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Structure, function, and mechanism of the TNFAIP8 (TIPE) family of proteins in cancer and inflammation

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Abstract: The multiple roles of the tumor necrosis factor (TNF)-α-inducible protein 8 (TNFAIP8), also named TIPE family of proteins have been shown in tumor and inflammation progression and regulation of cellular autophagy and apoptosis. In this review, we found that the TIPE family showed highly homologous sequences and conserved functional domains, such as the death effector domain (DED)-like domain but displayed different roles and mechanisms in different biological activities. For example, while TIPE is primarily associated with tumor progression and antitumor drug resistance, TIPE1 suppresses tumor progression in most instances. TIPE2 has multiple roles in tumor progression regulation, and antitumor drug resistance. Moreover, TIPE2 was also involved in inflammatory response regulation, tumor typing, and staging. A few studies reported that TIPE3 was engaged in tumor development by activating the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT) signaling pathway. The structure, function, and mechanism of the TIPE family in cancer and inflammation have been summarized in this review. This might serve as a reference for further research on the TIPE family and shed new light on the crosstalk among antitumor responses, inflammation, and immunology.

Introduction

Cancer usually progresses in multi-steps and is related to various etiologic factors (Jemal *et al.*, 2010). Most cancers are associated with somatic mutations and environmental factors, like cellular chronic inflammation (Coussens *et al.*, 2013). Chronic inflammation has been linked to cancer development at different levels, including cellular transformation, promotion, survival, proliferation, invasion, angiogenesis, and metastasis (Wu *et al.*, 2014). For example, mutagen-induced chronic inflammation can lead to sustained tissue damage and cell proliferation. Take the example of peroxynitrite, a DNA mutagenic agent which reacts with cellular DNA and causes its mutations, leading to the synthesis of tumor necrosis factor-alpha (TNF-α) and macrophage migration inhibitory factor (Pollard, 2004). The migration inhibitory factor contributes to tumorigenesis by impairing p53-dependent protective responses and interfering with the retinoblastoma (Rb)-adenoviral early region 2 binding factor (E2F) pathway (Singh *et al.*, 2019).

Moreover, abnormal activation of inflammatory cells such as tumor-associated macrophages and dendritic cells, in the tumor microenvironment contributes to tumor cell proliferation and ineffective responses to tumor antigens (Salmaninejad *et al.*, 2019). Further, pro-inflammatory cytokines and chemokines produced by tumor cells or tumor-associated immune cells, including TNF, interleukin-1 (IL-1), IL-6, and vascular endothelial growth factor (VEGF) have been reported to facilitate the antitumor immune response suppression and promote tumor development (Atretkhany *et al.*, 2016). In addition, the balance between apoptosis and proliferation of tumor cells is disturbed throughout the process of tumorigenesis. Multiple signal pathways have been implicated to be involved, such as the Wingless-Type MMTV Integration Site Family (Wnt) signal pathway, the janus kinase (JNK) signal pathway, the

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phosphatidylinositol-3-kinase (PI3K) signal pathway, and the Hippo signaling pathway (Vendramini-Costa and Carvalho, 2012). For example, the Wnt signaling pathway is often dysregulated in human cancers. It has three branches, the Wnt/β-catenin signaling pathway, the planar cell polarity (Wnt-PCP) pathway, and the Wnt-Ca^{2+} signaling pathway. An aberrant Wnt signaling pathway promotes cancer stem cell renewal, cell proliferation, and differentiation, thus playing a key role in tumorigenesis, and treatment response (Zhao *et al.*, 2022). The JNK signaling pathway mediates a wide range of cellular processes, including cell proliferation, survival, migration, cell apoptosis, senescence, and stress responses. As members of the mitogen-activated protein kinase (MAPK) family, c-Jun N-terminal Kinases (JNKs) have been identified as key disease drivers in some pathophysiological settings and central oncogenic signaling nodes in various cancers, for positively regulating cancer stem cell populations, promoting invasion and facilitating metastatic outgrowth (Latham *et al.*, 2022). The phosphatidylinositol-3-kinase (PI3K)/Protein kinase B (AKT) pathway controls hallmarks of cancer, including cell survival, metastasis, and metabolism. It plays essential roles in the tumor environment, functioning in angiogenesis and inflammatory factor recruitment. An aberrantly activated PI3K/AKT signaling pathway can recruit oncogenic signaling proteins, including the serine and threonine kinase Protein kinase B. Once activated, Akt phosphorylates several substrates, such as mammalian target of rapamycin (mTOR), one of the most common downstream effectors of Akt, which integrates many proteins to promote cancer progression (He *et al.*, 2021). The Hippo signaling pathway is associated with cellular mechanical strain, cell polarity/adhesion molecules, other signaling pathways (e.g., G protein-coupled receptor (GPCR), Epidermal growth factor receptor (EGFR), Wingless-Type MMTV Integration Site Family (WNT), Notch, and Transforming Growth Factor-β (TGFβ)/Bone Morphogenetic Protein (BMP)), and cellular metabolic status. As core components of the Hippo signaling pathway, the activation of the Yes-associated protein 1 (YAP) influences cell proliferation and resistance to apoptosis, which eventually leads to cancer development. The transcriptional coactivator with PDZ-binding motif (TAZ) stimulates the epithelial-to-mesenchymal transition (EMT) through transcriptional activation of zinc finger E-box binding homeobox 1/2 (ZEB1/2). Dysregulation of Hippo signaling generally results in aberrant YAP and TAZ transcriptional activity that enhances their oncogenic properties (Bae *et al.*, 2017). Besides, autophagy in tumor cells was upregulated in many cancers, promoting tumor cell survival, proliferation, and metastasis. This was through inhibition of p53 activation, sustaining redox homeostasis, maintenance of essential amino acids levels, and inhibition of antitumor immune responses (Usman *et al.*, 2021). Thus, cancers are linked to many factors including cell bio-activity, chronic inflammation, cell apoptosis, cell proliferation, and cell autophagy. This biological progress was not independent or individual but linked by different molecular hubs, signaling pathways, and crosstalk.

The tumor necrosis factor (TNF)-α-inducible protein 8-like is a recently identified protein family with four members, including the tumor necrosis factor (TNF)-α-inducible protein 8 (TNFAIP8, also called TIPE), tumor necrosis factor-α-inducible protein 8-like 1 (TNFAIP8L1 or TIPE1), tumor necrosis factor-α-inducible protein 8-like 2 (TNFAIP8L2, or TIPE2), and tumor necrosis factor-α-inducible protein 8-like 3 (TNFAIP8L3 or TIPE3). It has been reported that they were involved in cancer progression, inflammatory responses, and other biological processes (Hua *et al.*, 2021). They were regarded as important molecules linked to cancer and inflammation. The TIPE family members are similar in structure but vary significantly in terms of biological functions. For example, TIPE regulates cell proliferation and apoptosis (Niture *et al.*, 2018a). While TIPE1 was involved in cell autophagy (Liu *et al.*, 2020a), TIPE2 was reported to support cellular immunity (Sun *et al.*, 2008). The TIPE3 acts as a transporter of second messenger phosphatidylinositol (Fayngerts *et al.*, 2014). In this work, we reviewed recent progress on the structures, functions, and mechanisms of the TIPE family in cancer and inflammation. Understanding their role and molecular mechanism may shed new insights into initiating, progressing, and hence management of their related cancers and immunological diseases.

