



Review

TIPE Family of Proteins and Its Implications in Different Chronic Diseases

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Abstract: The tumor necrosis factor- α -induced protein 8-like (TIPE/TNFAIP8) family is a recently identified family of proteins that is strongly associated with the regulation of immunity and tumorigenesis. This family is comprised of four members, namely, tumor necrosis factor- α -induced protein 8 (TIPE/TNFAIP8), tumor necrosis factor- α -induced protein 8-like 1 (TIPE1/TNFAIP8L1), tumor necrosis factor- α -induced protein 8-like 2 (TIPE2/TNFAIP8L2), and tumor necrosis factor- α -induced protein 8-like 3 (TIPE3/TNFAIP8L3). Although the proteins of this family were initially described as regulators of tumorigenesis, inflammation, and cell death, they are also found to be involved in the regulation of autophagy and the transfer of lipid secondary messengers, besides contributing to immune function and homeostasis. Interestingly, despite the existence of a significant sequence homology among the four members of this family, they are involved in different biological activities and also exhibit remarkable variability of expression. Furthermore, this family of proteins is highly deregulated in different human cancers and various chronic diseases. This review summarizes the vivid role of the TIPE family of proteins and its association with various signaling cascades in diverse chronic diseases.

Keywords: TIPE; TIPE1; TIPE2; TIPE3; chronic diseases; cancer

1. Introduction

The tumor necrosis factor- α -induced protein 8 (TIPE/TNFAIP8/Oxi- α) family is a newly identified family of proteins that is involved in the regulation of immunity and tumorigenesis. This family is comprised of four members, namely, TIPE or TNFAIP8 (tumor necrosis factor- α -induced protein 8), TIPE1 (TNFAIP8-like 1, or TNFAIP8L1), TIPE2 (TNFAIP8-like 2 or TNFAIP8L2), and TIPE3 (TNFAIP8-like 3 or TNFAIP8L3) [1]. Despite the fact that all the four proteins of this family share a significant sequence homology (~54% sequence identity), they are involved in the regulation of different cellular activities [2–5].

TIPE, the most extensively studied member of this family, is a transcription factor nuclear factor- κ -B inducible, anti-apoptotic, and oncogenic molecule that is associated with prognosis of different malignancies. It is a 21-kDa cytoplasmic protein that was initially identified in human head and neck squamous cell carcinoma [5–10]. It is expressed in different human normal tissues with relatively higher levels in placenta and lymphoid tissues. The open reading frame of this protein bears a sequence in the amino terminus that displays a notable homology to the death effector domain II of the cell death regulatory protein, Fas-associated death domain-like interleukin-1 β -converting enzyme-inhibitory protein (FLIP) [11]. TIPE is associated with the immune regulation of CD4⁺ T lymphocytes and inhibits autophagy under oxidative stress through the mammalian target of rapamycin (mTOR)-dependent pathway [3,12,13]. Notably, different transcript variants of this TIPE gene were recently listed in the NCBI databank. However, currently no study has described their distinguished roles or depicted the factors that regulate their expression. A study by Lowe and group reported TIPE variant 2 as an oncogenic gene product that may regulate different processes in tumor cells such as proliferative signaling, resistance to cell death, and evasion of growth suppressors. On the other hand, other variants are normally downregulated in cancer (variant 1) or show minimal expression in cancer or normal tissues (variant 3–variant 6) [14].

TIPE1 (tumor necrosis factor- α -induced protein 8-like 1) is a recently identified member of the TIPE family that can act as a cell death regulator. It is regarded as a pro-apoptotic factor with the ability to cause increased apoptotic functions. Currently, there is little information available about the role of TIPE1. The information on its biological activity under both physiological and pathological conditions remains ambiguous [4,5,15–17]. It was reported to be distributed in different mouse tissues except for mature B and T lymphocytes. Further, TIPE1 was speculated to be associated with cardiac decompensation linked with diabetes and to interact with FBXW5 and caspase-8. Besides, different post-translational modifications were also predicted to exist in the case of TIPE1 [2,16].

TIPE2 (tumor necrosis factor- α -induced protein 8-like 2), the third member of this family, is a latterly discovered negative regulator of innate, as well as cellular immunity, with sizable sequence homology with the other members of the family [18–20]. It is a cytoplasmic protein consisting of 184 amino acids and is expressed preferentially in lymphoid tissues and some non-lymphoid tissues [19,21]. This protein was initially identified as an abnormally expressed gene in the inflamed spinal cord of experimental autoimmune encephalomyelitic mice [22,23]. Further, TIPE2 was found to be expressed in varied cell types such as neurons in the brain and brainstem; hepatocytes; squamous epithelial cells in the cervix and esophagus; glandular epithelial cells in the colon, stomach, and appendix; and transitional epithelial cells in the ureter and bladder [24]. It negatively regulates the functions of toll-like receptor (TLR) and T cell receptor, and its selective expression in the immune system averts hyper responsiveness and maintains immune homeostasis [22,23,25]. Further, it is an inhibitor of the nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B) and mitogen-activated protein kinase (MAPK) signaling pathways and contributes to the reduced activation of activator protein-1 (AP-1) and NF- κ B [5,26,27]. It also acts as an inhibitor of Rac, which is a GTPase involved in the promotion of

trailing-edge polarization [28]. A recent genome-wide expression profiling analysis reveals TIPE2 to function as an immune checkpoint regulator of inflammation and metabolism. This finding depicts that during the course of inflammation, the expression of TIPE2 may be downregulated plausibly due to its altered epigenetic status, which in turn results in the upregulation of the expression of lipid biosynthesis genes, mitochondrial respiration, and inflammation [29].

