

The Function Profiling of TIPE2 Reveals Links to its Potential Application

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Abstract

TIPE2, TNF- α -induced protein 8-like 2 (TNFAIP8L2), is a newly identified member of the TNFAIP8 family. Recent studies revealed that TIPE2 is a negative regulator of inflammation and carcinogenesis. TIPE2 deletion in mice causes fatal inflammation and its dysregulation in humans is associated with diseases, such as viral hepatitis, hepatocellular carcinoma, and atherosclerosis. The function profiling of TIPE2 in normal or pathological conditions indicates its potential application in immunotherapy.

Keywords: TIPE2 Reveals; Inflammation; Carcinogenesis

Introduction

The mammalian TNFAIP8 family consists of four members: TNFAIP8 (TIPE), TNFAIP8L1 (TNF- α -induced protein 8-like 1, TIPE1), TIPE2 and TIPE3, which share high degrees of sequence homology but possess different biological functions in the regulation of proliferation, cell death and immune homeostasis [1,2]. Among the four members, TIPE is the first identified member and acts as an oncogenic molecule by skewing the balance of cell survival and apoptosis [3]. TIPE1 induced apoptosis in HCC cells by negatively regulating Rac1 pathway [4]. Recent studies reveal that TIPE3 is a transfer protein of two lipid second messengers, PtdIns(4,5)P2 and PtdIns(3,4,5)P3, and is hijacked by cancer cells to cause malignant transformation [5]. However, more studies focus on TIPE2, another new identified member of TNFAIP8 family. TIPE2 is preferentially expressed in lymphoid tissues and required for maintaining immune homeostasis [1,6,7]. Emerging evidences demonstrate that TIPE2 not only acts as a negative regulator of inflammation and plays roles in inflammation associated diseases, such as viral hepatitis [8,9], diabetic nephropathy [10], colitis [11], stroke [12] and atherosclerosis [13,14], but also suppresses carcinogenesis [15-17]. In this review, we will summarize the known and potential roles of TIPE2 and predict its possible application in immune therapy.

Expression pattern of TIPE2 in mouse and human provides insights into its functions

TIPE2 was originally identified as a gene abnormally expressed in the inflamed spinal cord of mice with experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis, using a high-throughput gene microarray technology [18]. Initial studies demonstrated that TIPE2 mRNA was expressed in inflamed tissues, lymphoid tissues and several transformed cell lines [1]. Murine TIPE2 protein displayed a cytoplasmic distribution and was detected in the megakaryocytes and T cells but not in B-lymphoid cells [6], which may explain why TIPE2 deficiency preferentially influences cellular, but not humoral immunity in mice [1]. Interestingly, TIPE2 expression is not

only restricted in lymphocytes and myeloid cells, but can be observed in several types of endocrine cells, and somatic as well as germ cells of the reproductive organs [6]. Similar to murine TIPE2, human TIPE2 was also expressed in hematopoietic cells and a wide variety of non-hematopoietic cell types [7]. These findings not only support the view that TIPE2 plays roles in anti-inflammation and maintaining homeostasis, but also indicate that TIPE2 owns other potential functions beyond immune regulation.

TIPE2 and inflammation

TIPE2 is a key regulator of inflammatory responses and immune homeostasis. It suppresses hyper-inflammation by negatively regulating T cell receptor and Toll-like receptor (TLR) signaling [1,19]. Thus TIPE2-deficient mice suffer from fatal inflammation diseases and exhibit more sensitive to experimental stroke and hepatitis [1,8,9,12]. Abnormal expression of TIPE2 on PBMCs has been determined in patients with disease which T lymphocytes play important roles, such as systemic lupus erythematosus (SLE) [20], hepatitis B[8,9], transplantation rejection [21] and childhood asthma [22]. The downregulation of TIPE2 in HBV-specific cytotoxic CD8⁺ T cells induces higher levels of perforin, granzyme B, and IFN- γ . As a result, their cytolytic activity was markedly enhanced to contribute more severe pathological injury [9]. These studies indicate that TIPE2 may be a new target to treat these diseases by regulating cellular immunity.

TIPE2 can inhibit innate immunity by regulating Toll-like receptor signaling [1]. Macrophage is an important cell which participates in innate immunity and highly expresses TIPE2 protein [1]. Studies showed that TIPE2 can suppress inflammatory reaction by negatively regulating macrophage functions. For example, TIPE2 prevents atherosclerosis by negatively regulating macrophage responses to oxidized low-density lipoprotein [13]. TIPE2-deficient macrophages treated with ox-LDL produced more oxidative stress and proinflammatory cytokines. In addition, we also found that TIPE2 negatively regulates inflammation by switching arginine metabolism from nitric oxide synthase to arginase. TIPE2 deficiency in macrophages increased iNOS expression, NO production and enhanced antibacterial activity [23].

