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The translational values of TRIM family in pan-cancers: from functions and mechanisms to clinics

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Abstract

Cancer is the second leading cause of human death across the world. Tripartite motif (TRIM) family, with E3 ubiquitin ligase activities in majority of its members, is reported to be involved in multiple cellular processes and signaling pathways. TRIM proteins have critical effects in the regulation of biological behaviors of cancer cells. Here, we discussed the current understanding of the molecular mechanism of TRIM proteins regulation of cancer cells. We also

[1]Note: Zhao G and Liu C contributed equally to this work.

comprehensively reviewed published studies on TRIM family members as oncogenes or tumor suppressors in the oncogenesis, development, and progression of a variety of types of human cancers. Finally, we highlighted that certain TRIM family members are potential molecular biomarkers for cancer diagnosis and prognosis, and potential therapeutic targets.

Keywords: TRIM; cancer; prognosis; diagnosis; inhibitor; therapeutic targets

Abbreviations

AFP	Alpha-fetoprotein
AR	Androgen Receptor
Akt	protein kinase B
CDK	Cyclin Dependent Kinase
ccRCC	Clear Cell Renal Cell Carcinoma
CNS	Central Nerve System
CRC	Colorectal Cancer
CS	Cumulative Survival
CSS	Cancer Specific Survival
DFS	Disease Free Survival
E1	Ubiquitin-activating Enzyme 1

E2	Ubiquitin-activating Enzyme 2
E3	Ubiquitin Ligase 3
EMT	Epithelial Mesenchymal Transition
ERK	Extracellular Signal-Regulated Kinase
ER	Estrogen Receptor
ESR1	Estrogen Receptor 1
FoxM1	forkhead box M1
FRK	Fyn-related kinase
GC	Gastric Cancer
GLOBOCAN	WHO Global Cancer Observatory
GPER	G-Protein-Coupled Estrogen Receptor
GREB1	Growth Regulation by Estrogen in Breast Cancer 1
GSK-3β	glycogen synthase kinase-3β
HCC	Hepatocellular Carcinoma
HECT	Homologous to the E6AP Carboxyl Terminus
HER2	Human Epidermal growth factor Receptor 2

IHC	Immunohistochemistry
JAK	Janus Kinase
KI67	Protein Ki-67
LAC	Lung adenocarcinoma
MAPK	Mitogen-Activated Protein Kinases
miRNA	microRNA
MMP	Matrix Metalloproteinase
mTOR	mechanistic Target Of Rapamycin
NF-κB	Nuclear Factor Kappa B
Nrf	Nuclear related factor
NSCLC	Non-Small Cell Lung Cancer
PC	Prostate Cancer
OS	Overall survival
PFS	Progression Free Survival
PGF	Prostaglandin F
PKB	Protein Kinase B
PI3K	Phosphatidylinositol 3-Kinase

PML	promyelocytic leukemia
PML-RARA	promyelocytic leukemia-retinoic acid receptor alpha
PTC	Papillary Thyroid Carcinoma
PTEN	Phosphatase and tensin homolog deleted on chromosome TEN
PR	Progesterone Receptor
RCC	Renal Cell Carcinoma
RFS	Recurrence Free Survival/Relapse Free Survival
RING	Really Interesting New Gene
SOCS1	Suppressor Of Cytokine Signaling 1
SPHK	Sphingokinase
SPOP	Speckle-type POZ Protein
STAT	Signal Transducers and Activators of Transcription
TAM	Tamoxifen
TC	Thyroid Cancer

TDP	Transactive response DNA-binding Protein
TGF	Transforming Growth Factor
TNM	Tumor Node Metastasis
TRIM	Tripartite motif
TSC1	tuberous sclerosis complex subunit 1
VEGF	vascular endothelial growth factor
ZWINT	ZW10 Binding Factor
ZEB	Zinc finger E-box Binding homeobox.

Introduction

With increased incidence and mortality, cancers have become a worldwide threat to human health. According to the WHO Global Cancer Observatory (GLOBOCAN), there were 19.29 million new cancer cases and 9.96 million cancer deaths worldwide in 2020 (Sung, et al., 2021). There are mainly five types of cancer treatments: surgery, radiation, chemotherapy, immunotherapy and targeted therapy (Z. Li, Song, Rubinstein, & Liu, 2018). Although the above treatments have advanced much in recent couple of decades, the prognosis of cancer patients is still poor, and the five years survival rate remains at a low level (C. Wu, et al., 2019). This is mainly due to the molecular heterogeneity and late diagnosis of cancer (Z. Li, et al., 2018). Therefore, identification of cancer biomarkers for early detection, drug response prediction and progression monitoring of cancer are of great importance to the improvement and supervision of treatments.

Protein ubiquitination is one of the dynamic post-translational modifications involved in nearly all eukaryotic cells to regulate cellular processes (Swatek & Komander, 2016), including cell cycle, mitosis (Verdile & Merla, 2019), cell signaling transduction (Y. Kim & Jho, 2018), neuronal morphogenesis (Hamilton & Zito, 2013), autophagy (Grumati & Dikic, 2018), transcriptional regulation and protein quality control (Willis, Townley-Tilson, Kang, Homeister, & Patterson, 2010). During ubiquitination, an isopeptide bond is formed between the C terminus of ubiquitin and lysine residue of the target protein (Pickart, 2001). This process, also called ubiquitin conjugation, is catalyzed by the E1 ubiquitin-activating enzyme, followed by E2 ubiquitin-conjugating enzymes, and finally E3 ubiquitin ligases. E3 ubiquitin ligases are specifically responsible for recognizing target substrates (Deshaies & Joazeiro, 2009). Based on

domain structures, E3 ubiquitin ligases are classified into four families: HECT (homologous to the E6AP carboxyl terminus) family, the RING-finger-containing protein family, U-box family and plant homeodomain (PHD)-finger family (Bronner, et al., 2007; Hatakeyama & Nakayama, 2003; Y. Sun, 2003; N. Zheng & Shabek, 2017).

The tripartite motif (TRIM)-containing protein family members are characterized by an N-terminal TRIM region including a RING finger domain, one or two zinc-binding motifs (also known as B boxes (B1 box and B2 box)), and a coiled-coil region (Reymond, et al., 2001). TRIM proteins can be classified into subfamilies I to XI based on domain structures (Hatakeyama, 2011). There are more than 70 TRIM family members in humans (Hatakeyama, 2017). It has been reported that many oncogenes and tumor suppressors are regulated by the ubiquitin-proteasome system via altering the stability of ubiquitin E3 ligases (D. Wang, Ma, Wang, Liu, & Wei, 2017). Most of TRIM family members, like TRIM47, TRIM50, TRIM71, TRIM24 and TRIM59, with a RING-finger domain can be treated as E3 ubiquitin ligases, while some TRIM family members without RING-finger domain have not E3 ubiquitin ligase activity, such as TRIM14, TRIM16, TRIM20 and so on (Hatakeyama, 2011). Thus, certain number of TRIM family genes are considered to be involved in carcinogenesis and cancer progression.

In this paper, we review the TRIM family and discuss their regulatory role in cancers, as well as recent achievements in studying the clinical role of TRIM family. We concentrate on the crucial role of TRIM family for various signaling pathways, and summary current understanding about the function of TRIM family in breast, renal, thyroid, CNS, prostate, gastrointestinal, gynecological, lung and hepatocellular cancers. These cancer types were selected due to their high incidence and mortality (Sung, et al., 2021). Finally, we discuss the potential application of TRIM

family members as future biomarker and drug targets in several cancer types.

1. Materials and methods

2.1 Search strategy

The database of NCBI PubMed was systematically searched to identify all eligible article published up to March 21, 2021. Keywords and search terms include the following: “Motif Proteins, Tripartite” or “Proteins, Tripartite Motif” or “RBCC Proteins” or “Proteins, RBCC” or “RBCC Protein Family” or “Family, RBCC Protein” or “Protein Family, RBCC” or “TRIM Protein Family” or “Family, TRIM Protein” or “Protein Family, TRIM” or “TRIM Proteins” or “Proteins, TRIM”, “Neoplasm” or “Tumor” or “Cancer” or “Malignancy” or “Malignant Neoplasm”. These terms were applied to maximize the possibility of finding the appropriate articles. Besides, references in related articles were manually curated by Guo Zhao, Chuan Liu and Longxiang Xie. The languages of the retrieved studies were confined to English. Any discrepancy about inclusion and exclusion of articles would be resolved via group discussion.

2.2 Inclusion and exclusion criteria

The following criteria of eligible researches should be fulfilled: (1) full-text is available; (2) research about TRIM family and cancer; (3) studied the relationship between expression of TRIM proteins and clinicopathological parameters or survival of cancer, (4) reported an HR or OR value with 95% CIs or there were relevant data to calculate them. The exclusion criteria were as follows: (1) not written in English; (2) non-human researches; (3) reviews, comments, case reports, letters, and meta-analyses; (4) studies about other diseases not cancer; (5) not TRIM family studies; (6) studies lacked usable information, such as clinical features and survival curves. All of the evaluations were independently conducted by three individual researchers to ensure the accurate

inclusion of articles. Any conflicts were discussed by all authors to reach a consensus. The flow diagram of study is showed in **Figure S1**.

2.3 Data extraction

The following information was extracted from each included study: (1) basic information including first author's name, publication year, country, name of TRIM protein, cancer type, number of patients, expression of TRIM protein in tumor, detection methods, sample type, follow-up period, type of HR statistic, and type of survival analysis; (2) *p* values of the correlation between TRIM protein level and clinical features of tumors and the survival curve for calculating HRs and their 95% CIs; and (3) original data of HRs and their 95% CIs for survival analysis. If HRs were not directly accessible in the articles, Engauge Digitizer (Version 12.1) (http://markummitchell.github.io/engauge-digitizer/) was used to obtain the HRs and 95% CIs from Kaplan-Meier survival curves.

2.4 Statistical analysis

HRs with their 95% CIs was used for the survival analysis. When two or more different articles studied the same TRIM protein, a meta-analysis would be conducted to combine the effect size. All statistical analyses were done with the R studio-4.0.0. A p-value < 0.05 was considered statistically significant.

2. Expression of TRIM family members in various types of cancer

TRIM family members are found to be frequently dyregulated in various tumors. **Figure 1** summarizes the involvement of TRIM proteins in various human tumors via heatmap. Among 76 TRIM members, the expression level of 48 of them have been investigated by clinical and/or

laboratory methods. TRIM59 is most widely studied, and is found to be upregulated in eleven types of cancer such as lung cancer, ovarian cancer, colorectal cancer, and so on. Lung cancer is one of the most extensively studied cancers for TRIM members. In lung cancer, 18 TRIM proteins are found to be upregulated, while 10 members are down-regulated. Meanwhile, 11 TRIM proteins are up-regulated and 6 TRIM proteins are down-regulated in breast cancer. Both TRIM44 and TRIM59 are up-regulated while TRIM2, TRIM13, TRIM19 and TRIM28 are down-regulated in renal cell cancer. TRIM14, TRIM19 and TRIM44 are up-regulated and TRIM26 is down-regulated in papillary thyroid cancer. 13 TRIM proteins are overexpressed while 9 members are found to be down-regulated in CNS tumors. In colorectal cancer and gastric cancer, 17 and 11 TRIM family members and are reported to be overexpressed and 5 and 2 members are down-regulated, respectively. And TRIM25, TRIM31 and TRIM39 are overexpressed in pancreatic cancer. Moreover, 8 TRIM proteins are up-regulated and 2 TRIM proteins are down-regulated in prostate cancer. In addition, 5 and 4 TRIM family members are reported to be overexpressed and 2 and 4 members are down-regulated in cervical cancer and ovarian cancer, respectively. Finally, 13 TRIM proteins are revealed to be overexpressed while 7 members are down-regulated in liver cancer.

3. Regulation of TRIM family expression and the regulatory effect of TRIMs on multiple signaling pathways

4.1 Upstream regulators of TRIM

The expression of TRIM family members is regulated differently in various cellular processes through a complex transcriptional and post-transcriptional network. Although it is rather

elusive how TRIM-proteins are regulated, it is well documented that such processes involve interferon, transcription factors, signaling pathways microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), and circRNAs (circular RNAs) (**Table 1**).

Many TRIMs are induced by IFN-Is (Type I Interferons) and involve in regulating IFN-I-mediated innate immune by sumoylation and ubiquitination in most cases (L. Wang & Ning, 2021). For instance, expression of TRIM34/RNF21 is dramatically up-regulated in HeLa cells by IFN stimulation (Orimo, et al., 2000). TRIM22 can also be stimulated by IFN (Vicenzi & Poli, 2018). In 2009, Carthagena *et al.* showed that 16 of 72 human TRIM genes are up-regulated (TRIM5, 6, 14, 19, 20, 21, 22, 25, 26, 31, 34, 35, 38, 56, 58 and 69) by IFN-I and 7 TRIM genes (TRIM19, 20, 21, 22, 25, 56 and 69) can be induced by IFN-II (Carthagena, et al., 2009). Besides, interferon alpha (IFNα)-induced TRIM22 is revealed to interrupt HCV replication by ubiquitinating non-structural protein 5A (NS5A) (C. Yang, et al., 2016). Interestingly, upregulated PML (promyelocytic leukemia protein) by IFNβ in lung cancer cells can decrease MMP2 expression and cell invasion (Kuo, et al., 2014). This implies that TRIM proteins can be regulated by IFN and play crucial roles in regulating antiviral activities and cancer metastasis.

The expression of TRIM proteins is found to be regulated by several transcription factors. In the case of TRIM67, it has been shown that TRIM67 is down-regulated in colorectal tumors, and TRIM67 knockout increased the multiplicity, incidence and burden of colorectal tumors in $Apc^{Min/+}$ mice. Moreover, TRIM67 is regulated by p53 tumor suppressor. p53 can directly bind to the TRIM67 promoter upon cellular stress, and form a TRIM67/p53 self-amplifying loop that promotes p53-induced cell apoptosis and growth inhibition of colorectal cells (S. Wang, et al., 2019).

Nuclear related factor 1 and Nuclear related factor 2 (Nrf1 and Nrf2), which can regulate the activity of proteasome are two key regulators of intracellular antioxidant reaction. It has been shown that Nrf2 acts as a key transcription factor to upregulate the expression of TRIM11. Moreover, TRIM11 can significantly reverse the growth defects of Nrf2 deficient breast cancer cells (L. Chen, et al., 2017; Y. Zhang, et al., 2017).

The expression of TRIM proteins is also regulated by signaling pathways. For TRIM2, the activation of GPER and its downstream signal transduction MAPK/ERK signaling pathway leads to the increase of TRIM2 protein level and affects the binding of TRIM2 to Bim, a pro-apoptotic protein. This may lead to the degradation of Bim in tamoxifen-resistance breast cancer cells, thus causing tamoxifen resistance in breast cancer (H. Yin, et al., 2017). Hepatitis B protein X (HBx) can up-regulate the expression of TRIM52 via NF-κB signaling pathway, thus promoting tumor cell proliferation in HBV-related hepatocellular carcinoma (Y. Zhang, et al., 2017). Similarly, TRIM7 can also be induced by HBx in HBV-related hepatocellular carcinoma (X. Hu, Z. Tang, et al., 2019). What is more, both Feldmeyer *et al.* and Munding *et al.* showed that TRIM16 is actively secreted by keratinocyte under ultraviolet light in a caspase-1 dependent manner. And secreted TRIM16 binds to components of the pro-IL1β and inflammasome complex, which is involved in innate immune response in keratinocytes and skin cancer development (Feldmeyer, et al., 2007; Munding, et al., 2006; Sutton, et al., 2019). Another study reported that peroxide-induced p38 MAPK specifically induces TRIM28 Ser473 phosphorylation and the activation in CRC cells (L. T. Shen, Chou, & Kato, 2017). Meanwhile, zinc-finger protein 471 (ZNF471) recruits TRIM28 to the promoter of the target genes, thereby inducing enrichment of H3K9me3 for inhibiting expression of oncogenic protein AP-2 Alpha (TFAP2A) and plastin3

(PLS3) in gastric cancer (Cao, et al., 2018).

Last, the regulation of TRIM family expression also occurs at the post-transcriptional level by miRNAs, lncRNAs and circRNAs. miRNAs, a class of small noncoding RNAs, can fine tune the level of mRNAs. For TRIM11, two miRNAs (miR-24-3p and miR-5193) have been reported to control TRIM11 expression level. Yin *et al.* found that TRIM11 is specifically targeted by miR-24-3p, and the high expression of miR-24-3p reduces the TRIM11 expression in colon cancer (Y. Yin, et al., 2016). Pan *et al.* reported that miR-5193 targets the 3'-UTR of TRIM11, resulting in a down-regulation of TRIM11 expression (Y. Pan, et al., 2019).

Meanwhile, miR-135 can target TRIM16 to promote the sensitivity of non-small cell lung cancer to gefitinib (N. Wang & Zhang, 2018). Exogenous miR-519d can decrease the expression of TRIM32, thus promotes cisplatin-induced apoptosis of CRC cells (Su, Wang, Wang, & Wang, 2020). miR-873 can suppress expression of TRIM25, thus upregulates metastasis associated protein 1 (MTA-1) in HCC (Y. H. Li, Zhong, Zang, & Tian, 2018). Moreover, miR-365 suppresses the expression of TRIM25 and increases the expression of proapoptotic protein in NSCLC cells (Q. Han, Cheng, Yang, Liang, & Lin, 2019). And miR-24-3p downregulation can promote TRIM11 upregulation in CRC (Y. Yin, et al., 2016).

Furthermore, miR-101-3p, miR-195-5p and miR-3614-3p negatively regulated the mRNA and protein expression of TRIM44, TRIM14 or TRIM25 by interacting with their 3'- untranslated regions (UTRs), and inhibited the proliferation and migration of glioblastoma cells, gastric cancer cells or breast cancer cells, respectively (L. Li, Shao, Zou, Xiao, & Chen, 2019; F. Wang, Ruan, Yang, Zhao, & Wei, 2018; Z. Wang, et al., 2019).

Up to now, eight studies have revealed that lncRNAs can also regulate TRIM family

members in various cancers. Generally, NCK1-AS1, ZFPM2-AS1, DUXAP8, ELFN1-AS1, LINC00265 and TP73-AS1 can act as molecular sponge of miRNAs to increase level of TRIM24, TRIM29 or TRIM44 in glioma, CRC, and NSCLC (L. Huang, et al., 2020; Ji, Tao, Sun, Xu, & Ling, 2020; Lei, Feng, & Hong, 2020; S. Luo, Shen, Chen, Li, & Chen, 2020; S. Sun, Li, Ma, & Luan, 2020; M. Xiao, Liang, & Yin, 2021). In NSCLC, DUXAP8 and TP73-AS1 are reported to up-regulate expression of TRIM44 or TRIM19 by sponging and inhibiting miR-498 or miR-34a-5p, respectively (Ji, et al., 2020; S. Luo, et al., 2020). Similarly, ELFN1-AS1 act as a molecular sponge of miR-4644 to increase mRNA and protein level of TRIM44 in CRC cells (Lei, et al., 2020). And LINC00265 can directly bind to miR-216b-5p and inhibit miR-216b-5p, which increases the expression of TRIM44 in CRC cells (S. Sun, et al., 2020).

In addition, KCNQ1OT1 and LINC01857 can increase the expression of TRIM14 and TRIM65 in tongue cancer and glioma through sponging miRNAs, respectively (G. Hu, Liu, Wang, Wang, & Guo, 2019; Qiao, et al., 2020).

Notably, two circRNAs (circEPSTI1 and circNDUFB2) have been reported to control TRIM members' expression level. Downregulation of circEPSTI1 inhibits the proliferation and invasion of NSCLC cells by inhibiting TRIM24 expression via upregulation of level of miR-1248 (T. Yang, et al., 2020). Recently, circNDUFB2 was found to interact with TRIM25 and Insulin-like growth factor 2 messenger RNA-binding proteins (IGF2BPs) as a scaffold, enhancing ubiquitination and degradation of IGF2BPs, a driver of tumor malignant progression (B. Li, et al., 2021).

4.2 The regulatory effect of TRIMs on multiple signaling pathways

TRIM family is a multiple functional E3 Ubiquitin ligase family involved in a variety of cellular pathways (van Gent, Sparrer, & Gack, 2018). The development of cancer involves a

variety of signaling pathways (Dolcet, Llobet, Pallares, & Matias-Guiu, 2005; Tilborghs, et al., 2017), such as NF-κB pathway, AKT pathway, TGF-β pathway, β-catenin pathway, p53 pathway, JAK/STAT pathway, MAPK/ERK pathway, autophagic degradation pathway, DNA damage response pathway and EGF pathway. A number of studies had shown that TRIM proteins can modulate these pathways by regulating several downstream targets' expression in cancers (**Table 2**).

4.2.1 TRIM in NF-κB pathway

Nuclear factor kappa B (NF-κB) family plays a key role in regulating the immune response and inflammation, and is also closely associated with the proliferation, migration, and apoptosis of cancer cells (Dolcet, et al., 2005). Upstream molecules such as Ras, (epidermal growth factor receptor) EGFR, (placenta growth factor) PGF, and HER2 can influence the increase of NF-κB signal. And NF-κB pathway can stimulate proliferation regulating genes such as cyclin D1 and c-Myc, promote VEGF-dependent angiogenesis, and enhance the effect of telomerase on cell immortalization (Tilborghs, et al., 2017). TRIM family can also regulate innate immunity and adaptive immunity, such as regulating pattern recognition receptors and T cell development and activation (W. Yang, Gu, Zhang, & Hu, 2020). Furthermore, TRIM family play a crucial role in inflammatory and antiviral reaction through NF-κB signaling pathway (Uchil, et al., 2013). For instance, antiretroviral TRIM1 and TRIM62 proteins restrict murine leukemia virus (MLV) release by regulating NF-κB/AP-1 signaling (Uchil, et al., 2013). TRIM9 as a brain-specific negative regulator of NF-κB pro-inflammatory signaling pathway, significantly affects production of NF-κB-induced inflammatory cytokine (M. Shi, et al., 2014). However, overexpression of TRIM25 enhances K63-linked ubiquitination of TRAF2 and promotes TNF-α-induced NF-κB

signaling in human embryonic kidney 293T, HeLa cells, THP-1 cells, and PBMCs (Y. Liu, Liu, et al., 2020).

Numerous studies have shown that TRIM family is involved in the regulation and function of NF-κB signaling pathway, and thus plays a key role in the development of various cancers. **Figure 2** shows the relationship between the TRIM family and the NF-κB pathway in tumor progression.