TIPE3 (tumor necrosis factor- α -induced protein 8-like 3), the newest member of TIPE family, is located on human chromosome 15. It functions as a transfer protein for lipid second messengers PIP2 (phosphatidylinositol 4,5-bisphosphate) and PIP3 (phosphatidylinositol 3,4,5-trisphosphate), and enhances their level in the plasma membrane [1,30,31]. This protein is expressed in various human organs and is highly upregulated in several human cancers such as cervical cancer, colon cancer, esophageal cancer, and lung cancer [5,32].

Furthermore, the crystal structures of two members of the TIPE family, namely, TIPE2 and TIPE3 from *Homo sapiens*, have been determined. Both of them possess a central hydrophobic cavity that is proposed as a binding site for cofactors, occupied by two long electrostatic densities, which are plausibly phospholipid in nature [3,19,33,34]. Moreover, these phospholipids were observed to share similar binding modes that involve the exposure of the inositol head group outside and insertion of the lipid tails into the cavity. In addition, all the lipid molecules interact with the critical, positively charged residues as per molecular interaction studies, i.e., Arg 75 and -91 in TIPE2, and Arg 181 and 197 in TIPE3, indicating the similar binding fashion of the phosphoinositides to the TH domain of this protein family [35]. Interestingly, the high-resolution crystal structure of TIPE2 clearly reveals that it possesses a unique yet previously uncharacterized fold that gives TIPE2 a unique structure and topology that is different from that of death effector domain (DED). The structure of TIPE2, which comprises around 150 amino acids, is reasonably larger than that of the DED, as it usually contains a total of 90 amino acids. Again, the topology of TIPE2 is different from that of a DED, as it was observed that N-to-C arrangement of TIPE2 is identical to the C-to-N topology diagram of DED. Therefore, the topology of TIPE2 seems to be a mirror image of that of the DED [34]. Additionally, the crystal structure of TIPE from *Mus musculus* (mTIPE) was also determined. The overall shape of mTIPE bears a resemblance to a water dipper. Its cylindrical domain contains two long electron densities and has a dimension of $48 \times 31 \times 30 \text{ \AA}$ linked to an N-terminal grip-like domain of length $\sim 35 \text{ \AA}$ that comprises of 20 residues. It possesses a hydrophobic cavity of depth around 20 \AA , a diameter of around 7 \AA , and a volume of 837 \AA^3 , which is lined with highly conserved hydrophobic residues, thereby facilitating the binding of hydrophobic cofactors or substrates inside the cavity [3].

Aforementioned, different *in vitro* and *in vivo* studies have revealed that this family of proteins plays a crucial role in inflammatory responses and tumorigenesis (Table 1; [5]). Interestingly, the expression analyses in clinical settings have also demonstrated these proteins to be highly deregulated in different cancers and various chronic diseases (Figure 1).

Table 1. Different chronic diseases and signaling pathways with known associations with the TIPE family of proteins.

| Disease | Model | Protein Involved | Targets Associated/Outcome | References |
|---|--|--------------------------------|---|------------|
| Cancers | | | | |
| Bladder cancer | T24 cells | ↑TIPE3 | ↑PI3K-Akt, ↑MEK-ERK | [31] |
| Breast cancer | Tissue samples | ↑TIPE | tumor progression | [8] |
| | MDA-MB-231 and MCF-7 cells | ↑TIPE2 | ↓β-catenin, ↓cyclin D1, ↓c-Myc | [36] |
| | MDA-MB-231 cells transfected into the dorsal flank of female BALB/c nude mice (4–5 weeks old); two groups (vector group and TIPE2 group) | | ↓tumor growth | |
| | MCF-7 cells | ↓TIPE | ↑p21 | [14] |
| | MDA-MB-231 and LM2-4175 cells | ↓TIPE | ↑SNX1, ↑NR4A1, ↑AP2A1, ↓IL5 ↓SRC, ↓MAPT, ↓NEK2, ↓TRAF4, ↓PDCL, ↓GTF2F2, ↓GRAP2, ↓ABL1, ↓AKAP2, ↓GAP43, ↓PIK3CA, ↓EGFR, | [9] |
| | HS578T and MCF-7 cells | TIPE | - | [37] |
| Breast cancer | MDA-MB-435 cells | ↓TIPE | ↓VEGFR-2, ↓MMP-1, ↓MMP-9 | [38] |
| | MDA-MB 435 cells transfected via tail vein into female BALB/c mice (6–8 weeks old); eight animals in vector group and 12 animals in TIPE group | TIPE3 | ↑MMP2, ↑uPA, ↑AKT, ↑NF-κB | [32] |
| | MCF-7 and MDA-MB-231 | ↑TIPE | - | [39] |
| | MDA-MB-231 cells | | | |
| Cervical cancer | Tissue samples | ↑TIPE | platinum resistance | [40] |
| Colon cancer | CACO2 and HCT116 cells | ↑TIPE | ↑cyclin D1, ↑phospho-Rb | [41] |
| | HT-29 cells | ↓TIPE3 | ↓PI3K-Akt | [31] |
| | HCT116 cells | ↓TIPE | ↑p21 | [14] |
| | HCT116 cells | TIPE | - | [42] |
| Endometrial cancer | Tumor specimens | ↑TIPE | ↑Ki-67, ↑MMP-9 | [43] |
| ESCC | TE-1, TE-8, and TE-15 cells | ↑TIPE | - | [44] |
| | Eca109 cells | ↓TIPE | ↑apoptosis | [6] |
| Gastric cancer | AGS and HGC-27 cells | ↑TIPE2 | ↓Akt, ↓ERK1/2 | [45] |
| | AGS cells xenografted female BALB/c nude mice (4-week-old); Five mice in each group | | | |
| | AGS, HGC-27, and SGC-7901 cells | ↑TIPE2 | ↓Akt, ↑GSK3β | [46] |
| | BGC823 cells | ↓TIPE | caspase-3, -8, -9 | [47] |
| | BGC823 cells injected athymic nude mice; four groups containing six animals in each group | ↓TIPE | ↓tumor growth | |
| | Tissue samples | ↑TIPE | ↑metastasis, ↓prognosis | [48] |
| AGS, BGC-823, and SGC-7901 cells | TIPE1 | ↓Wnt/β-catenin, ↓MMP-2, ↓MMP-9 | [49] | |
| BGC-823 cells injected through tail vein into male nude mice (5–6 weeks old), four groups (including control group) | | | | |

