Journal of Contemporary Medical Practice (JCMP) ISSN: 2006-2745
DOI: 10.53469/jcmp.2024.06(11).44

Mechanisms and Progress of TIF1 Proteins in Digestive Tract Tumors

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Abstract: ***Digestive system cancers, including esophageal cancer, gastric cancer, and colorectal cancer, are common types of malignant tumors. Due to their relatively obscure early symptoms, they are often overlooked, leading to worsened conditions and poor prognosis. With improvements in medical technology, the prognosis for patients with digestive tract tumors has improved, but recurrence and metastasis rates remain high. The Transcription Intermediary Factor 1 (TIF1) family, consisting of TRIM24, TRIM28, TRIM33, and TRIM66, is a subfamily of the E3 ubiquitin ligase TRIM family involved in various biological processes such as cell signaling, immunity, and viral infection. A growing number of studies have shown that the TIF1 protein family regulates multiple biological activities and signaling cascades in digestive tract tumors, including immune engagement, metabolic reprogramming, and histone modifications. This review aims to explore the mechanisms and progress of TIF1 protein family members in the development of digestive tract tumors.***

Keywords: Digestive system cancers, TIF1 protein, TRIM protein**.**

1. Structure and Function of TIF1 Proteins

The TRIM protein family comprises over 80 proteins, typically characterized by a conserved N-terminal RBCC motif, which includes a RING domain, one or two B-boxes (B1 and B2), and a coiled-coil (CC) domain, followed by a highly variable C-terminal region [1]. The RING domain confers E3 ligase activity, capable of ubiquitinating substrates as part of the ubiquitin-proteasome system (UPS). The B-box motifs consist of small peptide sequences involved in target protein recognition. The coiled-coil region often participates in TRIM homooligomerization [2]. TRIM proteins are further classified into 11 subfamilies (C-I to C-XI) based on their variable C-terminal domains [3].

TRIM24 (TIF1α), TRIM28 (TIF1β/KAP1), and TRIM33 (TIF1γ) are categorized into the C-VI subfamily, based on the presence of plant homeodomain (PHD) and bromodomain at the C-terminus. Although TRIM66 lacks the RING domain, it similarly contains two B-boxes, a CC domain, and a PHD-bromodomain, and can be alternatively classified into the TIF1 protein family [4]. Increasing evidence suggests that TIF1 proteins are closely related to digestive tract tumors. Here, we review their roles in immune regulation, metabolic reprogramming, and histone modification in digestive tract tumors.

2. Immune Regulatory Role of TIF1 Proteins

The theory of tumor immune escape, originating from the "cancer surveillance hypothesis" first proposed by Burnet and Thomas, has attracted wide attention in recent years. The human immune system regularly monitors, identifies, and eliminates "non-self" components [5]. However, tumors can progress and metastasize by disrupting immune homeostasis or evading detection. TIF1 family proteins influence various pathogenic conditions at different levels, often by mediating specific proteasomal degradation or performing other substrate-dependent functions [6].

EMT is a key process in cancer progression and metastasis. As our understanding deepens, researchers have found that EMT is not only a core driver of tumors but also an important process for immune resistance and escape, serving as a powerful driver for activating the immunosuppressive network in the tumor immune microenvironment [7]. Altering the expression levels of specific TIF1 proteins promotes EMT, making tumor cells more prone to metastasis. For example, TRIM66 is significantly overexpressed in hepatocellular carcinoma cells, where it upregulates the expression of vimentin, Snail, and E-cadherin through the JAK2/STAT3 pathway, thereby promoting proliferation and metastasis of liver cancer [7]. In contrast, TRIM33 expression is significantly reduced in gastric cancer cells compared to normal gastric tissue. TRIM33 upregulates E-cadherin transcription by inhibiting TGF-β expression, and reduced TRIM33 expression promotes EMT in gastric cancer cells [8].

Immune checkpoints are inhibitory signaling pathways in the immune system that regulate the intensity, duration, and prevention of tissue damage and play a crucial role in maintaining self-antigen tolerance [9] A classic method for cancer cells is to express inhibitory ligands that suppress immune cell function or modulate self-tolerance. Ma et al. found that TRIM28 can inhibit T cell activation by upregulating PD-L1 abundance, thus promoting the escape of gastric cancer cells from immune surveillance [10].