TIPE family structures

Although the TIPE family proteins have different important roles in tumor homeostasis maintenance and autoimmunity, they have shown high amino acid sequence similarity and homologous structures (Figs. 1a and 1b). All TIPEs have a conserved C-terminus and a variable—terminus (Niture *et al.*, 2019). The C-terminus of TIPEs contained a TIPE homology (TH) domain characterized by six/seven α-helix structures (Zhang *et al.*, 2009). The TH homology domain contained a DED-like structure. It was reported that the DED-like domain of TIPE2 showed a mirror image of the classical DED structure and negatively regulated cellular apoptosis (Kumar *et al.*, 2000; Niture *et al.*, 2018a). Besides, TIPE3 has an N-terminal α0 helix connected with α1 via a flexible short hinge motif (Kim *et al.*, 2017). TIPE1 was homologous to other TIPEs with two transcript variants encoding one protein (Zhong *et al.*, 2021). Further, the α1-α6 helices of TIPE3 could be aligned with the helices α1-α6 of TIPE2 (Kim *et al.*, 2017). Unlike other TIPE family members, TIPE3 has a unique 19 amino acids N-terminal (NT) region (Fayngerts *et al.*, 2014). The crystal structures of TIPEs suggest that each TIPE family member contains a large hydrophobic central cavity, to which the phospholipid molecule binds (Fig. 1c) (Kim *et al.*, 2017). The TIPEs have highly similar DED-like and TH domains, but different structures in other regions, which may determine the great differences in their expression and functions. The D-Box motif of TIPE is a significant motif of the TIPE and is involved in cell cycle-related protein degradation (Niture *et al.*, 2018a). According to the NetOGlyc 4.0 Server and Prosite database predictions, T31, T36, T138, and S153 were predicted to be crucial amino acid residues of TIPE (Niture

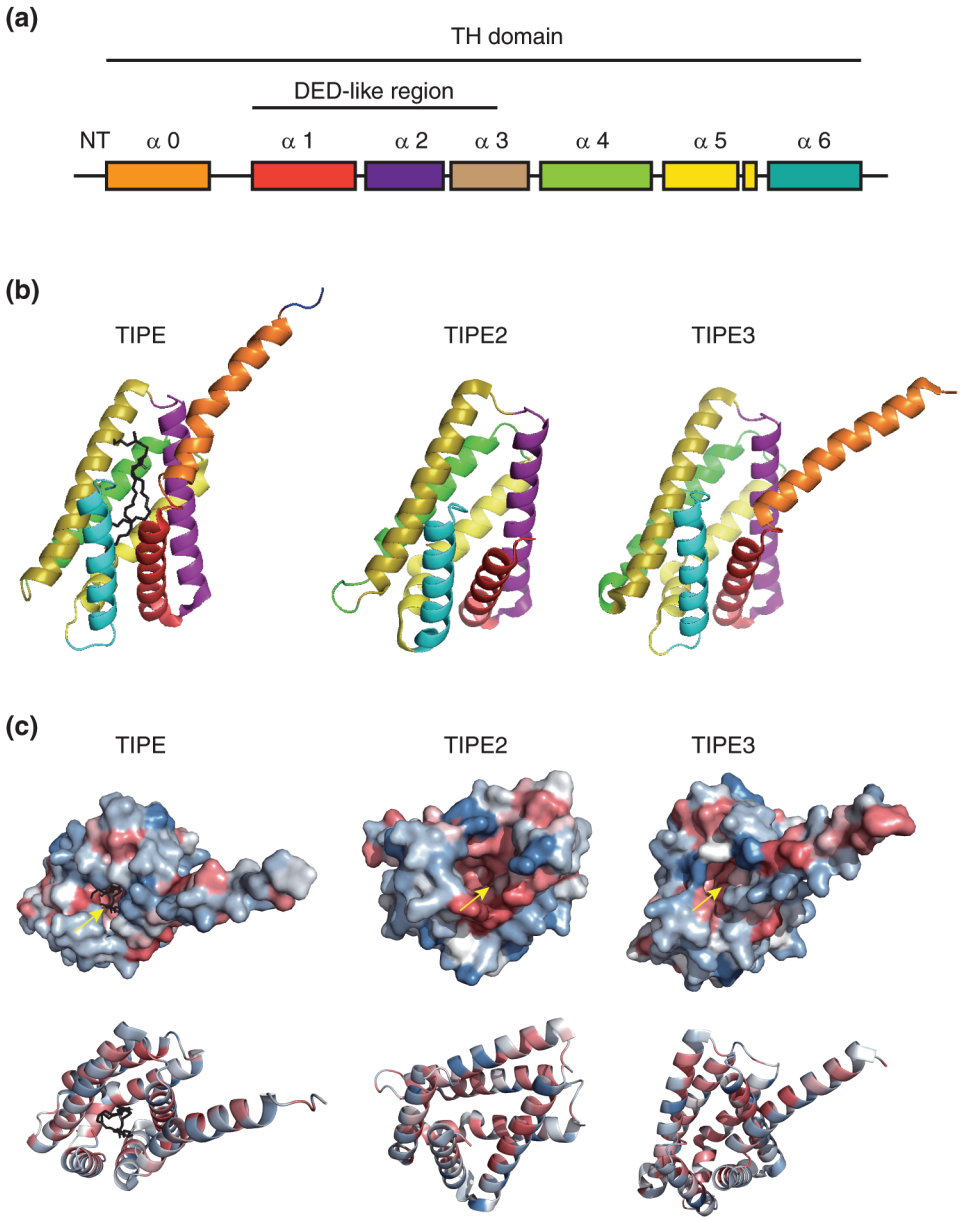

FIGURE 1. The structures of the TIPE family. (a) Schematic diagram of the TIPE family. (b) Cartoon presentation of TIPE homology (TH) domain of TIPEs. A Phosphatidylethanolamine (PE) has been shown in a black stick in the cavity of TIPE. (c) Cartoon and surface diagrams of the TH domain of TIPEs. Hydrophobic sections were represented by red, and hydrophilic ones were represented by blue. Yellow arrows indicate hydrophobic cavities. The PDB Numbers of TIPE, TIPE2, and TIPE3 are as follows: 5jxd, 3f4m, and 4q9v, respectively.

et al., 2018a). According to molecular modeling, His86 in mouse TIPE and Tyr76 in human TIPE could form hydrogen bonds with the phosphate group of phosphatidylethanolamine in the active cavity of TIPE. Therefore, these residues may be crucial for TIPE function (Niture *et al.*, 2018a). Further, it was reported that the Arg75 and Arg91 residues of TIPE2 interacted with the free hydroxyl groups in the TH domain cavity of the TIPE2 protein to bind the phosphoinositides (Antony *et al.*, 2016). Similarly, the Arg181 and Arg197 residues were also predicted to be crucial amino acid residues of TIPE3 that could bind with phosphoinositides (Antony *et al.*, 2016). Additionally, some highly conserved hydrophobic residues in the central cavity of TIPE family proteins may also be crucial, such as Gly97 of human TIPE2 and Thr203 and Phe145 of human TIPE3 (Kim *et al.*, 2017). However, only a few structures of TIPE1 have been reported until now.

TIPE plays many roles in tumor progression, antitumor drug resistance, antibacterial functions, and anti-inflammation

Like most TIPE family members, TIPE plays different roles in tumor progression and antitumor drug resistance (Fig. 2) (Zhang *et al.*, 2009). It is widely expressed in the gastrointestinal tract, lymphatic system, bone marrow, reproductive system, and mammary gland (Zhang *et al.*, 2009). Normally, the TIPE protein is a regulator of T lymphocytes in the lung mucosa, which is important in preventing bacterial infection (Li *et al.*, 2021a). It has also been reported that TIPE specifically regulates the directionality of lymphocyte migration with little effect on