Table 1. Cont.

| Disease | Model | Protein Involved | Targets Associated/Outcome | References |
|--|---|--------------------------------|---|------------|
| | MKN-28, SGC-7901, and MGC-803 cells | ↑TIPE | - | [50] |
| | Tissue samples | ↑TIPE | - | [51] |
| | AGS and HGC-27 cells | ↑TIPE2 | reversal of EMT | [52] |
| Glioma | U87, U251, and U373 MG cells | ↑TIPE2 | ↓Wnt/ β -catenin, ↓EMT | [53] |
| HCC | Bel7402, SK-Hep-1, HepG2, SMMC7721 and Huh7 cells | ↑TIPE | ↓YAP phosphorylation | [7] |
| | Bel7402, SMMC7721, QSG770, HepG2, and HepG2.2.1 cells | TIPE1 | ↓Rac1 | [16] |
| | Subcutaneously transplanted H22 cells into male BALB/c mice (6–8 weeks old); two groups (including control group) containing at least five mice in each cohort HepG2 cells | TIPE2 | ↓tumor growth and weight ↓Erk1/2-NF- κ B | [27] |
| Lung cancer | H292 and A549 cells | ↑TIPE1 | ↓cyclin D1, cyclin B1, ↓caspase3, ↓caspase 8, ↓MMP-2, ↓MMP-9 | [15] |
| | A549 cells engrafted into the flank of female BALB/c nude mice; two groups (control group and TIPE1 group) containing five mice in each group | ↑TIPE1 | ↓tumor growth | |
| | H460 and H1299 cells | ↑TIPE | ↓phosphorylated LATS1 | [54] |
| | A549 cells | ↓TIPE | ↑p21 | [14] |
| | H1299 cells | TIPE | - | [42] |
| | Tissue samples | ↑TIPE | - | [55] |
| | H1975 and A549 cells | ↑TIPE2 | ↓Rac1, ↓VEGF | [56] |
| | Tissue samples | ↑TIPE | - | [57] |
| | H1975 and A549 cells | ↑TIPE3 | ↑Akt, ↑ERK | [30] |
| | A549 cells transfected into flanks of male BALB/c nude mice (4–6 weeks old), two groups (mock and C-3 flag TIPE3) containing five mice in each group NCI-H727 cells | ↑TIPE3 | ↑tumor growth - | [31] |
| Tissue samples NCI-H460 and A549 cells | | - | | |
| A549 cells injected into flanks of female BALB/c nude mice (4–6 weeks old); two groups (Control and TIPE group) containing 10 mice in each group | ↓TIPE | ↓MDM2, ↓RAD51 ↓tumor volume | [58] | |
| Melanoma | MDA-MB-435 cells | ↓TIPE | ↑NR4A1, ↑AP2A1, ↓TOP2A, ↓EGFR ↓PDCL, ↓GTF2F2, ↓IL5, ↓GRAP2, ↓AKAP2, ↓GAP43, ↓ABL1 | [9] |
| NHL | Tissue samples | ↑TIPE2 | ↑prognosis | [59] |
| | 514 NHL patients and 557 cancer-free controls | TIPE | TIPE polymorphism rs1045241C > T | [60] |
| Osteosarcoma | 143b, LM7, HOS, SaOS-2, U2OS and MG-63 cells | ↑TIPE | Modulation of miR-138 | [61] |
| | KHOS, 143b, LM7, U2OS and MG-63 cells | ↑TIPE | Modulation of miR-99a | [62] |
| | U2OS cells | ↓TIPE | ↑p21 | [14] |

Table 1. Cont.

| Disease | Model | Protein Involved | Targets Associated/Outcome | References |
|------------------------------|--|------------------|---|------------|
| Ovarian cancer | Tissue samples | ↑TIPE | ↓survival | [63] |
| | OVCAR-3 cells | ↓TIPE | G0/G1 cell cycle arrest, ↑beclin 1, ↑LC II | [64] |
| | Tissue samples | ↑TIPE | - | [65] |
| Pancreatic cancer | Tissue samples | ↑TIPE | ↑EGFR | [66] |
| Prostate cancer | PC-3 cells | ↓TIPE | ↑IGFBP3, ↑NR4A1, ↑AP2A1, ↓IL5, ↓MAPT, ↓TOP2A, ↓TRAF4, ↓EGFR, ↓PDCL, ↓GTF2F2, ↓GRAP2, ↓ABL1, ↓GAP43, ↓AKAP2, ↓GRIP1 | [9] |
| | PC-3 cells | ↑TIPE2 | ↓PI3K/Akt signaling | [67] |
| | PC-3 cells | ↑TIPE | ↑MMPs, ↑VEGFR-2 | [68] |
| | PC-3 cells | TIPE | ↑autophagy | [69] |
| Renal cancer | RCC-RS cells | ↑TIPE | - | [39] |
| Thyroid cancer | Tissue samples | ↑TIPE | - | [70] |
| Inflammatory diseases | | | | |
| Atherosclerosis | <i>Ldlr</i> ^{-/-} female mice; two groups (wild type and TIPE2 ^{-/-}) containing eight mice in each group | ↓TIPE2 | ↑JNK, ↑NF-κB, ↑p38 | [71] |
| | VSMCs | ↓TIPE2 | ↓contractile proteins, ↑synthetic capacity for growth factors and cytokines | [72] |
| Colitis | DSS induced male C57BL/6 mice (8-12 weeks old); two groups (wild type and TIPE2 ^{-/-}) | ↓TIPE2 | ↓TNF-α, ↓IL-6, ↓IL-12 | [73] |
| | Colonic epithelial cells | ↓TIPE | ↑cell death | [74] |
| | DSS-induced mice (8–10 weeks old); two groups (wild type and TIPE2 ^{-/-}) | ↓TIPE | ↓survival rate, ↑body weight loss, ↑leukocyte infiltration, ↑bacterial invasion, ↑inflammatory cytokine production in the colon | |
| Rheumatoid arthritis | AA-FLSs | ↑TIPE2 | ↑DR5, ↑caspase, ↓NF-κB | [75] |
| | Synovial fibroblasts | ↑TIPE2 | ↓Rac signaling | [76] |
| Infectious diseases | | | | |
| AIH | PBMCs | ↓TIPE2 | ↑ALT, ↑AST | [77] |
| Hepatitis B | PBMCs | ↓TIPE2 | ↑perforin, ↑granzyme B, ↑IFN-γ | [78] |
| | PBMCs | ↓TIPE2 | ↑ALT, ↑AST, ↑total bilirubin | [79] |
| | Male C57BL/6 mice (10–12 weeks old); two groups (wild type and TIPE2 ^{-/-}) | ↓TIPE2 | ↑HBV load ↑hepatic inflammation | |
| Hepatitis B liver failure | PBMCs | ↑TIPE2 | ↓TNF-α, ↓IL-6 | [80] |
| Hepatitis B | PBMCs | ↑TIPE2 | ↓IL-6, ↓TNF-α, ↓IFN-γ | [81] |

