Histol Histopathol (2018) 33: 919-928

http://www.hh.um.es

Histology and Histopathology

From Cell Biology to Tissue Engineering

Review

Understanding the roles of negative immune regulator TIPE2 in different diseases and tumourigenesis

Zequn Li[1]*, Wenyu Jia[2,3]*, Jun Niu[4] and Lining Zhang[5]

[1]Department of General Surgery, Affiliated Hospital of Qingdao University, Qingdao, [2]Department of Endocrinology, Shandong Provincial Hospital affiliated to Shandong University, Jinan, [3]Institute of Endocrinology and Metabolism, Shandong Academy of Clinical Medicine, [4]Department of General Surgery, Qilu Hospital of Shandong University and [5]Department of Immunology, School of Basic Medical Sciences, Shandong University, Jinan, Shandong Province, P.R. China

*The two authors contributed equally to this work

Summary. Tumour necrosis factor (TNF)-alpha-induced protein 8-like 2 (TIPE2 or TNFAIP8L2) is a novel identified negative regulator of both innate and adaptive immunity, which participates in immune homeostasis. TIPE2 is expressed in both immune tissues and non-immune tissues. It is significantly down-regulated in patients with infectious and autoimmune diseases, and the depletion of TIPE2 causes severe inflammatory disease. In recent years, accumulating evidence has shown that TIPE2 serves as an ideal biomarker and as a tumour suppressor in several tumour types. In this review, we summarized the roles and corresponding mechanisms of TIPE2 in immune regulation and different diseases, especially in tumourigenesis.

Key words: TIPE2, Expression profile, Immune regulator, Inflammatory diseases, Tumourigenesis

Introduction

Tumour necrosis factor (TNF)-α-induced protein 8 (TNFAIP8)-like 2 belongs to the TNFAIP8 family, a novel identified group of proteins that consist of TNFAIP8 (TIPE), TIPE1 (TNFAIP8L1), TIPE2 (TNFAIP8L2), and TIPE3 (TNFAIP8L3). TIPE2 was initially identified as an abnormally expressed gene in the inflamed spinal cord of experimental autoimmune encephalomyelitis (EAE) mice (Freundt et al., 2008; Sun et al., 2008). TIPE2 is significantly down-regulated in patients with infectious or autoimmune diseases and primarily functions as an essential negative immune regulator of vital importance in maintaining immune homeostasis (Li et al., 2009; Xi et al., 2011). A recent study reported that TIPE2 is also involved in the development of a variety of tumours (Cao et al., 2013; Zhang et al., 2013; Li et al., 2016b). According to the most recent studies, we summarized the basic information, expression conditions, functions and

Offprint requests to: Jun Niu, Department of General Surgery, Qilu Hospital of Shandong University, 107# Wenhua Xi Road, Jinan, Shandong Province, P.R. China 250012. e-mail: sduniujun@163.com or Lining Zhang, Department of Immunology, School of Basic Medical Sciences, Shandong University, 44# Wenhua Xi Road, Jinan, Shandong Province, P.R. China 250012. e-mail: zhanglining@sdu.edu.cn

DOI: 10.14670/HH-11-977

Abbreviations. TIPE2, Tumour necrosis factor (TNF)-α-induced protein 8 (TNFAIP8) like 2; EAE, experimental autoimmune encephalomyelitis; DED, death effector domain; TGF-β, transforming growth factor-β; IL-10, interleukin-10; TLR, Toll-like receptor; Foxp3, forkhead box P3; ROS, reactive oxygen species; LPS, lipopolysaccharide; TCR, T cell receptor; IFN-γ, interferon-γ; CTLA4, cytotoxic T-lymphocyte-associated protein 4; PBMCs, peripheral blood mononuclear cells; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Tbil, total bilirubin; ACHBLF, acute-on-chronic hepatitis B liver failure; ox-LDL, oxidized low-density lipoprotein; PRR, pattern-recognition receptor; I/R, ischemia/reperfusion; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; AA-FLSs, adjuvant arthritis-fibroblast-like synoviocytes; DR5, death receptor 5; MG, Myasthenia gravis; CR, chronic rejection; DSS, dextran sodium sulfate; HCC, hepatocellular carcinoma; MMP9, matrix metallopeptidase 9; uPA, urokinase plasminogen activator; NSCLC, non-small cell lung cancer; TAMs, tumour-associated macrophages; SCC, skin squamous carcinoma; EMT, epithelial-mesenchymal transition.

corresponding mechanisms of TIPE2 in this review.

The gene location and protein structure of TIPE2

By aligning the murine and human TIPE2 sequences with murine and human genome databases, the chromosome location of TIPE2 was determined. Murine TIPE2 was identified on chromosome III (3f1–3f3), while human TIPE2 was identified on chromosome I (1q21.2–1q21.3) (Sun et al., 2008).

TIPE2 is a cytoplasmic protein that consists of 184 amino acids. Human TIPE2 shared approximately 53% identity and 78% similarity amino acid sequence with TNFAIP8, and 94% homologous with murine TIPE2 (Sun et al., 2008). The high-resolution crystal structure of TIPE2 showed that TIPE2 consists of six antiparallel a-helices. The helix a5 contains a kink, caused by Pro153, which disassociates the two helices, a5a and a5b. TIPE2 has a structure similar to a death effector domain (DED), referred to as a DED-like domain. Interestingly, in the topology of TIPE2, the DED-like domain appears as a mirror image of the DED domain of caspase-8 or c-FLIP (Zhang et al., 2009). Strikingly, TIPE2 contains a large, hydrophobic central cavity, which is proposed as a binding site for cofactors. These structural features are important for understanding the functions of TIPE2.

The expression and localization of TIPE2 in different tissues and cells

The expression of TIPE2 in humans and murine animals is not precisely the same, and differs in different tissues (Table 1). Zhang et al. generated a specific antibody to TIPE2 and detected TIPE2 expression in various murine tissues and a number of human cell lines (Zhang et al., 2010). TIPE2 has been identified as a cytoplasmic protein. TIPE2 is mainly expressed in the T cell zone in the spleens of mice. In murine lymphoid tissues, TIPE2 protein was mainly observed in the paracortical areas and reticular cells in the medullary cords. TIPE2 expression was negative in B-lymphoid cells in the bone marrow and germinal centre B cells in the spleen and lymph node. Moderate TIPE2 protein expression can be detected in bone marrow polymorphonuclear cells. Moreover, high TIPE2 expression can also be detected in monocyte/macrophage-derived human cell line THP1 and mouse cell lines RAW264.7 or J774A.1. Furthermore, TIPE2 is preferentially expressed in glandular epithelium, such as renal proximal tubules, glucocorticoid-secreting cells of the adrenal medulla, islets of pancreas, and parietal cells of the stomach, suggesting that TIPE2 may be involved in endocrine functions. TIPE2 was initially identified as a gene abnormally expressed in the inflamed spinal cord of mice with experimental autoimmune encephalomyelitis (EAE) (Sun et al., 2008). Interestingly, TIPE2 expression was negative in neuronal cells of the central nervous system. The increased TIPE2 expression in inflamed neural tissue may result from leukocyte infiltration. In addition, TIPE2 could also be detected in somatic and germ cells of both female and male

Table 1. TIPE2 protein expression profiles in different tissues and organs.

