Research Progress on Trigger Receptors of Myeloid Cells and Non-infectious Inflammatory Diseases

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Abstract

Triggering receptor expressed on myeloid cells (TREM-1) is an immunoglobulin expressed on some immune cells and parenchymal cells, which can amplify inflammation after activation. It was originally found to play a key role in infectious inflammatory diseases. In recent years, TREM-1 has been found to also play a key role in non-infectious inflammatory diseases such as atherosclerosis, trauma, autoimmune diseases, and tumors. This article reviews the research progress of TREM-1 and non-infectious inflammatory diseases.

Keywords

TREM-1; Non-infectious inflammatory diseases.

1. Introduction

Innate immune cells are the body's line of defense to recognize invading pathogens.Environmental signals at the site of inflammation mediate the rapid mobilization of immune cells and determine the differentiation process, so that these cells quickly participate in tissue healing, the removal of pathogens and dead cells, and the initiation of adaptive immunity [1]. *TREM-1* is an amplifying factor of the inflammatory response triggered by bacterial and fungal infections, and was originally found to play a role in infectious inflammatory diseases [2].The trigger receptor expressed in the myeloid cell (*TREM*) family is a member of the immunoglobulin superfamily, including at least two activating receptors, namely *TREM-1* and *TREM-2*, and called TREM-like transcripts (TLT)-1 [2,3].

2. Biological characteristics of TREM-1

2.1 Structure, distribution characteristics and form

TREM-1 is a member of the immunoglobulin superfamily. It is constitutively expressed on monocytes and neutrophils in peripheral blood; it can also be detected on certain parenchymal cells and immune cells during inflammation. Such as liver endothelial cells, airway epithelial cells, dendritic cells, natural killer cells and B and T lymphocytes [4,5]. It is mainly composed of three parts: the transmembrane domain of lysine residues, the V-type Ig-like extracellular domain and the cytoplasmic domain lacking signal motifs. [6].*TREM-1* activates myeloid cells through the adaptor protein *DAP12*, triggers phagocytes to secrete pro-inflammatory chemokines and cytokines, and amplifies inflammation induced by bacteria and fungi [7].

It has been confirmed that *TREM-1* exists in two forms, namely membrane-bound receptor protein and soluble protein (*sTREM-1*) [8] *sTREM-1* is a special form of *TREM-1* that can be directly detected in human body fluids. The level of *sTREM-1* may potentially be used for early diagnosis and prognosis prediction of some infectious diseases, including infectious pleural effusion,lung infections,Sepsis, bacterial meningitis,viral infections(such as Crimean Congo haemorrhagic fever and dengue fever),fungal infections such as Aspergillus infections and burn-related infections.For these infectious diseases, *sTREM-1* is a more sensitive and specific biomarker than traditional indicators(such as C-reactive protein and procalcitonin levels).Therefore, *sTREM-1* is a viable

biomarker for targeted therapy and rapid and early diagnosis of infectious diseases [9]. *sTREM-1* is an important part of the innate immune response, which leads to the release of pro-inflammatory cytokines and chemokines [10]. The serum level of *sTREM-1* increased early after the onset of severe sepsis/shock, but the gene expression of TREM-1 on monocytes did not increase in severe sepsis/shock. These findings have increased our understanding of the pathophysiology of sepsis [11] .

2.2 Ligand

Before 2015, the ligands of *TREM-1* were not very clear, and the lack of identified ligands prevented people from fully understanding the function of *TREM-1*. In 2015, Christine B.and others identified the complex formed by peptidoglycan recognition protein-1 (PGLYRP1) and bacterial-derived peptidoglycan (PGN), high mobility histone group Box 1(*HMGB1*) .Both are effective functional ligands of *TREM-1*, which can bind to *TREM-1* and activate the *TREM-1* signaling pathway [12]. Studies have shown that anti-*TREM-1* antibodies can inhibit the secretion of pro-inflammatory cytokines in inflammatory patients with elevated *PGLYRP-1*. *PGLYRP-1* and myeloperoxidase are potential biomarkers for predicting the effect of anti-*TREM-1* therapy [13].