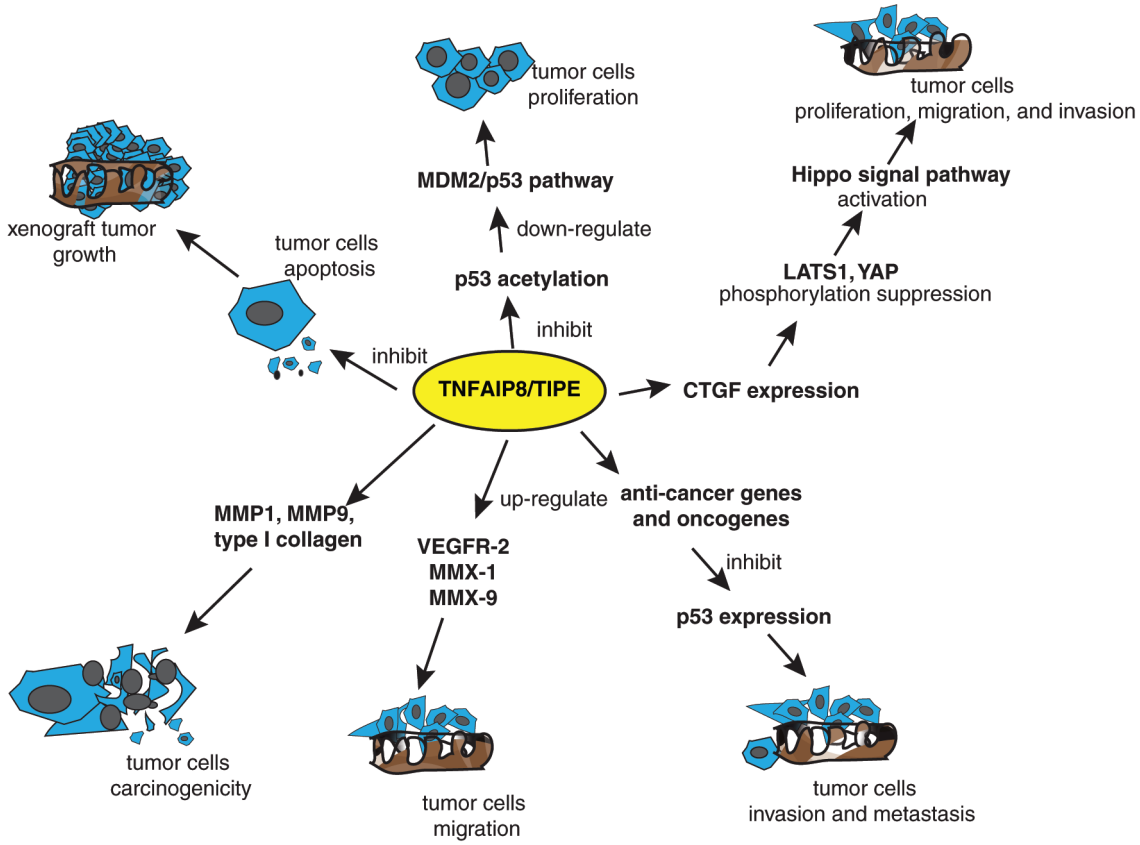

FIGURE 2. TIPE regulates tumor progression through different signaling pathways. TIPE impacted the murine double minute 2 (MDM2)/p53 and Hippo signal pathways to promote tumor cell proliferation, migration, and invasion. Further, TIPE promoted xenograft tumor growth by suppressing tumor cell apoptosis. TIPE promoted tumor cell carcinogenicity, migration, and invasion by regulating the expression of anti-cancer genes and oncogenes, such as *matrix metalloproteinase (MMP), vascular endothelial growth factor receptor (VEGFR), connective tissue growth factor (CTGF)*, and related genes.

the velocity (Sun *et al.*, 2020), and it could inhibit caspase-induced apoptosis (Sun *et al.*, 2015). Furthermore, TIPE is associated with glucocorticoid-mediated apoptosis in mouse thymocytes and acts as a promoter (Woodward *et al.*, 2010). Much evidence has demonstrated that TIPE can promote tumor cell survival, growth, proliferation, and invasion in cancers (Zhang *et al.*, 2009). For example, TIPE inhibits p53 acetylation and promotes the downregulation of the murine double minute 2 (MDM2)/p53 pathway in non-small cell lung cancer (NSCLC), leading to tumor cell proliferation induction and TIPE overexpression (Xing *et al.*, 2018). As a major effector downstream of the Hippo pathway, YAP can be directly phosphorylated by large tumor suppressor 1 and 2 (LATS1/2). Phosphorylated YAP is always ubiquitinated and degraded in the cytoplasm, thereby inhibiting the tumor cells growth-promoting and anti-apoptotic functions of YAP. The Hippo pathway negatively regulates YAP activity through this phosphorylation cascade. In turn, when the Hippo pathway is inhibited, YAP is transported to the nucleus and binds to transcription factors that promote the expression of target genes (Zhang *et al.*, 2006; Han *et al.*, 2018). TIPE has been shown closely related to the Hippo pathway to promote connective tissue growth factor (CTGF) protein expression in lung cancer cells, leading to the suppression of the phosphorylation of LATS1 and YAP (Dong *et al.*, 2017). Similarly, in hepatocellular carcinoma, TNFAIP8 acts in the same way as in non-small cell lung cancer (NSCLC), primarily by promoting tumor progression through inhibition of the Hippo signal pathway. While TIPE knockdown increased the G1 phase percentage and decreased the S phase percentage, its overexpression increased the S phase percentage and decreased G1 phase cells, accompanied by increased levels of cyclin D1 and cyclin E, with the downregulation of the p27 protein in TIPE-transfected SK-Hep-1 cells. In contrast, TIPE knockdown downregulated cyclin D1 and cyclin E, while the expression of p27 was upregulated. These results demonstrate that the TIPE promotes cell cycle progression at the G1/S transition (Dong *et al.*, 2017). Besides, TIPE was reported to promote xenograft tumor growth by lowering cell apoptosis (Zhang *et al.*, 2009).

Many researchers have suggested that the TIPE promoted tumor cell migration and progress by increasing the expression of metastasis-related molecules or collagen (Zhang *et al.*, 2006). For instance, in lung cancer cell metastasis, inhibition of TIPE expression reduced the expression of matrix metalloproteinase 1 (MMP1) and MMP9 (Zhang *et al.*, 2006). Similarly, TIPE promoted the expression of type I collagen and increased the proliferative capacity and oncogenicity of MDA-MB-435 cells (Zhang *et al.*, 2006). Furthermore, TIPE promoted tumor cell migration by upregulating the expression of vascular endothelial growth factor receptor 2 (VEGFR-2), MMP-1, and MMP-9 (Zhang *et al.*, 2006). Interestingly, TIPE has a

pair of homologous autophagy regulatory proteins namely Tnfaip8/Oxi-a and Tnfaip8l1/Oxi-b, which are homologous to dopamine neurons and have opposite effects on mammalian target of rapamycin (mTOR), an autophagy marker. Tnfaip8/Oxi-a activates mTOR and induces autophagy, while Tnfaip8l1/Oxi-b is a novel mTOR inhibitor that inhibits neuronal autophagy (Ha *et al*., 2014). Additionally, TIPE can upregulate autophagy by increasing the expression of autophagy effectors, including microtubule-associated protein1 light chain 3 (LC3)βI/II, Beclin1, eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1), p62, and sirtuin 1 (SIRT1) (Niture *et al*., 2018b). In addition, TIPE was reported to promote the migration and proliferation of thyroid cancer cells, but the relevant mechanism has not been clarified and needs further exploration (Yang *et al*., 2021). To summarize, TIPE may be an important therapeutic target for inhibiting cancer metastasis and progression (Kumar *et al*., 2004).

In addition to directly regulating tumor metastasis and progression, TIPE can regulate tumor progression by impacting the expression of anti-tumor genes and oncogenes (Day *et al*., 2017; Li *et al*., 2020b; Zhou *et al*., 2021). For example, TIPE knockdown enhanced the expression of anti-cancer genes, including *interleukin-24 (IL-24), Latrophilin 2 (LPHN2), FAT atypical cadherin 3 (FAT3), erythropoietin-producing hepatocellular carcinoma cell receptor A3 (EPHA3)*, and *fatty acid oxidation-related* genes, but decreased the expression of oncogenes, such as *nuclear factor of activated T cells 5* (*NFAT5), metastasis associated lung adenocarcinoma transcript 1 (MALAT1)*, and *mesenchymal to epithelial transition factor (MET)* (Day *et al*., 2017). Further, knockdown of TIPE by microRNA-138 promoted osteosarcoma cells to die (Zhou *et al*., 2021). However, lncRNA H19 upregulated TIPE and inhibited p53 expression, and promoted the invasion and migration of triple-negative breast cancer cells (Li *et al*., 2020b).