Tissues and Organs	TIPE2 expression (C57BL/6 mice) Zhang et al., 2010	TIPE2 expression (Human) Zhang et al., 2011
Lymph node		
T cell zone	++	++
Germinal center	-	-
Thymus	-	N.A.
Spleen		N.A.
T cell zone	++	
Germinal center	-	
Bone marrow		N.A.
Megakaryocytes	+	
Erythroid cell	-	
Cerebellum	-	-
Hippocampus	-	N.A.
Heart	-	+
Cardiovascular muscle	-	+
Skeletal muscle	+++	+
Smooth muscle	-	N.A.
Skin	-	+
Trachea	-	+
Lung	-	-
Esophagus	-	+++
Stomach		
Epithelium	-	-
Parietal cell	+	++
Chief cell	-	++
Small intestine		-
Enterocyte	±	
Crypt cell	-	
Granulocyte	++++	
Colon	N.A.	+++
Rectum	N.A.	-
Appendix	N.A.	+++
Liver	-	+
Pancreas		-
Exocrine portion	-	
Pancreatic islet	++	
Kidney		-
Glomerulus	++	
Proximal convoluted tubule	++	
Distal convoluted tubule	-	
Thyroid gland	±	-
Mammary gland	-	N.A.
Adrenal gland		N.A.
Cortex	-	
Medulla	+	
Ovary		N.A.
Primaryoocyte	+	
Follicular cell	++	
Granulose lutein cell	++	
Testis		++
Spermatogonium	-	
Spermatozoon	±	
Leydig cell	++	
Sertoli cell	-	
Epididymis	-	
Prostate	-	-
Bladder	N.A.	++
Uterus	-	++

reproductive organs (Zhang et al., 2010).

To determine the expression profile of human TIPE2, Zhang et al. generated a specific anti-human TIPE2 antibody and examined TIPE2 expression in various human tissues (Zhang et al., 2011). TIPE2 was expressed not only in monocytes and T cells but also in B cells, which are different from those in murine animals, as murine TIPE2 was not expressed in B cells. As to the non-immune tissues and cells, TIPE2 was preferentially expressed in stratified squamous epithelium, including stratum basal, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum, but not in simple epithelium, such as simple lung squamous epithelium, simple small intestine columnar mucous cells, and renal tubule cuboidal epithelium. Moreover, in the human oesophagus and cervix-stratified squamous epithelial tissues, TIPE2 was differentially expressed in the outer cells rather than in the inner cells. Consistent with that in murine animals, human TIPE2 was also selectively expressed in glandular epithelial tissues and certain types of cells that have secretory activity, suggesting the relationship of this protein with secretory functions. Unlike the expression conditions in murine animals, human TIPE2 was expressed in the neurons of the brain and brainstem. Additionally, TIPE2 was also expressed in liver hepatocytes and trachea chondrocytes (Zhang et al., 2010, 2011).

TIPE2 expression was low or negative in most human carcinoma cell lines but is highly expressed in monocyte/macrophage derived-cell lines, and SK-OV-3 originated from ovarian adenocarcinoma. We also found that TIPE2 was highly expressed in human endometrial carcinoma cell lines, Ishikawa and HEC-1A (Our unpublished data). In addition, TIPE2 could also be detected in Treg cells, which plays an important role in regulating the functions of Treg cells (Luan et al., 2011). Collectively, the expression profile of human TIPE2 and murine TIPE2 is different. TIPE2 protein was expressed in both immune and non-immune tissues, indicating that TIPE2 may have functions other than immune regulation.

Role of TIPE2 in immune regulation

The human defence against a number of pathogens primarily depends on the normal functions of the immune system, while immune homeostasis is important to maintain normal immunoreactions. The detailed mechanisms through which immune homeostasis is maintained are not fully understood. Recent studies have indicated the requirement of at least two classes of molecules (Sun et al., 2008). The first class of molecules mainly includes inhibitory cytokines, such as transforming growth factor-β (TGF-β) and interleukin-10 (IL-10), negative regulators of the antigen receptor and Toll-like receptor (TLR) signalling, such as CTLA-4, inhibitor-of-kB and Socs1, and repressive transcription factors, such as forkhead box P3 (Foxp3). These molecules could limit the activation and expansion of immune cells (Van Parijs and Abbas, 1998; Wahl et al., 2006). The second class of molecules includes Fas, Bim, Bax, caspase-8 and caspase-10, which are responsible for controlling cell death (Suda et al., 1995; Van Parijs and Abbas, 1998; Van Parijs et al., 1998). There are still a large number of genes have not yet been characterized. TIPE2 is a novel characterized negative immune regulator required for maintaining immune homeostasis (Sun et al., 2008).

TIPE2 is involved in regulating innate immunity

Phagocytosis and oxidative burst are two fundamental effector mechanisms of innate immunity (Diebold and Bokoch, 2005; Niedergang and Chavrier, 2005; Mao and Finnemann, 2015). Phagocytosis enables the monocytes and granulocytes of the immune system to engulf and contain infectious microbes in phagosomes. Oxidative burst subsequently results in the release of vacuole reactive oxygen species (ROS) that kill the microbes. Deficiencies in either of these innate immune mechanisms lead to immune deficiency and uncontrolled infections (Roberts et al., 1999; Ambruso et al., 2000; Heyworth et al., 2003; Assari, 2006).

TLR activates both phagocytosis and oxidative burst, and plays an important role in the pathogen recognition and innate immune responses. Sun et al. found that upon stimulation with lipopolysaccharide (LPS), macrophages derived from TIPE2$^{-/-}$ bone marrow produced significantly more IL-6 and IL-12 than wild-type cells. TIPE2 knockdown in RAW 264.7 macrophages significantly increased the expression of IL-6 at both mRNA and protein levels. Moreover, TIPE2 may regulate innate but not adaptive B cell responses, as TIPE2$^{-/-}$ splenic B cells significantly expressed more IL-1β and TNF-α than wild-type B cells upon stimulation with LPS or CpG (cytosine guanine nucleotides), while the proliferation, apoptosis, and Ig secretion of B cells treated with anti-IgM were not significantly different between wild type and TIPE2$^{-/-}$ groups. Wang et al. found that upon stimulation with the TLR4 ligand, TLR3 agonist, and TLR2 ligand, significantly increased the expression of IL-6, TNF-α and IFN-β1, while TIPE2 expression was significantly diminished (Sun et al., 2012).

Both phagocytosis and oxidative burst are controlled by the Rac proteins of the Ras small GTPase superfamily (Roberts et al., 1999; Ambruso et al., 2000; Diebold and Bokoch; 2005; Niedergang and Chavrier, 2005). Rac GTPases control phagocytosis by promoting actin polymerization, and these enzymes also mediate ROS production by binding and activating the NADPH oxidase complex (Diebold and Bokoch, 2005). RacGTPase deficiency in mice and humans leads to an immune-deficient syndrome characterized by defective phagocytosis and oxidative burst (Roberts et al., 1999; Ambruso et al., 2000; Heyworth et al., 2003; Assari, 2006). Wang et al. reported that TIPE2 binds to Rac

GTPases through a C-terminal CAAX motif, resulting in the inhibition of Rac membrane translocation, Rac activation and the downstream effects of Rac signalling (Such as the JNK and the PAK pathways). TIPE2-Rac interactions result in the inhibition of basal level phagocytosis, which also contributes to TLR-induced augmentation of phagocytosis. Similarly, TIPE2 also inhibits oxidative burst via binding with Rac, which subsequently leads to the TLR-induced augmentation of bactericidal activity (Sun et al., 2012; Wang et al., 2012).