TIPE2 promotes activated immune cell death

Apoptosis is a form of programmed cell death that plays a critical role in the regulation of immune homeostasis and the normal functioning of the immune system. In addition to inhibitory effects in immune activation, TIPE2 can also maintain immune homeostasis by promoting Fas-mediated apoptosis and antigen receptor-induced cell death (AICD) [1,24,25]. However, the underlying mechanism is not very clear. Studies demonstrated that TIPE2 did not recruit to caspase-8 in death-inducing signaling complex (DISC) because its distinct DED (Death Effector Domain)-like domain, which appears a mirror image of the classic DED, failed to interact with caspase-8 but bound to the DED of c-FLIP [1,26]. These findings exclude the possibility that TIPE2 regulates Fas-induced apoptosis by directly modulating the activities of caspase-8 in the DISC. TIPE2 can inhibit the activation of NF- κ B signaling pathway [1,2], an effective inhibitor of Fas-induced apoptosis [27]. Therefore, TIPE2 mediated NF- κ B inhibition may be responsible for Fas-induced apoptosis.

TIPE2 and carcinogenesis

Recent studies revealed that anti-inflammatory TIPE2 is a negative regulator of carcinogenesis [1,25]. TIPE2 binds the Ras interacting domain of the RalGDS family of proteins to prevent Ras from forming an active complex, thereby inhibiting the activation of the downstream signaling molecules Ral and AKT [25]. Ras is a major regulator of cell survival, proliferation, migration, and transformation. Thus, TIPE2 overexpression induced cell death and significantly inhibited Ras-induced tumorigenesis in mice [25]. Importantly, TIPE2 expression was either completely lost or significantly down-regulated in human hepatic cancer, gastric cancer, non-small cell lung cancer [16,25,28,29], which may be responsible for these tumor cells to escape apoptosis. Unlike murine TIPE2 that interacts with RalGDS family of proteins, human TIPE2 is an endogenous inhibitor of Rac1 in liver and attenuates invasion and metastasis of hepatocellular carcinoma [16]. These findings suggest that TIPE2 is an anti-tumor factor but usually down regulated in the process of carcinogenesis. Thus, upregulation of TIPE2 may be a new therapeutic strategy against tumors.

TIPE2 and cardiovascular diseases

Both of Ras and Rac signaling cascades are involved in various physiological and pathological conditions. As a novel regulator of Ras and Rac signaling, TIPE2 may participate in regulating the progress of other diseases. In fact, our previous studies demonstrated that murine TIPE2 plays an atheroprotective action by attenuating the phenotypic switching of VSMCs (vascular smooth muscle cells) in response to ox-LDL stimuli, which is dependent on P38 and ERK1/2 kinase signals [14]. TIPE2-deficient VSMCs treated with ox-LDL expressed lower levels of contractile proteins such as SM α A, SM-MHC and calponin, whereas the proliferation, migration and the synthetic capacity for growth factors and cytokines were increased remarkably [14]. Otherwise, murine TIPE2 inhibits experimental restenosis by attenuating VSMCs proliferation in a Rac1-dependent manner (unpublished data). Adenovirus-mediated overexpression of murine TIPE2 in vivo significantly blocked injury-induced restenosis (unpublished data). These data confirm the notion that TIPE2 has new functions beyond the roles in immunity and carcinogenesis. All that we have known may be only the tip of the iceberg.

The possible mechanism of TIPE2 functions

TIPE2 regulates TCR and TLR signaling by inhibiting MAPKs and NF- κ B signaling pathways, resulting in diminished activity of transcription AP-1 and NF- κ B [1,30]. Recent studies demonstrate that TIPE2 may control innate immunity to bacteria and dsRNA viruses by targeting the Rac GTPases [19,31]. Phagocytosis and oxidative burst are two major effector arms of innate immunity, both of which are regulated by Rac protein of the ras small GTPase superfamily [31-33]. TIPE2 binds to Rac1 and Rac2 GTPases through their C-Terminal CAAX Motif and directly inhibits Rac membrane translocation, activation, and downstream signaling, result in a negative regulation on phagocytosis and oxidative burst [31]. Rac3 is another member of Rac GTPases and share high sequence identity (88-92%) with Rac1 and Rac2 [34]. However, there is no direct evidence to describe the interaction of TIPE2 and Rac3. In addition to Rac, RalGDS family is another binding partner of TIPE2 [25]. TIPE2 binds the Ras interacting domain of the RalGDS family of proteins to prevent Ras from forming an active complex, thereby inhibiting the activation of the downstream signaling molecules Ral and AKT [25]. These data suggest that TIPE2 is a novel regulator of both Rac and Ras cascades and may play important roles in diseases associated with Rac and Ras dysfunction. However, these issues remain to be further discussed.

Summary

TIPE2 is a newly identified negative regulator of inflammation and carcinogenesis. However, the expression pattern of TIPE2 and emerging evidences outside the two aforementioned fields indicate that TIPE2 may not only involve in inflammation and carcinogenesis, but also play important roles in other Ras or Rac related diseases. Further studies should be done to reveal these issues. In addition, TIPE2 is a potential therapeutic target that may be utilized to treat these diseases in the future, but much remains to be done.

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