For TRIM52, Yang *et al.* found that the overexpression of it increases the expression of IKK, IKB, and nuclear protein p65, thus activating the NF-κB pathway in ovarian cancer cell line HO8910. Furthermore, TRIM52 downregulates the mRNA and protein levels of MMP9 and BCL2, and upregulates the expression of caspase-3, which is the downstream effectors of NF-κB signaling pathway (W. Yang, et al., 2018).

In the case of TRIM44, its knockdown significantly attenuates TNF-mediated NF-κB transcription, and reduces the phosphorylation of NF-κB subunit p65 in breast cancer cell lines MCF-7 and MDA-MB-231 (Kawabata et al., 2017). These results suggest that TRIM44 enhances the activity of NF-κB pathway in breast cancer cells. It was also found that TRIM44 upregulates the expression of CXCL10 and MMP9 by activating NF-κB signaling pathway in NSCLC, which promotes the migration and invasion of NSCLC (Q. Luo, et al., 2015).

TRIM71 is an E3 Ubiquitin ligase and its RING domain is important for ubiquitin-dependent degradation or stabilization of target proteins. TRIM71 interacts with iκBα through its RING domain to participate in iκBα dependent degradation, thus reduces the level of iκBα protein and promotes the activation of NF-κB pathway. In addition, TRIM71 overexpression can increase the phosphorylation of p65 and nuclear translocation, thus increase the activity of NF-κB pathway and accelerate the proliferation of NSCLC (Ren, et al., 2018).

Other studies show that TRIM proteins can also inhibit the activity of NF-κB pathway. For example, TRIM40 reduces the expression level of Kappab Kinase γ subunit (the key regulator of NF-κB activation) through ubiquitination and thus inhibits the activity of NF-κB (Noguchi, et al., 2011). In addition, low TRIM13 expression was found to be associated with high NF-κB and MMP-9 expressions based on the data from 87 RCC patients (H. Li, et al., 2020). TRIM13 acts as a tumor suppressor in NSCLC through inhibiting NF-κB pathway. Overexpression of TRIM13 increases NF-κB in cytoplasm and decreases NF-κB in nucleus (L. Xu, Wu, Zhou, Wu, & Fang, 2019). Meanwhile, an NF-κB inhibitor, PDTC, significantly attenuates the influence of TRIM13 knockdown on cell proliferation and apoptosis (H. Li, et al., 2020; L. Xu, et al., 2019).

4.2.2 TRIM in AKT signaling pathway

AKT serine/threonine Kinase B (PKB) regulates cell survival, proliferation, growth, apoptosis and glycogen metabolism (M. Song, Bode, Dong, & Lee, 2019). Phosphorylated AKT (p-AKT) is associated with cell apoptosis, proliferation, and movement disorders by inducing signals that interfere with the normal regulatory mechanisms of AKT signaling (M. Song, et al., 2019). Several studies have shown that TRIM family may directly or indirectly regulate AKT signaling to modulate the development of various cancers (**Figure 3**).

Knockdown of TRIM37 significantly decreases the level of phosphorylated PI3K and AKT in glioma cell lines. PI3K/AKT signaling activator SC79 can partially reverse the inhibitory effect of si-TRIM37 on the proliferation and migration of glioma cells (S. L. Tang, Gao, & Wen-Zhong, 2018).

Overexpression of TRIM13 weakens AKT signaling pathway by inhibiting phosphorylation of AKT, thus inhibiting cell migration and invasion (H. Li, et al., 2020). In *TRIM11* knockdown

lung cancer cells, PI3K/AKT activity is also inhibited (Y. Chen, Sun, & Ma, 2017; X. Wang, et al., 2016). Moreover, TRIM59 mediates AKT signaling. Silencing of TRIM59 inhibits the FAK/AKT/MMP pathway, and over-activation of FAK/AKT/MMP pathway plays a key role in the proliferation and invasion of ovarian cancer cells. Inhibition of TRIM59 significantly reduces the level of phosphorylated PI3K and AKT (P. Zhang, Zhang, Wang, Zhang, & Qi, 2019). Besides, the expression of TRIM59 is up-regulated in human cholangiocarcinoma (CCA) tissues. With the capacity of promoting CCA cell proliferation and regulating cell apoptosis via PI3K/AKT/m-TOR signaling pathway, TRIM59 could be a negative prognostic factor in patients with CCA (H. Shen, et al., 2019).

Under or over expression of TRIM31 can inhibit or promote the proliferation, invasion, and migration of glioma cells via AKT signaling pathway (G. Shi, et al., 2019a). Meanwhile, knockdown of TRIM31 inhibits the proliferation and invasion of gallbladder cancer cells by down-regulating MMP29 via PI3K/AKT signaling pathway (H. Li, et al., 2018).

TRIM44 promotes proliferation and invasion of prostate cancer cells by regulating AKT/mTOR signaling pathways and their downstream targets, such as STAT3, at least partially through activating PI3K/AKT signaling pathways (Y. Tan, Yao, Hu, & Liu, 2017; Xiong, et al., 2018).TRIM27 not only interacts with PTEN, but also promotes the ubiquitination of PTEN in ESCC cells and thus promotes ESCC cell proliferation (L. Ma, Yao, Chen, & Zhuang, 2019). In addition, TRIM27 can activate EMT and p-AKT in colorectal cancer (Y. Zhang, Feng, et al., 2018).

4.2.3 TRIM in TGF-β signaling pathway

TGF-β is one member of the growth-related factor superfamily. TGF-β pathway is involved

in cell proliferation, differentiation, apoptosis and migration. When TGF-β binds to its receptors, SMAD2, SMAD3, and SMAD4 migrate from the cytoplasm to the nucleus for transcriptional activation, and SMAD7 inhibits TGF-β signaling (Meng, Nikolic-Paterson, & Lan, 2016; Q. Yin, Wyatt, Han, Smalley, & Wan, 2020). TGF-β signaling pathway is suppressed in a variety of tumors. In healthy cells and early-stage cancer cells, this pathway inhibits tumor activity through cell cycle arrest and apoptosis. However, in advanced cancer, activation of TGF-β signaling may promote tumor development, including tumor cell proliferation, metastasis and drug resistance (Colak & Ten Dijke, 2017).

Recent studies have revealed various relationships between TRIM proteins and the TGF-β signaling (**Figure 4**). TRIM33 is identified as a SMAD4 independent regulator of TGF-β signaling pathway (Herquel, et al., 2011). Meanwhile, TRIM33 can regulate both the SMAD4 mononuclear diphosphate ligase and the phosphorylation of SMAD2/3 in TGF-β pathway (Herquel, et al., 2011). TRIM66, an oncoprotein, may partially promote cell invasion and inhibit cell apoptosis by activating TGF-β signaling in osteosarcoma (Y. Chen, et al., 2015). The down-regulation of TRIM59 reduces the level of p-SMAD2, thus inhibiting activity of TGF-β signaling in breast cancer (Y. Zhang & Yang, 2017). Zhu *et al.* reported that proteins associated with TGF-β signal transduction (BMP-4, p-SMAD2 and p-SMAD4) are regulated by TRIM25 (Z. Zhu, et al., 2016). Sun *et al.* showed that TRIM25 increases the phosphorylation of SMAD2 and SMAD4 in downstream of TGF-β pathway in colorectal cancer cells (N. Sun, Xue, Dai, Li, & Zheng, 2017).

4.2.4 TRIM in Wnt/β-catenin signaling pathway

β-catenin (CTNNB1 coding) is a subunit of the cadherin complex on the cell surface, acting as an intracellular signal transducer for Wnt signaling (Monga, 2015). Wnt/β-catenin signaling

pathway is an evolutionarily conserved pathway that regulates cell fate, organ development, tissue homeostasis, injury, and repair (Steinhart & Angers, 2018).

Several studies have shown that TRIM proteins are connected to the Wnt/β-catenin signaling pathway (**Figure 4**). TRIM44 silencing significantly down-regulates the expression of β-catenin thus inhibiting the Wnt/β-catenin signaling pathway in human thyroid cancer cells (Z. Zhou, Liu, Ma, & Chang, 2017). Knockdown of TRIM59 promotes excessive E-cadherin expression and decreases β-catenin expression, leading to high cell adhesion, low Wnt signaling, and high cell death, and ultimately reducing tumor formation and metastasis (H. Tan, et al., 2018). Moreover, TRIM59 increases the expression of Annexin A2, an activator of β-catenin signal in ovarian cancer (Y. Wang, et al., 2018). Overexpression of TRIM59 can up-regulate Survivin, β-catenin and c-Myc, and down-regulate Bax and Bim in neuroblastoma. These effects of TRIM59 can be blocked by Xav939, an inhibitor of Wnt/β-catenin signal pathway (G. Chen, Chen, Ye, Tan, & Jia, 2019). It was also found that TRIM29 regulates the β-catenin-dependent signaling pathway in pancreatic cancer and its interaction with β-catenin may stabilize β-catenin and activate Disheveled2 in pancreatic cancer (L. Wang, et al., 2009). Up-regulation of TRIM32 significantly enhances the expression of β-catenin and its downstream targets TCF1, cyclinD1, Axin2, and MMP7 (C. Wang, et al., 2018). Additionally, TRIM66 can promote the GSK-3β (glycogen synthase kinase-3β) dependent Wnt/β-catenin signaling pathway in HCC (Fan, Du, & Liu, 2019).

4.2.5 TRIM in p53 signaling pathway

Tumor suppressor gene *TP53* plays an important role in maintaining genomic stability and cancer prevention by regulating stress responses such as apoptosis, cell cycle arrest, and senescence. p53 achieves its tumor suppression function through a large number of p53 target

genes. Mutations in *TP53* gene alter the p53 response pathway and promote the development of many cancers. p53 is tightly regulated primarily through post-translational modifications, such as ubiquitination, to achieve its appropriate levels and normal function (Fischer, 2017; J. Liu, et al., 2014; Prokocimer, Molchadsky, & Rotter, 2017). Several studies revealed the roles of p53 signal pathway and TRIM family. And TRIM family can be divided into two types based on their roles in regulating p53 pathway: positive regulatory TRIM proteins and negative regulatory TRIM proteins (**Figure 5**).

p53 positive regulatory TRIM proteins

There are seven positive regulatory TRIM proteins for p53 signaling pathway. Overexpression of TRIM13 leads to p53 homeostasis and decreasing of AKT kinase activity in renal cell carcinoma (H. Li, et al., 2020). Knockdown of TRIM52 affects cell cycle progression in a p53 dependent manner, and *TP53* ablation inhibits the proliferation of TRIM52-knockdown glioblastoma multiforme cell lines (Benke, et al., 2018). Previous studies showed that p53 can be inhibited by MDM2 in two ways: by blocking the ubiquitin ligase activity of MDM2 and/or by directly binding to p53, masking transactivation domain of p53 (J. Di, Zhang, & Zheng, 2011). Besides, Wang *et al.* found that TRIM67 directly interacts with the C-terminal of p53, leading to disruption of the interaction between MDM2 and p53, thereby inhibiting MDM2-mediated p53 ubiquitination and increasing p53 protein levels in colorectal cancer (S. Wang, et al., 2019). Furthermore, TRIM19, TRIM13, and TRIM8 can improve the stability of p53 by interfering with the activity of MDM2. Interestingly, p53 can induce the expression of TRIM8, which in turn interacts directly with p53, and stabilizes p53 by impairing the interaction between p53 and MDM2 under stress (Caratozzolo, et al., 2012; Valletti, Marzano, Pesole, Sbisa, & Tullo, 2019; S.

Wang, et al., 2019).

p53 negative regulatory TRIM proteins

Other TRIM family members, including TRIM66 (Y. Chen, et al., 2015), TRIM59 (Aierken, Seyiti, Alifu, & Kuerban, 2017), TRIM32 (M. Ito, et al., 2017), TRIM31 (P. Guo, Qiu, et al., 2018), TRIM29 (C. Liu, Huang, Hou, Hu, & Li, 2015), TRIM24 (J. Wang, et al., 2014), TRIM21 (Z. Zhao, et al., 2020) and TRIM11 (J. Liu, et al., 2017), can act as negative regulators of p53.

TRIM66 silencing can significantly increase the expression of p53 in osteosarcoma (Y. Chen, et al., 2015). TRIM59 promotes p53 ubiquitination and degradation in cervical cancer (Aierken, et al., 2017). Meanwhile, TRIM59 negatively regulates p53 protein levels, but does not significantly affect mRNA levels in osteosarcoma cells (J. Liang, et al., 2016). TRIM32 promotes p53 degradation through ubiquitination and negatively regulates p53-mediated apoptosis, cell cycle arrest, and senescence (M. Ito, et al., 2017). In addition, TRIM31 directly affects the upstream inhibitor of p53, the AMPK pathway, and mediates the general degradation of p53 by K48 in a domain-dependent manner (Y. Chen, et al., 2015). TRIM29 binds to p53 and inhibits the expression of p53 regulatory genes, including p21 and NOXA (C. Liu, et al., 2015; X. Song, et al., 2015). TRIM24, another key regulator of p53, regulates the degradation of p53 loop domains (J. Wang, et al., 2014). TRIM21 regulates the cell proliferation, cell migration, and cell senescence through the p53-p21 pathway in glioma (Z. Zhao, et al., 2020). Recent studies have revealed the diverse functions of TRIM24, including not only regulating p53 and a PHD/bromine domain histone reader, but also activating estrogen-regulated transcriptional processes (L. Chen & Yang, 2019; Patel & Barton, 2016).

4.2.6 TRIM in JAK/STAT pathway

Effective cell-to-cell communication is critical for tissue and organ homeostasis, development and host defense. JAK/STAT pathway mediates direct signaling between transmembrane receptors and the nucleus, thus is important for cell communication (O'Shea, et al., 2015).

So far, 13 studies have reported that TRIM proteins regulate JAK/STAT pathway in tumors from different origins (**Figure 4**), including acute promyelocytic leukemia (APL) (Kawasaki, et al., 2003), breast cancer (G. Hu, Pen, & Wang, 2019), CRC (T. He, Cui, Wu, Sun, & Chen, 2019; Z. Jin, et al., 2018; S. Pan, et al., 2019; W. Xu, et al., 2016), esophageal cancer (Xiong, et al., 2018), lung cancer (Z. Cui, Liu, Zeng, Zhang, et al., 2019; H. Yin, Li, Chen, & Hu, 2019), glioblastoma (Sang, et al., 2018; Sang, et al., 2019), PTC (W. Sun, et al., 2020) and HCC (Kato, et al., 2015). Generally, TRIM14 (G. Hu, W. Pen, et al., 2019; Z. Jin, et al., 2018; W. Sun, et al., 2020), TRIM29 (W. Xu, et al., 2016), TRIM32 (H. Yin, et al., 2019), TRIM44 (Xiong, et al., 2018), TRIM52 (S. Pan, et al., 2019), TRIM59 (Z. Cui, Liu, Zeng, Zhang, et al., 2019; Sang, et al., 2018; Sang, et al., 2019), TRIM66 (T. He, et al., 2019) can positively regulate JAK/STAT3 pathway in various cancers, while PML negatively regulates JAK/STAT pathway in HCC (Kato, et al., 2015) and APL (Kawasaki, et al., 2003).

Overexpression of TRIM14 was found to increase the level of phosphorylated STAT3 (p-STAT3), thus activates JAK/STAT3 pathway in breast cancer (G. Hu, W. Pen, et al., 2019), PTC (W. Sun, et al., 2020) and CRC (Z. Jin, et al., 2018). In addition, TRIM14 (Z. Jin, et al., 2018), TRIM29 (W. Xu, et al., 2016), TRIM52 (S. Pan, et al., 2019) and TRIM66 (T. He, et al., 2019) can increase level of p-STAT3 or p-JAK2 and activate JAK/STAT3 pathway in CRC. Importantly, both

TRIM14 and TRIM52 can promote ubiquitination of SOCS1 or SHP2 (negative regulators of STAT3 activation) and decrease their expression in PTC (W. Sun, et al., 2020) or CRC (S. Pan, et al., 2019). And TRIM14 can increase level of SPHK1, a positive regulator of JAK/STAT3 pathway activation in CRC (Z. Jin, et al., 2018). Additionally, TRIM32 and TRIM59 were reported to promote tumorigenesis of glioblastoma (Sang, et al., 2018; Sang, et al., 2019) and lung cancer (Z. Cui, Liu, Zeng, Zhang, et al., 2019; H. Yin, et al., 2019) through activating JAK/STAT3 pathway. TRIM59 can induce ubiquitination and degradation of mH2A1, a tumor suppressive histone variant, and this leads to activation of STAT3 signaling and increased tumorigenicity of the glioblastoma (Sang, et al., 2019). Furthermore, TRIM59 can interact with nuclear STAT3 and prevent dephosphorylation of STAT3 through nuclear form of T-cell protein tyrosine phosphatase (TC45). This promotes tumorigenesis of glioblastoma (Sang, et al., 2018). TRIM59 can enhance gefitinib resistance of lung adenocarcinoma cells through activating STAT3 signaling (Z. Cui, Liu, Zeng, Zhang, et al., 2019).

However, PML/retinoic acid receptor alpha (PML-RARA) can dissociate PML from STAT3, which restores activity of STAT3 suppressed by PML in APL cells (Kawasaki, et al., 2003). Besides, endogenous PML is revealed to suppress phosphorylation and transcriptional activation of STAT3 in hepatoma cells (Kato, et al., 2015). Strikingly, JAK/STAT-mediated signaling pathway can up-regulate PML in cell senescence process triggered by various anti-cancer chemotherapeutics, such as etoposide (ET) and camptothecin (CPT) and so on (Hubackova, et al., 2010). This suggests that PML plays a crucial role in tumor inhibition by JAK/STAT3 signaling pathway.

4.2.7 TRIM in MAPK signaling pathway

Mitogen-activated protein kinase (MAPK) pathway is a crucial signaling pathway, which can regulate multiple biological processes, including cell proliferation, apoptosis, differentiation, stress responses and inflammation (Cuenda & Rousseau, 2007; Y. J. Guo, et al., 2020). There are three major subfamilies of MAPK: extracellular-signal-regulated kinases (ERK/MAPK, Ras/Raf1/MEK/ERK); the c-Jun N-terminal or stress-activated protein kinases (JNK or SAPK)); and MAPK14 (J. Y. Fang & Richardson, 2005). What is more, activation of ERK/MAPK signaling pathway can lead to transformation of normal cells into tumor cells (Y. J. Guo, et al., 2020). Fifteen studies have showed that TRIM family members affect MAPK signaling through different mechanisms in various tumors (**Table S2**).

As an important member of MAPK family, p38 kinase is widely involved in regulating stress-induced cell death and inflammation (Cuenda & Rousseau, 2007). Short isoform of TRIM9 (TRIM9s) was reported to promote phosphorylation of p38, and p38 activation, thus inhibits glioblastoma progression. Moreover, TRIM9s can stabilize MKK6 through promoting K48-K63 ubiquitination transition of MKK6 on Lys82. Interestingly, MKK6 enhances phosphorylation of TRIM9s to inhibit ubiquitination of TRIM9s through p38 signaling pathway. This generates a positive feedback loop between MKK6 and TRIM9s through p38 signaling pathway in glioblastoma (K. Liu, et al., 2018). Strikingly, receptor for activated C kinase (RACK1) is the target of TRIM45-mediated proteasomal degradation, which shows that overexpression of TRIM45 results in the development of melanoma through inhibition of the MAPK pathway (Sato, Takahashi, Hatakeyama, Iguchi, & Ariga, 2015).

Furthermore, the knockdown of TRIM44 inhibits the invasion and migration of intrahepatic cholangiocarcinoma (ICC) cells. And overexpression of TRIM44 was found to induce EMT by

activating MAPK signaling pathway, which lead to development of ICC (R. Peng, et al., 2018).

4.2.8 TRIM in autophagic degradation pathway

Autophagy is a major degradation system through delivering and degrading cytoplasmic materials in the lysosome (Mizushima & Komatsu, 2011), and is initiated by combination of ATG1 (autophagy related 1)/ULK1 (Unc-51 like autophagy activating kinase-1) complex and PI3K-III complex in response to stress and metabolic needs of cells (Bento, et al., 2016). PI3K/AKT/mTOR signaling and BECN1 phosphorylation were reported to play crucial roles in regulation of autophagy in mammalian cells (Menon & Dhanasekaran, 2018; Popova & Jucker, 2021). Many cancer cells have high autophagic flux, causing resistance to metabolic stress and apoptosis. Thus, autophagy components are promising targets for anti-cancer strategy (Bhat, et al., 2018).

Up to now, seven reports have shown that TRIM proteins regulate autophagy in tumors. Generally, TRIM19 can promote or inhibit autophagic activity in various hematological malignancy including acute myeloid leukemia (AML) (Q. Zou, et al., 2017), APL (Isakson, Bjoras, Boe, & Simonsen, 2010; Missiaglia, et al., 2016) and acute lymphoblastic leukemia (Laane, et al., 2009). Besides, TRIM59 and TRIM65 can degrade crucial autophagic regulator (BECN1 (T. Han, et al., 2018) and ATG7 (X. Pan, Chen, Shen, & Tantai, 2019)) or specific transcription factor (PDCD10 (P. Tan, et al., 2018)), then regulate tumor progression in breast cancer (P. Tan, et al., 2018) and non-small-cell lung cancer (T. Han, et al., 2018).

Overexpression of PML was reported to be involved in primary NPM1-mutated AML by stabilizing NPM1 (Q. Zou, et al., 2017). Meanwhile, expression of PML can enhance the autophagic activity of NPM1-mA knockdown cells through activating AKT signaling pathway (Q. Zou, et al., 2017). It was also revealed that PML can suppress autophagy by regulating

autophagosome formation in a p53-dependent manner at mitochondria-associated membranes of APL cells (Missiroli, et al., 2016). Remarkably, PML deletion can promote autophagy by activating AMPK/mTOR/Ulk1 signaling pathway, thus enhances occurrence of APL (Missiroli, et al., 2016). This indicates that targeting PML may be a potential way to treat APL.

However, fusion of PML and retinoic acid receptor alpha (RARA) can lead to clinical chemotherapy failure (Isakson, et al., 2010). Isakson et al. found that both all-trans retinoic acid and arsenic trioxide can induce autophagy through mTOR pathway in APL cells. And PML/RARA is degraded by autophagy through p62 and ULK1 (Isakson, et al., 2010). Another study found that PML can promote dexamethasone-induced autophagy, thus enhances the ability of dexamethasone to kill primary leukemic cells (Laane, et al., 2009). TRIM59 was also reported to promote breast cancer metastasis through inhibiting p62-selective autophagic degradation of programmed cell death protein 10 (PDCD10) (P. Tan, et al., 2018).