Apart from the regulation of tumor progression, much evidence has suggested that TIPE was involved in antitumor drug resistance. For example, TIPE promoted resistance to cisplatin treatment by inhibiting the expression of TNF-Iα in esophageal cancer (Zhang and Yang, 2020). When caspase-8/3 and p38 were knocked down, TIPE promoted cisplatin-induced apoptosis in tumor cells (Shi *et al*., 2013). Interestingly, TIPE could enhance glycemic metabolism and glycolytic metabolic rearrangement and improve metabolism-related product generation in prostate cancer cells, leading to a range of cellular metabolic changes and ATP generation (Niture *et al*., 2021). Thus, TIPE could induce antitumor drug resistance by mediating metabolic reactions and playing a carcinogenic role (Zhang *et al*., 2015c). Other reports have shown that TIPE participated in antitumor drug resistance by inducing autophagy or suppressing apoptosis in tumor cells. For example, TIPE activated the extracellular signal-regulated kinase (ERK) signal pathway by interacting with Ras-related C3 botulinum toxin sub-strate 1 (Rac1) to check tumor cell apoptosis and promote chemoresistance in acute myeloid leukemia (Pang *et al*., 2020). Furthermore, TIPE was reported to induce antitumor drug resistance and promote tumor cell survival by acting on the autophagy-related gene 3 (ATG3) protein (Niture *et al*., 2018b).

Moreover, TIPE has dual roles in antibacterial infection or anti-inflammation in addition to tumor progression and regulation of antitumor drug resistance. On one hand, TIPE mediates the lethal effect of bacteria and on the other hand, it exerts an indirect antibacterial effect. For example, in lung mucosa, TIPE selectively affected T lymphocyte subsets that highly expressed *Ccr9, Tcf7*, and *Rag1/2* genes to target bacteria (Li *et al*., 2021a). Besides, another study has shown that TIPE promoted the expression of chemokines in T cells and determined their migration (Sun *et al*., 2020). However, TIPE-deficient mice could resist lethal listeria infections, presumably because TIPE enhanced the antibacterial ability of the liver and spleen in these mice (Porturas *et al*., 2015). In addition, TIPE was reported to act as an important regulator in colitis-associated inflammation (Lou *et al*., 2022). TIPE activated nuclear factor kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3) signal pathways in the intestine, leading to the growth retardation of intestinal epithelial cells, thereby aggravating the chemotherapy-induced colitis (Sun *et al*., 2015).

TIPE1 normally acts as a suppressor in tumor progression and regulation

TIPE1 (TNFAIP8L1), a recently discovered TIPE family member, is known as a positive regulator in cell apoptosis in many cancers and is different from TIPE (Fig. 3) (Zhang *et al*., 2015c). Normally, TIPE1, as a regulator of necroptosis, can regulate programmed necroptosis and apoptosis in L929 cells or NIH3T3 cells (Hitomi *et al*., 2008). TIPE1 acted on multiple signaling pathways, such as the C-Jun N terminal kinase (C-JNK), Bcl2, and mTOR signaling pathways to induce cell apoptosis and inhibited tumor cell proliferation (Ha *et al*., 2014; Zhang *et al*., 2015c; Wang *et al*., 2016b). For example, TIPE1 inhibited JNK and p65 activities by interacting with Rac1, and it promoted apoptosis in primary hepatocellular carcinoma cells (Zhang *et al*., 2015c). Further, in hematological malignancy, over-expression of TIPE1 increased the expression of pro-apoptotic related Bcl-2 family of proteins, such as Bcl-2, Bax, p53, and Bik, and promoted the tumor cells apoptosis (Wang *et al*., 2016b). Besides, tuberous sclerosis complex 2 (TSC2) is a negative regulatory factor of mTOR. TIPE1 could downregulate the mTOR expression by upregulating TSC2 expression, ultimately leading to neuronal apoptosis (Ha *et al*., 2014). Overall, TIPE1 promoted tumor cell apoptosis by acting on different signaling pathways.

In addition to mediating apoptosis in tumor cells, TIPE1 suppressed tumor progress through different mechanisms. For example, TIPE1 was reported to reduce macrophage infiltration and inhibit osteosarcoma cell growth by downregulating monocyte chemotaxis protein-1 expression (Chen *et al*., 2019). TIPE1 regulated the ERK signaling pathway and inhibited tumor cell proliferation and migration in breast cancer by decreasing the protein kinase phosphorylation level (Hu *et al*., 2019). Further, TIPE1 is reportedly involved in cancer metastasis regulation. A report showed that the higher the TIPE1 expression, the lower is

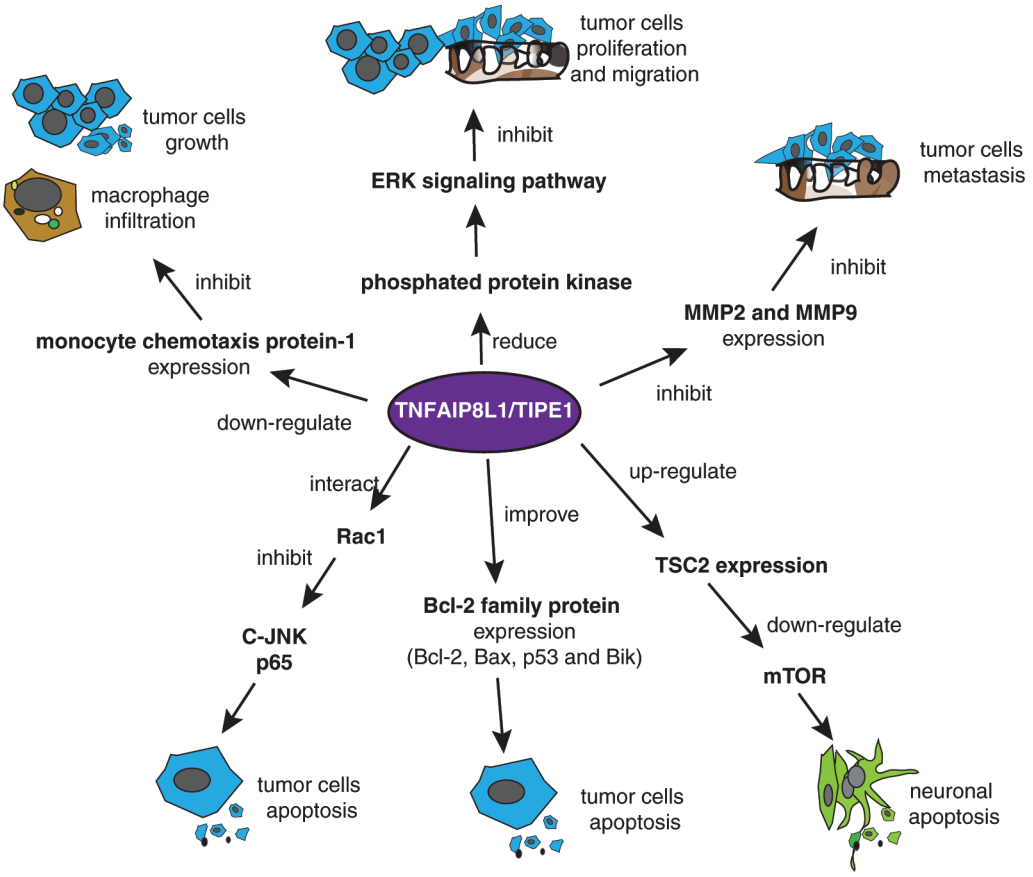

FIGURE 3. TIPE1 usually acts as a suppressor of tumor progression. TIPE1 inhibits tumor progression by mediating tumor cell apoptosis and suppressing tumor cell growth, proliferation, migration, and metastasis. TIPE1 initiates tumor cell apoptosis by acting on multiple signaling pathways, such as C-JNK, Bcl2 signaling pathway, and the mammalian target of rapamycin (mTOR) signaling pathway. TIPE1 mediates tumor initiation and progression suppression by inhibiting monocyte chemotaxis protein-1, matrix metalloproteinase 2 (MMP-2), and MMP-9 expression or decreasing protein kinase phosphorylation levels.

the lymphatic metastasis in primary hepatocellular carcinoma cells (Zhang *et al.*, 2015c). Moreover, TIPE1 suppressed gastric cancer cell metastasis by inhibiting MMP-2 and MMP-9 expression (Ha *et al.*, 2014; Wang *et al.*, 2016b; Liu *et al.*, 2018). Additionally, evidence has shown that TIPE1 could promote tumor cell proliferation and enhance their activity. For example, TIPE1 promoted tumor cell proliferation in cervical cancer by inhibiting p53 acetylation (Zhao *et al.*, 2019).