The effects of TIPE2 on adaptive immunity

Sun et al. found that TIPE2$^{-/-}$ could augment both CD4+ and CD8+ T cell immune responses. T cells derived from TIPE2$^{-/-}$ mice were hyper-reactive to T cell receptor (TCR) ligation and the production of Th17 cytokines, and Th1 cytokines (IFN-γ) and Th2 cytokines (IL-4) were also significantly increased. The expression of CD25, CD44 and CD69 was also significantly increased in TIPE2$^{-/-}$ T cells. In addition, TIPE2 overexpression in haematopoietic cells markedly reduced the expression of CD69 and IFN-γ after stimulation with antigens. This evidence indicates that TIPE2 suppresses TCR-mediated T cell activation.

Further investigation revealed that TIPE2 is a negative regulator of NF-κB, JNK and p38 pathways. Caspase-8 is an apoptosis initiator that plays important roles in lymphocyte and myeloid cell activation and inducing apoptosis. Caspase-8-deficient immune cells are defective in response to both TLR and antigen receptor stimulations (Chun et al., 2002; Salmena and Hakem, 2005; Su et al., 2005; Tang et al., 2005; Bidere et al., 2006; Lemmers et al., 2007). TIPE2 regulates the NF-κB pathway by binding to caspase-8. However, the effect of TIPE2 on MAPK might be independent of caspase-8. Moreover, TIPE2 is involved in the regulation of Fas-mediated apoptosis and activation-induced cell death of T cells. By regulating the expression of cytotoxic T-lymphocyte-associated protein 4 (CTLA4), Foxp3, TGF-β and IL-10, TIPE2 can maintain the immunosuppressive properties of CD4+CD25+ regulatory T cells (Luan et al., 2011). In addition, TIPE2 inhibits inducible nitric oxide synthase and nitric oxide generation, which consequently suppresses inflammation by switching arginine metabolism from nitric oxide synthase to arginase (Lou et al., 2014).

Roles of TIPE2 in different diseases

TIPE2 was initially identified as an abnormally expressed gene in the inflamed spinal cord of EAE mice. Since then, a number of studies have been focused on the roles of TIPE2 in different diseases. Accumulating evidence has shown that immunological factors are the key points for numerous diseases, indicating that the functions of TIPE2 are ubiquitous. Table 2 summarizes the recent advances on the expression conditions and roles of TIPE2 in different diseases.

TIPE2 in infectious diseases

TIPE2 has been demonstrated as a key molecule in regulating both innate and adaptive immunity, which determined its role in infectious diseases. Sun et al. reported that TIPE2-deficient mice are hypersensitive to septic shock, and consistently undergo fatal inflammatory diseases (Sun et al., 2008). By using a mouse sepsis model, Liu et al found that down-regulated TIPE2 expression was associated with decreased apoptosis and increased Th1 cytokines, which enhances the immune capacity of the host against sepsis (Liu et al., 2015a).

A number of studies have focused on the effect of TIPE2 in hepatitis. TIPE2 expression was down-regulated in the peripheral blood mononuclear cells (PBMCs) of hepatitis B patients, and TIPE2 expression was negatively correlated with the blood levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (Tbil) as well as the HBV load of the patients. TIPE2-deficient mice developed more severe hepatic inflammation than wild-type mice. Moreover, TIPE2 down-regulation preferentially occurred in cytotoxic CD8+ T cells, with increased expression of perforin, granzyme B and IFN-γ, indicating that TIPE2 is involved in regulating the functions of HBV-specific CD8+T lymphocytes (Xi et al., 2011, Wang et al., 2015).

TIPE2 was demonstrated as a biomarker in predicting the prognosis of patients with hepatitis B infections. Wang et al. reported that TIPE2 might be involved in the pathogenesis of acute-on-chronic hepatitis B liver failure (ACHBLF) by negatively regulating immune responses, as TIPE2 mRNA expression was higher in patients with ACHBLF, and TIPE2 expression serves as a potential indicator for the prognosis of patients with ACHBLF (Wang et al., 2014). By a prospective single-centre study, Fan et al demonstrated that TIPE2 mRNA level in PBMCs serves as a novel biomarker in predicting 3-month mortality of ACHBLF (Fan et al., 2015). In addition, TIPE2 expression was significantly decreased in the PBMCs of chronic hepatitis C patients. TIPE2 was also negatively correlated with serum ALT, AST and HCV RNA levels. Moreover, the expression of TIPE2 increased after anti-virus treatment, suggesting that TIPE2 is also involved in hepatitis C infection, and its expression may serve as a marker of the viral load (Kong et al., 2013).

TIPE2 in cardiovascular disease

Atherosclerosis is a key aetiology of several cardiovascular diseases, and this condition has been widely recognized as an inflammatory disease of the arterial wall. As an anti-inflammatory protein, TIPE2 is also involved in the development of atherosclerosis. Macrophages are considered essential for the development of atherosclerosis. Lou et al. found that macrophages from TIPE2$^{-/-}$ mice produced more

oxidative stress and pro-inflammatory cytokines after treatment with oxidized low-density lipoprotein (ox-LDL), which resulted in exacerbated atherosclerosis development, indicating that TIPE2 expression in macrophages may play an atheroprotective role by negatively regulating ox-LDL-induced inflammatory responses (Lou et al., 2013).

Yi et al found that genetic ablation of TIPE2 significantly increased the cerebral volume of infarction and neurological dysfunction in mice after cerebral ischaemia reperfusion induced by middle cerebral artery occlusion, suggesting that TIPE2 is involved in the signal transduction pathway linking the inflammatory immune response to specific conditions after cerebral ischaemia (Zhang et al., 2012). TIPE2 also acts as a negative regulator linking NOD2, an intracellular pattern-recognition receptor (PRR), and inflammatory responses. The TIPE2-NOD2 interaction plays an important role in the pathogenesis of myocardial ischaemia/reperfusion (I/R) injury (Zhang et al., 2015a). These studies suggest that TIPE2 is an important regulator in the progression of cardiovascular diseases.

TIPE2 in autoimmune diseases

As an essential negative regulator of inflammation and immune homeostasis, TIPE2 is involved in a variety of immune related diseases. Both TIPE2 mRNA and protein expression were decreased in asthmatic children. The levels of IgE, EO and IL-4 in the children with asthma were obviously higher than those in normal controls. While the expression level of TIPE2 mRNA was negatively correlated with IgE, EO and IL-4 (Ma et al., 2013). TIPE2 mRNA expression in the PBMCs of systemic lupus erythaematosus (SLE) patients was also significantly decreased, and the TIPE2 mRNA expression level was negatively correlated with the SLE disease activity index (SLEDAI). Moreover, TIPE2 alleviates experimental SLE by inducing macrophage polarization to a M2 phenotype (Li et al., 2009, 2016a). TIPE2 may also be involved in the pathogenesis of rheumatoid arthritis, as TIPE2 increased the apoptosis of adjuvant arthritis-fibroblast-like synoviocytes (AA-FLSs) by enhancing death receptor 5 (DR5) expression levels, which subsequently promoted the activation of

Table 2. Expression, functions and related mechanisms of TIPE2 in different diseases.