Moreover, overexpression of TRIM59 was revealed to significantly increase Tumor necrosis factor receptor-associated factor 6 (TRAF6)-induced ubiquitination of BECN1, thus inhibits autophagy in NSCLC. This suggests that TRIM59 can affect autophagy through regulating transcription and ubiquitination of BECN1 in NSCLC (T. Han, et al., 2018). In addition, TRIM65 can induce ubiquitination and degradation of trinucleotide repeat-containing gene 6A (TNRC6A), and then inhibit the expression of miR-138-5p. Inhibition of miR-138-5p can induce the expression of ATG7 (a crucial autophagy mediator), thereby increasing autophagy in NSCLC (X. Pan, et al., 2019).

4.2.9 TRIM in EGF signaling pathway

Epidermal growth factor (EGF) pathway plays a role in epithelial tissue development and

homeostasis as well as tumorigenesis (Sigismund, Avanzato, & Lanzetti, 2018). Some members of TRIM family are found to interact with factors associated with EGF of various tumors, such as glioma (K. Di, Linskey, & Bota, 2013), lung adenocarcinoma (Kuo, et al., 2014), head and neck squamous cell carcinoma (HNSCC) (Klanrit, et al., 2009).

EGFR activity is frequently abnormally upregulated in lung adenocarcinoma (LAC) and thus is considered to be a driving oncogene for LAC. PML was found to inhibit nuclear EGFR (nEGFR) in LAC to promote expression of cyclin D1 (CCND1), thus promotes the growth of LAC cells (Kuo, et al., 2014). Similarly, PML isoform IV was reported to link with decreased expression of nEGFR target gene CCND1 and suppress the growth of the lung cancer cells (Kuo, et al., 2013). PML can reduce nuclear EGFR-mediated activation of matrix metalloprotease-2 (MMP2), which inhibits lung cancer metastasis (Kuo, et al., 2014). Moreover, transactivating isoforms of p73 (TAp73), especially TAp73beta, can induce PML and result in the inhibition of EGFR promoter. This significantly downregulates EGFR protein expression, inducing apoptosis in HNSCC cell(Klanrit, et al., 2009). Another study found that PML can interact with early region 1A (E1A) gene and downregulate EGFR in HNSCC cells (Flinterman, Gaken, Farzaneh, & Tavassoli, 2003).

Other TRIM family members were also reported to play important roles in regulation of EGF pathway in tumors. For instance, the overexpression of TRIM59 significantly promotes cell viability and suppresses cell apoptosis in gefitinib resistance EGFR mutant LAC cells (Z. Cui, Liu, Zeng, Zhang, et al., 2019). Overexpression of TRIM11 is associated with increased expression of EGFR and upregulated mRNA levels of HB-EGF (heparin-binding EGF-like growth factor) in glioma cells (K. Di, et al., 2013). Besides, TRIM59 overexpression induced by EGFR can promote tumorigenesis in glioblastoma, which is regulate by SOX9 (Sang, et al., 2018).

4.2.10 TRIM in DNA damage response pathway

DNA damage and repair process is a complicated cellular behavior, involved in balance of cell survival and death (Roos, Thomas, & Kaina, 2016). Some members of TRIM family have been reported to play important roles in DNA damage and repair in esophageal cancer (G. Wu, et al., 2018), HCC (Chung & Wu, 2013), ovarian cancer (W. W. Pan, Zhou, et al., 2013) and so on.

TRIM19 (PML) was described as a tumor suppressor in APL (Roos, et al., 2016). PML nuclear bodies (NBs) disruption can increase exchange of sister-chromatid and abnormalities of chromosome and elevate the possible pathogenesis of APL (Vois et, et al., 2018). Interestingly, up-regulation of PML and HBV exacerbation are reactive to DNA damage in normal liver tissue. However, nuclear PML are non-response to DNA damage in HCC cells that lost HBV DNA and HBsAg. This shows that PML deficiency enhances genomic instability and promotes HBV-related hepatocarcinogenesis (Chung & Wu, 2013). Similarly, inhibition of PML by HBsAg interferes DNA damage and repair and finally facilitates hepatocarcinogenesis (Chung, 2013). Moreover, PML can protect cancer cells from DNA damage. Pan *et al.* found that PML is co-localized with death-associated protein DAXX, an oncoprotein in ovarian cancer. DAXX can protect ovarian cancer cells from DNA damage in a PML NBs depended way (W. W. Pan, Yi, et al., 2013). Another study showed that overexpression of DAXX protects ovarian cancer cells from DNA damage induced by x-irradiation and chemotherapy, depending on interaction with PML (W. W. Pan, Zhou, et al., 2013). Besides, down-regulation of PML can disrupt the response to genotoxic stress, then inhibits growth of mutant p53-expressing cancer cells (Haupt, et al., 2009).

Several other TRIM family members are also reported to play a role in DNA damage of cancers. For instance, increased expression of TRIM37 was associated with increased resistance to

the DNA-damaging anticancer drug cisplatin by activating the NF-κB pathway in esophageal cancer cells (G. Wu, et al., 2018). Another study found that TRIM32 is induced by p53 in stress response process, and overexpression of TRIM32 can promote the tumorigenesis and oncogenic transformation of mice by downregulating p53 (J. Liu, et al., 2014). TRIM24 also targets activated p53 for degradation to inhibit p53-regulated response to DNA damage (Jain, Allton, Duncan, & Barton, 2014). Notably, TRIM37 was revealed to interact with double-strand break (DSB) repair factors (BMI1 and FRA3B) and promote the doxorubicin-induced DNA damage repair in triple-negative breast cancer (TNBC) (Przanowski, et al., 2020).

4.2.11 TRIM in other pathways

Apart from the main pathways mentioned above, some TRIM proteins are also involved in the growth of tumor cells through other pathways and their substrates.

Expression of TRIM28 is positively correlated with glioblastoma malignancy and there is a negative correlation between TRIM28 expression and p21 expression in glioblastoma multiforme patients (Z. X. Qi, et al., 2016). TRIM44 modulates Fyn-related kinase (FRK) in patients with RCC (Yamada, et al., 2020). TRIM44 also significantly decreases cyclinD1 and c-Myc expression in PTC cells. TRIM44 partially mediates the mTOR pathway in human esophageal cancer (Patel & Barton, 2016; Xiong, et al., 2018; Z. Zhou, et al., 2017). TRIM31 directly interacts with the upstream inhibitory TSC1 and TSC2 complexes of the mTORC1 pathway to promote ubiquitination and degradation of K48 ligands (P. Guo, Ma, et al., 2018). Interestingly, TRIM59 can suppress nitric oxide (NO) production through promoting the binding of PIAS1 and STAT1, which inhibits the activation of JAK2-STAT1 signaling pathway in macrophages of melanoma (Su, Zhang, et al., 2020). Moreover, TRIM59 regulate the Ras/Braf/MEK/ERK signaling pathway by

linking to the SV40 Tag/pRB/p53 pathway to promote prostate cancer progression (Valiyeva, et al., 2011).

In addition to the role of oncogenes, many TRIM proteins also play a role as tumor suppressor. TRIM36 significantly down-regulates T-cell receptor signaling and enhances anti-androgen effect by inhibiting MAPK/ERK signaling in prostate cancer (Kimura, et al., 2018). Besides, overexpression of TRIM3 can up-regulate caspase-3 activity and increase the cleaved caspase-3 and p53 expression as well as decreased the p38 phosphorylation level in cervical cancer cells (Y. Song, Guo, Gao, & Hua, 2018). Furthermore, TRIM3 can block p21 and prevent it from promoting the accumulation of cyclin D1-CDK4 (Angelo, Vargas, Lee, Bigio, & Gioux, 2016; T. He, et al., 2019; W. Y. Lin, et al., 2016).

In summary, TRIM family and the involved signaling pathway are not a simple one-way relationship. In fact, the same TRIM molecule may directly or indirectly participate in multiple signaling pathways, acting both as an oncogene and a tumor suppressor gene. Also, one signaling pathway may require multiple molecules to precisely regulate each step of the cell life cycle. Understanding the regulatory network of TRIM family is the basis of developing related therapies.

4. The role of TRIM in different types of cancer

This section summarizes the biological function (cell proliferation, cell invasion, cell migration, cell apoptosis and EMT) of TRIM family in various cancer types (**Figure 6 and Table S3**). And TRIM family can be divided into oncogene or tumor suppressor based specific functions (**Figure 7**). Several cancer types are selected according to the incidence and mortality reported by the GLBOCAN database as shown in the **Table 3.**

5.1 Breast cancer

Breast cancer is the most widespread invasive cancer in female, with high rate of distant metastasis and 5-year survival rate of just 26% (Kozlowski, Kozlowska, & Kocki, 2015; Peart, 2017; H. B. Wang, et al., 2019). Breast cancer is classified into five molecular subtypes according to immunohistochemistry (IHC) markers including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and protein Ki-67 (KI67). The clinical outcome and prognosis of different subtypes vary: luminal A ($ER^+/PR^+/HER2^-/KI67^-$) has good prognosis; luminal B ($ER^+/PR^+/HER2^-/KI67^+$) and normal like ($ER^+/PR^+/HER2^-/KI67^-$) have general prognosis, while basal ($ER^-/PR^-/HER2^-$/basal marker$^+$), HER2 subtype ($ER^-/PR^-/HER2^+$) and luminal B ($ER^+/PR^+/HER2^+/KI67^+$) are with poor prognosis (X. Dai, et al., 2015).

Thirty studies have discussed the role of TRIM in breast cancer. TRIM11 (L. Chen, et al., 2017; X. Dai, Geng, Li, & Liu, 2019), TRIM14 (G. Hu, W. Pen, et al., 2019), TRIM25 (Ikeda, Orimo, Higashi, Muramatsu, & Inoue, 2000; Suzuki, et al., 2005; Urano, et al., 2002; Z. Wang, et al., 2019), TRIM27 (Townson, Kang, Lee, & Oesterreich, 2006), TRIM28 (Addison, et al., 2015; Czerwinska, et al., 2017; Daniheni, et al., 2017; J. Li, et al., 2017; C. Wei, et al., 2016), TRIM37 (Bhatnagar, et al., 2014; X. Hu, D. Xiang, et al., 2019; Przanowski, et al., 2020; Yeow, et al., 2020), TRIM44 (Kawabata, et al., 2017), TRIM47 (Y. Wang, Liu, Xie, & Lu, 2020), TRIM59 (Y. Liu, et al., 2018; P. Tan, et al., 2018), and TRIM63 (K. Li, et al., 2019) act as oncogenic proteins, and were all found to be overexpressed in breast cancer.

The ability to degrade misfolded proteins is enhanced in the process of tumorigenesis, and decreased in tumor differentiation (F. Huang, Wang, & Wang, 2018). TRIM-mediated degradation of misfolded proteins is involved in tumorigenesis (Jena, Kolapalli, Mehto, Chauhan, & Chauhan,

2018). Chen *et al.* indicated that over expression of TRIM proteins, especially TRIM11 plays a critical role in the anti-oxidant defense of breast cancer cells via Nrf2/TRIM11 axis (L. Chen, et al., 2017). Besides, downregulation of TRIM11 and TRIM14 inhibit cell proliferation and promotes cell apoptosis in breast cancer cells (X. Dai, et al., 2019; G. Hu, W. Pen, et al., 2019). Downregulation of TRIM11 upregulates phosphatase, PTEN, p53 and Bcl-2-associated X protein, but downregulates Bcl-2, phosphorylated c-Jun N-terminal kinase 1/2 (p-JNK1/2) and phosphorylated extracellular signal-regulated kinases 1/2 (p-ERK1/2) (X. Dai, et al., 2019). And downregulation of TRIM14 increases expression of BAX and SHP-1, but down-regulates expression of BCL2 and p-STAT3 (G. Hu, W. Pen, et al., 2019).

High level of estrogen receptor (ER) is considered to be one of the causes of breast cancer (Yip & Rhodes, 2014). TRIM25 mRNA is expressed in human breast cancer and induced expression by estrogen in MCF-7 cell line. Meanwhile, TRIM25 promoter activity is increased through estrogen-responsive element dependent on estrogen and estrogen receptor (Ikeda, et al., 2000). Urano *et al.* revealed that TRIM25-overexpressing MCF7 cells promote breast tumors without involvement of estrogen in mice models. Knockdown of TRIM25 in mouse embryonic fibroblasts causes the accumulation of 14-3-3 sigma, a negative cell cycle regulator (Urano, et al., 2002). Another study reported that immunoreactivity of TRIM25 is positively correlated with estrogen receptor alpha level and negatively associated with 14-3-3 sigma immunoreactivity in 151 breast cancer specimens (Suzuki, et al., 2005). Recently, Wang *et al.* showed that miR-3614-3p can inhibit expression of TRIM25 by binding to its 3'- UTR, thus inhibits breast cancer cell growth. However, IGF2BP3 competitively occupies this binding site and inhibits TRIM25 degradation, thereby promotes the proliferation of breast cancer cells (Z. Wang, et al.,

2019). In addition, TRIM27 is widely expressed in breast cancer cell lines including MCF-7 and MCF10A cells, and TRIM27 is located to the TFF1 promoter (an ESR1(estrogen receptor 1) -regulated gene) as a part of ESR1 regulatory complex (Townson, et al., 2006).

TRIM28 (KAP1) knockdown reduces the proliferation of breast cancer cells and inhibits growth and metastasis of tumor xenografts (Addison, et al., 2015). TRIM28 is an essential corepressor of KRAB family zinc finger proteins (KRAB-ZNF). And TRIM28 directly interacts with KRAB-ZNF to promote its stabilization, thus stimulates cell proliferation and growth of breast cancer (Addison, et al., 2015). Another study found that TRIM28 directly interacts with TWIST1 and stabilizes TWIST1 to enhance metastasis of breast cancer (C. Wei, et al., 2016). Three studies found that TRIM28 are associated with stemness of breast cancer (Czerwinska, et al., 2017; Damineni, et al., 2017; J. Li, et al., 2017). Downregulation of TRIM28 inhibits ability of cancer stem cells (CSCs) to self-renew and stemness in breast cancer (Czerwinska, et al., 2017; Damineni, et al., 2017). In addition, TRIM28 knockdown represses the enhancer of zeste homolog 2 (EZH2) recruitment to chromatin and expression of EZH2, which decreases CD44hi/CD24lo mammosphere formation (J. Li, et al., 2017).

In 2014, Bhatnagar and co-workers found that TRIM37, polycomb repressive complex 1 (PRC1) and polycomb repressive complex 2 (PRC2) are co-bound to specific target genes in breast cancer cells, including multiple tumor suppressors. Promoters of these tumor suppressors are bound by TRIM37 and enriched for ubiquitinated H2A, resulting in transcriptional silencing of these tumor suppressors (Bhatnagar, et al., 2014). Histone demethylase LSD1 can suppress expression of TRIM37 to inhibit breast cancer progression (X. Hu, D. Xiang, et al., 2019). Remarkably, TRIM37-mediated histone H2A monoubiquitination enhances DNA repair and

promotes resistant to chemotherapy of TP53-mutant TNBC cells. And chemotherapeutic drugs enhance expression of TRIM37 in chemoresistant cancer cells via ATM/E2F1/STAT signaling pathway, forming a positive feedback loop. Additionally, overexpression of TRIM37 promotes metastatic phenotype of TNBC cells and inhibition of TRIM37 reduces the *in vivo* metastasis of TNBC cells (Przanowski, et al., 2020). Recently, another study found that overexpression of TRIM37 leads to genomic instability by delaying the centrosome maturation and the separation at mitotic entry, thus increases frequency of mitotic errors in breast cancer (Yeow, et al., 2020).

The level of TRIM44 mRNA in breast cancer tissues is higher than that in paracancerous tissues and the decrease of TRIM44 upregulates CDK10 level and downregulates MMP1 expression in breast cancer cell line, MDA-MB-231. Mechanism study showed that TRIM44 is involved in the development of breast cancer by promoting cell proliferation and migration as a regulator of NF-κB signal pathway (Kawabata, et al., 2017).

TRIM59 is increased in breast cancer cells. TRIM59 knockdown in breast cancer inhibits cell proliferation, migration, and invasion *in vitro* as well as tumor growth *in vivo* and decreases the level of p-Smad2 and thus inhibits the activation of transforming growth factor-β (TGF-β) signaling (Y. Zhang & Yang, 2017). Another study also showed that TRIM59 is a key regulator for controlling the contraction and adhesion of metastatic breast cancer cells through the TRIM59/PDCD10 axis (P. Tan, et al., 2018). Importantly, TRIM59 expression is also increased in TNBC tissues, and overexpressed TRIM59 promotes proliferation, invasion, migration and paclitaxel resistance in breast cancer cells. Mechanically, TRIM59 overexpression upregulates expression of cyclin A, cyclin E, Bcl-xl, Bcl-2, p-AKT, and downregulates expression of p21, p27, p53 (Y. Liu, et al., 2018).TRIM proteins including TRIM16 (P. Y. Kim, et al., 2016) (J. Yao, et al.,

2016), TRIM17 (Horie-Inoue, 2013), TRIM19 (Bao-Lei, et al., 2006; Le, Vallian, Mu, Hung, & Chang, 1998; Son, et al., 2007), TRIM22 (Y. Sun, et al., 2013) and TRIM29 (J. Liu, Welm, Boucher, Ebbert, & Bernard, 2012), also act as a tumor suppressor to inhibit the progression of breast cancer.

Downregulation of TRIM22 expression is associated with a lack of p53 in breast cancer (Y. Sun, et al., 2013). Moreover, loss of TRIM29 contributes to malignant transformation of breast cells and leads to progression of invasive ER^+ breast cancer (J. Liu, et al., 2012). The breast cancer suppressor effect of TRIM16 is achieved by interacting with transactive response DNA-binding protein43 (TDP43) and thus affecting the protein level of E2F1 and pRb, cell cycle regulatory proteins (P. Y. Kim, et al., 2016). Another study showed that TRIM16 directly regulates degradation of Gli-1 (a key molecule in sonic hedgehog pathway) through ubiquitin-proteasome pathway and suppresses CSCs properties of breast cancer cells (J. Yao, et al., 2016). Similarly, TRIM17 stimulates the degradation of kinetochore protein ZWINT and regulates the cell proliferation of breast cancer (Horie-Inoue, 2013).

PML/TRIM19 was found to suppresses growth and tumorigenicity of human breast cancer cells by inducing G1 cell cycle arrest and apoptosis (Le, et al., 1998). And TRIM19 knockdown inhibits p53 signaling pathway and suppresses irradiation induced apoptosis in breast cancer cells (Bao-Lei, et al., 2006). Another study reported that TRIM19 can activate ERK1/2, p38 MAPK and p21; thus, results in cell cycle arrest and cell death (Son, et al., 2007).Therefore, these data suggest that the TRIM proteins play both oncogenic and suppressor roles in breast cancer. Mechanism studies show that the TRIM family is involved in multiple signaling pathways in the genesis and progression of breast cancer.

5.2 Renal cell carcinoma (RCC)

Renal cell carcinoma (RCC) represents about 85% of all solid kidney cancers (Sims, et al., 2018). Major histological subtypes of RCC include clear cell renal cell carcinoma (ccRCC), papillary RCC (pRCC), and chromophobe RCC (chRCC) (Linehan & Ricketts, 2019; Prasad, et al., 2006). According to GLOBOCAN 2020, there are about 431,288 new RCC cases (2.2% of all new cases) and 179,368 deaths (1.8% of all death cases) caused by RCC per year worldwide (Sung, et al., 2021).

Up to now, only four studies have revealed the potential roles of TRIM family in tumorigenesis and malignant behaviors of RCC (S. H. Hu, Zhao, Wang, Xu, & Wang, 2017; H. Li, et al., 2020; W. Xiao, Wang, Wang, & Xing, 2018; Yamada, et al., 2020) (Diets, et al., 2019; Halliday, et al., 2018; W. J. Kim, et al., 2015; Shtutman, Zhurinsky, Oren, Levina, & Ben-Ze'ev, 2002). TRIM44 and TRIM59 act as oncogenic proteins, and are both found to be overexpressed in RCC tissues. TRIM44 facilitates cell proliferation and migration of RCC cell lines Caki1 and 769P. Further microarray analysis showed that FRK, under expressed in RCC than normal renal tissues, is a crucial target gene of TRIM44 (Yamada, et al., 2020). TRIM59 mRNA in RCC tissues is 2-fold higher as compared with that in paracancerous tissues. And TRIM59 knockdown inhibits cell proliferation, migration and invasion in RCC cell line, 786-O, and suppresses tumor growth *in vivo* (S. H. Hu, et al., 2017)

The cancer inhibitory role of TRIM family has also been studied in RCC. TRIM2 and TRIM13 act as tumor-suppressors and were found to be downregulated in RCC tissues and cell lines. TRIM2 is under-expressed in both ccRCC tissues and RCC cell lines. Besides, TRIM2

overexpression in RCC inhibits cell proliferation, migration, and invasion (W. Xiao, et al., 2018). Expression of TRIM13 is significantly decreased in RCC tissues. Exogenous overexpression of TRIM13 in 786-O cells inhibits cell migration and invasion, and decreases NF-κB, MMP-9 and p-AKT levels (H. Li, et al., 2020). Besides, germline loss of mutations in TRIM28 predispose children to Wilms tumor, which become homozygous in tumor tissues (Diets, et al., 2019; Halliday, et al., 2018). And nuclear WTX (also known as *AMER1*/*FAM123B*, a tumor suppressor in somatic Wilms tumors) interacts with coiled coil domain of TRIM28, thus promotes TRIM28-mediated transcriptional repression of the specific chromatinized target sequences (W. J. Kim, et al., 2015).

Therefore, these data suggest that TRIM protein may act as vital pro-oncogenic factors or tumor suppressors in the progression of RCC. This indicates that some members of TRIM family may be promising therapeutic targets for RCC. More studies validating the role of the TRIM family in RCC are needed.

5.3 Thyroid cancer

Thyroid cancer (TC) is classified into four main subtypes: papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), medullary thyroid carcinoma (MTC), and anaplastic thyroid carcinoma (ATC) (Khatami & Tavangar, 2018). PTC is the most common subtype, accounting for 80–90% of all TC (Abdullah, et al., 2019). The standard treatment (surgery followed by either radioactive iodine or observation) is effective for most early-stage TC patients (Cabanillas, McFadden, & Durante, 2016). Molecular targeted therapy is a promising treatment for advanced TC and radioiodine refractory (RAI-R) patients (Aashiq, Silverman, Na'ara, Takahashi, & Amit, 2019).