Table 1. Cont.

| Disease | Model | Protein Involved | Targets Associated/Outcome | References |
|---|---|------------------|--|------------|
| Hepatitis-C induced hepatic inflammation | PBMCs | ↓TIPE2 | ↑TLR signaling | [82] |
| Listeria infection | HEPA1-6 cells | ↓TIPE | ↑apoptosis, deregulated Rac1-GTP | [83] |
| Liver fibrosis | HSC-T6 cells | ↑TIPE2 | ↓β-Catenin, ↓cmyc, ↓cyclin D1 | [84] |
| Neuromuscular and neurodegenerative diseases | | | | |
| Myasthenia Gravis | PBMCs | ↓TIPE2 | ↑IL-6, ↑IL-17, ↑IL-21 | [85] |
| Parkinson's disease | Dopaminergic neurons | ↑TIPE1 | ↑autophagy, ↓mTOR phosphorylation | [86] |
| Other diseases | | | | |
| CNV | RPE cells | ↓TIPE2 | ↑TNF-α, ↑IL-1β, ↑VEGF | [87] |
| Diabetes Mellitus | PBMCs | ↑TIPE2 | ↓TNF-α, ↓IL-6 | [88] |
| Diabetic nephropathy | Mesangial cells | ↑TIPE | modulation of NADPH oxidase-mediated signaling pathway | [89] |
| | Male Sprague-Dawley diabetic rats | ↑TIPE | | |
| Restenosis | VSMCs | ↓TIPE2 | ↑cyclin D1, ↑cyclin D3 ↑severity of disease | [90] |
| | Male C57BL/6J mice (8–12 weeks old); two groups (wild type and TIPE2 ^{-/-}) | ↓TIPE2 | | |