Immune cells are the natural guardians of the human body, responsible for detecting and eliminating malignant cells and controlling tumor progression. However, cancer cells have developed multiple strategies to evade the host immune system, including unrecognition, reverse inhibition, and apoptosis [11]. Park et al. found that TRIM28 negatively correlates with infiltrating CD8+ T cells and DCs in tumors, while RIPK3 shows the opposite trend. Mechanistically, RIPK3 activation hinders the binding of TRIM28 to chromatin, which activates the transcription of cytokines and thereby promotes immune-related regulation of anti-cancer responses [12]. In addition to immune cells, other stromal cells, such as cancer-associated fibroblasts and angiogenesis-related cells, also affect immune escape. Fibroblasts, as important components of the tumor immune microenvironment, actively participate in tumor growth and

progression. Through transcriptome analysis, researchers have found that TRIM28 transcripts are significantly associated with fibroblasts, and TRIM28 has been shown to correlate with poor prognosis in colon cancer [13].

In addition to their indirect roles in digestive tract tumor cells, TIF1 proteins can also directly affect immune cells themselves, thereby influencing tumor immune escape, with macrophages and NK cells being typical examples. Macrophages can secrete various inflammatory mediators and play a crucial role in the activity of tumor cells, while NK cells participate in tumor immune responses by eliminating target cells and secreting cytokines [14]. However, in immunosuppressive tumor microenvironments, the function of NK cells is disrupted due to contact with inhibitory molecules produced by tumor cells, leading to tumor immune escape [15]. Su et al. pointed out that there is a significant correlation between high expression of TRIM24 and TRIM66 and the infiltration of macrophages and NK cells in liver cancer [16,17]. Peng et al. found that Sophoridine, an active quinoline alkaloid, can inhibit chemotaxis and M2 polarization in macrophages, thereby remodeling the immune microenvironment of gastric cancer [18].

3. Metabolic Reprogramming

Metabolic reprogramming refers to the metabolic changes that cells undergo in response to various stress stimuli. It is prevalent in multiple diseases, involving metabolic pathways such as glucose metabolism, lipid metabolism, amino acid metabolism, and is closely linked to the development and progression of diseases [11]. Among them, the Warburg effect is a primary characteristic, which means that even in the presence of sufficient oxygen, tumor cells mainly metabolize glucose through glycolysis to produce lactic acid, favoring tumor metastasis [19]. Fructose-1,6-bisphosphatase (FBP1) is a rate-limiting enzyme in gluconeogenesis, converting fructose-1,6-bisphosphate to fructose-6-phosphate. Jin et al. found that TRIM28, a member of the TIF1 family, targets FBP1 for degradation by exerting its ubiquitination function, thereby promoting the Warburg effect in liver cancer cells and facilitating their progression [20].

Ni et al. discovered that salt-inducible kinase 2 (SIK2) promotes glycolysis in colon cancer cells. Bioinformatics analysis predicted an interaction between SIK2 and TRIM28, and further research revealed that TRIM28 overexpression can reverse the effects of SIK2 silencing on cellular glycolysis [21]. Due to drug resistance, the clinical benefits of tyrosine kinase inhibitor-based systemic therapy for advanced hepatocellular carcinoma are limited. Ding et al. identified a role for unconventional prefolding protein RPB5 interactor (URI)-mediated lipid metabolism reprogramming in liver cancer. Mechanistically, URI directly interacts with TRIM28 and promotes p53 ubiquitination and degradation in a TRIM28-MDM2-dependent manner, leading to lipid metabolism reprogramming and ferroptosis in liver cancer cells [22]. Furthermore, the tumor suppressor p53 plays a key role in glycolysis, OXPHOS, glutaminolysis, lipid metabolism, and antioxidant defense, impacting cellular metabolism and redox balance. TRIM24, as an E3-ubiquitin ligase, can target p53 for protein degradation [23]. Related literature also reports that the absence of Trim24 expression increases the expression of hepatic lipase and inflammatory signaling genes while inhibiting de novo lipogenesis, steroid and lipid metabolism, and transport. The hepatic accumulation of lipids, fibrosis, and infiltration of inflammatory macrophages can lead to the development of liver cancer [24]. Jiang et al. further supported this view by finding that TRIM24 overexpression leads to hepatic lipid accumulation, inflammation, and liver cancer in mice [24].