The effect of TRIM family in TC remains unclear, and only four studies have referred to this field so far. In 2000, Yu *et al.* found that TRIM19 is overexpressed in all papillary carcinomas of diffuse or ball-shaped patterns, while it is either not detectable or lower in medullary carcinomas compared to that in non-neoplastic thyroids (E. Yu, Lee, & Lee, 2000). Zhou *et al.* found that TRIM44 is overexpressed in both human PTC tissues and cell lines compared with normal samples. Further experiments showed that the knockdown of TRIM44 inhibits PTC malignant behaviors including the proliferation, migration and invasion of PTC cells by suppressing the Wnt/β-catenin signaling pathway (Z. Zhou, et al., 2017). Recently, Sun *et al.* found that TRIM14 is upregulated in PTC tissues, compared with normal paracancerous tissues. TRIM14 knockdown inhibits proliferation, induces cell apoptosis of human PTC K1 cells and human PTC TPC1 cells *in vitro* and represses tumor growth in nude mice. Furthermore, they found that knockdown of TRIM14 also increases the level of SOCS1, a negative regulator of STAT3 activation, through inhibiting SOCS1 ubiquitination (W. Sun, et al., 2020). Additionally, TRIM26 is significantly downregulated in PTC tissues and cell lines. And overexpression of TRIM26 can decrease glucose uptake and lactate production in PTC cells through inhibiting activation of PI3K/Akt pathway (K. Wang, et al., 2019).

The role of TRIM family in TC is still unclear. Therefore, further studies in the field of TC are needed.

5.4 Central nervous system (CNS) tumors

CNS tumors mainly include diffuse gliomas, medulloblastomas and neuroblastoma, etc. (Komori, 2017). Studies about the role of TRIM proteins in CNS tumors are mainly focusing on

gliomas, glioblastoma and neuroblastoma.

Eleven TRIM members, including TRIM11 (K. Di, et al., 2013), TRIM14 (Feng, et al., 2019) (Z. Tan, et al., 2018), TRIM21 (Z. Zhao, et al., 2020), TRIM24 (L. H. Zhang, et al., 2015), TRIM31 (G. Shi, et al., 2019b), TRIM37 (S. L. Tang, et al., 2018), TRIM44 (L. Li, et al., 2019; X. Zhou, et al., 2019), TRIM52 (Benke, et al., 2018), TRIM28 (Z. Qi, et al., 2016; Z. X. Qi, et al., 2016), TRIM59 (Sang, et al., 2018) and TRIM65 (G. Hu, N. Liu, et al., 2019) were found to be overexpressed and act oncogenic role in human glioblastoma or other CNS tumors tissues and cell lines, while six TRIM members, including TRIM3 (Y. Liu, et al., 2014), TRIM8 (Bhaduri & Merla, 2020), TRIM9s (K. Liu, et al., 2018), TRIM19 (E. Yu, Choi, & Kim, 2003; J. H. Yu, et al., 2004), TRIM32 (Izumi & Kaneko, 2014) and TRIM35 (Xue, et al., 2015) were found to be downregulated and play a tumor suppressor role in CNS tumors.

Both TRIM11 and TRIM32 were reported to regulate stemness of glioma and neuroblastoma through different mechanism (K. Di, et al., 2013; Izumi & Kaneko, 2014). Overexpression of TRIM11 promotes tumorsphere formation *in vitro* and enhances glial tumor growth in mice (K. Di, et al., 2013), while TRIM32 suppresses tumorsphere formation of neuroblastoma-initiating cells by degrading MYCN (Izumi & Kaneko, 2014).

TRIM14 is upregulated in human glioblastoma samples and LN229 and U251cell lines, and knockdown of TRIM14 facilitates zinc finger E-box binding homeobox 2 (ZEB2) (a transcription factor involved in EMT) ubiquitination and degradation and consequently inhibit cell invasion and migration of glioblastoma (Feng, et al., 2019). Besides, TRIM14 can also activates Wnt/β-catenin signaling via stabilizing dishevelled (Dvl2), thus promotes chemoresistance in gliomas (Z. Tan, et al., 2018).

Downregulation of TRIM28 leads to cell cycle arrest at G1 phase by increasing p21 level *in vitro* and suppresses glioma growth *in vivo* (Z. X. Qi, et al., 2016). Another study found that miR-491 can downregulate TRIM28 to inhibit proliferation of glioma cells (Z. Qi, et al., 2016). Similarly, miR-101-3p inhibits EMT, proliferation and metastasis of glioblastoma by downregulating TRIM44 (L. Li, et al., 2019).

Further mechanism study revealed that TRIM24, TRIM31, TRIM37, TRIM44 and TRIM47 regulate 'malignant behaviors' of glioma cells through inactivating or activating Akt signaling pathway (G. Shi, et al., 2019a), NF-κB pathway (L. Zhou, et al., 2019) or Wnt/β-catenin pathway (L. Chen, Li, Li, Xu, & Zhong, 2020).

Both TRIM24 and TRIM37 are overexpressed in human glioma tissues and cell lines and promote malignancy behaviors of glioma cells by activating PI3K/Akt signaling pathway (S. L. Tang, et al., 2018; L. H. Zhang, et al., 2015). Moreover, TRIM44 can decrease p21/p27 (negative cell cycle regulators) and activate Akt signaling to promote cell proliferation and cell cycle progression of gliomas (X. Zhou, et al., 2019). TRIM31 overexpression promotes glioma cell proliferation and invasion by activating NF-κB pathway (L. Zhou, et al., 2019). TRIM47 and TRIM59 may exert carcinogenic effects through activation of the Wnt/β-catenin pathway in glioma and neuroblastoma, respectively (G. Chen, et al., 2019; L. Chen, et al., 2020)...

The loss of heterozygosity at the TRIM3 site in human glioblastomas is about 20%, suggesting that TRIM3 might be a tumor suppressor of glioblastoma. Meanwhile, TRIM3 knockdown can increase the incidence of glioma in mice. Further experiments showed that TRIM3 could prevent the accumulation of cyclin D1-CDK4 by sequestering p21, a CDK inhibitor, thereby inhibits tumor growth (Y. Liu, et al., 2014). Similarly, mutual stabilization between

TRIM9s and MKK6 promotes p38 signaling to inhibit glioblastoma (K. Liu, et al., 2018).

Interestingly, EGFR signaling can upregulate TRIM59 through SOX9, and this upregulation enhances interaction between TRIM59 and nuclear STAT3. This interaction maintains transcriptional activation of STAT3 and promotes gliomagenesis (Sang, et al., 2018).

TRIM16 is highly expressed in differentiating ganglia cell nucleus but not in tumor-initiating cells (Bell, Malyukova, Kavallaris, Marshall, & Cheung, 2013). Consistent with this, overexpressed TRIM16 inhibits neuroblastoma cell growth, promotes retinoid-induced differentiation and reduces tumorigenicity *in vivo*. Furthermore, TRIM16, as a tumor suppressor, regulates neurotic differentiation, cell migration and replication through regulating cytoplasmic vimentin and nuclear E2F1 in neuroblastoma cells (Marshall, et al., 2010).

Importantly, expression of PML/TRIM19 increases during the differentiation of human neuroblastoma cells (E. Yu, et al., 2003). And increase of PML-NBs in neuroblastoma cells enhances retinoic acid responsiveness and induces cellular differentiation (J. H. Yu, et al., 2004).

The above studies show that various TRIM proteins, acting as oncogenic proteins or tumor suppressors, regulate diverse cellular processes of CNS tumors through vital signal pathways and critical protein-protein interactions.

5.5 Prostate cancer

Prostate cancer (PC) accounts for more than 380,000 deaths annually worldwide. It is estimated that prostate cancer is the fifth leading cause of cancer death in males in 2020 (Sung, et al., 2021). Twelve studies have revealed important roles of TRIM proteins in the development and progression of prostate cancer.

TRIM11 (Y. Pan, et al., 2019), TRIM24 (Groner, et al., 2016), TRIM25 (Takayama, et al., 2018; S. Wang, et al., 2016), TRIM28 (Fong, Zhao, Song, Zheng, & Yu, 2018), TRIM44 (Y. Tan, et al., 2017), TRIM59 (Valiyeva, et al., 2011) and TRIM68 (Miyajima, et al., 2008) act as oncogenic proteins, and all were found to be overexpressed in prostate cancer tissues or cell lines.

Pan *et al.* found that overexpression of TRIM11 enhances the proliferation of prostate cancer cell lines, DU145 and PC3 (Y. Pan, et al., 2019). Another study reported that TRIM24 protein as an oncogenic transcriptional activator is stabilized by recurrent PC-driver mutations in speckle-type POZ protein (SPOP). The interaction of TRIM24 bromodomain and the AR-interacting motif promotes proliferation of castration-resistant cells (Groner, et al., 2016). Notably, TRIM28 can interact with TRIM24 to prevent TRIM24 ubiquitination and degradation by SPOP in PC. And TRIM28 can promote the proliferation of PC cells *in vitro* and tumor growth *in vivo* (Fong, et al., 2018). TRIM44 knockdown dramatically decreases the levels of phosphorylated PI3K and AKT in PC-3 cells, thus attenuates the proliferation, invasion and migration of prostate cancer cells *in vitro*, as well as inhibits the tumorigenesis *in vivo* (Y. Tan, et al., 2017). TRIM59 knockdown inhibits cell proliferation, colony formation, and cell cycle *in vitro* and suppresses tumor growth *in vivo*. In terms of molecular mechanism, knockdown of TRIM59 inhibits the expression of cycle regulators CDC2, CDC25A, and cyclin B1, thus interrupt the cell cycle of prostate cancer cells (W. Y. Lin, et al., 2016).

Interestingly, TRIM25 was reported to interact with GTPase-activating protein-binding protein 2 (G3BP2) to negatively regulate p53 nuclear export. This promotes cell proliferation as well as cell migration and inhibits p53 activity as well as docetaxel-induced apoptosis of PC cells (Takayama, et al., 2018). Another study showed that TRIM25 can also target Ets related gene

(ERG), a cancer driver, for degradation, however, ERG levels may be reduced when USP9X, an ERG-stabilizing deubiquitinase is also expressed. Strikingly, ERG can upregulate TRIM25 in PC. This could be a negative feedback loop to maintain physiological ERG protein levels in PC (S. Wang, et al., 2016). Moreover, TRIM68 interacts with TIP60 and p300, coactivators of androgen receptor (AR), and promotes transcriptional activity of AR in PC (Miyajima, et al., 2008). Both TRIM24 and TRIM28 are also found to enhance AR signaling in PC progression (Fong, et al., 2018).

TRIM16 (Qi, Lu, Sun, Song, & Xu, 2016), TRIM29 (Kano, et al., 2014) and TRIM36 (Kimura, et al., 2018) were found to be downregulated in PC tissues and cell lines. Overexpression of TRIM16 inhibits migration, invasion and EMT process of PC cells, whereas TRIM16 knockdown enhances these processes. Mechanically, TRIM16 inhibits EMT in PC cells through inhibiting snail signaling pathway (L. Qi, et al., 2016). Besides, TRIM29 expression is detected in basal cells of normal prostatic glands in all cases, but not or rarely detected in prostate cancer tissues. This result indicates that TRIM29 might be used to distinguish prostate cancers from benign tissues (Kano, et al., 2014). TRIM36 might act as tumor-suppressor by promoting apoptosis in PC. Overexpression of TRIM36 inhibits proliferation and migration of PC cells lines, 22Rv1, LNCaP, and DU145. Further microarray analysis showed that TRIM36 overexpression dramatically upregulates the apoptosis-related pathway (Kimura, et al., 2018).

In brief, studies show the involvement of TRIM proteins in the development and progression of prostate cancer. And it is possible to target TRIM family to treat patients with PC in the future.

5.6 Gastrointestinal cancers

Gastric cancer, colon cancer, colorectal cancer and pancreatic cancer are the major subtypes of gastrointestinal cancers. And gastrointestinal cancers are responsible for relatively high cancer-related morbidity and mortality amongst all cancer types (Rahbari, Rahbari, Reissfelder, Weitz, & Kahlert, 2016). Discovering effective therapeutic targets is of great significance for patients with gastrointestinal cancers.

TRIM29, TRIM31 and TRIM37 play oncogenic role and promote cell proliferation and motility in pancreatic cancer (Jiang, Tian, Yu, Chen, & Sun, 2016; L. Wang, et al., 2009; C. Yu, Chen, Guo, & Sun, 2018). Mechanically, TRIM29 activates Wnt/β-catenin/TCF signaling via stabilizing β-catenin and Disheveled-2 in pancreatic cancer (L. Wang, et al., 2009). TRIM31 upregulates nuclear p65 by promoting K63-linked polyubiquitination of TRAF2 and activating NF-κB signaling pathway in pancreatic cancer cells (C. Yu, et al., 2018). TRIM37 interacts with β-catenin and activates β-catenin /TCF complex as well as expression of β-catenin downstream genes (Jiang, et al., 2016).

In gastric cancer (GC), TRIM14 (F. Wang, et al., 2018), TRIM15 (W. Zhou, Chen, Ruan, Zeng, & Liu, 2020), TRIM16 (Yan, et al., 2015), TRIM23 (Y. Yao, et al., 2018), TRIM24 (Z. Fang, et al., 2017; Miao, et al., 2015), TRIM25 (Z. Zhu, et al., 2016), TRIM29 (Kosaka, et al., 2007; F. Qiu, Xiong, Deng, & Xiang, 2015), TRIM31 (Sugiura, 2011), TRIM32 (J. Wang, Fang, & Liu, 2020),TRIM44 (Kashimoto, et al., 2012) and TRIM59 (Z. Zhou, et al., 2014) were found to be increased in cancer tissues or cell lines.

TRIM14 and TRIM24 promotes cell migration, invasion and metastasis of GC *in vitro* and *in vivo*. (F. Wang, et al., 2018) (Z. Fang, et al., 2017). And TRIM14, TRIM24 and TRIM29 promote the aggression of GC via activating Akt or Wnt/β-catenin signaling pathway (Z. Fang, et al., 2017;

Miao, et al., 2015; F. Qiu, et al., 2015).

Interestingly, TRIM31 is overexpressed in GC, but it negatively regulated the growth of GC cell line, AsPC-1. Further evidence demonstrates that posttranslational modification via proteasome pathway controls the intracellular abundance of TRIM31, which also depends on the process of alternative splicing and inducible transcription (Sugiura, 2011).

Silencing of TRIM29 inhibits cell proliferation and colony formation, and induce apoptosis as well as G1-S cell cycle arrest *in vitro*. Meanwhile, TRIM29 is identified as a target of miR-185 in GC, and overexpression of miR-185 in MGC803 cells inhibits TRIM29 expression and Wnt/β-catenin signal pathway (F. Qiu, et al., 2015). The role of TRIM32 has been intensively investigated. Silencing of TRIM32 inhibits the proliferation and induces apoptosis of GC cells *in vitro* (M. Ito, et al., 2017). Furthermore, knockdown of TRIM32 significantly inhibits the proliferation, invasion, and migration of GC cells *in vitro* and tumor growth *in vivo*, through promoting expression of β-catenin and its downstream targets cyclin D1, TCF1, MMP7 and Axin2 (C. Wang, et al., 2018). Additionally, TRIM32 may regulate the metabolism of glycolysis via targeting GLUT1 and HK2 and involve in the activation of Akt pathway in GC cells (J. Wang, et al., 2020).

Importantly, TRIM32 and TRIM59 were found to be up-regulated in CRC or GC and promote ubiquitination and degradation of p53, promoting progression of CRC or GC, respectively (J. Liu, et al., 2014; Z. Zhou, et al., 2014).

Regarding the role of TRIM15 and TRIM25 in GC, current research results are inconsistent. Zhou *et al.* showed that the expression level of TRIM15 in GC tissues is higher than adjacent non-cancerous tissues. Furthermore, TRIM15 promotes cell invasion, migration and EMT process

of GC (W. Zhou, et al., 2020). However, Chen *et al.* reported that TRIM15 is overexpressed in normal stomach tissues compared with tumor tissues. Overexpression of TRIM15 inhibits cell invasion of GC *in vitro* (W. Chen, Lu, & Hong, 2018). This result indicates that TRIM15 exerts anti-cancer effects in GC. In addition, TRIM25 is overexpressed in human GC tissues and enhances migration and invasion of GC cells via TGF-β signaling (Z. Zhu, et al., 2016). However, recently, expression of TRIM25 is found to be lower in GC tissues than in paired normal tissues. And TRIM25 promotes ubiquitination of SP1 at K610, suppressing expression of MMP2 and inhibiting angiogenesis in GC (J. J. Chen, et al., 2020), suggesting there is a complex network between TRIM family and GC. Further studies are needed to clarify these inconsistent results.

18 members including TRIM2 (Xia, Zhao, & Yang, 2020), TRIM6 (S. Zheng, et al., 2020), TRIM11 (Y. Yin, et al., 2016), TRIM14 (Z. Yin, et al., 2018), TRIM23 (Y. Han, et al., 2020), TRIM24 (J. Wang, et al., 2014; W. Xie, et al., 2020), TRIM25 (N. Sun, et al., 2017), TRIM27 (Y. Zhang, Feng, et al., 2018), TRIM28 (Fitzgerald, et al., 2013), TRIM29 (W. Xu, et al., 2016), TRIM32 (J. Liu, et al., 2014) (J. Liu, et al., 2014), TRIM37 (C. E. Hu & Gan, 2017; P. Zhao, et al., 2017), TRIM47 (Q. Liang, et al., 2019), TRIM52 (S. Pan, et al., 2019), TRIM59 (Y. Sun, et al., 2017; W. Wu, et al., 2017), TRIM65 (D. Chen, et al., 2019), TRIM66 (T. He, et al., 2019), and TRIM68 (Z. Tan, et al., 2017) were found to be significantly elevated in CRC tissues or cell lines.

Knockdown of TRIM6 inhibits cell proliferation, increases sensitivity to oxaliplatin and 5-fluorouracil and induces cell cycle arrested at G2/M phase of CRC cells (S. Zheng, et al., 2020). Further experiment showed that the overexpression of TRIM6 lead to decreased protein stability of TIS21 through ubiquitination. Meanwhile, overexpression of TRIM6 increases the level of FoxM1, thus enhancing the proliferative activity of CRC cells.

Another study found that TRIM47 increases Smad4 ubiquitination and degradation, and thus enhances invasion and growth in human CRC cells via CCL15/CCR1 signaling pathway (Q. Liang, et al., 2019). Similarly, TRIM65 targets ARHGAP35, a Rho GTPase-activating protein for ubiquitination and degradation. This elevates Rho GTPase activity and promotes CRC metastasis(D. Chen, et al., 2019).

TRIM14 can promote invasion and migration of CRC cells by increasing protein levels of sphingosine kinase-1 (SPHK1) and p-STAT3 and activating SPHK1/STAT pathway (Z. Jin, et al., 2018). Meanwhile, knockdown of TRIM29 significantly reduces phosphorylation levels of JAK2 and STAT3 and then affects JAK2/STAT3 signal pathway in CRC (W. Xu, et al., 2016). Additionally, knockdown of TRIM66 also suppresses the activation of JAK2/STAT3 signaling pathway in CRC cell.

Both TRIM37 and TRIM59 can promote EMT process to enhance invasion and migration of CRC cells (C. E. Hu & Gan, 2017; Y. Sun, et al., 2017). Knockdown of TRIM59 attenuates cell proliferation via the induction of apoptosis and significantly suppresses invasion and migration *in vitro* through regulating the EMT-related proteins (E-cadherin, Snail and vimentin) (Y. Sun, et al., 2017). Furthermore, TRIM59 can also promote migration and invasion of CRC cells through PI3K/AKT signaling pathway (Y. Sun, et al., 2017). TRIM59 knockdown promotes apoptosis of CRC cells by decreasing cell cycle regulators CDC25C, cyclin B1, cyclin D1 and enhancing cleavage of caspase-3 and PARP (W. Wu, et al., 2017). Knockdown of TRIM37 can also inhibit expression of β-catenin, cyclin D1, and c-Myc in CRC cells to inhibit proliferation and tumorigenesis of CRC cells (P. Zhao, et al., 2017).

Overexpression of TRIM25 enhances the capacities of proliferation and migration of CRC *in*

vitro via TGF-β signaling pathway (N. Sun, et al., 2017). Another study showed that TRIM25 can also negatively regulate with caspase-2 translation to affect resistance of CRC cells to drug-induced apoptosis (Nasrullah, et al., 2019). TRIM15 (Lee, et al., 2015), TRIM21 (G. Zhou, et al., 2020), TRIM58 (M. Liu, et al., 2018) and TRIM67 (S. Wang, et al., 2019) were found to act as tumor suppressors by inhibiting the progression of CRC. Expression of TRIM15 was found to be downregulated in colon cancer (Lee, et al., 2015). And TRIM15 significantly suppresses cell migration via co-localizing to focal adhesions through homo-dimerization process (Lee, et al., 2015). Ectopic expression of TRIM58 remarkably inhibits invasion of CRC cells, while has minimal effects on cell proliferation, migration and colonization *in vitro*. Moreover, knockdown of TRIM58 promotes EMT process and the expression of MMP genes of CRC (M. Liu, et al., 2018). In addition, TRIM67 can interact directly with the C-terminus of p53, inhibiting p53 degradation by its ubiquitin ligase MDM2, inhibiting CRC progression (S. Wang, et al., 2019).

To sum up, it would be interesting to investigate more about role of TRIM proteins in gastrointestinal cancers and the clinical application.

5.7 Gynecological cancers

Gynecologic cancer, originating from women's reproductive system, cover cervical, ovarian, uterine and so on (Ledford & Lockwood, 2019). According to GLOBOCAN, gynecological cancers are responsible for about 14.4% of all new cancers and 12.4% of deaths caused by cancer among women worldwide in 2020 (Sung, et al., 2021).

Research about the role of TRIM family in gynecological cancers mainly focused on human ovarian and cervical cancers. Functions of TRIM3 (Y. Song, et al., 2018), TRIM11(Y. Chen, J. Sun, et al., 2017), TRIM14 (Diao, et al., 2020), TRIM16 (H. Tan, Qi, Chu, & Liu, 2017), TRIM28

(Deng, et al., 2017; F. Li, Wang, & Lu, 2018), TRIM50 (Y. Qiu, et al., 2019), TRIM52 (W. Yang, et al., 2018), TRIM56 (L. Zhao, Wang, Zhang, Yu, & Su, 2019; L. Zhao, Zhang, Su, & Zhang, 2018), TRIM59 (Aierken, et al., 2017; Tong, Mu, Zhang, Zhao, & Wang, 2020), TRIM62 (T. Y. Liu, et al., 2016) and TRIM71 (Y. Chen, et al., 2019) were studied in ovarian and cervical cancers.