Disease	Source	TIPE2 expression	Experimental data	Mechanisms	References
Hepatitis B	PBMCs (Human)	Decreased	TIPE2 expression is negatively correlated with hepatic enzymes and HBV load	Regulating the functions of CD8+T lymphocytes	Xi et al., 2011; Wang et al., 2015
ACHBLF	PBMCs (Human)	Decreased	TIPE2 is a prognostic biomarker	Negatively regulates immune reactions such as IL-6 and TNF-α expression	Wang et al., 2014; Fan et al., 2015
Hepatitis C	PBMCs (Human)	Decreased	TIPE2 expression is negatively correlated with ALT, AST and HCV RNA levels	N.A.	Kong et al., 2013
Atherosclerosis	Macrophages (Mice)	High	Inhibits the development of atherosclerosis	Inhibits oxidative stress and expression of inflammatory cytokines, regulates the functions of macrophage	Lou et al., 2013
Stroke	Brain (Mice)	Deficiency	TIPE2 deficiency exacerbates stroke outcomes	TIPE2 deficiency increases inflammatory cytokine expression and alters cerebral inflammatory cell infiltration	Zhang et al., 2012
I/R injury	N.A.	N.A.	TIPE2 is negatively mediated by NOD2, and TIPE2 silencing counteracted the reduced inflammation and myocardial injury in ischemic mice	Inhibits NOD2-induced activation of MAPK and NF-κB signaling pathways, thus reducing the production of proinflammatory cytokines in macrophages	Zhang et al., 2015a
Asthma	PBMCs (Human)	Decreased	TIPE2 expression is negatively correlated with IgE, EO and IL-4	N.A.	Ma et al., 2013
SLE	PBMCs (Human)	Decreased	TIPE2 expression is negatively correlated with the SLE disease activity index	TIPE2 alleviates experimental SLE by inducing macrophage polarization to a M2 phenotype	Li et al., 2009; Li et al., 2016a
Rheumatoid arthritis	FLSs (Rats)	Decreased	Promotes AA-FLS apoptosis	Regulates the DR5-caspase-NF-κB pathway	Shi et al., 2016
Myasthenia gravis	PBMCs (Human)	Decreased	TIPE2 expression is negatively correlated with IL-6, IL-17 and IL-21, TLR4 activation could down-regulate TIPE2 expression	Negatively regulates TLR4-mediated autoimmune T helper 17 cell responses	Zhang et al., 2015b
Primary biliary cirrhosis	PBMCs (Human)	Decreased	TIPE2 expression is negatively correlated with ALT, ALP, GGT, TNF-α, IL-1β, IL-8 levels	Suppresses NF-κB pathways	Quin et al., 2016
Chronic kidney allograft rejection	PBMCs and renal tissues (Human)	Increased (PBMCs) Decreased (Renal tissues)	TIPE2 in the blood samples could serve as a diagnostic marker in clinical monitoring kidney chronic rejection	N.A.	Jia et al. 2013
Colitis	Colon (Mice)	Deficiency	Promotes colitis	Inhibits mucosal immunity to commensal bacteria	Lou et al., 2014a

Abbreviations: PBMCs, peripheral blood mononuclear cells; ACHBLF, acute-on-chronic hepatitis B liver failure; I/R injury, ischemia/reperfusion injury; SLE, systemic lupus erythematosus; FLSs, fibroblast-like synoviocytes.

caspase and inhibited the activation of NF-ϰB in AA-FLSs (Shi et al., 2016).

Myasthenia gravis (MG) is an autoimmune-mediated neuromuscular disease (Heldal et al., 2009). Recently, Zhang et al. reported that TIPE2 mRNA expression was significantly reduced in MG patients, and TIPE2 expression was closely related to the clinical manifestations of this disease. TIPE2 may be involved in the pathogenesis of MG via negatively regulating TLR-mediated autoimmune T helper 17 cell responses (Zhang et al., 2015b).

TIPE2 might be involved in the hyper-reactivity of monocytes to TLR ligands in primary biliary cirrhosis, a typical organ-specific autoimmune disease characterized by the immune-mediated destruction of small intrahepatic bile-duct, cholestasis, fibrosis and cirrhosis (Selmi et al., 2011). The expression of TIPE2 was significantly decreased in primary biliary cirrhosis, and TIPE2 expression is negatively correlated with the expression levels of ALT, ALP, GGT, TNF-α, IL-1β, and IL-8. Moreover, TIPE2 expression is significantly increased after ursodeoxycholic acid treatment (Qin et al., 2016).

Jia et al. detected the expression of TIPE2 in the

Table 3. Expression, functions and corresponding signaling pathways of TIPE2 in human cancers.

Cancer types	TIPE2 level	Sample size	Detection methods	Functions	Signaling pathways	Ref.
Gastric cancer	Decreased	Tumour (n=15) v.s. adjacent paraneoplastic tissue (n=15)	IHC and qRT-PCR	Suppresses tumour cell proliferation	Upregulates p27	Zhao et al., 2015
Gastric cancer	Decreased	Gastric cancer cell lines (n=3) v.s. normal gastric mucous epithelial cells (n=1)	qRT-PCR	Inhibits tumour cell growth and induces tumour cell apoptosis	Upregulation of Bax, cleaved Caspase-9, cleaved Caspase-3, cleaved poly ADP ribose polymerase as well as downregulation of Bcl-XL, p-PKB/AKT and p-ERK1/2	Zhu et al., 2016
Gastric cancer	Decreased	Gastric cancer cell lines (n=3) v.s. normal gastric mucous epithelial cells (n=1)	RT-PCR	Suppresses tumour cell migration and invasion	Downregulation of β-catenin signaling through inhibiting AKT and activating GSK3β	Wu et al., 2016
Hepatocellular carcinoma	Decreased	Tumour tissues (n=115)	IHC	Inhibits tumour cell proliferation, migration and invasion	Targeting Rac1 and then reduces F-actin polymerization and expression of MMP-9 and uPA	Cao et al., 2013
Hepatocellular carcinoma	N.A.	N.A.	N.A.	Suppresses TNF-α induced hepatocellular carcinoma metastasis	Decreasing the expression of MMP-13/MMP-3 through inhibiting ERK1/2 and NF-κB activation	Zhang et al., 2015c
Hepatocellular carcinoma	Decreased	Tumour tissues (n=10) and pericarcinomatous liver tissues (n=10)	IHC and Western blot	Maintains genomic DNA stability and suppresses tumour development	N.A.	Wang et al., 2016
Colon cancer	Increased	Tumour tissues (n=52) v.s. healthy controls (n=30), colon cancer cell line (HT-29)	IHC and qRT-PCR	Serves as tumour suppressor	Inhibits TLR4-mediated tumourigenesis via caspase-8	Li et al., 2014
Non-small cell lung cancer	Increased	Tumour tissues (n=85) v.s. adjacent normal tissues (n=85)	IHC, qRT-PCR and Western blot	Suppresses tumour invasiveness and angiogenesis	Inhibits the activation of Rac1 and subsequently weakening its downstream effects, including F-actin polymerization and VEGF expression	Li et al., 2016b
Glioma cancer	Decreased	Glioma cell lines (n=3) and normal human astrocytes	qRT-PCR and Western blot	Inhibits hypoxia-induced migration, invasion and the EMT process	Inhibits hypoxia-induced activation of Wnt/beta-catenin pathway	Liu et al., 2016
Renal cell carcinoma	Increased	Tumour tissues (n=46) v.s. control (n=39)	qRT-PCR	N.A.	N.A.	Zhang et al., 2013
Prostate cancer	Decreased	Tumour tissues, prostate cancer cell lines (n=3) and the normal prostate cell line (n=1)	qRT-PCR and Western blot	Suppresses the proliferation, migration, invasion and the EMT process	Inhibits the PI3K/AKT signaling pathway	Lu et al., 2016
Skin squamous carcinoma	Increased	Tumour tissues (n=40)	qRT-PCR	Induces polarization of macrophages to a M2 phenotype	N.A.	Li, 2016
Osteosarcoma	Decreased	Tumour tissues (n=36) v.s. adjacent non-cancer bone tissues (n=36) and osteosarcoma cell lines (n=2)	qRT-PCR and Western blot	Suppresses tumour cell invasiveness	Decreasing the expression of MMP-13	Deng et al., 2015