3.1 Metabolic Reprogramming and Immune Microenvironment

Furthermore, TIF1 family proteins influence the composition and characteristics of the tumor immune microenvironment through metabolic reprogramming to achieve immune evasion. For instance, inflammatory mediators can lead to the accumulation of oxygen and nitrogen free radicals, causing abnormal oxidative stress in the microenvironment and inhibiting the function of immune cells. The hypoxic and acidic tumor immune microenvironment resulting from extensive aerobic glycolysis due to tumor metabolic reprogramming can suppress normal metabolism of immune cells and T-cell function [25]. Tumor angiogenesis involving TIF1 family proteins can also lead to immune evasion, with abnormal and uneven vascular distribution, disrupted adjacent endothelial cell and pericyte structure, resulting in impaired vascular perfusion and increased vascular permeability. Meanwhile, the low levels of cell adhesion-related molecules produced by tumor-associated endothelial cells block the infiltration of immune cells. Over time, hypoxia, acidosis, and necrosis occur in tissues, which worsen the hypoxic and acidic conditions of the tumor immune microenvironment and inhibit the function of immune cells [26]. For example, studies have shown that TRIM28 plays a crucial role in T-cell development and activation. T-cell-specific deletion of TRIM28 leads to a lack of invariant natural killer T cells due to altered usage of the T-cell receptor α chain and the development of autoimmunity due to TGFβ3 overexpression and dysregulation of the Th17 pathway. It was demonstrated that due to early defects in glycolytic metabolic reprogramming, TRIM28 and HP1β/γ prevent T cells from differentiating into helper cells and Tregs [27]. Gehrmann U et al. found that defects in metabolic reprogramming are caused by impaired TCR/CD28 signaling through the PI3K-Akt-mammalian target of rapamycin (mTOR) axis, and these defects are associated with impaired epigenetic silencing of a defined set of Treg signature genes by TRIM28 and HP1β/γ in distal regulatory regions, which is essential for proper T-cell metabolic reprogramming [28]. Additionally, the molecular mechanisms of tumor metabolic reprogramming are complex. Genetic changes in the tumor immune microenvironment disrupt the homeostatic balance of metabolism between cells and the body, leading to metabolic reprogramming. Taking the typical oncogene C-myc as an example, it can simultaneously affect both catabolic and anabolic processes of carbohydrates, promoting aerobic glycolysis and regulating the pentose phosphate pathway (PPP) to increase ribose production and enhance NADPH production for lipid synthesis [25]. For instance, Ding and colleagues found that TRIM33 is highly expressed in liver cancer, and C-myc, as a downstream protein, is upregulated, promoting cancer cell proliferation, migration, and metastasis [29].

4. TIF1 Proteins and Histone Modifications

The core of chromatin is the nucleosome, consisting of an octamer of four core histones (H3, H4, H2A, and H2B) around which DNA is wrapped. Histones undergo post-translational modifications, which regulate chromatin dynamics and underlying DNA activity. These histone modifications are fundamental for maintaining genome stability and include phosphorylation, ubiquitination, SUMOylation, acetylation, and methylation. Dysregulation of this post-translational modification signaling is associated with various diseases [4].