TRIM11 expression is significantly higher in ovarian cancer tissues than that in normal tissues. Silencing of TRIM11 significantly inhibits proliferation and invasion in A2780 and SK-OV-3 ovarian cancer cells, affects the level of cell apoptosis-related proteins (Bcl-2 and Bax), and invasion-related proteins (MMP-2 and MMP-9), and decreases the phosphorylation levels of ERK and AKT (Y. Chen, J. Sun, et al., 2017).

Moreover, overexpression of TRIM16 suppresses the cell migration, invasion and EMT progression of ovarian cancer through suppressing the sonic hedgehog signaling pathway *in vitro* (H. Tan, et al., 2017).TRIM52, as an oncogenic protein, promotes the progression of ovarian cancer through NF-κB signal pathway (W. Yang, et al., 2018). Another study showed that TRIM28, as an oncogenic protein, promotes migration, invasion and EMT of ovarian cancer cells through activating Wnt/β-catenin signaling pathway (Deng, et al., 2017).

TRIM56 can inhibit migration and invasion of ovarian cancer cells by degrading vimentin protein (L. Zhao, et al., 2018). Recently, they found that silencing of poly r(C) binding protein 1 (PCBP1) or overexpression of TRIM56 significantly decreases cell migration and invasion of SKOV-3 cells. Interestingly, PCBP1 was found to mediate translational repression of TRIM56, thus increases expression of vimentin and promote metastasis of ovarian cancer (L. Zhao, et al., 2019).

Moreover, Silencing TRIM59 can significantly inhibit the epithelial ovarian cancer (EOC)

cells *in vitro* through FAK/AKT/MMP pathway (P. Zhang, et al., 2019). Besides, TRIM59 increases levels of c-Myc and lactate dehydrogenase A and decreases MKP3 through ubiquitination, thus activates ERK signaling pathway in ovarian cancer (Tong, et al., 2020). Notably, TRIM59 knockdown can also significantly suppress cell proliferation, invasion and clone formation of ovarian cancer *in vitro* and *in vivo* through inducing expression of an oncoprotein - Annexin A2 (Christensen, Hogdall, Jochumsen, & Hogdall, 2018; Y. Wang, et al., 2018).

TRIM50 targets Src protein via inducing RING domain-dependent K48-linked poly-ubiquitous modification, thus suppresses ovarian cancer progression (Y. Qiu, et al., 2019). Similarly, TRIM71, as a tumor suppressor in ovarian cancer, was found to reduce mutant p53 protein stability through inducing its ubiquitination and proteasomal degradation (Y. Chen, et al., 2019).

Five studies were conducted to explore the role of TRIM proteins in the development of cervical cancer. TRIM24 enhances migration and invasion of cervical cancer cells through the NF-κB and Akt signaling pathways (L. Lin, Zhao, Sun, Wang, & Liu, 2017). And overexpression of TRIM28 promotes proliferation, colony formation ability and cell cycle progression of cervical cancer cells by activating mTOR signaling pathway (F. Li, et al., 2018). Another study found that expression of TRIM59 is higher in cervical cancers than normal tissues. And TRIM59 knockdown significantly inhibits the capacities of proliferation, invasion and migration as well as colony formation of cervical cancer cells (Aierken, et al., 2017).

TRIM3 as a tumor suppressor can inhibit cell proliferation in cervical cancer via inactivating p38 signaling pathway (Y. Song, et al., 2018). Besides, overexpression of TRIM62 significantly inhibits proliferation, migration and invasion of cervical cancer cells. Mechanically, TRIM62

suppresses EMT by inhibiting c-Jun/Slug signaling pathway, thus regulates cell cycle related proteins cyclinD1 and p27 (T. Y. Liu, et al., 2016). Due to the varieties and complicated etiologies of gynecological cancers, functions of TRIM family in gynecological cancers need to be further explored.

5.8 Lung cancer

Lung cancer is the most prevalent cancer in the world, with an estimated 2,206,771 new cases (11.4% of total new cases) and 1,796,144 deaths (18.0% of total cancer-related deaths) in 2020 worldwide, ranking first in the causes of cancer mortality (Sung, et al., 2021). Unfortunately, nearly 85% of all lung cancer is diagnosed at an advanced stage, with an extremely low five-year survival rate of 4% (Mallow, et al., 2018).

35 studies have shown that TRIM11(X. Wang, et al., 2016), TRIM23 (Y. Zhang, et al., 2020), TRIM24 (H. Li, et al., 2012), TRIM25 (Q. Han, et al., 2019; Y. Qin, Cui, & Zhang, 2016), TRIM27 (Iwakoshi, et al., 2012), TRIM28 (L. Chen, et al., 2012; L. Chen, Munoz-Antonia, & Cress, 2014; L. Liu, et al., 2017; L. Liu, et al., 2018; L. Liu, et al., 2013), TRIM29 (C. Liu, et al., 2015), TRIM32 (H. Yin, et al., 2019), TRIM35 (J. Zhang, Xu, Yu, Xu, & Yu, 2020), TRIM37 (Y. Li, et al., 2018), TRIM44 (Ji, et al., 2020; Q. Luo, et al., 2015; Xing, et al., 2016; P. Zou, et al., 2019), TRIM52 (Mu, Li, Zhou, & Xu, 2019), TRIM58 (Kajiura, et al., 2017), TRIM59 (W. Zhan, et al., 2015) (Z. Cui, Liu, Zeng, Chen, et al., 2019; Z. Cui, Liu, Zeng, Zhang, et al., 2019; Geng, et al., 2019; T. Han, et al., 2018; R. He & Liu, 2020; Lou, et al., 2020; Tian, et al., 2020), TRIM65 (G. Chen, Zhou, Liu, & Yu, 2018; Y. Li, et al., 2016; X. Pan, et al., 2019; X. L. Wang, et al., 2016), TRIM66 (Y. Ma, Dai, Zhang, & Zhao, 2017), TRIM67 (R. Liu, et al., 2019), TRIM69 (Sinnott, et al., 2014), and TRIM71 (Ren, et al., 2018) are overexpressed or act as oncoproteins in lung cancer

tissues or cell lines.

TRIM11 knockdown inhibits cell proliferation and EMT process by affecting the levels of proliferation-related proteins, including cyclin D1 and (proliferating cell nuclear antigen) PCNA, and EMT-related proteins, including VEGF, MMP-2, MMP-9, Twist1, Snail and E-cadherin. Further investigation demonstrated that TRIM11 may facilitate the motility and invasion of cancer cells through AKT pathway (X. Wang, et al., 2016).

TRIM24 knockdown inhibits growth and invasion of NSCLC cells and induces cell cycle arrest at the G1/S phase and cell apoptosis. Mechanically, TRIM24 knockdown decreases levels of cyclin A, cyclin B, cyclin D1, cyclin E and p-Rb and increases p27 expression (H. Li, et al., 2012).

TRIM25 can form a complex with p53 and murine double minute 2 homolog (MDM2) and decreases expression of p53 in both human lung cancer tissues and cells. This promotes proliferation and migration of lung cancer cells (Y. Qin, et al., 2016). TRIM65 negatively regulates p53 via ubiquitination (Y. Li, et al., 2016). Furthermore, another study showed that TRIM65 can also bind to N-terminus of p53, thus competes with MDM2 for p53 binding to promote resistance to Nutlin-3a (an MDM2 inhibitor) in lung cancer cell line (G. Chen, et al., 2018).

TRIM28 knockdown can decrease expression of Bcl-2 and increases gene and protein levels of Bcl-2 associated X protein, and p53. This increases apoptosis of NSCLC cells (L. Liu, et al., 2018). Another study found that TRIM28 knockdown can also increase sensitivity to etoposide by upregulating E2F1 in NSCLC cells (L. Liu, et al., 2017). Strikingly, Chen *et al.* found that TRIM28 is up-regulated in lung cancer tissues, however, TRIM28 may have a tumor suppressing role in early stages of lung cancer (L. Chen, et al., 2012). Subsequently, Chen and his colleagues

reported that TRIM28 is involved in TGF-β-induced EMT process and depletion of TRIM28 reduces migration and invasion of lung cancer cells (L. Chen, et al., 2014).

TRIM32 and TRIM44 can also regulate the motility of lung cancer cells by upregulating the level of CXCL16 and MMP9, thus activating JAK2/STAT3 signaling pathway and NF-κB signaling pathway (Q. Luo, et al., 2015; H. Yin, et al., 2019). Another study showed that TRIM44 can also promote proliferation and metastasis in NSCLC via activating mTOR signaling pathway (Xing, et al., 2016).

TRIM29 overexpression was found to be related with invasive tumor behaviors and ultimately affect clinical outcomes (X. Song, et al., 2015). Zhou *et al.* reported that TRIM29 may play an oncogenic role in NSCLC through β-catenin, a crucial molecule in Wnt signaling pathway (Z. Y. Zhou, Yang, Zhou, & Yu, 2012). Moreover, Liu *et al.* demonstrated that silencing of TRIM29 inhibits cell proliferation and invasion *in vitro* (C. Liu, et al., 2015). And TRIM29 knockdown increases chemosensitivity of NCI-H520 cells (C. Liu, et al., 2015). Furthermore, overexpression of TRIM52 promotes proliferation and invasion of lung cancer cells through activating Wnt/β-catenin pathway (Mu, et al., 2019).

TRIM59 was found to be overexpressed and primarily located in cytoplasm of NSCLC cells (Lou, et al., 2020). Besides, TRIM59 knockdown significantly inhibits the proliferation and migration of NSCLC cells through arresting the cell cycle in G2 phase via affecting the expression of cell cycle proteins including CDC25C and CDK1 (W. Zhan, et al., 2015). Another study found that up-regulation of TRIM59 also induces significant increases in CDK6 expression in NSCLC cells (Geng, et al., 2019). And TRIM59 can also modulate autophagy of NSCLC cells through regulating both transcription and the ubiquitination of beclin 1 (BECN1) (T. Han, et al., 2018).

Silencing of TRIM66 inhibits EMT progression through downregulating N-cadherin and vimentin and upregulating E-cadherin, thus reduces the capacities of proliferation, invasion and migration of NSCLC cells (H. Y. Dai, Ma, Da, & Hou, 2018). Similarly, Ren *et al.* reported that TRIM71 may play a role of carcinogenesis through promoting the proliferation of NSCLC cells via κB-α/NF-κB pathway (Ren, et al., 2018).

Ten TRIM members including TRIM7 (J. Jin, et al., 2020), TRIM13 (L. Xu, et al., 2019), TRIM14 (Hai, et al., 2017), TRIM16 (Huo, et al., 2015; N. Wang & Zhang, 2018), TRIM19 (P. Zhang, et al., 2000), TRIM28 (L. Chen, et al., 2012), TRIM31 (H. Li, et al., 2014), TRIM58 (Kajiura, et al., 2017), TRIM62 (Quintas-Cardama, et al., 2014) and TRIM71 (J. Yin, et al., 2016) show anti-cancer effects in lung cancer.

Both mRNA and protein expressions of TRIM13 are decreased in NSCLC tissues and cell lines. TRIM13 overexpression inhibits cell proliferation and induces cell apoptosis through caspase-3-dependent pathway and NF-κB pathway (L. Xu, et al., 2019). TRIM16 inhibits EMT and metastasis of NSCLC cells by downregulating sonic hedgehog pathway (Huo, et al., 2015). Moreover, overexpression of TRIM71 decreases Lin28B expression through ubiquitination-mediated degradation, thus inhibits let-7 and HMGA2, which inhibits growth of NSCLC cells (J. Yin, et al., 2016). Interestingly, TRIM28 was found to be up-regulated in lung cancer tissue, however, TRIM28 acts as a tumor suppressor by interacting with HDAC1/E2F axis in early-stage lung adenocarcinomas (L. Chen, et al., 2012). Moreover, CGI hypermethylation of TRIM58 might be associated with the carcinogenesis of early-stage LADC (Kajiura, et al., 2017).

The above findings indicate that TRIM family might be promising therapeutic targets for lung cancer.

5.9 Liver cancer

According to GLOBOCAN 2020, primary liver cancer has become the sixth most commonly diagnosed cancer (fifth in males and ninth in females) and the fourth cause of cancer death (second in males and sixth in females) worldwide in 2020, with about 905,677 newly diagnosed cases and 830,180 deaths each year(Sung, et al., 2021). Primary liver cancer includes hepatocellular carcinoma (HCC) (75%--85%), intrahepatic cholangiocarcinoma (10% - 15%) and other rare types (Sung, et al., 2021). Unfortunately, prognosis of advanced liver cancer is extremely poor, with an average 5-year survival rate of less than 10% (Sung, et al., 2021). Because of the risk of recurrence (Brown, Greten, & Heinrich, 2019) and the emergence of sorafenib resistance (Y. J. Zhu, Zheng, Wang, & Chen, 2017), therapeutic breakthroughs are urgently needed.

TRIM7 (X. Hu, Z. Tang, et al., 2019), TRIM11 (J. Liu, et al., 2017; Z. Zhang, et al., 2017), TRIM24 (X. Liu, et al., 2014; Y. Zhu, Zhao, Shi, Huang, & Chen, 2018), TRIM25 (Y. Liu, Tao, et al., 2020; Yuan, Zheng, & Tang, 2020), TRIM31 (P. Guo, Qiu, et al., 2018; T. Lv, Jiang, Kong, & Yang, 2020), TRIM37 (Jiang, Yu, Chen, Tian, & Sun, 2015; G. Tan, et al., 2021), TRIM44 (X. Zhu, et al., 2016), TRIM52 (Y. Zhang, Tao, et al., 2018), TRIM59 (G. Sun, et al., 2017), TRIM65 (Y. F. Yang, Zhang, Tian, & Zhang, 2017) and TRIM66 (Fan, et al., 2019) are found to be involved in the progression of HCC, acting as oncoproteins.

The level of TRIM11 is significantly overexpressed in HCC tissues compared with paracancerous tissues (Y. Chen, Li, Qian, Ge, & Xu, 2017; Z. Zhang, et al., 2017). Similar results about high expression are also observed for TRIM7 (X. Hu, Z. Tang, et al., 2019), TRIM14 (Dong

& Zhang, 2018), TRIM24 (X. Liu, et al., 2014; Y. Zhu, et al., 2018), TRIM25 (Y. Liu, Tao, et al., 2020; Yuan, et al., 2020), TRIM31(P. Guo, Ma, et al., 2018; T. Lv, et al., 2020), TRIM32 (X. Cui, et al., 2016), TRIM37 (J. Jiang, et al., 2015; G. Tan, et al., 2021), TRIM44 (X. Zhu, et al., 2016), TRIM52 (Y. Zhang, et al., 2017), TRIM59 (G. Sun, et al., 2017), TRIM65 (Y. F. Yang, et al., 2017) and TRIM66 in HCC (Fan, et al., 2019).

Overexpression of TRIM7 promotes cell cycle progression, cell proliferation as well as p38 activation and enhances polyubiquitination and degradation of dual specificity phosphatase 6 (DUSP6) in HCC (X. Hu, Z. Tang, et al., 2019). Similarly, TRIM25 is significantly increased under ER stress. TRIM25 directly targets Keap1 by ubiquitination and degradation and activates Nrf2, leading to the enhancement of HCC anti-oxidant defense (Y. Liu, Tao, et al., 2020). Another study found that TRIM25 knockdown reduces ubiquitination of PTEN and affects epirubicin resistance of HCC (Yuan, et al., 2020). TRIM31 can induce ubiquitination of the upstream suppressor of mTORC1 pathway, TSC1-TSC2 complex, thus promoting HCC progression (P. Guo, Ma, et al., 2018). TRIM31 also degrades p53 via ubiquitination and subsequently over activate AMPK pathway to promote anoikis-resistance of HCC (P. Guo, Qiu, et al., 2018). TRIM24 also promotes HCC progression via activating AMPK signaling pathway (Y. Zhu, et al., 2018).

Additionally, downregulation of TRIM11 decreases the level of p-PI3K and p-Akt in HCC cells and thus inhibits activation of PI3K/Akt signaling pathway in HCC (Z. Zhang, et al., 2017). TRIM37 upregulates the activity of Akt and phosphorylates Akt, thereby activates Akt signaling and enhances sorafenib resistance in HCC (G. Tan, et al., 2021). TRIM52 knockdown inhibits proliferation, migration as well as invasion and induces cell cycle arrest in HCC both *in vitro* and *in vivo*. TRIM52 knockdown can inhibit the ubiquitination of PPM1A, a Rela phosphatase with

tumor suppressor-like activity in HCC (Y. Zhang, Tao, et al., 2018). Ectopic expression of HBx increases TRIM52 expression in HepG2 cells, and TRIM52 promotes the proliferation of HepG2.2.15 *in vitro*. Further experiments showed that HBx might affect TRIM52 through the NF-κB signaling pathway in HBV-associated HCC (Y. Zhang, et al., 2017). Moreover, overexpression of TRIM44 can enhance doxorubicin resistance of HCC via activating NF-κB signaling (X. Zhu, et al., 2016). Silencing of TRIM59 reduces the level of E-cadherin and elevates vimentin and N-cadherin expression. And TRIM59 as an oncogenic protein may reinforce cell proliferation and metastasis of HCC by p53 signaling pathway (G. Sun, et al., 2017). In addition, TRIM37, TRM65 andTRIM66 are found to promote malignant behaviors in HCC through activating Wnt/β-catenin signaling pathway (Fan, et al., 2019; J. Jiang, et al., 2015; Y. F. Yang, et al., 2017).

TRIM7 (L. Zhu, et al., 2020), TRIM16 (L. Li, et al., 2016), TRIM19 (Chan, Chin, Liew, Chang, & Johnson, 1998; Herzer, Weyer, Krammer, Galle, & Hofmann, 2005; Son, Yu, Choi, Lee, & Choi, 2005; Yoon & Yu, 2001), TRIM25 (Y. H. Li, et al., 2018; Zang, Ren, Cao, & Tian, 2017), TRIM26 (Y. Wang, et al., 2015), TRIM50 (X. Ma, et al., 2018), TRIM55 (X. Li, Huang, & Gao, 2019) and TRIM58 (X. Qiu, Huang, Zhou, & Zheng, 2016) are reported to be down-regulated in HCC tissues and cell lines.

PML/TRIM19 was found to be overexpressed in neoplastic cells at the periphery of tumors, however, progressively decreased in cells at center of tumor (Chan, et al., 1998). Another study showed that the amount of PML as well as number and size of PML NBs gradually increased through progression from liver cirrhosis (LC), dysplastic nodules (DNs) to HCC, indicating that PML is involved in early stage of multistep hepatocarcinogenesis (Yoon & Yu, 2001). Furthermore,

overexpressed PML can induce G1 cell cycle arrest and triggers cell death in all liver cancer cell lines, irrespective of their p53 status (Son, et al., 2005). Similarly, hepatitis C virus (HCV) core protein can inhibit PML-IV-induced apoptosis and interfere with coactivator function of PML-IV for proapoptotic p53 target genes, CD95 (Fas/APO-1). This promotes HCV-associated development of HCC (Herzer, et al., 2005).

Li *et al*. revealed that TRIM16 knockdown enhances EMT process of HCC both *in vitro* and *in vivo*. And TRIM16 can inhibit the expression of E-cadherin via suppressing ZEB2 expression, thus promotes cell invasion and migration of HCC (L. Li, et al., 2016). TRIM26 knockdown promotes the proliferation, invasion, migration and colony formation in cell lines Bel-7402 and HepG2 of HCC *in vitro*. Through bioinformatics analysis, TRIM26 was found as a tumor suppressor to regulate diverse metabolism related signaling pathways in HCC (Y. Wang, et al., 2015). Loss of TRIM24 confers oncogenic activity to retinoic acid receptor alpha in HCC (RARA) (Khetchoumian, et al., 2007). TRIM24 was also shown to be potent liver-specific tumor suppressor by attenuating RARA-mediated transcription (Khetchoumian, et al., 2008). TRIM24 also directly and indirectly inhibits hepatic lipid accumulation and the development of HCC in mice (S. Jiang, et al., 2015).

In addition, TRIM25 can directly interact with MTA1 and increase polyubiquitinated MTA1, thus inhibits migration and invasion of HCC cells (Y. H. Li, et al., 2018; Zang, et al., 2017). TRIM50 directly targets snail protein via K48-linked ubiquitination and degradation. Targeting on snail protein inhibits snail-mediated EMT process of HCC *in vitro* and *in vivo* (X. Ma, et al., 2018).

Thus, TRIM proteins have been shown to have both tumor suppressive and tumor promoting

functions in HCC, and it is important to explore the mechanism of TRIM proteins function in different conditions.

5.10 TRIM family in regulation of epithelial-mesenchymal plasticity of tumors

Epithelial–mesenchymal transition (EMT) is a transitional process that epithelial cells lose intercellular adhesion and polarity, and transit to more motile and invasive mesenchymal-line cells (B. Du & Shim, 2016). EMT has been reported to be associated with many characteristics of cancers, especially the drug resistance (B. Du & Shim, 2016), recurrence and metastasis (Aiello & Kang, 2019), it is a common cause of death in cancer patients (Hua, Ten Dijke, Kostidis, Giera, & Hornsveld, 2020). Therefore, EMT can be a potential target for cancer therapy.

Up to now, 19 TRIM proteins were found to be associated with EMT in various types of cancers, such as breast cancer (C. Wei, et al., 2016), colorectal cancer (M. Liu, et al., 2018), gastric cancer (F. Wang, et al., 2018), glioblastoma (L. Li, et al., 2019), hepatocellular carcinoma (X. Liu, et al., 2014; Z. Zhang, et al., 2017), lung cancer (X. Wang, et al., 2016) and ovarian cancer (Deng, et al., 2017). Generally, TRIM11 (Lan, et al., 2021), TRIM14 (F. Wang, et al., 2018), TRIM15 (L. Zhang, et al., 2021), TRIM24 (T. Jiang, et al., 2020; X. Liu, et al., 2014), TRIM28 (Damineni, et al., 2017), TRIM37 (C. E. Hu & Gan, 2017), TRIM44 (L. Li, et al., 2019), TRIM47 (Y. Wang, et al., 2020), TRIM59 (Y. Sun, et al., 2017), TRIM65 (Wei, et al., 2018), TRIM66 (T. He, et al., 2019) and TRIM67 (J. Jiang, et al., 2020) can promote EMT process in various types of tumors. However, TRIM16 (L. Li, et al., 2016), TRIM26 (K. Wang, et al., 2019), TRIM50 (X. Ma, et al., 2018), TRIM55 (X. Li, et al., 2019), TRIM56 (L. Zhao, et al., 2018), TRIM58 (M. Liu, et al., 2018) and TRIM62 (T. Y. Liu, et al., 2016) can inhibit tumor progression by suppressing EMT

process.