PBMCs and kidney biopsy samples from 96 recipients of kidney transplants. TIPE2 expression in the PBMCs of patients with chronic rejection (CR) was significantly higher than that of the healthy controls, indicating that the detection of TIPE2 in the blood samples may serve as a diagnostic marker in clinical monitoring chronic kidney rejection (Jia et al., 2013). In addition, using an experimental colitis model induced by dextran sodium sulfate (DSS), Lou et al. found that TIPE2 promotes colitis by inhibiting mucosal immunity to commensal bacteria (Lou et al., 2014b).

TIPE2 and tumourigenesis

Subsequent studies further found that unlike murine TIPE2, which is preferentially expressed in haematopoietic cells, human TIPE2 is expressed in a wide variety of nonhaematopoietic cell types, implying a new function in addition to immune modulation (Zhang et al., 2010, 2011). TIPE2 is not detectable or weakly expressed in most human cancer cells, suggesting that TIPE2 alteration may be involved in human cancer progression. Accumulating evidence has demonstrated that TIPE2 exhibits effects not only in inflammation but also in cancer. We previously investigated the expression of TIPE2 in 112 primary hepatocellular carcinoma (HCC) tissues and found that TIPE2 expression was significantly decreased in HCC tissues, and TIPE2 expression was significantly associated with tumour metastasis. Mechanically, TIPE2 inhibits the migration and invasion of HCC cells through targeting Rac1 and then reduces F-actin polymerization and expression of matrix metallopeptidase 9 (MMP9) and urokinase plasminogen activator (uPA) (Cao et al., 2013). Additionally, Zhang et al found that TIPE2 could significantly suppress the TNF-α-induced HCC metastasis via inhibiting ERK1/2 and NF-ϰB activation (Zhang et al., 2015c). A recent study also demonstrated that TIPE2 down-regulation was associated with genomic DNA instability and HCV-induced HCC development (Wang et al., 2016).

Interestingly, although TIPE2 expression is increased in non-small cell lung cancer (NSCLC), this protein was negatively associated with the primary tumour size, lymph node metastasis, and advanced clinical stage, which can be used to predict lymph node metastasis. TIPE2 also serves as a tumour suppressor, as TIPE2 significantly suppresses the migration, invasion and colony formation of NSCLC cells (Li et al., 2016b). Li et al. reported that TIPE2 functions through reducing the expression of Bcl-XL and N-cadherin and increasing the expression of cleaved caspase-9, cleaved caspase-3 and E-cadherin (Li et al., 2015). Liu et al demonstrated that TIPE2 promoted lung cancer cell apoptosis by regulating caspase-3, caspase-9, Bcl-2 and Bax (Liu et al., 2015a,b). Additionally, we demonstrated that TIPE2 serves as a tumour suppressor via inhibiting Rac1 activity in NSCLC. Moreover, TIPE2 suppressed the

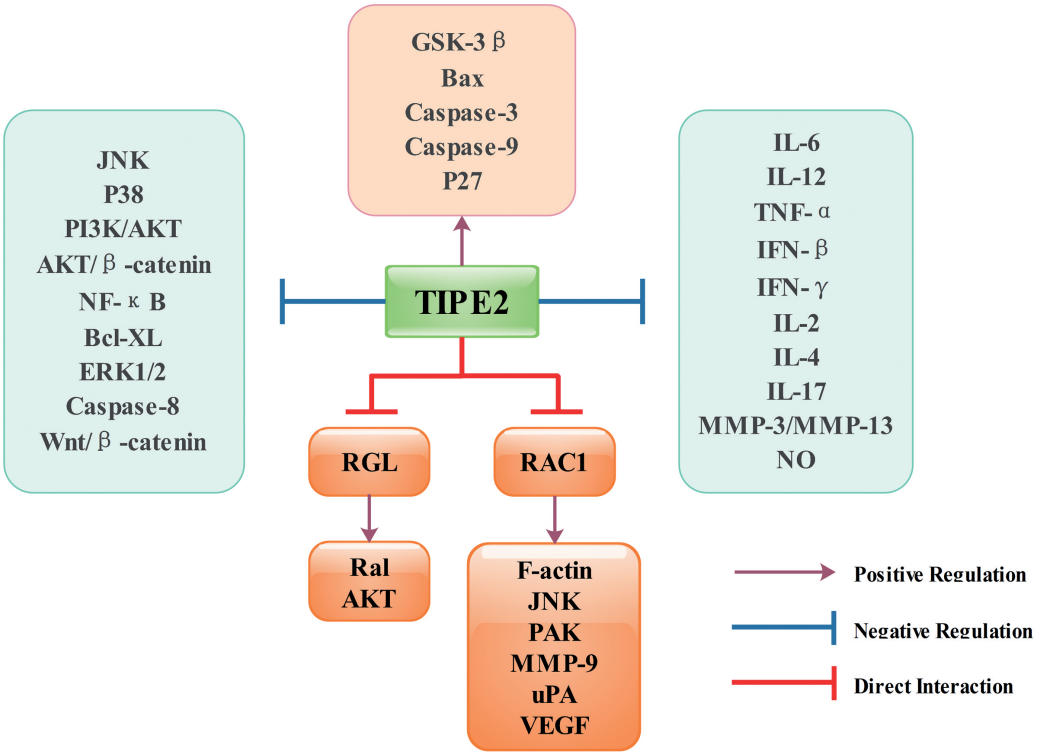

Fig. 1. Proposed molecular mechanism for TIPE2 mediated effects in immune regulation and tumourigenesis. TIPE2 primarily serves as a negative immune regulator by suppressing the expression of a number of inflammatory and pro-inflammatory cytokines. TIPE2 is also involved in apoptosis via regulating several related molecules, such as Bcl-2, Bax and caspases. By interacting with RGL and RAC1, TIPE2 regulates various classical signalling pathways that contribute to inflammation and tumourigenesis.

proliferation, migration, and tube formation of vascular endothelial cells, primarily due to its inhibitory effect on the secretion and expression of VEGF (Li et al., 2016b). This anti-angiogenesis property may account for the suppressive effect of TIPE2 on tumour metastasis.

By upregulating p27, TIPE2 could significantly suppress the proliferation of gastric cancer cells (Zhao et al., 2015). TIPE2 overexpression also increased the expression of Bax, cleaved caspase-9, cleaved cspase-3, cleaved poly ADP ribose polymerase, activated GSK3β and decreased the expression of Bcl-XL, p-PKB/AKT, p-ERK1/2 in gastric cancer cells (Wu et al., 2016; Zhu et al., 2016).