TIF1 proteins have a PHD domain and a bromodomain at their C-terminus, often serving as "readers" of histones. The bromodomain of TIF1 family proteins can recognize acetylated lysine residues on H3 and H4, while the PHD domain can recognize methylated lysine marks, particularly methylated lysine marks on H3K4 [30]. Histone modifications are one of the important mechanisms for gene expression regulation, in which TIF1 family proteins play a crucial role. Lysine Acetyltransferase 6A (KAT6A) is a MYST-type histone acetyltransferase (HAT) enzyme that contributes to histone modifications and cancer development [31]. Zhao et al. demonstrated that KAT6A acetylates lysine 23 of histone H3 (H3K23), thereby enhancing the binding of the nuclear receptor-binding protein TRIM24 to H3K23ac, further activating SOX2 transcription and expression, leading to liver cancer [32]. The tumor suppressor p53 controls the expression of numerous genes involved in DNA repair, cell cycle arrest, and cell death. The p53 signaling pathway is frequently involved in the initiation and progression of gastrointestinal tumors. For example, Trim24 binds to p53 and unmethylated histone 3 lysine 4 (H3K4), thereby preferentially localizing to p53 sites residing in closed chromatin, while H3K4 methylation prevents its entry into chromatin [33]. Meanwhile, Li et al. confirmed that in liver cancer, the interaction between TRIM28 and histone deacetylase 6 (HDAC6) accelerates the ubiquitination and degradation of HDAC6, promoting the progression of liver cancer through histone ubiquitination modifications [34]. Additionally, Chen et al. found that in DNA damage, H3K56ac is rapidly deacetylated and then restored in the later stages of DNA repair. The absence of TRIM66 in embryonic stem cells leads to the retention of H3K56ac and elevated levels of DNA damage [35]. The bromodomain of TRIM66 recognizes H3K56ac at damaged sites and recruits the deacetylase Sirt6 to chromatin, thereby activating DDR. TRIM66 can also read unmodified H3R2K4 in response to damage through its PHD finger. Collectively, this proposes a model where TRIM66, as a dual reader of H3K56ac and unmodified H3R2K4, recruits Sirt6 upon damage and ultimately maintains genome stability through histone deacetylation [35].

4.1 Histone Modifications and Metabolic Reprogramming

Metabolic reprogramming and epigenetic remodeling are closely related and reciprocally regulated, representing a well-known hallmark of cancer, with histone modifications falling under the category of epigenetics. Recent evidence suggests that many metabolites can serve as substrates or cofactors for chromatin-modifying enzymes due to the translocation or spatial compartmentalization of enzymes or metabolites [36]. It has been reported that various metabolic alterations and histone modifications also drive immune evasion or hinder immune surveillance in certain cases, playing a crucial role in tumor progression. Recent evidence indicates that many metabolites can act as substrates or cofactors for chromatin-modifying enzymes due to the translocation or spatial compartmentalization of enzymes or metabolites. Jiang et al. reported that in liver cancer, the PHD/bromodomain at the C-terminus of TRIM28 interacts with specific histone post-translational modifications to regulate lipid metabolism in the liver, promoting the onset of liver cancer [24]. Meanwhile, studies have found that TRIM24 also plays a bridging role between histone modifications and metabolic reprogramming in other gastrointestinal tumors [37].

5. Prospects

In recent years, an increasing number of studies have found that TIF1 family proteins play crucial roles in the initiation and progression of gastrointestinal tumors. In these tumors, specific TIF1 protein members regulate functions such as ubiquitination, deubiquitination, stabilization, and co-repression through their N-terminal RBCC structure and variable C-terminus, thereby extensively participating in the regulatory network of cellular signaling pathways.

Gastrointestinal tumor immune cell activity and distribution are manipulated to evade immune surveillance, inhibit immune responses, and promote tumor cell growth and metastasis. Similarly, immune cells also affect tumor cell growth and metastasis by releasing various cytokines and mediators. Metabolism not only plays a crucial role in cancer signaling that maintains the initiation and survival of gastrointestinal tumors but also influences the expression of immune molecules by releasing metabolites. The TIF1 family proteins, through their C-terminal bromodomain and PHD domain, act as histone readers, interacting with cellular metabolism and histone modifications in a bidirectional manner and intertwining with genetic and molecular drivers of cancer regulation. However, many mechanisms remain unclear. Future research will further explore the specific mechanisms of TIF1 proteins in gastrointestinal tumors and other types of tumors, as well as how they can be harnessed to develop more effective treatment strategies, improving patient survival and quality of life.

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