Overexpression of TRIM11 (Z. Zhang, et al., 2017), TRIM14 (F. Wang, et al., 2018), TRIM15 (L. Zhang, et al., 2021), TRIM28 (Damineni, et al., 2017), TRIM37 (C. E. Hu & Gan, 2017), TRIM44 (Xiong, et al., 2018), TRIM47 (Y. Wang, et al., 2020), TRIM59 (Geng, et al., 2019), TRIM65 (Wei, et al., 2018), TRIM66 (T. He, et al., 2019) and TRIM67 (J. Jiang, et al., 2020) can decrease the expression of epithelial marker (E-cadherin) and increase the expression of mesenchymal marker (N-cadherin). Besides, overexpression of TRIM11 (Z. Zhang, et al., 2017), TRIM14 (F. Wang, et al., 2018), TRIM15 (L. Zhang, et al., 2021), TRIM24 (T. Jiang, et al., 2020), TRIM28 (Deng, et al., 2017), TRIM37 (S. L. Tang, et al., 2018), TRIM44 (L. Li, et al., 2019), TRIM47 (Y. Wang, et al., 2020), TRIM59 (Y. Sun, et al., 2017), TRIM65 (Wei, et al., 2018), TRIM66 (T. He, et al., 2019) and TRIM67 (J. Jiang, et al., 2020) can elevate another mesenchymal marker, vimentin protein. In addition, some mesenchymal markers such as β-catenin (T. Jiang, et al., 2020; X. Liu, et al., 2014), Slug (Damineni, et al., 2017; X. Liu, et al., 2014), fibronectin (Damineni, et al., 2017), VEGF, MMP-2, MMP-9, Snail and Twist1 (X. Liu, et al., 2014; X. Wang, et al., 2016) are also increased in tumors. Notably, some transcription factor interacted with TRIM family are also involved in EMT process of tumors. Zinc finger E-box binding homeobox 2 (ZEB2) is a downstream target of TRIM14. And overexpression of ZEB2 can reverse inhibition of EMT caused by the inhibition of TRIM14 in glioblastoma (Feng, et al., 2019).

Overexpression of TRIM16 (L. Li, et al., 2016) and TRIM26 (K. Wang, et al., 2019) can increase expression of E-cadherin and decrease expression of N-cadherin in PTC and HCC. Furthermore, overexpression of TRIM16 (L. Qi, et al., 2016) and TRIM62 (T. Y. Liu, et al., 2016)

can increase another epithelial marker α-catenin in cervical cancer and prostate cancer. And TRIM62 can decrease some other mesenchymal markers such as vimentin, Twist and Snail in lung cancer (Quintas-Cardama, et al., 2014). Additionally, TRIM62 can inhibit EMT through ubiquitination and degradation of SMAD3, which is the main effector of TGF-β-SMAD3 signaling pathway (N. Chen, et al., 2013). Sonic hedgehog pathway is involved in embryogenesis and development, metastasis, and drug resistance of tumors (H. Zhang, et al., 2020). Remarkably, TRIM16 inhibits EMT and metastasis by down-regulating sonic hedgehog pathway in NSCLC (Huo, et al., 2015).

5.11 TRIM family in regulation of cancer stem cells (CSCs)

Cancer stem cells (CSCs) are defined as one cell type with self-renewal (Shibue & Weinberg, 2017). They are identified in various liquid and solid cancers, and contributed to tumor growth, metastasis, drug resistance, and recurrence after therapy (Shibue & Weinberg, 2017). CSCs originate from progenitor cells or non-malignant stem cells. And dysregulated signaling pathways crucial for stem cell homeostasis can lead to the production of CSCs (Clara, Monge, Yang, & Takebe, 2020). In CSCs, JAK/STAT3, EGFR, AMPK and Notch pathways are found to be vital for maintaining self-renewal (Cai, et al., 2019; Pei, et al., 2018; Talukdar, Emdad, Das, & Fisher, 2020; T. Wang, et al., 2018).

To date, seventeen studies have demonstrated that TRIM proteins can regulate CSCs stemness acquisition or maintenance. Generally, TRIM proteins promote CSCs progression by positively regulating core transcription factors (i.e., EZH2 (J. Li, et al., 2017), ISG15 (J. Sun, et al., 2020) and c-Myc (C. Zhang, et al., 2017)), or activating specific signaling pathways such as

JAK/STAT3 (C. Zhang, et al., 2017) and EGFR (K. Di, et al., 2013; D. Lv, et al., 2017). However, several TRIM proteins were found to negatively regulate stem cell self-renewal by ubiquitin-mediated degradation of specific transcription factors (Gli-1 (J. Yao, et al., 2016) and Oct-1 (L. Du, et al., 2016) or inhibition of some signaling pathways (i.e., Notch pathway (Quintas-Cardama, et al., 2015)).

To better understand it, we discussed the roles of TRIM family members in CSCs stemness or self-renewal in details. Both TRIM8 and TRIM24 were found to activate STAT3 signaling in glioma stem cells (D. Lv, et al., 2017; C. Zhang, et al., 2017). Overexpression of TRIM11 increases EGFR level and MAPK activity, and promotes tumorsphere formation (a stem-like phenotype) in high-grade gliomas (K. Di, et al., 2013). Another study found that TRIM24 promotes EGFR/EGFRvIII signaling in patient-derived glioma stem cells, thereby enhances EGFR-driven tumorigenesis in gliomas (D. Lv, et al., 2017).

Additionally, TRIM25 and TRIM28 were revealed to promote the stemness of breast cancer stem cell (Czerwinska, et al., 2017; J. Li, et al., 2017; Walsh, et al., 2017). TRIM25 can upregulate expression of POU5F1, NANOG, and SOX2 to maintain quiescent CSC-like phenotypes and stemness in breast cancer (Walsh, et al., 2017). TRIM28 knockdown weaken the self-renew ability of CSCs by reducing the stability of AMPK protein, thus inhibits the growth of breast cancer (Czerwinska, et al., 2017). Similarly, TRIM28 can interact with EZH2 and SWI/SNF to promote the stem cell maintenance of breast cancer (J. Li, et al., 2017). TRIM32 was found to promote neural differentiation by increasing the stability of retinoic acid receptor α (RARα) in neuroblastoma cells (Sato, et al., 2011). Moreover, TRIM32 can promote CSC stemness by degrading ARID1A in a ubiquitination manner and upregulating SDC2 expression in squamous

cell carcinoma (Q. Luo, et al., 2020).

Remarkably, miR-551b suppresses TRIM31 and forkhead box protein O3 (FOXO3) to promote proliferation, invasion and chemoresistance of ovarian cancer stem cells (Z. Wei, et al., 2016). Another study reported that miR-15b inhibits CSC stemness by suppressing TRIM14 in tongue squamous cell carcinoma (X. Wang, Guo, Yao, & Helms, 2017). Interestingly, TRIM19 both positively and negatively regulate stem cell phenotype (Mathieu, et al., 2014; H. Tang, et al., 2016). Besides, sodium arsenite and As2O3 can reduce CSCs stemness by inhibiting TRIM19 in hepatocellular carcinoma and glioblastoma (H. Tang, et al., 2016; W. Zhou, et al., 2015). Studies discussed above provide an insight to target cancer stem cells by TRIM proteins.

5. Clinical perspectives of TRIM family

In the above sections, the roles of different TRIM proteins in various cancer types are described. Exploring the function of TRIM proteins in these processes usually needs molecular methods to overexpress and/or knock down the expression of TRIM members in cancer cell lines, as well as to test the influence in xenograft tumors of mice. Together with the observations of overexpression/down-regulation of many TRIM family members in diverse cancer subtypes, this information paves the way for the development of assays to use TRIM proteins as the diagnostic prognostic biomarkers, as well as development of new cancer therapy by targeting a particular TRIM member.

6.1. TRIM as biomarkers for diagnosis

TRIM members have been examined in human cancer at the DNA, mRNA and protein levels, and are potential diagnosis markers.

The t(15;17) translocation encodes PML(TRIM19)-RARα fusion protein, occurring in 95% of APL patients, and is considered as diagnostical biomarker (Lutz, Moog-Lutz, & Cayre, 2002). Tests like droplet-reverse transcription-polymerase chain reaction (droplet-RT-PCR), instant quality-fluorescence in situ hybridization (IQ-FISH) and morphological examination of blood smears can detect and quantify the PML-RARA fusion protein in patients with APL within 4h (Shigeto, et al., 2016).

An exome sequencing study showed that 21 of 33 patients with Wilms tumor have a mutation in TRIM28. Importantly, there is a strong parent-of-origin effect with ten inherited mutations being transmitted from their mothers (Mahamdallie, et al., 2019).

Many tissue biomarkers are also identified as diagnostic makers in various cancers (Khatamianfar, et al., 2012). TRIM59 protein is 2–3-fold increased in NSCLC tissues than adjacent tissues based on 140 NSCLC tissues and 10 normal tissue (Hao, Du, & Xi, 2017). TRIM59 is also markedly overexpressed in HCC tissues (n=11) than normal tissues (Ying, et al., 2020). Another study showed that TRIM59 is upregulated in CRC tissues (n=90) compared with corresponding normal colorectal mucosa by RT-PCR (Y. Sun, et al., 2017). Combining these three studies, TRIM59 may be a potential diagnostic biomarker for patients with lung cancer, HCC and CRC (Hao, et al., 2017) (Y. Sun, et al., 2017; Ying, et al., 2020).

Recently, epigenetic signatures, like methylation have emerged as efficient biomarkers in various tumors (J. Huang, Soupir, & Wang, 2021). Diaz-Lagares *et al.* reported that TRIM58 was hypermethylated in 237 stage I NSCLC samples than 25 matched normal lung samples. The area under the curve (AUC) is 0.97 calculated based on 122 stage I NSCLC and 79 nonmalignant lung tissues (Diaz-Lagares, et al., 2016). TRIM58 is also significantly hypermethylated in HCC tissues

(n=181) compared with adjacent normal tissues (n=172) (X. Qiu, et al., 2016).

TRIM28 is significantly overexpressed in NSCLC tissues than in noncancerous tissues. Importantly, the overall TRIM28-positive detection rate was 30.4% (42 of 138) in peripheral blood of NSCLC patients and was 29.9% (29 of 97) in early-stage NSCLC patients (L. Liu, et al., 2013). Another study reported that serum levels of TRIM72 are lower in patients with colon cancer. And the AUC of serum TRIM72 is 0.829 and the combination of TRIM72 with carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA199) exhibits a higher diagnostic value for colon cancer (AUC = 0.928) (Z. Chen, et al., 2018).

In brief, some members of TRIM family show a promising diagnostic value by detecting epigenetic signatures or peripheral blood of patients with cancers.

6.2 TRIM as tissue biomarkers for prognosis

TRIM proteins were found to be associated with several important clinicopathological characteristics and prognosis **(Table S4 and Table S5).** In addition, TRIM14, TRIM25, TRIM32, TRIM44, TRIM59, and TRIM29 are abnormally expressed in various types of cancer and are found to be associated with prognosis. Here, we focus on TRIM14, TRIM25 and TRIM32, which are most frequently related with prognosis in cancers (**Table 4**).

TRIM14 located in 9q22.33, is up-regulated in several types of cancer including papillary thyroid carcinoma (W. Sun, et al., 2020), glioblastoma (Feng, et al., 2019), gastric cancer (F. Wang, et al., 2018), osteosarcoma (G. Xu, et al., 2017) and colorectal cancer (Z. Jin, et al., 2018). Its expression is correlated with several clinicopathological characteristics of various cancers and is a potential prognostic biomarker.

To evaluate the association between the expression level of TRIM14 and overall survival (OS) in cancer patients, we collected data of HRs and 95%CIs for OS from 4 studies with a total of 1267 patients to perform meta-analysis. Wang *et al.* revealed that the elevated expression of TRIM14 was associated with unfavorable OS in patients with gastric cancer (F. Wang, et al., 2018). Sun *et al.* observed that in a group with 89 patients with papillary thyroid carcinoma, the elevated expression of TRIM14 was correlated with poor recurrence-free survival (HR=0.22, 95%CI: 0.083-0.59, p=0.027) (W. Sun, et al., 2020). Additionally, Feng *et al.* mentioned that OS of patients with glioblastoma was poorer in the group of high expression of TRIM14 than that in the low expression group (p=0.0340) (Feng, et al., 2019). Xu *et al.* conducted a study of 45 patients with osteosarcoma, and found that OS in the TRIM14-positive group was statistically unfavorable than that in the TRIM14-negative group (p=0.043) (G. Xu, et al., 2017). Finally, we found that there is a significant association between high TRIM14 expression and poor OS in cancer patients through the application of the random-effects model (pooled HR = 1.22, 95% CI: 1.05–1.42, p<0.05, **Figure 8A**).

Similarly, TRIM25 located in 17q22, is elevated in three cancers including HCC (Y. Liu, Tao, et al., 2020), gastric cancer (Z. Zhu, et al., 2016), and colorectal cancer (N. Sun, et al., 2017). Moreover, its expression is associated with poor prognosis in HCC (Y. Liu, Tao, et al., 2020), and gastric cancer (Z. Zhu, et al., 2016). To verify the association between the expression level of TRIM25 and OS in cancer patients, we collected data of HRs and 95%CIs for OS from 2 studies with a total of 1149 patients to perform meta-analysis. Liu *et al.* studied 90 HCC patients, and found that OS was poorer in group with high expression of TRIM25 than that in the low expression group (p=0.0092). In addition, OS and disease-free survival were also poorer in high

expression of TRIM25 group (n = 146) compared with low expression of TRIM25 group (n = 218) in HCC patients from TCGA cohort (p=0.013, p=0.023, respectively) (Y. Liu, Tao, et al., 2020). In addition, Zhu *et al.* conducted a study with 90 gastric cancer patients and reported that the elevated expression of TRIM25 was linked with poor OS (p=0.012) (Z. Zhu, et al., 2016). Ultimately, we found that there was a significant association between high TRIM25 expression and poor OS in cancer patients through using the random-effects model (pooled HR = 2.83, 95% CI: 1.33–5.88, p<0.05, **Figure 8B**).

Additionally, TRIM32 located in 9q33.1, is up-regulated in two types of cancers including gastric cancer (M. Ito, et al., 2017), and lung cancer (H. Yin, et al., 2019). Its high expression is usually associated with poor prognosis in patients with these two cancers (M. Ito, et al., 2017).

In order to explore the relationship between TRIM32 and prognosis of cancer patients, we collected data of HRs and 95%CIs for OS from 4 studies with a total of 2725 patients to conduct meta-analysis. Wang *et al.* conducted a study of 61 patients with gastric cancer, showed that the elevated expression of TRIM32 was linked with an unfavorable OS (p=0.0361) (C. Wang, et al., 2018). Furthermore, a study conducted by Wang *et al.* revealed that the increased expression of TRIM32 was associated with unfavorable OS in 534 gastric cancer patients (p=0.0042) (J. Wang, et al., 2020). And Ito *et al.* revealed that elevated expression of TRIM32 was correlated with poor OS (p=0.006) and low recurrence-free survival (p=0.01) in 142 patients with gastric cancer (M. Ito, et al., 2017). In addition, Yin *et al.* found that high expression of TRIM32 was also associated with unfavorable OS in patients with lung cancer (H. Yin, et al., 2019). Finally, we revealed that there was a significant association between high TRIM32 expression and poor OS in patients with cancer through the application of the random-effects model (pooled HR = 1.21, 95% CI:

1.05–1.39, $p<0.05$, **Figure 8C**).

We also found that overexpression of TRIM29, TRIM44, and TRIM59 are associated with poor prognosis in patients with cancer through systematically analysis of multiple studies. Detailed information is shown in **Figure S2 and Table S4**. In brief, based on the expressions of different TRIM proteins with prognosis role, we can make a more accurate risk classification for patients early and conduct customized treatment and medical management to improve the survival of patients.

6.3 TRIM as tissue biomarkers for chemoresistance

Tumor cells often have or develop resistance to cytotoxic drugs, and this is the main cause of treatment failure in cancer patients (Fontana, Cariolo, Melling, & Carter, 2021). Following studies are about TRIM and related types of drug resistance, the specific mechanisms about how TRIM influenced drug resistance in cancers (**Table 5**).

TRIM8 (Mastropasqua, et al., 2017), TRIM11 (R. Zhang, et al., 2020), TRIM14 (Qiao, et al., 2020), TRIM23 (Y. Zhang, et al., 2020), TRIM25 (X. Qin, Qiu, & Zou, 2017), TRIM29 (C. Liu, et al., 2015), TRIM31 (Z. Wei, et al., 2016), TIM37 (G. Wu, et al., 2018), TRIM59 (R. He & Liu, 2020), and TRIM65 (Y. Li, et al., 2016; X. Pan, et al., 2019) were reported to influence cisplatin resistance in clear cell renal cell carcinoma and colorectal cancer, nasopharyngeal carcinoma, tongue cancer, ovarian cancer, esophageal cancer and lung cancer.

To be more specific, miR-17-5p/miR-106b-5p downregulates TRIM8, then inhibits p53 signaling pathway, which induces cisplatin resistance in ccRCC and CRC (Mastropasqua, et al., 2017). TRIM25 and TRIM65 promote cisplatin resistance through p53 pathway. TRIM25

increases the expression of MDM2 and cleaved-capsese3 and downregulates 14-3-3σ and p53 in NSCLC. Moreover, TRIM65 suppresses expression of miR-138-5p through promoting degradation and ubiquitination of TNRC6A, thus decreases expression of ATG7, an autophagy mediator in NSCLC. This leads to cisplatin resistance (Y. Li, et al., 2016). Apart from that, TRIM37 can promote cisplatin resistance through activating NF-κB signaling pathway by monoubiquitylation of NEMO in esophageal cancer (G. Wu, et al., 2018). TRIM23 can inhibit glucose uptake via activating NF-κB signaling pathway to promote cisplatin resistance in lung adenocarcinoma (Y. Zhang, et al., 2020). TRIM59 activates PTEN ubiquitination, then regulates the phosphorylation of AKT (p-AKT) and expression of hexokinase 2 (HK2) to promote cisplatin resistance in NSCLC (R. He & Liu, 2020). Besides, miR-551b inhibits the expression of Foxo3 and TRIM31, thus promotes cisplatin resistance in ovarian cancer (Z. Wei, et al., 2016). Knockdown of TRIM65 increases cisplatin-induced apoptosis, inhibits autophagy and decreases cisplatin resistance through regulating miR-138-5p/ATG7 (an important autophagy mediator) in NSCLC (X. Pan, et al., 2019). TRIM11 was found to degrade Daple in a p62-selective manner, which activates Wnt/β-catenin signaling pathway to induce ABCC9. This enhances cisplatin resistance in nasopharyngeal carcinoma cells (R. Zhang, et al., 2020).

Both TRIM16 and TRIM59 contribute to gefitinib resistance in NSCLC cells through activating JAK/STAT pathway (Z. Cui, Liu, Zeng, Zhang, et al., 2019; N. Wang & Zhang, 2018). Meanwhile, TRIM8 (Mastropasqua, et al., 2017) and TRIM37 (G. Tan, et al., 2021) were found to be involved in sorafenib resistance in ccRCC, CRC and HCC, respectively.

Both TRIM14 (Z. Tan, et al., 2018) and TRIM21 (Z. Zhao, et al., 2020) can induce temozolomide resistance in glioma. For instance, TRIM14 activates Wnt/β-catenin signaling via stabilizing Dvl2,

then contributes to temozolomide resistance in glioma (Z. Tan, et al., 2018).

Besides, TRIM25 (Nasrullah, et al., 2019), TRIM37 (Przanowski, et al., 2020) and TRIM44 (X. Zhu, et al., 2016) are also associated with doxorubicin resistance in TNBC and HCC. TRIM37 activates JAK/STAT and inhibits p53 signaling pathway, thus increases H2Aub and induces doxorubicin resistance in triple-negative breast cancer (Przanowski, et al., 2020). Moreover, knockdown of TRIM25 sensitizes colon cancer cells to doxorubicin or etoposide-induced apoptosis by increasing caspase-2 translation (Nasrullah, et al., 2019). And TRIM44 overexpression enhances doxorubicin resistance through activating NF-κB signaling pathway in HCC (X. Zhu, et al., 2016).

In addition, TRIM28 promotes etoposide, 5-fluorouracil and methotrexate resistance in HCC and breast cancer through inhibiting expression of E2F1 (L. Liu, et al., 2017), activating CD44 and Bim1 and increasing stem-like cell population (Damineni, et al., 2017), respectively. TRIM31 activates NF-κB signaling pathway and upregulates p65 by promoting K63-linked polyubiquitination of TNF receptor-associated factor 2. This promotes gemcitabine resistance in pancreatic cancer (C. Yu, et al., 2018).

Thus, TRIM family members play important roles in tumor chemotherapy failure, and may be potential therapeutic targets for chemoresistant cancer. However, studies about TRIM family and chemoresistance are relatively scarce, especially those about the relationship between TRIM family and multidrug resistance (MDR) in tumor.

6.4 Targeting TRIM for cancer treatment

It had been demonstrated that several TRIM family members play crucial roles in cancer

progression (Hatakeyama, 2011). Upregulation of these members promote the proliferation, migration, and invasion of various cancer cells, while their downregulation shows anti-tumor effect. These finding make TRIM family attractive targets for cancer treatment.

As the upstream regulator, miRNAs and lncRNAs can directly regulate expression of TRIM members. For example, TRIM29 and TRIM14, which regulate the development of GC, were identified as the targets of miR-185 and miR-195-5p, respectively (F. Qiu, et al., 2015; F. Wang, et al., 2018). In addition, TRIM44 can be induced by DUXAP8, FLJ21511-AS1 and LINC00265 in CRC or NSCLC (Ji, et al., 2020; Lei, et al., 2020; S. Sun, et al., 2020). Therefore, discovering more miRNA, lncRNAs and circRNAs targeting TRIM family is of great importance for cancer treatments, and it appears reasonable to target the dysregulated TRIM to inhibit the progression of cancer.