TIPE2 is involved in tumor progression, regulation, antitumor drug resistance, tumor subtyping, and tumor staging

TIPE2 (TNFAIP8L2), like TIPE1 also generally acts as a tumor suppressor by promoting the apoptosis of tumor cells (Gu *et al.*, 2020). Many reports have shown that TIPE2 was involved in regulating tumor progression by activating or suppressing multiple signaling pathways (Fig. 4). Under normal conditions, TIPE2 regulates two signaling pathways, the Ral guanine nucleotide dissociation stimulators (Ras-RalGDS)/Ral guanine nucleotide exchange factors (Ral-GEFs) pathway and the Ral signaling pathway, thereby inhibiting the action of Ras and acting as a tumor suppressor (Wang *et al.*, 2018b). Additionally, TIPE2 acts as an inhibitor of Rac, a GTPase that promotes trailing edge polarization during cell migration (Fayngerts *et al.*, 2017). For example, TIPE2 can suppress tumor cell growth, migration, and invasion by affecting downstream molecules of the Ras-related C3 botulinum toxin sub-strate 1 (Rac1) signal pathway, inhibiting the progress of non-small cell lung cancer (Li *et al.*, 2016). Moreover, TIPE2 inhibited the expression of the downstream genes of the Rac1 signal pathway, such as the MMP-9 and urokinase-type plasminogen activator fibrinogen activator (uPA). This resulted in the suppression cell migration and invasion in hepatocellular carcinoma (Gus-Brautbar *et al.*, 2012). On similar lines, TIPE2 mediated the inhibition of tumor cell invasion in papillary thyroid carcinoma (Zhao *et al.*, 2018).

In addition to the Rac1 signal pathway, TIPE2 suppressed tumor progression by regulating the Wnt/β-catenin signaling pathway and its relevant signal pathways. For example, evidence from TIPE2-expressing EC9706 cells and xenograft tumor models have suggested that overexpression of TIPE2 suppressed the expression of β-catenin, c-myc, cyclinD1 in esophageal squamous cell carcinoma, thereby suppressing cancer development by inhibiting the Wnt/β-catenin signaling pathway (Zhu *et al.*, 2018). Interestingly, when TIPE2 was overexpressed in glioma cells, it suppressed the hypoxia-induced activation of the Wnt/β-catenin pathway and was also associated with cyclin D1, c-myc, and epithelial-mesenchymal transition (Li *et al.*, 2016). Moreover, in addition to suppressing the expression of Wnt3a, phospho(p)-β-catenin, and p-glycogen

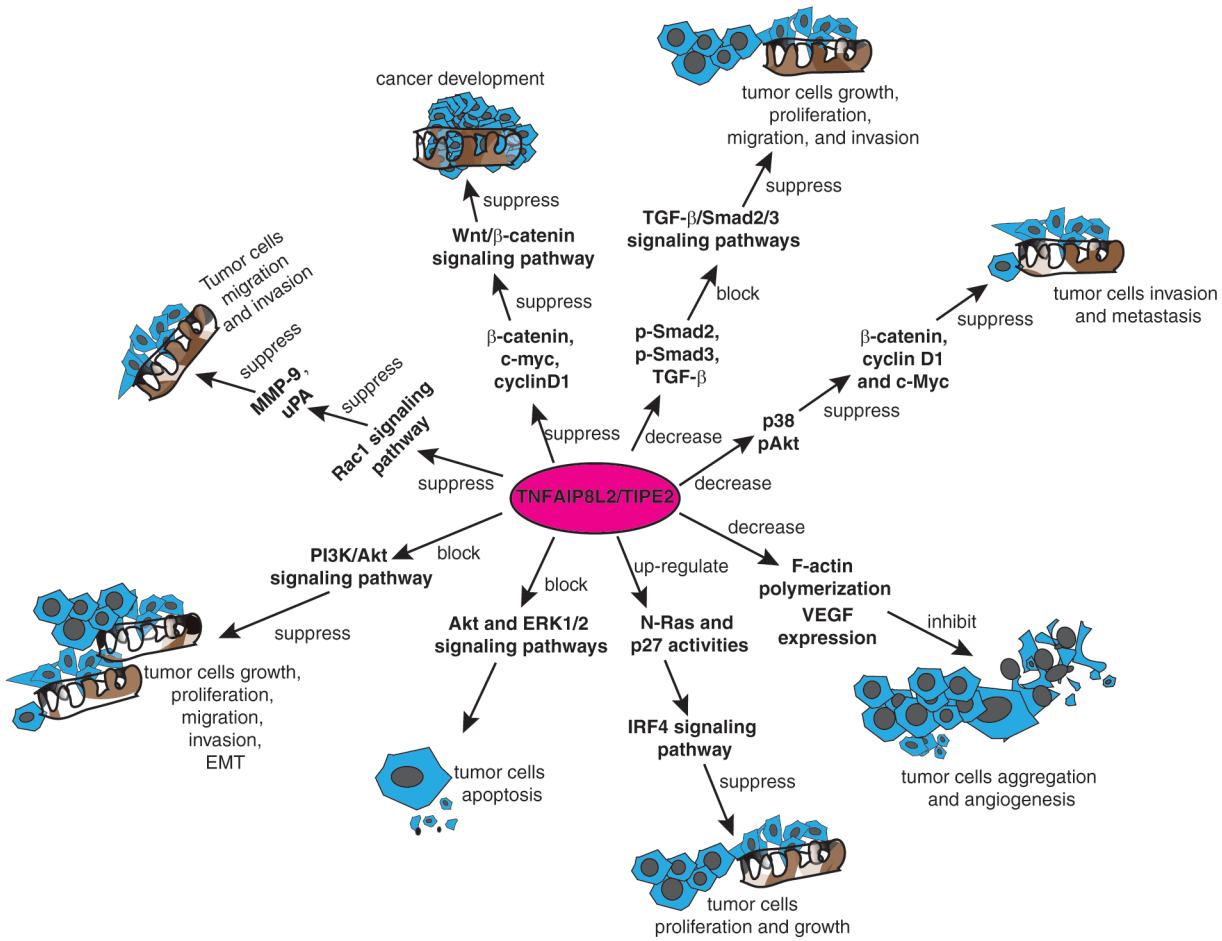

FIGURE 4. TIPE2 regulates tumor progression through multiple signaling pathways. TIPE2 suppressed the growth, proliferation, migration, and invasion of different kinds of tumor cells by suppressing the Ras-related C3 botulinum toxin sub-strate 1 (Rac1) signaling pathway, Wnt/β-catenin signaling pathway, transforming growth factor-beta (TGF-β)/Sma and Mad protein 2/3 (Smad2/3) signaling pathway, Protein kinase B (AKT) and extra-cellular signal-regulated protein kinase (ERK)1/2 signaling pathways, or interferon regulatory factor 4 (IRF4) signaling pathway. Other mechanisms include downregulation of F-actin polymerization, and decreasing the expression of vascular endothelial growth factor.

synthase kinase-3β, overexpression of TIPE2 also reduced the expression levels of phospho-Sma and Mad protein 2 (p-Smad2), phospho-Sma and Mad protein 3 (p-Smad3), and transforming growth factor-beta (TGF-β) in rectal adenocarcinoma cells. To summarize, TIPE2 suppressed cellular autophagy and the growth, proliferation, migration, and invasion of rectal adenocarcinoma cells by blocking both Wnt/β-catenin and TGF-β/Smad2/3 signaling pathways (Wu *et al.*, 2019).

TIPE2 also modulates tumor progression through the PI3K/Akt and other related signal pathways. For example, TIPE2 suppressed the expression of β-catenin, cyclin D1 and c-myc in breast cancer cells by reducing the expression of p38 and phosphorylated Akt to significantly inhibit cancer cell invasion and migration (Lu *et al.*, 2016; Zhang *et al.*, 2016). Furthermore, TIPE2 inhibited tumor cell proliferation and growth by binding to β-catenin and reducing its nuclear translocation in endometrial cancer (Liu *et al.*, 2020b). Similarly, overexpression of TIPE2 blocked the PI3K/Akt signaling pathway and suppressed the growth, proliferation, migration, invasion, and epithelial-mesenchymal transition (EMT) of prostate cancer cells (Lu *et al.*, 2016). Moreover, TIPE2 was reported to be involved in cell apoptosis by blocking the Akt and extra-cellular signal-regulated protein kinase (ERK)1/2 signaling pathways in gastric cancer (Zhu *et al.*, 2016). Additionally, there is evidence that TIPE2 suppressed the proliferation and growth of gastric cancer cells by modulating the activity of N-Ras and p27 in the interferon regulatory factor 4 (IRF4) signaling pathway (Zhao, 2020). Further, TIPE2 inhibited tumor cell aggregation and angiogenesis by downregulating F-actin polymerization and vascular endothelial growth factor expression (Li *et al.*, 2016).