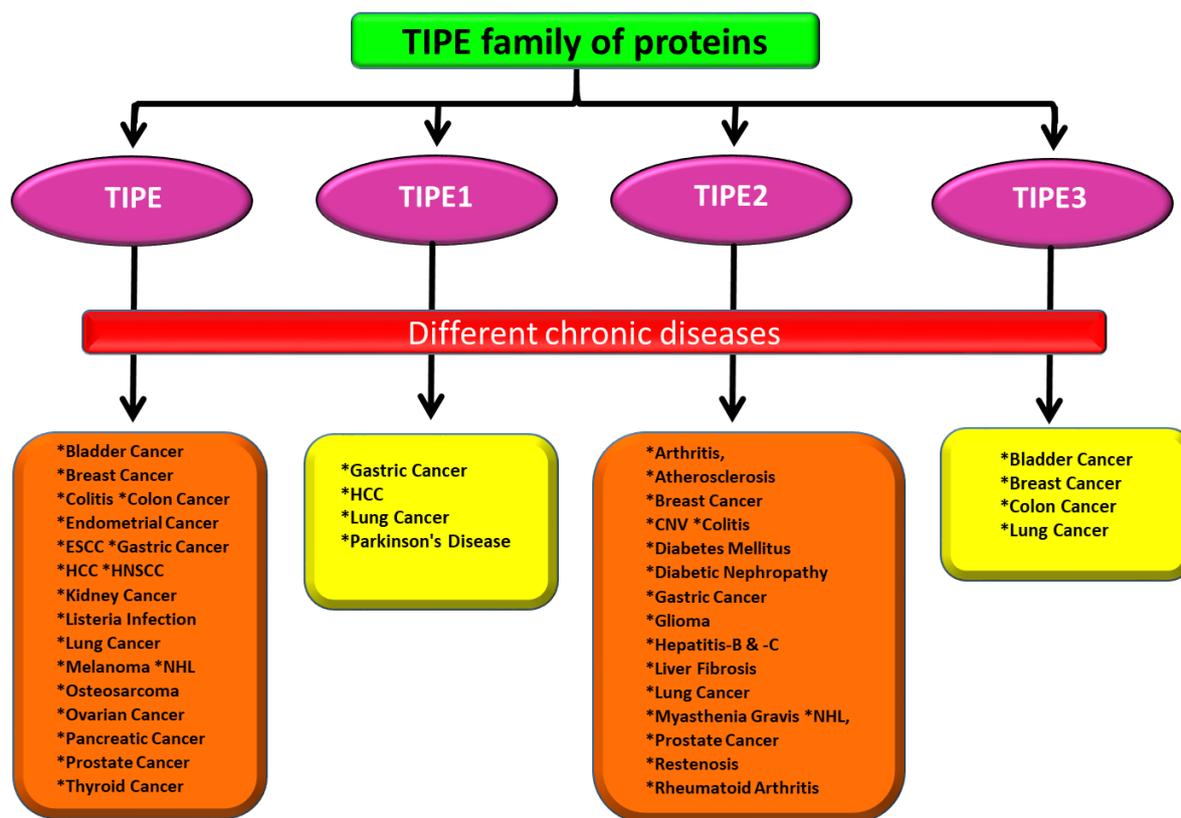


Figure 1. Various chronic diseases associated with TIPE family of proteins.

This review summarizes the role of this TIPE family of proteins in different chronic diseases, their molecular targets and associated signaling cascades in different chronic diseases based on existing literature.

2. Role of TIPE Family of Proteins in Different Chronic Diseases

2.1. TIPE Family of Proteins and Cancers

Cancer, which stems from the perturbations of multiple signaling pathways, affects people of all ages and is a major health concern worldwide [5,91,92]. The TIPE family of proteins plays a vital role in carcinogenesis and metastasis through its deregulated expression and function. It has been found to be strongly associated with cancers of breast, bone, brain, cervix, colon, esophagus, endometrium, liver, lung, stomach, and thyroid. Overall, the potential crosstalk of the four different TIPE proteins with various signal transduction cascades in different cancers has been reviewed by our group [5] previously.

2.2. TIPE Family of Proteins and Inflammatory Diseases

TIPE and TIPE2, the regulators of immunity, have been demonstrated to protect against inflammatory diseases such as atherosclerosis, colitis, and rheumatoid arthritis.

2.2.1. Atherosclerosis

Atherosclerosis is widely known as an inflammatory disease of the arterial wall in which macrophages play an important role. Notably, TIPE2 exhibits a high expression level in resting macrophages and has been found to exhibit a potent atheroprotective role by regulating macrophage responses to oxidized low-density lipoprotein (ox-LDL). When macrophages lacking TIPE2 were treated with ox-LDL, it resulted in enhanced production of oxidative stress and pro-inflammatory cytokines, as well as activation of NF- κ B, JNK, and p38 signaling cascades. These results clearly implied

TIPE2, a new-found inhibitor of atherosclerosis, to be an effective target against this disease [71]. Further, TIPE2 displayed its atheroprotective role through modulation of phenotypic switching of vascular smooth muscle cells (VSMCs), which plays a vital role in the development of atherosclerosis in response to ox-LDL stimuli. Ox-LDL treated TIPE2-deficient VSMCs were found to have lower expression of contractile proteins such as smooth muscle-myosin heavy chain (SM-MHC), smooth muscle α -actin (Sm α A), and calponin, while proliferation, migration, and the synthetic ability for cytokines and growth factors were found to increase significantly [72] (Figure 2A). Thus, these findings clearly imply that TIPE2 is an atheroprotective protein that may serve as a potent drug candidate for protection against this inflammatory disease.

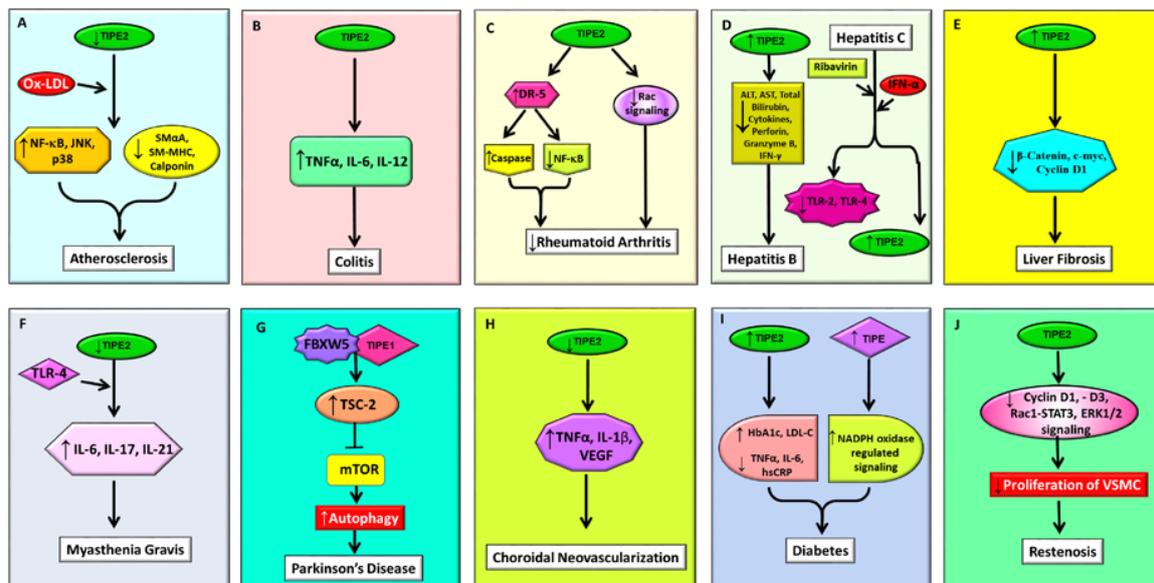


Figure 2. Role of TIPE family of proteins and their molecular mechanisms in different chronic diseases; (A). Atherosclerosis, (B). Colitis, (C). Rheumatoid Arthritis, (D). Hepatitis B and C, (E). Liver Fibrosis, (F). Myasthenia Gravis, (G). Parkinson's Disease, (H). Choroidal Neovascularization, (I). Diabetes, (J). Restenosis