Up to now, carfilzomib (Kyprolis®) and bortezomib (Velcade®) are the only two approved drugs that target the proteasome and are used to treat multiple myeloma (S. Ito, 2020). They suggest the possibility of cancer treatment by targeting RING E3 ligases, for instance, TRIM proteins. Since TRIM family members are strongly related with diverse human cancer, developing TRIM inhibitors for cancer therapy is currently gaining pharmaceutical attentions (D'Amico, Mukhopadhyay, Ovaa, & Mulder, 2021) (**Table 6**).

TRIM24 has been recurrently reported to play oncogenic role in many tumors (Appikonda, Thakkar, & Barton, 2016). And TRIM24 can target endogenous p53(an important cell apoptosis regulator) for degradation (Allton, et al., 2009). Meanwhile, it is also a histone 'reader' through ubiquitination and a co-regulator of nuclear receptor-mediated transcription (Musselman & Kutateladze, 2018). TRIM24 contains a PHD/bromodomain, which offers the opportunity to

design inhibitors that block the interaction site of bromodomain. Three small molecule inhibitors (IACS-6558, "compound 34" and IACS-9571) have been developed for the inhibition of TRIM24 activity. In 2015, Zhan *et al.* developed IACS-6558 targeting bromodomain of TRIM24 through cellular histone-binding and chromatin-displacement assays (Y. Zhan, et al., 2015). Moreover, Bennett *et al.* discovered a potent acetyl-lysine mimetic benzimidazolones TRIM24 bromodomain inhibitor through screening 1,3-dimethyl-benzimidazolone scaffolds (KAc mimicry). The best compound, compound 34, is a selective dual BRPF-1 (Bromodomain protein family 1B)/TRIM24 BRD (bromodomains) inhibitor that bound with a K_D of 131 and 222nM, respectively. What is more, myeloma MM1S model exhibited modest sensitivity to compound 34 (GI50 > 10μM) (Bennett, et al., 2016). Similarly, Palmer and colleagues identified IACS-9571 through optimization of the same N, N'-dimethyl-benzimidazolone motif. Further experiments found that IACS-9571 was a selective inhibitor for TRIM24 and BRPF-1 with low nanomolar affinities (K_D = 31nM or 14nM, respectively). In addition, the bioavailability of IACS-9571 is 29% in female CD1 mice, making it useful for *in vivo* studies (Palmer, et al., 2016).

In addition to small molecular inhibitors that directly target TRIM proteins, numerous natural organic and inorganic matter have been reported to inhibit tumor through directly or indirectly targeting TRIM proteins. Detailed information is as follows:

Arsenic trioxide (As2O3) has been confirmed to target PML and/or PML-RARα proteins in APL cells (Z. G. Wang, et al., 1998). And As2O3 treatment is an effective and relatively safe drug in APL patients resistant to all-trans retinoic acid and conventional chemotherapy (Z. X. Shen, et al., 1997). Treatment with As2O3 had dual effects on malignant lymphocytes: (1) inhibiting growth through ATP depletion and prolongation of cell cycle time; (2) inducing cell apoptosis (X.

H. Zhu, et al., 1999). In 2004, Hayakawa *et al.* found that As2O3 treatment induces phosphorylation of PML and PML-RARα protein through MAPK pathway. And increased PML phosphorylation promotes PML-mediated apoptosis in cancer cells (Hayakawa & Privalsky, 2004). As2O3 was also revealed to downregulate PML for leukemia-initiating cells (LICs) eradication (K. Ito, et al., 2008). In addition, red orpiment, dexamethasone and genistein can be promising to treat APL (Laane, et al., 2009; Ng, et al., 2007; Zhong, Chen, Han, Shao, & Ouyang, 2003). Red orpiment can degrade PML-RARα fusion protein in APL cells (Zhong, et al., 2003). Similarly, genistein can up-regulate the expression of PML and promotes degradation of PML-RARα in NB4 cells. Moreover, genistein can significantly reverse PML-RAR-induced misfolding protein by inhibiting phosphorylation-dependent binding of N CoR and PML-RARα (Ng, et al., 2007). Interestingly, dexamethasone treatment leads to upregulation of PML and upregulation of PML enhance ability of dexamethasone to kill primary leukemic cells (Laane, et al., 2009). Notably, As2O3 can inhibit glioma stem cells through promoting PML degradation (W. Zhou, et al., 2015). This may disturb fusion of PML-RARα proteins, thus inhibiting glioma growth.

Furthermore, sodium arsenite treatment was reported to inhibit PML expression at the transcriptional level, thus inhibiting CD133+CD13+ hepatocytes, a type of CSCs in primary HCC tumors (H. Tang, et al., 2016). Another study found that a tyrosine kinase inhibitor, named methyl 2,5-dihydromethylcinnimate (2,5-MeC), can enhance the expression and/or stability of PML proteins and induced PML- nuclear bodies (nuclear structure consisting of numerous proteins such as PML, p53 and SUMO-1) formation in NSCLC and OS cells (Komura, Asakawa, Umezawa, & Segawa, 2007). Liang *et al.* showed that verteporfin inhibits PD-L1 through autophagy and STAT1-IRF1-TRIM28 signaling axis, exerting its antitumor function (J. Liang, et al., 2020).

13-Chlorine-3,15-dioxy-gibberellic acid methyl ester (GA-13315) was also reported to promote TRIM67 expression to increase expression of FAS and cell apoptosis in lung cancer (R. Liu, et al., 2019). Moreover, eugenol suppresses p65 expression, subsequently decreasing TRIM59 expression to inhibit NSCLC progression (Z. Cui, Liu, Zeng, Chen, et al., 2019). Recently, withaferin A was found to activate TRIM16, thus exhibiting potent cytopathic effects on melanoma cells (Nagy, et al., 2020).

In conclusion, above methods such as targeting the bromodomain used in searching for small molecule inhibitors of TRIM24 are promising to be applied in cancer treatment and would be interesting to be applied to other TRIM proteins to develop novel anti-cancer methods.

However, multi-domain of TRIMs and the off-target effects of inhibitors imply that targeting just one domain of TRIMs may not be sufficient to get the expectant therapeutic effects. Moreover, As2O3 and red orpiment exhibit a powerful anticancer effect in APL through targeting PML (Z. X. Shen, et al., 1997), suggesting some chemicals and natural products can be used to treat malignancies in clinics. However, related studies about targeting TRIM family in clinics is still unknown. Therefore, further study is urgently needed to functionally characterize TRIM family in detail and subsequently regulate their activity with effective targeting strategies for pharmaceutical applications.

6. Conclusions and outlook

This review of TRIM family highlights their important roles in the development and progression of various cancers, and discusses the regulatory mechanism and potential clinical implications of the TRIM family members. However, the biological function of TRIM members in

prostate and thyroid cancer is especially rarely studied. Therefore, the potential value of TRIM proteins in clinic needs further extensive research. In summary, TRIM family members are involved in diverse important processes in cancer development, exhibiting oncogenic and tumor-suppressive capacities in different human cancer types, and showing as potential tissue biomarkers for prognosis and chemoresistance (**Table 4-5)**. For instance, TRIM59 is a potential diagnostical biomarker for lung cancer, HCC and CRC (Hao, et al., 2017; Y. Sun, et al., 2017; Ying, et al., 2020), and it also could predict the poor prognosis in cancer patients (**Figure S2**). However, small molecule inhibitor targeting TRIM59 remains to be established. By targeting TRIM24 PHD/bromodomain, three small molecule inhibitors (IACS-6558, "compound 34" and IACS-9571) have been developed to inhibit TRIM24 activity, even though studies of the diagnosis and prognosis value of TRIM24 are still scarce. Serous TRIM28 exhibits a high diagnostical value in early-stage NSCLC (L. Liu, et al., 2013). Importantly, TRIM28 also contains a PHD/bromodomain, therefore, it is interesting to investigate the therapeutic value of TRIM28 in cancers. TRIM family inhibitors are potential therapy for cancer patients with TRIM family overexpression. Development of molecular therapy targeting on TRIM family will definitely benefit cancer patients.

At present, several critical questions need to be addressed. Few studies explore the function of other TRIM family members such as TRIM6 (S. Zheng, et al., 2020), TRIM21 (G. Zhou, et al., 2020), and TRIM23 (Y. Han, et al., 2020) in carcinogenesis. What are the direct substrates of TRIM family, and whether different TRIM members have the same substrates? Many studies concentrate on the downstream targets of TRIM family, but how TRIM members are regulated by upstream regulators is largely elusive. Whether TRIM protein is present in the body fluids of

cancer patients also requires further investigation.

To address these concerns, conditional engineered mouse models (tissue-specific knockout mouse models or transgenic mouse models) are favorable approaches. They can be used to clarify the function of TRIM proteins in tumorigenesis *in vivo* (Cheon & Orsulic, 2011). Besides, high-throughput sequencing technology could be helpful in determining the molecular mechanism of TRIM-involved tumorigenesis *in vitro* (Cheon & Orsulic, 2011). Moreover, systematic approaches are needed to screen the substrates of TRIM in human cancers (Iconomou & Saunders, 2016). Furthermore, the application of tissue and plasma proteomics are crucial for discovering potential biomarkers and drug targets (L. Peng, et al., 2018). Overall, more translational studies and clinical trials are required to develop TRIM-based novel biomarkers and therapeutics for cancer patients.

Figure S1: The flow diagram of study selection in this review. n=number of records.

Figure S2: Forest plot of the pooled HRs of six TRIM proteins expression for overall survival in different cancer types. (A): Forest Plot of the associations between the elevated expression of TRIM29 and cancer overall survival. (B) Forest Plot of the associations between the elevated expression of TRIM44 and cancer overall survival. (C) Forest Plot of the associations between the elevated expression of TRIM59 and cancer overall survival. Abbreviations: CI, confidence interval; HR, hazard ratio.

Table S1: The upstream regulation of TRIM family in various cancers.

Table S2: The regulatory effect of TRIMs on multiple signaling pathways in various cancers.

Table S3: Summary of TRIM family expression, gene type, cell function and mechanism in various types of human cancers.

Table S4: Summary of relationship between TRIM family and cancer prognosis.

Table S5: Summary of TRIM family and clinicopathologic characteristics of cancer.

Declaration of competing interest

The authors declare that they have no competing interests.

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Table 1: The upstream regulation of TRIM family in various cancers.

TRIM family	Cancer type	Upstream	Mechanism	PMIDs
TRIM19	Lung cancer	IFNβ	Upregulating expression of TRIM19.	(Kuo, et al., 2014)
TRIM52	Liver cancer	HBx	Upregulating expression of TRIM52 via NF-κB signaling pathway.	(Y. Zhang, et al., 2017)
TRIM67	Colorectal cancer	p53	Upregulating expression of TRIM67.	(S. Wang, et al., 2019)
TRIM25	Breast cancer	miR-3614-3p	Inhibiting expression of TRIM25 by binding to its 3'-UTR.	(Z. Wang, et al., 2019)
TRIM31	Liver cancer	miR-29c-3p	Directly bounding to TRIM31 and suppressing TRIM31 expression.	(T. Lv, et al., 2020)
TRIM31	Ovarian cancer	miR-551b	Inhibiting expression of Foxo3 and TRIM31.	(Z. Wei, et al., 2016)
TRIM14	Tongue cancer	KCNQ1OT1	Sponging miR-124-3p to regulate TRIM14 expression.	(Qiao, et al., 2020)
TRIM24	Colorectal cancer	ZFPM2 - AS1	Promoting expression of TRIM24 by sponging miR-137.	(M. Xiao, et al.,

				2021)
TRIM44	Colorectal cancer	LINC00265	Directly bounding to miR-216b-5p and negatively regulating miR-216b-5p.	(S. Sun, et al., 2020)
TRIM24	Lung cancer	circEPSTI1	Inhibiting miRNA-1248 and upregulating TRIM24	(T. Yang, et al., 2020)
TRIM25	Lung cancer	circNDUFB2	Interacting with TRIM25 and IGF2BPs, enhancing ubiquitination and degradation of IGF2BPs.	(B. Li, et al., 2021)

IFNβ: Interferon β; HBx: Hepatitis B protein X; IGF2BPs: Insulin-like growth factor 2 messenger RNA-binding proteins.

Table 2: The regulatory effect of TRIMs on multiple signaling pathways in various cancers.

TRIM family	**Cancer type**	**Downstream targets**	**Pathway affected**	**Positive/Negative**	**References**
TRIM37	Lung cancer	TRAF2, p-IKKβ, p-IKBα and p65	NF-κB signaling pathway	Positive	(Y. Li, et al., 2018)
TRIM52	Ovarian cancer	p-IKKβ, p-IKBα and p65	NF-κB signaling pathway	Positive	(W. Yang, et al., 2018)
TRIM8	Colorectal cancer	MDM2	p53 signaling pathway	Positive	(Caratozzolo, et al., 2012)

TRIM21	Glioma	p53 and p21	p53 signaling pathway	Negative	(Z. Zhao, et al., 2020)
TRIM22	Chronic myeloid leukemia	p-Akt, p-mTOR	Akt signaling pathway	Positive	(L. Li, et al., 2018)
TRIM25	Liver cancer	p-Akt and PTEN	Akt signaling pathway	Positive	(Yuan, et al., 2020)
TRIM24	Liver cancer	β-catenin	Wnt/β-catenin pathway	Positive	(X. Liu, et al., 2014)
TRIM26	Bladder cancer	p-GSK3β, β-catenin	Wnt/β-catenin pathway	Positive	(X. Xie, Li, Pan, & Han, 2021)
TRIM14	Breast cancer	p-STAT3	JAK/STAT pathway	Positive	(G. Hu, W. Pen, et al., 2019)
TRIM16	Lung cancer	p-JAK1, p-STAT1, and p-STAT2	JAK/STAT pathway	Negative	(N. Wang & Zhang, 2018)
TRIM25	Colorectal cancer	Smad2, Smad4	TGF-β pathway	Positive	(N. Sun, et al., 2017)
TRIM62	Adenocarcinoma	Smad3	TGF-β pathway	Negative	(N. Chen, et al., 2013)
TRIM11	Glioma	EGFR	EGF pathway	Positive	(K. Di, et al., 2013)
TRIM59	Lung cancer	EGFR	EGF pathway	Positive	(Z. Cui, Liu, Zeng, Zhang, et

					al., 2019)
TRIM7	Liver cancer	p-p38	MAPK pathway	Positive	(X. Hu, Z. Tang, et al., 2019)
TRIM44	Intrahepatic cholangiocarcinoma	p-MEK and p-ERK	MAPK pathway	Positive	(R. Peng, et al., 2018)
TRIM59	Lung cancer	BECN1	Autophage	Negative	(T. Han, et al., 2018)
TRIM65	Lung cancer	ATG7	Autophage	Positive	(X. Pan, et al., 2019)
TRIM19	Ovarian cancer	DAXX	DNA damage response pathway	Negative	(W. W. Pan, Yi, et al., 2013)
TRIM37	TNBC	BM1 and ERA3B	DNA damage response pathway	Positive	(Przanowski, et al., 2020)

Table 3: Summary of TRIM family in various types of human cancers (Top 3 studies of TRIM family in various cancers).

TRIM family	**Tumor**	**Expression**	**Gene type**	**Cell functions**	**References**
TRIM19	Breast cancer	Down	Tumor suppressor	Cell proliferation and apoptosis	(Le, et al., 1998)

TRIM19	Breast cancer	Down	Tumor suppressor	Cell apoptosis	(Bao-Lei, et al., 2006)
TRIM19	Breast cancer	Down	Tumor suppressor	Cell apoptosis	(Son, et al., 2007)
TRIM25	Breast cancer	Up	Oncogene	Cell proliferation.	(Ikeda, et al., 2000)
TRIM25	Breast cancer	Up	Oncogene	Cell proliferation	(Urano, et al., 2002)
TRIM25	Breast cancer	Up	Undefined	Cell metastasis and stemness	(Walsh, et al., 2017)
TRIM25	Breast cancer	Up	Oncogene	Cell proliferation	(Z. Wang, et al., 2019)
TRIM28	Breast cancer	Up	Oncogene	Cell invasion, EMT, migration	(Damineni, et al., 2017)
TRIM28	Breast cancer	Up	Oncogene	Cell proliferation and metastasis	(Addison, et al., 2015)
TRIM28	Breast cancer	Up	Oncogene	Cell migration and invasion	(C. Wei, et al., 2016)
TRIM28	Breast cancer	Up	Oncogene	Stemness and EMT	(Czerwinska, et al., 2017)
TRIM14	Cervical cancer	Up	Oncogene	Cell proliferation and apoptosis	(Diao, et al., 2020)
TRIM24	Cervical cancer	Up	Oncogene	Cell migration and invasion	(L. Lin, et al., 2017)
TRIM62	Cervical cancer	Down	Tumor suppressor	Cell proliferation, migration, invasion and EMT	(T. Y. Liu, et al., 2016)

TRIM25	Colorectal cancer	NA	Oncogene	Cell apoptosis	(Nasrullah, et al., 2019)
TRIM25	Colorectal cancer	Up	Oncogene	Cell proliferation and migration	(N. Sun, et al., 2017)
TRIM25	Colorectal cancer	NA	Oncogene	Cell apoptosis	(Nasrullah, et al., 2019)
TRIM37	Colorectal cancer	Up	Oncogene	Cell proliferation, migration and invasion	(P. Zhao, et al., 2017)
TRIM37	Colorectal cancer	Up	Oncogene	Cell proliferation, migration, invasion and EMT	(C. E. Hu & Gan, 2017)
TRIM59	Colorectal cancer	Up	Oncogene	Cell proliferation, apoptosis, migration and invasion	(Y. Sun, et al., 2017)
TRIM59	Colorectal cancer	Up	Oncogene	Cell proliferation, migration, apoptosis and invasion	(W. Wu, et al., 2017)
TRIM15	Gastric cancer	Up	Oncogene	Cell migration, invasion and EMT	(W. Zhou, et al., 2020)
TRIM15	Gastric cancer	Down	Tumor suppressor	Cell invasion	(W. Chen, et al., 2018)
TRIM24	Gastric cancer	Up	Oncogene	Cell proliferation	(Miao, et al., 2015)
TRIM24	Gastric cancer	Up	Oncogene	Cell proliferation, migration, invasion and apoptosis.	(Z. Fang, et al., 2017)
TRIM32	Gastric cancer	Up	Oncogene	Cell proliferation and apoptosis	(J. Wang, et al., 2020)
TRIM32	Gastric cancer	Up	Oncogene	Cell proliferation, migration and invasion	(C. Wang, et al., 2018)

TRIM32	Gastric cancer	Up	Oncogene	Cell proliferation and apoptosis	(M. Ito, et al., 2017)
TRIM24	Glioblastoma	Up	Oncogene	Cell proliferation	(L. H. Zhang, et al., 2015)
TRIM44	Glioblastoma	Up	Oncogene	Cell proliferation, invasion, migration and EMT	(L. Li, et al., 2019)
TRIM59	Glioblastoma	Up	Oncogene	Cell proliferation, migration and stemness	(Sang, et al., 2018)
TRIM11	Glioma	Up	Oncogene	Cell proliferation, invasion, migration and stemness	(K. Di, et al., 2013)
TRIM31	Glioma	Up	Oncogene	Cell proliferation, invasion and migration	(G. Shi, et al., 2019a)
TRIM31	Glioma	Up	Oncogene	Cell proliferation and invasion	(L. Zhou, et al., 2019)
TRIM31	Glioma	Up	Oncogene	Cell proliferation, invasion and migration	(G. Shi, et al., 2019a)
TRIM65	Glioma	Up	Oncogene	Cell proliferation, migration and invasion	(G. Hu, N. Liu, et al., 2019)
TRIM19	Liver cancer	Down	Tumor suppressor	Cell proliferation and apoptosis	(Chan, et al., 1998)
TRIM19	Liver cancer	Down	Undefined	NA	(Yoon & Yu, 2001)
TRIM19	Liver cancer	Down	Tumor suppressor	Cell apoptosis	(Herzer, et al., 2005)
TRIM19	Liver cancer	Down	Tumor suppressor	Cell apoptosis	(Son, et al., 2005)

TRIM25	Liver cancer	Up	Oncogene	Cell migration and invasion	(Zang, et al., 2017)
TRIM25	Liver cancer	Up	Oncogene	Cell migration and invasion	(Y. H. Li, et al., 2018)
TRIM25	Liver cancer	Up	Oncogene	Cell apoptosis	(Y. Liu, Tao, et al., 2020)
TRIM25	Liver cancer	Up	Oncogene	Cell apoptosis	(Yuan, et al., 2020)
TRIM31	Liver cancer	Up	Oncogene	Cell proliferation and migration	(T. Lv, et al., 2020)
TRIM31	Liver cancer	Up	Oncogene	Cell proliferation and invasion	(P. Guo, Qiu, et al., 2018)
TRIM31	Liver cancer	Up	Oncogene	Cell proliferation and invasion	(P. Guo, Ma, et al., 2018)
TRIM28	Lung cancer	Up	Oncogene	Cell migration, invasion and EMT	(L. Chen, et al., 2014)
TRIM28	Lung cancer	Up	Tumor suppressor	Cell proliferation	(L. Chen, et al., 2012)
TRIM65	Lung cancer	Up	Oncogene	Cell proliferation	(Y. Li, et al., 2016)
TRIM65	Lung cancer	Up	Oncogene	Cell apoptosis	(X. Pan, et al., 2019)
TRIM71	Lung cancer	Down	Tumor suppressor	Cell proliferation and invasion	(J. Yin, et al., 2016)
TRIM71	Lung cancer	Up	Oncogene	Cell proliferation	(Ren, et al., 2018)

TRIM16	Neuroblastoma	Down	Tumor suppressor	Cell proliferation and viability	(P. Y. Kim, et al., 2016)
TRIM16	Neuroblastoma	Down	Tumor suppressor	Cell proliferation and migration	(Marshall, et al., 2010)
TRIM16	Neuroblastoma	Down	Tumor suppressor	Cell proliferation	(Bell, et al., 2013)
TRIM32	Neuroblastoma	Down	Tumor suppressor	Cell proliferation	(Izumi & Kaneko, 2014)
TRIM59	Neuroblastoma	Up	Oncogene	Cell proliferation and apoptosis	(G. Chen, et al., 2019)
TRIM56	Ovarian cancer	Down	Tumor suppressor	Cell migration, invasion and EMT	(L. Zhao, et al., 2018)
TRIM56	Ovarian cancer	Down	Tumor suppressor	Cell migration and invasion	(L. Zhao, et al., 2019)
TRIM59	Ovarian cancer	Up	Oncogene	Cell invasion	(Tong, et al., 2020)
TRIM59	Ovarian cancer	Up	Oncogene	Cell proliferation, invasion and migration	(P. Zhang, et al., 2019)
TRIM59	Ovarian cancer	Up	Oncogene	Cell proliferation and invasion	(Y. Wang, et al., 2018)
TRIM71	Ovarian cancer	Down	Tumor suppressor	Cell proliferation and invasion	(Y. Chen, et al., 2019)
TRIM29	Pancreatic cancer	Up	Oncogene	Cell proliferation	(L. Wang, et al., 2009)
TRIM31	Pancreatic cancer	Up	Oncogene	Cell proliferation and motility	(C. Yu, et al., 2018)

TRIM37	Pancreatic cancer	Up	Oncogene	Cell proliferation and migration	(Jiang, et al., 2016)
TRIM14	Thyroid cancer	Up	Oncogene	Cell proliferation and apoptosis	(W. Sun, et al., 2020)
TRIM26	Thyroid cancer	Down	Tumor suppressor	Cell proliferation, EMT, and invasion	(K. Wang, et al., 2019)
TRIM44	Thyroid cancer	Up	Oncogene	Cell proliferation, migration, invasion and EMT	(Z. Zhou, et al., 2017)
TRIM25	Prostate cancer	Up	Oncogene	Cell proliferation and apoptosis	(Takayama, et al., 2018)
TRIM36	Prostate cancer	Up	Tumor suppressor	Cell proliferation, migration and apoptosis	(Kimura, et al., 2018)
TRIM59	Prostate cancer	Up	Oncogene	Cell proliferation	(W. Y. Lin, et al., 2016)
TRIM2	Renal cell carcinoma	Down	Tumor suppressor	Cell proliferation, migration and invasion	(W. Xiao, et al., 2018)
TRIM13	Renal cell carcinoma	Down	Tumor suppressor	Cell migration and invasion	(H. Li, et al., 2020)
TRIM59	Renal cell carcinoma	Up	Oncogene	Cell proliferation, migration and invasion	(S. H. Hu, et al., 2017)

NA: Not mentioned, EMT: Epithelial-mesenchymal transition.