In addition to regulating tumor progression, TIPE2 has been reportedly involved in antitumor drug resistance. For example, TIPE2 blocked multi-drug resistance1 gene (*MDR1*) transcription and enhanced patient sensitivity to the cisplatin-mediated treatment in osteosarcoma by inhibiting the transforming growth factor-β-activated kinase 1 (Tak1/NF-κB) and activating protein-1 (AP-1) signaling pathways (Zhao *et al.*, 2018). Besides, TIPE2 was reported to induce cellular autophagy and reduce cisplatin-mediated drug resistance in lung cancer cells by regulating the mTOR signaling pathway (Guo *et al.*, 2020).

Much evidence has suggested that TIPE2 is correlated with tumor staging and subtyping. For example, it has been

documented that TIPE2 was barely expressed in hepatocellular carcinoma (Gus-Brautbar *et al.*, 2012), non-small cell lung cancer (Liu *et al.*, 2016), esophageal squamous cell carcinoma (Zhu *et al.*, 2018), oral tongue squamous cell carcinoma (Zhao, 2020), and gastric cancer (Zhao *et al.*, 2015). However, TIPE2 was highly expressed in colon cancer tissues and non-Hodgkin's lymphoma (NHL) (Zhang *et al.*, 2013). Many reports have shown that the expression of TIPE2 was positively correlated with the Tumor Node Metastasis (TNM) staging in renal cell carcinoma and lymph node metastasis of colon cancer (Zhang *et al.*, 2013). Further, a high expression of TIPE2 was negatively correlated with tumor size, envelope infiltration, peripheral infiltration, and tumor T-stage in thyroid adenocarcinoma (Jia *et al.*, 2018). TIPE2 was more expressed in early-stage tumor tissues than in advanced-stage tumor tissues in pancreatic ductal adenocarcinoma (PDAC) (Sun *et al.*, 2021). The expression was negatively correlated with the TNM stage and lymph node metastasis of PDAC (Sun *et al.*, 2021). TIPE2 was upregulated in the normal columnar epithelium and squamous epithelium of early-stage tumor tissues but downregulated in advanced NSCLC tumor tissues with lymph node metastasis (Li *et al.*, 2016). Moreover, as a biomarker correlating with tumor staging and subtyping, TIPE2 showed different carcinogenic effects on tumor staging and subtyping (Li *et al.*, 2016). For example, in diffuse large B-cell lymphoma (DLBCL) and peripheral T-cell lymphoma, TIPE2 was more expressed in germinal-center B-cell (GCB) phenotypes than non-GCB phenotypes, suggesting that TIPE2 may act as an oncogenic gene in the progression of these tumors (Hao *et al.*, 2016). Besides, TIPE2 expression patterns were different in different lung cancer tissue subtypes. For example, TIPE2 showed low expression in squamous and small-cell lung cancer but was strongly expressed in lung adenocarcinoma (Zhao, 2020). In addition, recent research on oral tongue squamous cell carcinoma (OTSCC) patients showed that high expression of TIPE2 inhibited the progression of OTSCC and was correlated with patient prognosis in terms of the TNM stage and degree of tumor differentiation (Zhao, 2020). To summarize, TIPE2 is important in cancer progression, staging, and classification.

TIPE2 acts as a negative regulator in inflammation and immune-related diseases

TIPE2 has been reported to be expressed in different cells, such as neurons, hepatocytes, colon cells, stomach gland cells, ureter cells, and bladder transitional epithelium (Hao *et al.*, 2016). It normally acts as a negative regulator in innate and adaptive immunity and is highly expressed in our immune systems, such as lymphoid tissues and bone marrow (Zhang *et al.*, 2011). Much evidence has demonstrated that the absence of TIPE2 could induce immune dysregulation and inflammation to cause damage, such as multi-organ inflammation, splenomegaly, and premature death (Sun *et al.*, 2008). For example, the expression of TIPE2 was much higher in acute-on-chronic hepatitis B liver failure (ACHBLF) patients than that in chronic hepatitis B and normal subjects. This suggested that TIPE2 may serve as a predictor for disease onset and progression in ACHBLF patients (Wang *et al.*, 2014). TIPE2 was also reported to reduce inflammation by inhibiting the nucleotide-binding oligomerization domain protein 2 (NOD2)-induced activation of mitogen-activated protein kinase (MAPK) and NF-κB signaling pathways. This is given that deletion of the NOD2 led to lowered myocardial ischemia-induced injury (Wang *et al.*, 2014). Hence, TIPE2 can be a negative regulator linked to NOD2 and inflammatory responses (Zhang *et al.*, 2015a). Moreover, TIPE2 was reported to be involved in the pathogenesis of patients with different types of asthma like eosinophilic asthma (EA), neutrophilic asthma (NA), mixed granulocytic asthma (MA), paucigranulocytic asthma (PA) by regulating the activities and functions of multiple inflammatory cells (Shi *et al.*, 2020).

In addition to being involved in inflammation, TIPE2 is also a negative regulator of immune disorders. For example, TIPE2 has been shown to inhibit the development of Toll-like receptor 4 (TLR4)-mediated autoimmune inflammation in patients with myasthenia gravis (Li *et al.*, 2018). Further, TIPE2 regulated TLR4 receptor-mediated inflammatory response pathways in murine colitis-associated colon cancer by inhibiting caspase-8 activity (Li *et al.*, 2014). Besides, TIPE2 improved the activity of caspases to induce adjuvant arthritic fibroblast-like synoviocyte apoptosis by promoting the expression of death receptor 5 (DR5). Additionally, TIPE2 suppressed the activation of the NF-κB signal pathway in the adjuvant arthritis model (Shi *et al.*, 2016). In systemic lupus erythematosus (SLE), the expression of TIPE2 was suppressed, which increased the expression of interleukins (IL): IL-6, IL-17, IL-21, and aggravated the inflammation (Li *et al.*, 2018). Moreover, recent research has shown that TIPE2 influenced the *in vitro* biological activity of OTSCCs by negatively regulating the activities of $Foxp^{3+}$ Treg cells (Zhao, 2020). In addition, overexpression of TIPE2 in the tumor micro-environment enhanced the activity of immune cells, such as the $CD8^{+}$ cells and natural killer (NK) cells (Zhang *et al.*, 2017). In a recent report, knockout of TIPE2 improved the progression of mature NK cells and elevated the expression of tumor infiltration effectors in NK cells (Bi *et al.*, 2021). Moreover, TIPE2 deletion enhanced the antineoplastic activity and the antitumor function of NK cells (Bi *et al.*, 2023). To summarize, TIPE2 plays important roles in inflammation, immune diseases, and tumor immunology and may be a crosstalk massager linked to inflammation, immune disorders, and tumor progression.