TIPE2 is also involved several other types of tumours, such as colon cancer, skin squamous cell carcinoma and osteosarcoma. Li et al. demonstrated that TIPE2 expression is upregulated and related to lymph node metastasis and Dukes stage in colon cancer. In colon cancer cells, TIPE2 binds to caspase-8 and regulates the TLR4 inflammatory effect (Li et al., 2014). Also, Li found that TIPE2 regulates tumour-associated macrophages (TAMs) in skin squamous carcinoma (SCC), and patients with high-TIPE2 TAMs had a poor 5-year survival, indicating that the roles of TIPE2 may differ among different tumours (Li, 2016). Another study showed that TIPE2 expression was significantly decreased in osteosarcoma specimens, and TIPE2 could effectively mediate the suppressive effects of Shikonin on the invasiveness of osteosarcoma cells by decreasing MMP-13 expression (Deng et al., 2015). Recent studies have demonstrated that TIPE2 suppressed the epithelial-mesenchymal transition (EMT) process of glioma cells and also acts as a tumour suppressor by inhibiting the PI3K-AKT signalling pathway in prostate cancer cells (Liu et al., 2016; Lu et al., 2016). The expression, functions and mechanisms of TIPE2 in different tumours are summarized in Table 3.

Conclusions and perspectives

In this review, we briefly summarized the expression and functions of TIPE2, and the related mechanisms are summarized in Fig. 1. We conclude that TIPE2 is a key molecule in regulating immune homeostasis, as TIPE2 is involved in both innate and adaptive immune reactions, which determined the role of TIPE2 in infectious diseases and inflammatory diseases, such as in hepatitis, SLE and MG (Zhang et al., 2009; Xi et al., 2011; Sun et al., 2012; Zhang et al., 2015b; Li et al., 2016a). Currently, an increasing number of diseases have been considered as immune-related diseases. For example, inflammatory reactions and immune cells are essential for the development of atherosclerosis, while TIPE2 has been implicated as important in regulating the differentiation of immune cells and secretion of related cytokines (Lou et al., 2013). Indeed, TIPE2 is tightly associated with a number of immune related diseases, which deserves further investigation.

Inflammation is tightly correlated with tumourigenesis. In recent years, there has been a marked increase in understanding its wealth of correlations and potential roles in cancer (Gus-Brautbar et al., 2012; Cao et al., 2013; Li et al., 2016a,b; Liu et al., 2016; Lu et al., 2016). TIPE2 expression is typically decreased in tumour tissues, and TIPE2 regulates various classical signalling pathways that are essential for tumourigenesis. Given its critical roles in the development and progression of a number of tumours, TIPE2 may be considered a novel therapeutic target in cancer treatment. However, studies of TIPE2 in tumour are in the initial stages, and the different roles of TIPE2 in different tumours need further investigation. Moreover, as an immune regulator, the roles of TIPE2 in inflammation-associated cancer initiation and progression and in the immune therapy value of TIPE2 are not clear. To translate the laboratory findings into clinical applications, additional research is warranted to identify the precise mechanism of TIPE2 in cancer development.

We have to focus on the relationship between the structure and functions of TIPE2, as TIPE2 has a DED-like domain, of which the functions are still unknown. Moreover, the role of the large hydrophobic central cavity should also be further investigated (Zhang et al., 2009). In addition, there are four members of the TIPE family, and these members show high homology. However, the functions of these members are completely different (Cui et al., 2011, 2015; Lou and Liu, 2011; Fayngerts et al., 2014; Zhang et al., 2015d; Hu et al., 2016). Exploring the key structural factors and other factors that may affect the functions of the TIPE family is of high research value.

Except for immune regulation and tumour development, studies have focused on the other aspects of TIPE2 in recent years. In a recent study, we showed that TIPE2 is also involved in autophagy and lipid metabolism. Moreover, it seems that TIPE2 may function through different signalling pathways, which deserves further investigation.

Acknowledgements: This work was supported by grants from the National Key Research and Development Plan of China (No. 2016YFC1303400), the National Natural Science Foundation of China (81572414, 31470856 and 91439124) and Natural Science Foundation of Shandong Province (2014GGE27393).

Conflicts of Interest: The authors declare no conflict of interest.

References

Ambruso D.R., Knall C., Abell A.N., Panepinto J., Kurkchubasche A., Thurman G., Gonzalez-Aller C., Hiester A., deBoer M., Harbeck R.J., Oyer R., Johnson G.L. and Roos D. (2000). Human neutrophil immunodeficiency syndrome is associated with an inhibitory rac2 mutation. Proc. Natl. Acad. Sci. USA 97, 4654-4659.

Assari T. (2006). Chronic granulomatous disease; fundamental stages in our understanding of cgd. Med. Immunol. 5, 4.

Bidere N., Snow A.L., Sakai K., Zheng L. and Lenardo M.J. (2006).

Caspase-8 regulation by direct interaction with TRAF6 in T cell receptor-induced NF-kappaB activation. Curr. Biol. 16, 1666-1671.

Cao X., Zhang L., Shi Y., Sun Y., Dai S., Guo C., Zhu F., Wang Q., Wang J., Wang X., Chen Y.H. and Zhang L. (2013). Human tumor necrosis factor (TNF)-alpha-induced protein 8-like 2 suppresses hepatocellular carcinoma metastasis through inhibiting rac1. Mol. cancer 12, 149.

Chun H.J., Zheng L., Ahmad M., Wang J., Speirs C.K., Siegel R.M., Dale J.K., Puck J., Davis J., Hall C.G., Skoda-Smith S., Atkinson T.P., Straus S.E. and Lenardo M.J. (2002). Pleiotropic defects in lymphocyte activation caused by caspase-8 mutations lead to human immunodeficiency. Nature 419, 395-399.

Cui J., Zhang G., Hao C., Wang Y., Lou Y., Zhang W., Wang J. and Liu S. (2011). The expression of tipe1 in murine tissues and human cell lines. Mol. Immunol. 48, 1548-1555.

Cui J., Hao C., Zhang W., Shao J., Zhang N., Zhang G. and Liu S. (2015). Identical expression profiling of human and murine tipe3 protein reveals links to its functions. J. Histochem. Cytochem. 63, 206-216.

Deng B., Feng Y. and Deng B. (2015). Tipe2 mediates the suppressive effects of shikonin on MMP13 in osteosarcoma cells. Cell. Physiol. Biochem. 37, 2434-2443.

Diebold B.A. and Bokoch G.M. (2005). Rho GTPases and the control of the oxidative burst in polymorphonuclear leukocytes. Curr. Top. Microbiol. Immunol. 291, 91-111.

Fan Y.C., Wang N., Sun Y.Y., Xiao X.Y. and Wang K. (2015). TIPE2 mRNA level in pbmcs serves as a novel biomarker for predicting short-term mortality of acute-on-chronic hepatitis b liver failure: A prospective single-center study. Medicine (Baltimore) 94, e1638.

Fayngerts S.A., Wu J., Oxley C.L., Liu X., Vourekas A., Cathopoulis T., Wang Z., Cui J., Liu S., Sun H., Lemmon M.A., Zhang L., Shi Y. and Chen Y.H. (2014). TIPE3 is the transfer protein of lipid second messengers that promote cancer. Cancer Cell 26, 465-478.

Freundt E.C., Bidere N. and Lenardo M.J. (2008). A different tipe of immune homeostasis. Cell 133, 401-402.