Table 4: Summary of the relationship between three TRIM family and prognosis.

TRIM family	Tumor	Unfavorable/Favorable	Type of prognosis	Univariate		Multivariate		Sum	References
				HR	95CI%	HR	95CI%		
TRIM14	Gastric cancer	Unfavorable	OS	NA	*p*=0.0002	NA	NA	117	(F. Wang, et al., 2018)
TRIM14	Glioblastoma	Unfavorable	OS	NA	*p* = 0.0469	NA	NA	227	(Feng, et al., 2019)
TRIM14	Glioblastoma	Unfavorable	OS	NA	*p* = 0.0340	NA	NA	284	(Feng, et al., 2019)
TRIM14	Glioblastoma	Unfavorable	OS	NA	*p* = 0.0489	NA	NA	594	(Feng, et al., 2019)
TRIM14	Osteosarcoma	Unfavorable	OS	NA	*p*=0.043	NA	NA	45	(G. Xu, et al., 2017)
TRIM25	Gastric cancer	Unfavorable	OS	NA	*p*=0.012	NA	NA	90	(Z. Zhu, et al., 2016)
TRIM25	Hepatocellular carcinoma	Unfavorable	OS	NA	*p*=0.0092	NA	NA	90	(Y. Liu, Tao, et al., 2020)
TRIM25	Hepatocellular carcinoma	Unfavorable	OS	NA	*p*=0.013	NA	NA	364	(Y. Liu, Tao, et al., 2020)
TRIM32	Gastric cancer	Unfavorable	OS	1.29	1.08-1.54, *p*=0.0042	NA	NA	534	(J. Wang, et al., 2020)
TRIM32	Gastric cancer	Unfavorable	OS	NA	*p*=0.008	NA	NA	142	(M. Ito, et al., 2017)

TRIM32	Gastric cancer	Unfavorable	OS	NA	*p*=0.0361	NA	NA	61	(C. Wang, et al., 2018)
TRIM32	Lung cancer	Unfavorable	OS	NA	*p*=0.0318	NA	NA	500	(H. Yin, et al., 2019)
TRIM32	Lung cancer	Unfavorable	OS	NA	*p*=0.0024	NA	NA	994	(H. Yin, et al., 2019)
TRIM32	Lung cancer	Unfavorable	OS	NA	*p*=0.0089	NA	NA	494	(H. Yin, et al., 2019)

NA: Not mentioned; OS: Overall survival; DFS: Disease-free survival; PFS: Progression-free survival, CSS: Cancer-specific survival; CS: Cumulative survival; RFS: Recurrence free survival; RFS': Relapse free survival.

Table 5: The relationship between TRIM family and drugs resistance in cancers

TRIM Family	Therapeutic Compound	Target	Type of cancer	Experimental Model	Signaling Affected	Mechanism	References
TRIM8	Cisplatin	p53 (downstream); miR-17-5p, miR-106b-5p (upstream)	CRC and ccRCC	Renal cell carcinoma RCC-Shaw, BHD origin UOK-257 cells and colon cancer cell line, HCT116 cells, CD1 nude mice	p53 pathway	Knockdown of miR-17-5p/miR-106b-5p upregulates TRIM8, then activates p53 signaling pathway.	(Mastropasqua, et al., 2017)
TRIM11	Cisplatin	Daple (downstream)	Nasopharyngeal carcinoma	Human nasopharyngeal carcinoma cell lines, CNE1 and CNE2	Wnt/β-catenin pathway	Inhibiting Daple through p62-selective way, which activates Wnt/βcatenin pathway to induce ABCC9.	(R. Zhang, et al., 2020)
TRIM14	Cisplatin	LncRNA KCNQ1OT1 (upstream)	Tongue cancer	Tongue cancer lines, CAL27 and SCC9 cells	NA	Knockdown of LncRNA KCNQ1OT1 increases miR-124-3p to upregulate TRIM14 expression.	(Qiao, et al., 2020)

TRIM21	Cisplatin	p53 (downstream)	Glioma	Human malignant glioma cell lines, U87-MG, U251, U373 cells	p53 pathway	Inhibiting p53-p21 signaling pathway.	(Z. Zhao, et al., 2020)
TRIM23	Cisplatin	GLUT1/3, NF-κB (downstream)	Lung adenocarcinoma	Human bronchial epithelial cell line, 16HBE and lung adenocarcinoma cell lines, A549 cells; BALB/c nude mice	NF-κB pathway	Promoting glucose uptake via activating NF-κB signaling pathway.	(Y. Zhang, et al., 2020)
TRIM25	Cisplatin	14-3-3σ (downstream)	NSCLC	Human lung adenocarcinoma A549 cell	p53 pathway	Increasing MDM2 and cleaved-capsese3 and downregulating 14-3-3σ and p53.	(X. Qin, et al., 2017)
TRIM29	Cisplatin	NA	Lung squamous cancer	Human lung squamous cancer cell lines, NCI-H520 cells	NA	NA	(C. Liu, et al., 2015)
TRIM31	Cisplatin	miR-551b (upstream)	Ovarian cancer	Primary OVCa cells and SCID mice	NA	miR-551b inhibits Foxo3 and TRIM31.	(Z. Wei, et al., 2016)

TRIM37	Cisplatin	NEMO (downstream)	Esophageal cancer	Human esophageal cancer cell line, Eca109 cells	NF-κB pathway	Activating NF-κB signaling pathway through monoubiquitylation of NEMO.	(G. Wu, et al., 2018)
TRIM59	Cisplatin	PTEN/AKT/HK2 (downstream)	NSCLC	Human lung adenocarcinoma cell lines, A549 and 293 cells; BALB/c nude mice	Akt pathway	Activating PTEN ubiquitination, then activating AKT pathway and increasing HK2.	(R. He & Liu, 2020)
TRIM65	Cisplatin	miR-138-5p, ATG7 (downstream)	NSCLC	Human NSCLC A549 cell lines	NA	Inhibiting miR-138-5p and upregulating ATG7.	(X. Pan, et al., 2019)
TRIM65	Cisplatin	p53 (downstream)	NSCLC	Human NSCLC H460, A549 and H1299 cell lines	p53 pathway	Inhibiting p53 through facilitating p53 poly-ubiquitination and proteasome-mediated degradation.	(Y. Li, et al., 2016)
TRIM16	Gefitinib	miR-135 (upstream)	NSCLC	Human NSCLC cell lines, A549, H1650, H1975, H157, and	JAK/STAT pathway	Knockdown of miR-135 upregulates TRIM16, thus inhibits JAK/STAT signaling	(N. Wang & Zhang,

				H4006cells		pathway.	2018)
TRIM59	Gefitinib	STAT3 (downstream)	NSCLC	Human EGFR mutant lung adenocarcinoma cell lines, HCC827 and PC9 cells	JAK/STAT pathway	Activating JAK/STAT pathway.	(Z. Cui, Liu, Zeng, Zhang, et al., 2019)
TRIM8	Sorafenib	p53 (downstream); miR-17-5p, miR-106b-5p (upstream)	CRC and ccRCC	Renal cell carcinoma RCC-Shaw, BHL origin UOK-257 cells and colon cancer cell line, HCT116 cells; CD1 nude mice	p53 pathway	Knockdown of miR-17-5p/miR-106b-5p upregulates TRIM8, then activates p53 signaling pathway.	(Mastropasqua, et al., 2017)
TRIM37	Sorafenib	Akt (downstream)	HCC	Human HCC cell lines, Huh7, HepG2, Hep3B cells	Akt pathway	Activating Akt signaling pathway.	(G. Tan, et al., 2021)
TRIM14	Temozolomide	Dvl2 (downstream)	Glioma	Glioma cell lines, LN229, T98G,	Wnt/β-catenin	Activating Wnt/β-catenin signaling via	(Z. Tan, et

				U87, LN-18 and A-172, U251MG cells	pathway	stabilizing Dvl2.	al., 2018)
TRIM21	Temozolomide	p53 (downstream)	Glioma	Human malignant glioma cell lines, U87-MG, U251, U373 cells	p53 pathway	Inhibiting p53-p21 pathway.	(Z. Zhao, et al., 2020)
TRIM28	Doxorubicin	CD44 and Bmi1 (downstream)	Breast cancer	Human breast cancer cell lines , MDA-MB-231 and BT-474 cells; athymic nude mice	NA	Increasing expression of CD44, Bim1, and stem-like cell population.	(Damineni, et al., 2017)
TRIM37	Doxorubicin	H2Aub, p53 (downstream)	TNBC	TNBC cell lines MDA-MB-231-luc-D3H2LN-BMD2b; MDA MB 231, MDA MB 468 and HCC1806 cells	JAK/STAT pathway; p53 pathway	Inhibiting JAK/STAT signaling pathway and p53 pathway, increasing H2Aub.	(Przanowski , et al., 2020)
TRIM44	Doxorubicin	NF-κB	HCC	Human HCC cell lines, Huh7,	NF-κB pathway	Activating NF-κB signaling pathway.	(X. Zhu, et

		(downstream)		HepG2, Hep3B cells			al., 2016)
TRIM2	Tamoxifen	Bim (downstream)	Breast cancer	Human breast cancer cell lines, MCF-7 cells	MAPK pathway	MAPK pathway upregulates TRIM2, leading to degradation of Bim.	(H. Yin, et al., 2017)
TRIM8	Axitinib (A)	p53 (downstream); miR-17-5p, miR-106b-5p (upstream)	CRC and ccRCC	Renal cell carcinoma RCC-Shaw, BHD origin UOK-257 cells and colon cancer cell line, HCT116 cells; CD1 nude mice	p53 pathway	Knockdown of miR-17-5p/miR-106b-5p upregulates TRIM8, then activates p53 signaling pathway.	(Mastropasqua, et al., 2017)
TRIM8	Nutlin-3	p53 (downstream); miR-17-5p, miR-106b-5p (upstream)	CRC and ccRCC	Renal cell carcinoma RCC-Shaw, BHD origin UOK-257 cells and colon cancer cell line, HCT116 cells; CD1 nude mice	p53 pathway	Knockdown of miR-17-5p/miR-106b-5p upregulates TRIM8, then activates p53 signaling pathway.	(Mastropasqua, et al., 2017)

TRIM25	Epirubicin	p-Akt; PTEN (downstream)	HCC	Human hepatocyte L02 cells and hepatocellular carcinoma cell lines, HepG2 and Huh7	Akt pathway	Inhibiting Akt signaling pathway and increasing PTEN.	(Yuan, et al., 2020)
TRIM28	Etoposide	E2F1 (downstream)	NSCLC	Human NSCLC cell lines, PAa cells; BALB/c nude mice	NA	Inhibiting expression of E2F1.	(L. Liu, et al., 2017)
TRIM28	5-fluorouracil	CD44 and Bmi1 (downstream)	Breast cancer	Human breast cancer cell lines , MDA-MB-231 and BT-474; athymic nude mice	NA	Increasing expression of CD44, Bim1, and stem-like cell population.	(Damineni, et al., 2017)
TRIM28	Methotrexate	CD44 and Bmi1 (downstream)	Breast cancer	Human breast cancer cell lines , MDA-MB-231 and BT-474; athymic nude mice	NA	Increasing expression of CD44, Bim1, and stem-like cell population.	(Damineni, et al., 2017)
TRIM31	Gemcitabine	p65 (downstream)	Pancreatic cancer	Human pancreatic cell lines, PANC-1, CFPAC-1, BxPC-3,	NF-κB pathway	Activating the NF-κB signaling pathway and upregulating p65 by promoting K63-linked	(C. Yu, et al., 2018)

			AsPC-1, Capan-1, Capan-2, MIA PaCa-2, Hs 766T, and MIN6 cells; (HPDECs) BALB/c nude mice	polyubiquitination of tumor necrosis factor receptor-associated factor 2.	
TRIM32	Oxaliplatin	p53 (downstream)	HCC	Human HCC cell lines, Huh7, HepG2, Hep3B	Inhibiting p53 with a negative feedback loop formed with p53 downregulating cleaved caspase-3. (X. Cui, et al., 2016)

NA: Not mentioned

Table 3: The inhibitors of TRIM family.

Inhibitors	**Chemical formula**	**Targets/activity**	**Cancer type**	**References**
IACS-6558	C24H29N5O5S	TRIM24/ Kd in mM level	NA	(Y. Zhan, et al., 2015)
Compound 34	C25H27N3O6S	TRIM24/ Kd=222nM	NA	(Bennett, et al., 2016).
IACS-9571	C32H42N4O8S	TRIM24/ Kd=31 nM; EC50 = 50 nM and IC50 = 8nM	NA	(Palmer, et al., 2016).

Arsenic trioxide	As2O3	TRIM19	Acute promyelocytic leukemia	(Z. G. Wang, et al., 1998)
Arsenic trioxide	As2O3	TRIM19	Glioma	(W. Zhou, et al., 2015)
Red orpiment	As2H6S3	TRIM19	Acute promyelocytic leukemia	(Zhong, et al., 2003)
Genistein	C15H10O5	TRIM19	Acute promyelocytic leukemia	(Ng, et al., 2007)
Dexamethasone	C22H29FO5	TRIM19	Acute B-lymphocytic leukemia	(Laane, et al., 2009)
Sodium arsenite	AsNaO2	TRIM19	Hepatocellular carcinoma	(H. Tang, et al., 2016)
2,5-MeC	C11H12O4	TRIM19	Lung cancer and osteosarcoma	(Komura, et al., 2007)
Verteporfin	C82H84N8O16	TRIM28	Melanoma and lung cancer	(J. Liang, et al., 2020)
GA-13315	C19H17ClO6	TRIM67	Lung caner	(R. Liu, et al., 2019)
Eugenol	C10H12O2	TRIM59	Lung caner	(Z. Cui, Liu, Zeng, Chen, et al., 2019)
Withaferin A	C28H38O6	TRIM16	Melanoma	(Nagy, et al., 2020)

Figure 1. The heatmap of TRIM family in human cancers. Red represents up-regulated genes, yellow represents down-regulated genes and blue represents up-regulated or down-regulated genes. Heatmap was created using cluster 3.0 (http://bonsai.hgc.jp/~mdehoon/software/cluster/) and Java TreeView (https://sourceforge.net/projects/jtreeview/).

Figure 2. Action modes of TRIM family in NF-κB signaling pathway of cancers.

Activation of TNF receptor, Toll-like receptor and IL-1 receptor can activate the IKKs complex, that consists of IKKα, IKKβ and IKKγ (NEMO). The IKKs phosphorylate the NF-κB inhibitors IκBα, which marks them for ubiquitination and subsequent proteasomal degradation. Then, p50/p65 (NF-κB factor) is translocated into the nucleus, thus activated the target gene expression to inhibit cell apoptosis. TRIM proteins are linked to NF-κB signaling pathway, including TRIM14, TRIM23, TRIM31 and so on. TRIM14 can active the IKKs complex to promote ubiquitination and degradation of IκBα, thus activate NF-κB signaling pathway. TRIM23 can promote the nuclear translocation of p50/p65 to activate NF-κB signaling pathway. TRIM31 can promote the expression of p65 to enhance NF-κB signaling pathway.

Abbreviations: IKKs, IκB kinase; NF-κB, Nuclear factor-κB; TNF, Tumor necrosis factor.

Figure 3. Action modes of TRIM family in Akt signaling pathway of cancers.

After growth factors stimulate, PI3K activates PIP3. PTEN can inhibit PIP3, thus negative regulates Akt signaling. PIP3 activates PDK1, thus activates Akt. Then, Akt activates mTORC1, while mTORC2 directly phosphorylates Akt at Ser473 residue. Finally, activation of Akt signaling promotes the target gene expression. TRIM proteins are associated with Akt signaling pathway. For example, TRIM11 and TRIM14 can increase p-Akt and p-PI3K, thereby promote Akt signaling pathway. TRIM25 can inhibit PTEN, thus increase the expression of PIP3 to activate Akt

signaling pathway.

Abbreviations: Akt: Protein kinase B; mTORC1: Mammalian target of rapamycin complex 1; mTORC2: Mammalian target of rapamycin complex 2; PDK1: Phosphoinositide-dependent kinase-1; PI3K: Phosphatidylinositol-4,5- bisphosphate 3-kinase; PIP3: Phosphatidylinositol (3,4,5)- trisphosphate; PTEN: Phosphatase and tensin homolog; RTK, receptor tyrosine kinase.

Figure 4. Action modes of TRIM family in Wnt/β-catenin, TGF-β and JAK/STAT signaling pathway of cancers.

When the Wnt ligand is activated, it binds to the LRP5/6 co-receptor, thus recruits Dvl protein, disrupts the destruction complex (GSK3β complex) and increases the level of β-catenin. In the nucleus, β-catenin binds to LEF/TCF and CBP, thereby activates the transcription of Wnt target genes including cyclin D1, c-Myc and Axin2. TRIM proteins, including TRIM24, TRIM26, TRIM29 and so on, are linked to Wnt/β-catenin signaling pathway functions. TRIM24 can stabilize and increase β-catenin levels. TRIM26 disrupts the GSK3β complex and promote the level of β-catenin. TRIM29 can activate Disheveled2, thus promotes Wnt/β-catenin signaling pathway.

The TGF-β activated TGFBR1 phosphorylates the SMAD2/3 complex, then SMAD2/3 complex binds to SMAD4. Finally, SMAD2/3 complex and SMAD4 translocate to the nucleus to regulate the targeted genes expression (e.g., p15, p21, snail and vimentin). TRIM proteins, including TRIM25, TRIM59, TRIM62 and TRIM66, are associated with TGF-β signaling pathway functions. TRIM25, TRIM59 and TRIM66 can promote the p-SMAD2/3, thus active TGF-β signaling pathway. TRIM62 can decrease the level of p-SMAD2/3 to inhibit TGF-β signaling pathway.

Growth factors bind to transmembrane receptors, thus activate receptor-associated JAKs. JAKs phosphorylate the receptor's cytoplasmic tails, recruit and phosphorylate cytoplasmic STATs. Activated STATs dimerize and translocate into the nucleus, activate expression of target genes. SOCS can negatively regulate JAK/STAT pathway, and PIAS can inhibit activated STAT. TRIM proteins, including TRIM8, TRIM14, TRIM24 and so on, are related with JAK/STAT signaling pathway functions. TRIM8 and TRIM14 can inhibit SOCS and PIAS to activate JAK/STAT signaling pathway, while TRIM24 can increase the p-STAT to activate JAK/STAT pathway.

Abbreviations: CBP, CREB-binding protein; Dvl, Dishevelled; GSK3β, Glycogen synthase kinase 3β; JAK, Janus kinase; LEF/TCF, Lymphoid enhancer factor/T cell factor; LRP5/6, Low density lipoprotein receptor-related protein 5/6; P, phosphorylation; PIAS, protein inhibitor of activated STAT; SOCS, Suppressors of cytokine signaling; STAT, Signal transducer and activator of transcription; TGF-β, Transforming Growth Factor-β; TGFBR1: Type I TGF-β Receptor; TGFBR2, Type II TGF-β Receptor

Figure 5. Action modes of TRIM family in p53 signaling pathway of cancers.

P38 can activates p53, thus increases p21 expression. And MDM2 interacts with p53, marking p53 for ubiquitination and subsequent proteasomal degradation to inhibit cell apoptosis. Abbreviations: Mouse double minute 2 (MDM2). TRIM proteins are related with p53 signaling pathway. For instance, TRIM7 can inhibit the expression of p53. TRIM19 can sequester MDM2 into the nucleus, thus enhances the stability of p53. TRIM28 directly interacts with MDM2 to promote p53 ubiquitylation and degradation.

Figure 6. The schematic diagram of TRIM family regulating various malignant behaviors (cell proliferation, invasion, migration, apoptosis and EMT) in tumors. Red represents

positive regulator and blue represents negative regulator. The Schematic diagram was created using Cytoscape 3.8.2 (https://cytoscape.org/download.html).

Figure 7. The Schematic diagram of TRIM family regulates tumor progression via acting oncogene or tumor suppressor. The left represents oncogene and the right represents tumor suppressors in various cancers. Parts of the figure were drawn by using pictures from "Servier Medical Art" (http://www.servier.com).

Figure 8. Forest plots of the pooled HRs of three TRIM proteins expression for overall survival in different cancer types. (A): Forest Plot of the associations between the elevated expression of TRIM14 and cancer overall survival. (B): Forest Plot of the associations between the elevated expression of TRIM25 and cancer overall survival. (C): Forest Plot of the associations between the elevated expression of TRIM32 and cancer overall survival. Abbreviations: CI, confidence interval; HR, hazard ratio.