TIPE3 is linked to the PI3K/Akt and related signaling pathways for regulating tumor progression

TIPE3 (TNFAIP8L3) is a novel TIPE family member that was identified recently (Fayngerts *et al.*, 2014). Much evidence has suggested that TIPE3 is highly expressed in human cervical cancer, colon cancer, NSCLC, breast cancer, esophageal cancer, and glioblastoma (Fayngerts *et al.*, 2014; Cui *et al.*, 2015). It was reported that TIPE3 could activate the PI3K/Akt signaling pathway, converting phosphatidylinositol diphosphate (PIP2) to phosphatidylinositol triphosphate (PIP3) for further signaling transduction, and is considered as a second messenger phosphatidyl inositol transporter

TABLE 1

Overview of the function and mechanism of the tumor necrosis factor-α-induced protein 8-like (TIPE) family of proteins

TIPE family member	Expression level in a tumor	Functions	Mechanisms	References
TIPE	Gastric cancer ↑	Involved in the occurrence and progression of gastric cancer.	Overexpression of microRNA-9 directly inhibits the expression of TNFAIP8.	Gao *et al.* (2017), Uhlén *et al.* (2015)
	Thyroid cancer ↑	Enhance tumor metastasis, migration, and proliferation.	It may promote the expression of TNFAIP8 protein.	Duan *et al.* (2014)
	Non-small cell lung cancer ↑	Promotion of tumor cell proliferation and migration.	Involved in MDM2/p53 pathway and promoted the expression of transfer molecules MMP-1 and MMP-9.	Kim *et al.* (2017), Zhang *et al.* (2006)
	Breast cancer ↑	Improve the MDA-MB-435 cell proliferation and carcinogenicity.	Increased type I collagen expression.	Kumar *et al.* (2004), Zhang *et al.* (2006)
	Liver cancer ↑	Promotion of tumor cells proliferation, migration, and invasion.	Involved in the Hippo pathway, inhibition of LAST1 and YAP phosphorylation.	Niture *et al.* (2018a)
	Cervical cancer ↑	Promotion of tumor occurrence.	SNP of TNFAIP8 miRNA binding sites affects the affinity of miR-22 binding to TNFAIP8 3′UTR. Thus, it promotes TNFAIP8 protein expression and cervical cancer progression.	Shi *et al.* (2013)
	Prostate cancer ↑	Induce drug resistance and promote tumor cells survival, carcinogenic effect.	Interacted with ATG3 protein. Promoted glycolysis metabolism rearrangement and related metabolites generation. Activated the PI3K/AKT pathway.	Niture *et al.* (2018a, 2021, 2018b)
	Skin cancer ↑	Promotion of cancer cell survival and growth, and paclitaxel-mediated drug resistance.	Overexpression of miR-205-5p directly inhibits the effect of TNFAIP8 on tumors.	Ge *et al.* (2021)
	Acute myeloid leukemia ↑	Inhibition of tumor cell apoptosis and chemotherapy resistance.	Interacted with Rac1 and activated ERK pathway.	Pang *et al.* (2020), Uhlén *et al.* (2015)
	Esophageal carcinoma ↑	TIPE high expression was associated with TNM stage, tumor depth, lymph node metastasis, distant metastasis, lymphatic invasion and venous invasion, and low survival rate.	Associated with the TNF-Iα expression.	Hadisaputri *et al.* (2012), Sun *et al.* (2016), Zhang and Yang (2020)
TIPE1	Primary liver cancer ↓	Inhibiting liver cancer cell activity, growth, and lymph metastasis promoted cell apoptosis.	TIPE1 interacts with Rac1 and inhibits its activation; moreover, it affects the Rac1 downstream, such as p65 and c-Jun N-terminal kinase pathways.	Wu *et al.* (2017), Zhang *et al.* (2011), Zhang *et al.* (2015c)
	Non-small cell lung cancer ↓	Induced lung cancer cell apoptosis.	Regulated the expression of cyclin D1, cyclin B1, caspase 8, caspase 3, MMP-2, and MMP-9.	Wu *et al.* (2017)
	Gastric cancer ↓	Inhibition of the metastasis, growth, and proliferation of gastric cancer cells.	Suppressed MMP-9 and mediated Wnt/β-Catenin signal conduction suppression in EMT progress.	Cui *et al.* (2011), Liu *et al.* (2018)
	Osteosarcoma ↓	Inhibition of osteosarcoma tumor progression.	MCP-1 expression inhibition and ccr2 positive macrophage infiltration.	Chen *et al.* (2019)
	Ovarian cancer ↓	Suppressed ovarian cancer cell proliferation, migration, and aggregation and inhibited ovarian cancer damage.	Increased E-Cadherin but suppressed the expression of N-Cadherin, Slug, and Snail.	Li *et al.* (2020a), Yeung *et al.* (2015)

(Continued)

Table 1 (continued)

TIPE family member	Expression level in a tumor	Functions	Mechanisms	References
	Parkinson's disease ↑	Induce neuronal apoptosis and stabilize the disease.	Upregulated TSC2 expression and downregulated the mTOR expression, TIPE1 stabilizes the disease by competing with FBXW5 protein for TSC2 binding.	Cui *et al.* (2011), Ha *et al.* (2014)
	Breast cancer ↓	Inhibited breast cancer cell proliferation.	Downregulated ERK phosphorylation.	Hu *et al.* (2019)
	Cervical cancer ↓	Promotion of cervical cancer proliferation.	p53 activity inhibition.	Padmavathi *et al.* (2018)
	Nasopharyngeal Carcinoma ↑	Accelerated nasopharyngeal carcinoma cells proliferation.	Through AMPK/mTOR signal pathway.	Liu *et al.* (2020a)
TIPE2	Liver cancer ↓	Inhibition of tumor occurrence, proliferation, invasion, and migration.	Inhibition of AP-1 protein and NF-κB expression. Promotes fas-induced apoptosis. Inhibition of Rac1. Inhibits metastasis molecules MMP-9 and uPA, growth molecules EGF and PDGF.	Cao *et al.* (2013), Gus-Brautbar *et al.* (2012), Wang *et al.* (2018b), Wang *et al.* (2016a), Zhang *et al.* (2015b)
	Non-small cell lung cancer ↓	Inhibition of tumor cell proliferation, migration, invasion, lymph node metastasis, and cisplatin-mediated drug resistance.	Inhibition of Rac1 and downregulates F-actin polymerization and VEGF expression.	Li *et al.* (2018)
	Thyroid cancer ↑	Inhibition of tumor cells proliferation, migration, and invasion.	Inhibition of Rac1, uPA, MMP-9 expression.	Jia *et al.* (2018)
	Esophageal squamous cell carcinoma ↓	Inhibition of tumor proliferation, invasion, migration, and EMT.	Inhibition of Wnt/β proliferation. Reduces the expression of c-myc and cyclinD1.	Zhu *et al.* (2018)
	Glioma ↓	Inhibition of tumor proliferation, invasion, migration, and EMT.	Suppressed Wnt/β-catenin, cyclin D1, and c-myc expression.	Li *et al.* (2016)
	Rectal cancer ↑	Inhibition of tumor occurrence, proliferation, invasion, and migration.	Inhibition of Wnt/β occurrence, proliferation, invasion, and migrat expression.	Wu *et al.* (2019)
	Gastric cancer ↓	Inhibition of tumor proliferation, invasion, migration, EMT, and lymph node metastasis.	Suppressed PI3K/Akt/GSK3β/ERK1/2,Wnt/β- Catenin, IRF4 signal pathways, and upregulated N-Ras and p27 activities.	Li *et al.* (2014), Yin *et al.* (2017), Zhao (2020)
	Prostate cancer ↓	Inhibition of tumor proliferation, invasion, migration, and EMT.	Inhibition of PI3K/Akt signaling pathway.	Lu *et al.* (2016)
	Breast cancer ↓	Inhibition of tumor proliferation, invasion, migration, and EMT.	Inhibition of PI3K/AKT signaling pathway and the expression of/AKT signaling pathwayion, miand p38.	Wang *et al.* (2017), Zhang *et al.* (2016)
	Endometrial carcinoma ↓	Inhibition of tumor proliferation, invasion, migration, and EMT.	Inhibition of β-catenin expression.	Liu *et al.* (2020b)
	Osteosarcoma ↓	Promotion of tumor cell apoptosis and increased cisplatin sensitivity to tumor cells.	Inhibition of Tak1/NF-κB increased cisplatin sensitive Inhibits the MDR1 transcription pathway and reduces MMP-13 protein expression.	Zhao *et al.* (2018)
	Colon cancer ↑	Promotion of tumor cell proliferation, migration, and invasion, and promoted tumor staging and lymph node metastasis.	Inhibition of caspase-8 activity and TLR4-mediated inflammation.	Li *et al.* (2014)

(Continued)

Table 1 (continued)