Gus-Brautbar Y., Johnson D., Zhang L., Sun H., Wang P., Zhang S., Zhang L. and Chen Y.H. (2012). The anti-inflammatory TIPE2 is an inhibitor of the oncogenic ras. Mol. Cell 45, 610-618.

Heldal A.T., Owe J.F., Gilhus N.E. and Romi F. (2009). Seropositive myasthenia gravis: A nationwide epidemiologic study. Neurology 73, 150-151.

Heyworth P.G., Cross A.R. and Curnutte J.T. (2003). Chronic granulomatous disease. Curr. Opin. Immunol. 15, 578-584.

Hu R., Qiu X., Hong S., Meng L., Hong X., Qiu J., Yang J., Zhuang G. and Liu Z. (2016). Clinical significance of tipe expression in gastric carcinoma. Onco Targets Ther. 9, 4473-4481.

Jia L., Gui B., Tian P., Yao G., Fu R., Wang L., Ge H. and Ou Y. (2013). TIPE2, a novel biomarker for clinical chronic kidney allograft rejection. Artif. Organs 37, 221-225.

Kong L., Liu K., Zhang Y.Z., Jin M., Wu B.R., Wang W.Z., Li W., Nan Y.M. and Chen Y.H. (2013). Downregulation of TIPE2 mRNA expression in peripheral blood mononuclear cells from patients with chronic hepatitis C. Hepatol. Int. 7, 844-849.

Lemmers B., Salmena L., Bidere N., Su H., Matysiak-Zablocki E., Murakami K., Ohashi P.S., Jurisicova A., Lenardo M., Hakem R. and Hakem A. (2007). Essential role for caspase-8 in toll-like receptors and NFkappaB signaling. J. Biol. Chem. 282, 7416-7423.

Li X. (2016). Tipe2 regulates tumor-associated macrophages in skin squamous cell carcinoma. Tumour biology. 37, 5585-5590.

Li D., Song L., Fan Y., Li X., Li Y., Chen J., Zhu F., Guo C., Shi Y. and Zhang L. (2009). Down-regulation of TIPE2 mRNA expression in peripheral blood mononuclear cells from patients with systemic lupus erythematosus. Clin. Immunol. 133, 422-427.

Li X.M., Su J.R., Yan S.P., Cheng Z.L., Yang T.T. and Zhu Q. (2014). A novel inflammatory regulator TIPE2 inhibits TLR4-mediated development of colon cancer via caspase-8. Cancer Biomark. 14, 233-240.

Li Y., Li X., Liu G., Sun R., Wang L., Wang J. and Wang H. (2015). Downregulated TIPE2 is associated with poor prognosis and promotes cell proliferation in non-small cell lung cancer. Biochem. Biophys. Res. Commun. 457, 43-49.

Li F., Zhu X., Yang Y., Huang L. and Xu J. (2016a). TIPE2 alleviates systemic lupus erythematosus through regulating macrophage polarization. Cell. Physiol. Biochem. 38, 330-339.

Li Z., Guo C., Liu X., Zhou C., Zhu F., Wang X., Wang Q., Shi Y., Wang J., Zhao W. and Zhang L. (2016b). TIPE2 suppresses angiogenesis and non-small cell lung cancer (NSCLC) invasiveness via inhibiting rac1 activation and vegf expression. Oncotarget 7, 62224-62239.

Liu M.W., Su M.X., Zhang W., Zhang L.M., Wang Y.H. and Qian C.Y. (2015a). Rhodiola rosea suppresses thymus T-lymphocyte apoptosis by downregulating tumor necrosis factor-alpha-induced protein 8-like-2 in septic rats. Int. J. Mol. Med. 36, 386-398.

Liu Q.Q., Zhang F.F., Wang F., Qiu J.H., Luo C.H., Zhu G.Y. and Liu Y.F. (2015b). TIPE2 inhibits lung cancer growth attributing to promotion of apoptosis by regulating some apoptotic molecules expression. PLoS One 10, e0126176.

Liu Z.J., Liu H.L., Zhou H.C. and Wang G.C. (2016). TIPE2 inhibits hypoxia-induced wnt/beta-catenin pathway activation and emt in glioma cells. Oncol. Res. 24, 255-261.

Lou Y. and Liu S. (2011). The TIPE (TNFaip8) family in inflammation, immunity, and cancer. Mol. Immunol. 49, 4-7.

Lou Y., Liu S., Zhang C., Zhang G., Li J., Ni M., An G., Dong M., Liu X., Zhu F., Zhang W., Gao F., Chen Y.H. and Zhang Y. (2013). Enhanced atherosclerosis in TIPE2-deficient mice is associated with increased macrophage responses to oxidized low-density lipoprotein. J. Immunol. 191, 4849-4857.

Lou Y., Zhang G., Geng M., Zhang W., Cui J. and Liu S. (2014a). TIPE2 negatively regulates inflammation by switching arginine metabolism from nitric oxide synthase to arginase. PLoS One 9, e96508.

Lou Y., Sun H., Morrissey S., Porturas T., Liu S., Hua X. and Chen Y.H. (2014b). Critical roles of TIPE2 protein in murine experimental colitis. J. Immunol. 193, 1064-1070.

Lu Q., Liu Z., Li Z., Chen J., Liao Z., Wu W.R. and Li Y.W. (2016). TIPE2 overexpression suppresses the proliferation, migration, and invasion in prostate cancer cells by inhibiting PI3K/AKT signaling pathway. Oncol. Res. 24, 305-313.

Luan Y.Y., Yao Y.M., Zhang L., Dong N., Zhang Q.H., Yu Y. and Sheng Z.Y. (2011). Expression of tumor necrosis factor-alpha induced protein 8 like-2 contributes to the immunosuppressive property of CD4(+)CD25(+) regulatory T cells in mice. Mol. Immunol. 49, 219-226.

Ma Y., Liu X., Wei Z., Wang X., Wang Z., Zhong W., Li Y., Zhu F., Guo C., Zhang L. and Wang X. (2013). The expression and significance of TIPE2 in peripheral blood mononuclear cells from asthmatic children. Scand. J. Immunol. 78, 523-528.

Mao Y. and Finnemann S.C. (2015). Regulation of phagocytosis by rho GTPases. Small GTPases 6, 89-99.

Niedergang F. and Chavrier P. (2005). Regulation of phagocytosis by

rho GTPases. Curr. Top. Microbiol. Immunol. 291, 43-60.

Qin B., Wei T., Wang L., Ma N., Tang Q., Liang Y., Yang Z., Zhou L. and Zhong R. (2016). Decreased expression of TIPE2 contributes to the hyperreactivity of monocyte to toll-like receptor ligands in primary biliary cirrhosis. J. Gastroenterol. Hepatol. 31, 1177-1183.

Roberts A.W., Kim C., Zhen L., Lowe J.B., Kapur R., Petryniak B., Spaetti A., Pollock J.D., Borneo J.B., Bradford G.B., Atkinson S.J., Dinauer M.C. and Williams D.A. (1999). Deficiency of the hematopoietic cell-specific Rho family GTPase Rac2 is characterized by abnormalities in neutrophil function and host defense. Immunity 10, 183-196.

Salmena L. and Hakem R. (2005). Caspase-8 deficiency in T cells leads to a lethal lymphoinfiltrative immune disorder. J. Exp. Med. 202, 727-732.

Selmi C., Bowlus C.L., Gershwin M.E. and Coppel R.L. (2011). Primary biliary cirrhosis. Lancet 377, 1600-1609.