2.2.2. Colitis

TIPE2 plays a vital role in inflammatory cell function and commensal bacteria dissemination regulation in dextran sodium sulfate (DSS)-induced colitis. Lou and group observed that mice with TIPE2 deficiency in the hematopoietic compartment survived longer compared to the wild types upon treatment with DSS. Further, it was observed that the degree of severity of colitis, as well as colonic damage in TIPE2-deficient mice, was notably less and was plausibly attributed to the decreased colonic expression of inflammatory cytokines TNF- α , interleukin (IL)-6, and IL-12. In addition, it was observed that TIPE2-deficient mice with ameliorated DSS-induced colitis also displayed a weaker systemic inflammatory response together with reduced local dissemination of commensal bacteria [73]. Another study investigated the role of TIPE in DSS-induced colitis in which TIPE-deficient mice were reported to be more prone to DSS-induced colitis, and that lack of expression of TIPE in non-hematopoietic cells was found to play a vital role. In TIPE knockout mice, a great reduction in body weight, the occurrence of severe diarrhea, rectal bleeding, and increased mortality was observed, exemplifying the role of TIPE in protection against DSS-induced colitis [74] (Figure 2B). Altogether, these two findings indicate that both TIPE and TIPE2 play important roles in the maintenance of colon homeostasis and the prevention and treatment of colitis. However, further in-depth studies are required to clearly understand the exact molecular mechanism(s) of actions of these proteins against colitis.

2.2.3. Rheumatoid Arthritis

Rheumatoid arthritis is a chronic inflammatory illness characterized by joint tenderness, joint swelling, and synovial joint destruction, resulting in severe disability and premature mortality [93]. Fibroblast-like synoviocytes (FLSs) play an important role in the pathology of rheumatoid arthritis. The study conducted by Shi and group indicated that TIPE2 increased adjuvant arthritis (AA)-FLSs apoptosis through enhanced DR5 expression levels, thus inhibiting NF- κ B activation and promoting the activation of caspase in AA-FLSs. [75]. Further, TIPE2 was found to regulate lipopolysaccharide-induced rat rheumatoid arthritis immune responses via activation of Rac and phosphorylation of interferon regulatory factor 3. This study depicted TIPE2 to be inversely associated with cytokine gene expression in synovial fibroblasts after lipopolysaccharide stimulation. Thus, TIPE2 plays a negative role in the activation of the Rac signaling pathway, as well as initiation of the immune response via reduced function of pro-inflammatory cytokines [76] (Figure 2C). Thus, using this novel target, TIPE2, therapeutic strategies against rheumatoid arthritis can be designed and used for protection against this disease.

2.3. TIPE Family of Proteins and Infectious Diseases

Various studies were performed to evaluate the association of the TIPE family of proteins and different infectious diseases such as hepatitis B, hepatitis C, listeria infection, and liver fibrosis.

2.3.1. Hepatitis B

Hepatitis B virus (HBV)-induced hepatic inflammation affects a vast majority of people across the world and is also recognized as a prime cause of hepatic cancer. It has been reported that TIPE2, a regulator of immune receptor signaling, can control HBV-induced hepatitis. Xi and colleagues reported that patients with chronic hepatitis B exhibited remarkably decreased TIPE2 expression in their peripheral blood mononuclear cells (PBMCs) compared to healthy individuals. Further, the expression of TIPE2 negatively correlated with the blood levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and the HBV load of the patients, suggesting that TIPE2 is an important marker in HBV-induced hepatic inflammation [79]. In addition, the expression of TIPE2 was found to be relatively higher in acute-on-chronic hepatitis B liver failure (ACHBLF) patients compared to healthy controls, which positively correlated with total serum bilirubin, international normalized ratio, and the model for end-stage liver disease scores. Additionally, the TIPE2 mRNA level was significantly higher in non-survivors compared to survivors in patients with ACHBLF, and the TIPE2 mRNA level was found to be reduced progressively in survivors together with signs of recovery from patients with ACHBLF. Further, lipopolysaccharide stimulation in ACHBLF patients resulted in reduced levels of IL-6, as well as TNF- α , which displayed a negative association with TIPE2 [80]. Another study investigated the expression of TIPE2 in mice PBMCs with autoimmune hepatitis (AIH) and its involvement in the pathogenesis of AIH. The results showed that TIPE2 was expressed less in AIH mice, whereas in the case of concanavalin A-induced AIH, TIPE2-deficient mice exhibited enhanced levels of serum ALT, AST, pro-inflammatory cytokines, and severe hepatic inflammation [77]. Zhang and group reported that the TIPE2 protein level in PBMCs of hepatitis B patients was significantly less and negatively associated with the aminotransferases sera values. Notably, CD8⁺T cells, which express a low level of TIPE2, produced significantly high granzyme B, perforin, and interferon- γ , resulting in their enhanced cytolytic effect [78]. Further, in chronic hepatitis B (CHB) patients, TIPE2 mRNA level in immune clearance phases was notably more compared to the immune tolerance phase, indicating that TIPE2 might be involved in immune clearance of patients with CHB. In addition, TNF- α , interferon- γ , and HBV DNA load were also observed to be independently linked with the level of TIPE2 in CHB patients [81] (Figure 2D).

2.3.2. Hepatitis C

Approximately 80% of chronic hepatitis cases are caused due to infection with Hepatitis C virus (HCV). TIPE2 has been found to play an important role in chronic hepatitis C (CHC) infection. Kong et al. showed that in CHC patients, TIPE2 gets significantly downregulated, whereas TLR2 and TLR4 show upregulation when compared to healthy controls. Further, the mRNA expression level of TIPE2 was found to be negatively associated with serum ALT, AST, and HCV RNA levels, as well as TLR2 and TLR4 mRNA levels in CHC patients. In addition, treatment of HCV patients with ribavirin and interferon- α led to the upregulation of TIPE2 mRNA and downregulation of TLR2 and TLR4 mRNA level [82] (Figure 2D).