TIPE family member	Expression level in a tumor	Functions	Mechanisms	References
	Renal cell carcinoma ↑	Promoted tumor TNM staging.	Reduced IFN-I levels and downregulated MX1 expression.	Zhang *et al.* (2013)
	Oral tongue squamous cell carcinoma ↓	Inhibition of tumor proliferation, migration, and invasion.	Reduced the level of $FoxP_3^+$ Treg.	Zhao (2020)
	Non-Hodgkin's lymphoma ↑	Unknown	Unknown	Hao *et al.* (2016)
TIPE3	Gastric cancer ↓	Promoted tumor cell proliferation, migration, and invasion.	Activated the PI3K/Akt signaling pathway.	Cui *et al.* (2015), Fayngerts *et al.* (2014), Gao *et al.* (2020)
	Cervical cancer ↑	Unknown	Unknown	Cui *et al.* (2015), Fayngerts *et al.* (2014)
	Colon cancer ↑	Unknown	Unknown	Cui *et al.* (2015), Fayngerts *et al.* (2014)
	Non-small cell lung cancer ↑	Promotion of tumor cell proliferation, migration, and invasion.	Through AKT/ERK1/2GSK3 β axis, the β-catenin, Snail1, and Slug transcription signals were activated.	Cui *et al.* (2015), Fayngerts *et al.* (2014), Li *et al.* (2021b)
	Esophageal carcinoma ↑	Unknown	Unknown	Cui *et al.* (2015), Fayngerts *et al.* (2014)
	Breast cancer ↑	Promotion of tumor cells proliferation, migration, and invasion.	Improved MMP-2 and uPA expression, activated AKT, ERK, and NF-κB signaling.	Cui *et al.* (2015), Fayngerts *et al.* (2014), Lian *et al.* (2017), Wang *et al.* (2018a)
	Rectal cancer ↓	Unknown	Unknown	Gao *et al.* (2020)
	Hepatocellular carcinoma-?	Unknown	Unknown	Gao *et al.* (2020)
	Glioma ↑	Inhibition of tumor cells apoptosis.	Inhibition of the p38 MAPK signaling pathway.	Cui *et al.* (2015), Fayngerts *et al.* (2014), Yuan *et al.* (2019)
	Pancreatic cancer ↑	Promotion of tumor cell proliferation and migration.	Upregulated Rac1 expression.	Li *et al.* (2022)

Abbreviations: MDM2, murine double minute 2; MMP, matrix metalloproteinase; SNP, single nucleotide polymorphism; miRNA, micro RNA; UTR, untranslated Region; LATS1, phosphorylation of large tumor suppressor gene 1; YAP, Yes-associated protein; ATG3, autophagy-related protein 3; PI3K, phosphatidylinositol-3-kinase; AKT, protein kinase B; Rac1, Ras-related C3 botulinum toxin sub-Strate 1; ERK, extra-cellular signal-regulated protein kinase; TNM, Tumor Node Metastasis; TNF, Tumor Necrosis Factor; EMT, epithelial-mesenchymal Transition; ccr2, Recombinant Chemokine C-C-Motif Receptor 2; MCP-1, monocyte chemotactic protein-1; TSC2, tuberous sclerosis complex 2; mTOR, mammalian target of Rapamycin; FBXW5, F-box/WD repeat-containing protein 5; AMPK, AMP-activated protein kinase; AP-1, activating protein-1; EGF, endothelial growth factor; PDGF, Platelet-Derived Growth Factor; VEGF, vascular endothelial growth factor; Wnt, Wingless-Type MMTV Integration Site Family, GSK3β, Glycogen Synthase Kinase 3 Beta; IRF4, interferon regulatory factor 4; MDR-1, Multi-Drug Resistance Gene-1; TLR4, Toll-like Receptor 4; IFN-I, Type I interferon; Mx1, myxovirus resistance 1; PI3K, phosphatidylinositol-3-kinase; AKT, Protein kinase B; uPA, urokinase-type plasminogen activator fibrinogen activator; NF-κB, nuclear factor kappa-B; Tak1, transforming growth factor-β-activated kinase 1; MAPK, mitogen-activated protein kinase.

(Zhang *et al.*, 2017). TIPE3 activated the phosphatidylinositol-3-kinase (PI3K)-mediated signaling pathway and promoted tumor cell growth, proliferation, migration, and invasion by regulating phosphatidylinositol diphosphate (PIP2) and phosphatidylinositol triphosphate (PIP3) (Wang *et al.*, 2018a). However, TIPE3 activated PI3K/Akt signaling and promoted tumor cell migration and invasion in gastric cancer, which is different from the roles of TIPE2 (Gao *et al.*, 2020). Further, TIPE3 has reported to be involved in MMP and urokinase-type plasminogen activator fibrinogen activator (uPA) expression in breast cancer (Lian *et al.*, 2017). TIPE3 promoted breast cancer cell migration by activating the Akt and NF-κB signaling pathways (Moniz and Vanhaesebroeck, 2014). In addition, TIPE3 promoted malignant glioma development by inhibition of p38 phosphorylation (Yuan *et al.*, 2019). Overall, similar to the role of other TIPEs, TIPE3 may also be an oncogenic molecule and associated with PI3K/Akt and related signal pathways in tumor progression.

Discussion

The TIPE family of proteins is a recently discovered group with numerous roles in regulating immune, inflammation, and tumor development (Table 1). Many studies have focused on TIPE and TIPE2, while few have studied TIPE1 and TIPE3. Although there are some similarities in the structure and expression of the TIPE proteins, they have different biological activities in different cells and tissues (Gu *et al.*, 2020). According to recent studies, there is

increasing evidence that TIPE and TIPE3 promote tumor initiation and progression, while TIPE1 and TIPE2 inhibit tumor progression in most cases (Gus-Brautbar *et al*., 2012; Fayngerts *et al*., 2014; Zhang *et al*., 2015c; Day *et al*., 2017). The differences in the structures of the TIPE proteins may be related to their different roles in tumor progression, which may require further research in the future. Inhibiting or blocking TIPE or TIPE3 has been predicted to inhibit tumor progression and reduce antitumor drug resistance in cancer therapy (Fayngerts *et al*., 2014; Day *et al*., 2017). Discovering and designing inhibitors targeting TIPE or TIPE3 in the development of antitumor drugs may be a feasible strategy for antitumor therapy. TIPE1 and TIPE2 have been regarded as tumor suppressors in most studies. Various factors and signaling pathways were involved in the expression regulation of TIPE1 and TIPE2 in different cancers (Gu *et al*., 2020; Zhang *et al*., 2021). Further elucidation of the regulatory aspects of TIPE1 and TIPE2 in different cancers may support positive approaches for tumor prevention and treatment.

Interestingly, although TIPE1 and TIPE2 act as tumor suppressors in most cases, there is also some evidence that TIPE1 can act as an oncogenic factor to promote tumor cell growth and proliferation by inhibiting the acetylation of p53 in cervical cancer (Zhao *et al*., 2019). Moreover, TIPE2 shows low expression in bladder cancer, cervical cancer, and ovarian cancer, and the roles and related mechanisms in these cancers remain unclear (Zhang *et al*., 2011; Jiang *et al*., 2022; Zhang *et al*., 2022). Currently, the functions and mechanisms of TIPE3 have been reported to a lower extent. The roles and mechanisms of the TIPE family in cancer can be deduced as intricate.

In addition to its diverse regulatory roles in cancer, TIPE2 is highly expressed in the immune system, such as lymph and bone marrow, where it is involved in inflammation and immune regulation (Sun *et al*., 2008). Studying the role and mechanism of TIPE2 in immune and inflammatory diseases may be a future direction for treating immune disorders, such as eczema, psoriasis, rheumatoid arthritis, and chronic hepatitis. At the same time, given the established connection between inflammation and tumors, studies on TIPE2-related signaling pathways may help us further understand the interaction between inflammation and tumor progression. As mentioned earlier, TIPE2 inhibits natural killer cell maturation and further reduces antitumor immunity, which may be a good basis to understand these aspects. Furthermore, developing TIPE2 agonists or inhibitors may be helpful for antitumor and immunological disease therapies.

In summary, the roles and mechanisms of the TIPE family in cancer and inflammatory responses are not yet fully understood. Deeper studies on the structure, function, and mechanism of the TIPE family may help us better understand the relationship among inflammation, immune responses, and tumor progression. This will provide us with more clues and ideas for the treatment and prognosis of tumors or related immune diseases. In addition, as a family with high amino acid sequence similarity (Niture *et al*., 2018a), whether there exists an interaction between different TIPE members and crosstalk mechanisms among the TIPE family may also be another noteworthy avenue of research.

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