Shi C., Zhang S., Hong S., Pang J., Yesibulati Y., Yin P. and Zhuang G. (2016). The pro-apoptotic effects of TIPE2 on AA rat fibroblast-like synoviocytes via regulation of the DR5-caspase-NF-kappaB pathway in vitro. Onco. Targets Ther. 9, 993-1000.

Su H., Bidere N., Zheng L., Cubre A., Sakai K., Dale J., Salmena L., Hakem R., Straus S. and Lenardo M. (2005). Requirement for caspase-8 in NF-kappaB activation by antigen receptor. Science 307, 1465-1468.

Suda T., Okazaki T., Naito Y., Yokota T., Arai N., Ozaki S., Nakao K. and Nagata S. (1995). Expression of the Fas ligand in cells of T cell lineage. J. Immunol. 154, 3806-3813.

Sun H., Gong S., Carmody R.J., Hilliard A., Li L., Sun J., Kong L., Xu L., Hilliard B., Hu S., Shen H., Yang X. and Chen Y.H. (2008). TIPE2, a negative regulator of innate and adaptive immunity that maintains immune homeostasis. Cell 133, 415-426.

Sun H., Zhuang G., Chai L., Wang Z., Johnson D., Ma Y. and Chen Y.H. (2012). TIPE2 controls innate immunity to RNA by targeting the phosphatidylinositol 3-kinase-rac pathway. J. Immunol. 189, 2768-2773.

Tang J., Kawadler H. and Yang X. (2005). Lymphocyte life and death: The caspase-8 connection. Cancer Biol. Ther. 4, 700-702.

Van Parijs L. and Abbas A.K. (1998). Homeostasis and self-tolerance in the immune system: Turning lymphocytes off. Science 280, 243-248.

Van Parijs L., Biuckians A. and Abbas A.K. (1998). Functional roles of fas and bcl-2-regulated apoptosis of t lymphocytes. J. Immunol. 160, 2065-2071.

Wahl S.M., Wen J. and Moutsopoulos N. (2006). TGF-beta: A mobile purveyor of immune privilege. Immunol. Rev. 213, 213-227.

Wang Z., Fayngerts S., Wang P., Sun H., Johnson D.S., Ruan Q., Guo W. and Chen Y.H. (2012). TIPE2 protein serves as a negative regulator of phagocytosis and oxidative burst during infection. Proc. Natl. Acad. Sci. USA 109, 15413-15418.

Wang L.Y., Fan Y.C., Zhao J., Gao S., Sun F.K., Han J., Yang Y. and Wang K. (2014). Elevated expression of tumour necrosis factor-alpha-induced protein 8 (TNFaip8)-like 2 mRNA in peripheral blood mononuclear cells is associated with disease progression of acute-on-chronic hepatitis b liver failure. J. Viral Hepat. 21, 64-73.

Wang C., Yan G., Zhang Y., Jia X. and Bu P. (2015). Long non-coding RNA MEG3 suppresses migration and invasion of thyroid carcinoma by targeting of Rac1. Neoplasma 62, 541-549.

Wang Y., Jiang Y., Zhou J., Song W., Li J., Wang M., Chen J., Xu R., Zhang J., Ma F., Chen Y.H. and Ma Y. (2016). Hepatitis C virus promotes hepatocellular carcinogenesis by targeting TIPE2, a new regulator of DNA damage response. Tumour Biol. 37, 15265-15274.

Wu J., Zhang H., Xu C., Xu H., Zhou X., Xie Y. and Tao M. (2016). TIPE2 functions as a metastasis suppressor via negatively regulating beta-catenin through activating GSK3beta in gastric cancer. Int. J. Oncol. 48, 199-206.

Xi W., Hu Y., Liu Y., Zhang J., Wang L., Lou Y., Qu Z., Cui J., Zhang G., Liang X., Ma C., Gao C., Chen Y. and Liu S. (2011). Roles of TIPE2 in hepatitis B virus-induced hepatic inflammation in humans and mice. Mol. Immunol. 48, 1203-1208.

Zhang X., Wang J., Fan C., Li H., Sun H., Gong S., Chen Y.H. and Shi Y. (2009). Crystal structure of TIPE2 provides insights into immune homeostasis. Nat. Struct. Mol. Biol. 16, 89-90.

Zhang G., Hao C., Lou Y., Xi W., Wang X., Wang Y., Qu Z., Guo C., Chen Y., Zhang Y. and Liu S. (2010). Tissue-specific expression of tipe2 provides insights into its function. Mol. Immunol. 47, 2435-2442.

Zhang L., Shi Y., Wang Y., Zhu F., Wang Q., Ma C., Chen Y.H. and Zhang L. (2011). The unique expression profile of human TIPE2 suggests new functions beyond its role in immune regulation. Mol. Immunol. 48, 1209-1215.

Zhang Y., Wei X., Liu L., Liu S., Wang Z., Zhang B., Fan B., Yang F., Huang S., Jiang F., Chen Y.H. and Yi F. (2012). TIPE2, a novel regulator of immunity, protects against experimental stroke. J. Biol. Chem. 287, 32546-32555.

Zhang Z., Qi H., Hou S. and Jin X. (2013). TIPE2 mrna overexpression correlates with TNM staging in renal cell carcinoma tissues. Oncol. Lett. 6, 571-575.

Zhang H., Zhu T., Liu W., Qu X., Chen Y., Ren P., Wang Z., Wei X., Zhang Y. and Yi F. (2015a). TIPE2 acts as a negative regulator linking NOD2 and inflammatory responses in myocardial ischemia/reperfusion injury. J. Mol. Med. (Berl.) 93, 1033-1043.

Zhang Y., Shao Z., Zhang X., Jia X., Xia Y., Zhang Y., Xin N., Guo M., Chen J., Zheng S., Wang Y., Fu L., Dong R., Xiao C., Geng D. and Liu Y. (2015b). TIPE2 play a negative role in TLR4-mediated autoimmune T helper 17 cell responses in patients with myasthenia gravis. J. Neuroimmune Pharmacol. 10, 635-644.

Zhang Y.H., Yan H.Q., Wang F., Wang Y.Y., Jiang Y.N., Wang Y.N. and Gao F.G. (2015c). TIPE2 inhibits TNF-alpha-induced hepatocellular carcinoma cell metastasis via ERK1/2 downregulation and NF-kappaB activation. Int. J. Oncol. 46, 254-264.

Zhang Z., Liang X., Gao L., Ma H., Liu X., Pan Y., Yan W., Shan H., Wang Z., Chen Y.H. and Ma C. (2015d). TIPE1 induces apoptosis by negatively regulating Rac1 activation in hepatocellular carcinoma cells. Oncogene 34, 2566-2574.

Zhao Q., Zhao M., Dong T., Zhou C., Peng Y., Zhou X., Fan B., Ma W., Han M. and Liu S. (2015). Tumor necrosis factor-alpha-induced protein-8 like-2 (TIPE2) upregulates P27 to decrease gastic cancer cell proliferation. J. Cell. Biochem. 116, 1121-1129.

Zhu Y., Tao M., Wu J., Meng Y., Xu C., Tian Y., Zhou X., Xiang J., Zhang H. and Xie Y. (2016). Adenovirus-directed expression of TIPE2 suppresses gastric cancer growth via induction of apoptosis and inhibition of AKT and ERK1/2 signaling. Cancer Gene Ther. 23, 98-106.

Accepted February 26, 2018