Taken together, TIPE2 possesses a strong correlation with the infection with hepatitis virus, and hence it can be used as a target to develop strategies for the management of hepatitis-infected patients.

2.3.3. Listeria Infection

TIPE was reported to regulate infection with *Listeria monocytogenes* by controlling pathogen invasion and host cell apoptosis in a Rac1 GTPase-dependent manner. Notably, TIPE-knockout mice were found to be resistant to lethal *Listeria monocytogenes* infection, and they exerted a decreased bacterial load in the liver and spleen. In addition, knockdown of TIPE in murine liver cells resulted in enhanced apoptosis, reduction in bacterial invasion into cells, and deregulated Rac1 activation [83]. These findings provide understanding towards the role of TIPE2 in the pathogenesis of listeria infection, and thus it can be used as a therapeutic target for listeriosis.

2.3.4. Liver Fibrosis

TIPE2 possesses a protective effect on liver fibrosis and hence may serve as a potent target against this disease. TIPE2 diminished liver fibrosis through reversal of activated hepatic stellate cells. Xu et al. demonstrated low expression of TIPE2 in CCl₄-treated murine primary HSCs and activated HSC-T6 cells. Overexpression of TIPE2 hindered the activation and proliferation of HSC-T6 cells, as well as the expression of c-myc, cyclin D1, and β -catenin, whereas its inhibition displayed the reverse effect [84] (Figure 2E). Thus, owing to its protective effect, TIPE2 displays potential as an effective target against liver fibrosis.

2.4. TIPE Family of Proteins in Neuromuscular and Neurodegenerative Diseases

TIPE2 and TIPE1 have been found to exert their effect in Myasthenia Gravis and Parkinson's disease, respectively, and thus can serve as important targets for therapies against these diseases.

2.4.1. Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune neuromuscular disease, the incidence of which is increasing. TIPE2 has been found to play a role in MG via modulation of autoimmune T helper 17 cell responses mediated by TLR4 [85]. The study showed downregulation of TIPE2 in MG compared to normal controls. Furthermore, TIPE2 exerted a negative association with the levels of IL-6, -17, and -21 in the serum of MG patients. In cultured MG PBMC, TLR4 activation caused downregulation of TIPE2, whereas ROR γ t expression and IL-6, -17, -21 production was enhanced. Nevertheless, overexpression of TIPE2 abrogated the TLR4 activation-induced effects [85] (Figure 2F). Collectively, this study provides evidence that targeting TIPE2, which functions as a negative regulator of immunity, may offer protection against this autoimmune disease.

2.4.2. Parkinson's Disease

Parkinson's disease is a long-term degenerative disorder that involves the central nervous system. Altered regulation of TIPE1 may contribute to deregulated autophagy seen in dopaminergic neurons under pathogenic oxidative stress, which is especially observed in post-mortem brains in Parkinson's

disease. This protein binds to FBXW5, a tuberous sclerosis complex 2 (TSC2; a negative regulator of mTOR) binding receptor present in CUL4 E3 ligase complex, resulting in enhanced autophagy via activation of TSC2 in a Parkinson's disease model. Further, oxidative, stress-induced TIPE1 caused stabilization of TSC2 protein, reduction in mTOR phosphorylation, and an increase in autophagy [86]. Another study conducted by Kouchaki and group attempted to evaluate the association between the serum levels and circulatory gene expression of TIPE2 with severity of Parkinson's disease by enrolling a total of 43 patients. The results implied that no significant differences were noted between the mean serum levels and TIPE2 expression in patients compared to the healthy individuals. They further showed that enhanced serum levels of TIPE2 possess a direct correlation with age and severity of patients with Parkinson's diseases. Besides, TIPE2 expression was also found to be strongly linked with the age of the patients [94] (Figure 2G).

2.5. The TIPE Family of Proteins and Other Chronic Diseases

Apart from the abovementioned, this newly discovered family of proteins is strongly involved in various other diseases such as choroidal neovascularization, restenosis, and metabolic disease-like diabetes.

2.5.1. Choroidal Neovascularization (CNV)

Choroidal neovascularization (CNV), a pathological condition commonly occurring in ocular diseases, is primarily characterized by vasculogenesis and angiogenesis of the neuroretina, with the retinal pigment epithelium (RPE) as a major target. TIPE2, a negative regulator of immunity, has been found to play a role in CNV, as inflammation and immunity are critical in the early development of CNV. Suo and group conducted a study that reported that TIPE2 is present in human RPE cells in the cytoplasm, as well as the nucleus, and was downregulated in the inflammatory condition, with a subsequent reduction in cell viability. Further, knock-down of TIPE2 resulted in the upregulation of TNF- α , IL-1 β , and VEGF, especially under lipopolysaccharide induced stimuli. As TIPE2 displays potent anti-angiogenic properties and VEGF plays a vital role in the final stage of neovascularization, TIPE2 might take part in CNV formation [87] (Figure 2H). However, comprehensive studies are vital to decipher the underlined molecular mechanisms through which TIPE2 function and help in the development of CNV.

2.5.2. Diabetes

Diabetes is a type of metabolic disease associated with high blood sugar levels. Although TIPE2 plays a key role in inflammatory homeostasis, its exact role in type 2 diabetes mellitus (T2DM) remains unknown. Liu and group reported that TIPE2 is involved in T2DM via modulation of TNF- α . They observed an increased level of TIPE2 in T2DM patients that was positively associated with hemoglobin A1c and low-density lipoprotein cholesterol, while it negatively correlated with serum TNF- α , IL-6, and hsCRP concentrations in the diabetic patients. Further, treatment with high glucose concentrations resulted in the upregulation of TIPE2 and cytokine secretion in differentiated THP-1 human monocyte cells. Additionally, TIPE2 adenovirus infection reversed the enhanced TNF- α level, whereas treatment with siTIPE2 aggravated the enhanced level of TNF- α and IL-6 in differentiated THP-1 cells under high glucose conditions [88]. Again, TIPE serves as a vital component of a signaling cascade linking mesangial cell proliferation and diabetic renal injury. The study conducted by Zhang and colleagues showed that in response to high glucose, TIPE was upregulated in mesangial cells, and the expression of TIPE was directly correlated with mesangial cell proliferation mediated via an NADPH oxidase-regulated signaling pathway [89] (Figure 2I).

The above studies illustrated the critical role of the two TIPE family of proteins, namely, TIPE and TIPE2 in diabetes and diabetic nephropathy. Hence, they may serve as effective targets against diabetes mellitus and may aid in the development of therapeutic strategies for the prevention and treatment of this metabolic disorder.

2.5.3. Restenosis

Restenosis is a disease characterized by smooth muscle cell hyperplasia and neointimal formation. Zhang and group reported that TIPE2 repressed injury-induced restenosis through inhibited proliferation of vascular smooth muscle cells (VSMCs) via modulation of ERK1/2 and Rac1-STAT3 signaling cascades. The study reported that enforced TIPE2 expression suppressed the proliferation and blocked cell cycle progression in VSMCs, while deficiency of TIPE2 induced proliferation of VSMCs and upregulation of cyclin D1 and cyclin D3 [90] (Figure 2J). Therefore, targeting TIPE2 might help in designing novel approaches against restenosis.

Altogether, this family is evinced to have profound role in different chronic diseases. Interestingly, the function of TIPE and TIPE2 in different chronic diseases and their mode of action have been studied extensively. However, focus needs to be given to unveil the role of TIPE in various chronic diseases other than cancer. In addition, much comprehensive studies are immensely critical to elucidate the roles of the other two members of this family of proteins such as TIPE1 and TIPE3 in the development of different chronic diseases and to unveil their underlined molecular mechanisms. This would help us not only to understand their exact functions, but also to develop novel therapeutic approaches for the prevention and treatment of diverse chronic diseases effectively.

3. Conclusions

The TIPE protein family presents a novel group of proteins discovered just a decade ago. Expression studies of these proteins show remarkable variability among themselves. Interestingly, although the proteins of this family were initially depicted as the modulators of tumorigenesis, inflammation, and cell death, they were also found to possess various other functions. For instance, TIPE and TIPE1 function as autophagy inhibitors and activators in experimental models of Parkinson's disease. Further, they are involved in the transfer of lipid secondary messengers PIP2 and PIP3. Members of the TIPE family have been associated with the regulation of immune function and homeostasis and the development of diverse cancer types. Most importantly, the members of this family share a significant sequence homology but are involved in different biological activities. For instance, TIPE1 exhibits a high degree of sequence homology with TIPE2. Despite the existence of a common fold, TIPE2 plays a vital role in immune homeostasis, whereas TIPE1 may not play an essential role in immunity. Despite the existing knowledge on this protein family in the literature, a lot more needs to be elucidated. Though this family of proteins plays an important role in carcinogenesis, metastasis, and development of different human chronic diseases either through up- or downregulation, its exact molecular functions, detailed mechanism of action, and the plausible crosstalk between its members remain ambiguous. Therefore, more comprehensive studies are imperative for better understanding of this important family of proteins, which would provide key insights for biomarker discovery and treatment strategies for a wide array of chronic diseases.

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Abbreviations

| | |
|-----------------|--|
| TIPE or TNFAIP8 | Tumor necrosis factor- α -induced protein 8 |
| TIPE1 | Tumor necrosis factor- α -induced protein 8-like 1 |
| TIPE2 | Tumor necrosis factor- α -induced protein 8-like 2 |
| TIPE3 | Tumor necrosis factor- α -induced protein 8-like 3 |
| TLR | Toll-like receptor |
| TNF- α | Tumor necrosis factor- α |
| FLIP | Fas-associated death domain-like interleukin-1 β -converting enzyme-inhibitory protein |
| mTOR | Mammalian target of rapamycin |
| NF- κ B | Nuclear factor κ -light-chain-enhancer of activated B cells |
| MAPK | Mitogen-activated protein kinase |
| MMP | Matrix metalloproteinase |
| VEGF | Vascular endothelial growth factor |
| DLBCL | Diffuse large B-cell lymphoma |
| EMT | Epithelial-to-mesenchymal transition |
| EC | Endometrial carcinoma |
| ESCC | Esophageal squamous cell carcinoma |
| ERK1/2 | Extracellular signal-regulated kinase 1/2 |
| HCC | Hepatocellular carcinoma |
| NHL | Non-Hodgkin's lymphoma |
| PTCL | Peripheral T-cell lymphoma |
| NSCLC | Non-small cell lung cancer |
| OS | Osteosarcoma |
| CNV | Choroidal neovascularization |
| T2DM | Type 2 diabetes mellitus |
| MG | Myasthenia gravis |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| AIH | Autoimmune hepatitis |
| AST | Aspartate aminotransferase |
| ALT | Alanine aminotransferase |
| PBMCs | Peripheral blood mononuclear cells |
| DSS | Dextran sodium sulfate |
| IL-6 | Interleukin-6 |
| Ox-LDL | Oxidized low-density lipoprotein |
| VSMCs | Vascular smooth muscle cells |
| SM-MHC | Smooth muscle-myosin heavy chain |
| Sm α A | Smooth muscle α -actin |
| FLSs | Fibroblast-like synoviocytes |
| AA | Adjuvant arthritis |
| RPE | Retinal pigment Epithelium |

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