2.3 Signal Transduction

Because the *TREM-1* cytoplasmic domain lacks any signal transduction mediator docking motif, it must be combined with the signal unit to induce activation of the next-level intracellular pathway [4]. There are conserved lysine residues in the transmembrane domain of *TREM-1* that are positively charged, which can be non-cooperative with a negatively charged transmembrane adaptor protein called DNAX-activating protein 12 (*DAP12*). In combination with valence, *DAP-12* carries the cytoplasmic immune receptor Tyrosine-based Activation Motif (*ITAM*). When *TREM-1* is cross-linked with *DAP12*, the cytoplasmic part of *DAP12* will be phosphorylated by tyrosine kinase and act as a docking site for kinases to initiate a series of phosphorylation events to activate intracellular signaling pathways and induce the production of chemokines And cytokines [14].

In the early stages of infection,*TREM-1* receptor activation can induce Ca2 + mobilization, and activation of transcription factors such as nuclear factor of activating T cell (*NFAT*), Activator protein 1 (*AP1*), *NF-κB* and other transcription factors to make cells synthesize Release large amounts of pro-inflammatory cytokines to form an inflammatory cascade [14]. On the other hand, *TREM-1* can also coordinately activate the The pro renin receptor (*PRR*) signaling pathway, including Toll-like receptors (*TLRs*) and nucleotide binding oligos Nucleotide-binding oligomerization domain-NOD-receptors (*NLRs*) pathway.Further enhance the effects produced by the above signal pathways, leading to the production of inflammatory mediators and cytokine storms [9] Moreover, *TREM-1* activation of polymorphonuclear neutrophils (PMN) can induce rapid degranulation of cells,release IL-8,myeloperoxidase (MPO), and express large amounts of adhesion molecules, triggering Respiratory burst and enhanced phagocytosis, up-regulating the pro-inflammatory effect of TLR4 signaling pathway [6]. In addition, the activation of TLR and IL-1R signaling pathways can also up-regulate the expression of *TREM-1* in neutrophils and monocytes by mediating *NF-κB* activation, forming closed-loop positive feedback regulation, and promoting the pathological changes from SIRS to MODS progress [15,16].

3. TREM-1 and non-infectious inflammatory diseases

In 2000, Axel Bouchon et al. discovered that *TREM-1* interacts with the inflammatory pathway of microbial products as an amplifier of inflammation. Its response to lipopolysaccharide (LPS) is up-regulated, and at the same time it exhibits protective ability against septic shock of E. coli. Show that it is one of the important therapeutic targets for septic shock disease [17]. However, recent evidence also points to the beneficial effects of TREM-*1* inhibition during aseptic inflammation, such as IR, emphasizing the potential therapeutic benefit of *TREM-1* inhibition in aseptic inflammation [18]. During aseptic kidney injury, the *TLR-2/TLR-4 TREM-1* signaling pathway is unnecessary in inflammatory bone marrow cells [19].

3.1 Trauma, surgical tissue damage and burns

The current paradigm of immune response to severe trauma is regarded as an early systemic inflammatory response, followed by a temporary compensatory anti-inflammatory response and suppression of adaptive immunity. And it is believed that serious complications are usually related to the "second blow" (for example, infection or surgical stress) during the compensation period, leading to more severe inflammation. For example, early brain injury caused by major trauma mainly leads to the adverse consequences of subarachnoid hemorrhage, which is closely related to inflammation. et al. found that the expression of *TREM-1* in the cerebrospinal fluid of patients with early brain injury increased [20] Induction of RNA-binding protein-derived peptides by extracellular cold can inhibit the expression of *TREM-1* to reduce inflammation, reduce lung injury, and improve intestinal ischemia-reperfusion injury [21]. Wenzhong et al. put forward a new paradigm for human immune response to severe trauma [22]. The heat injury is followed by a complex immune response. Studies have found that innate and adaptive immune responses may vary significantly depending on the intensity and time of exposure to heat injury, and *TREM-1* is upregulated in the case of aseptic heat injury, indicating that non-infectious molecular structures can activate this *PRR* [23].

3.2 Thromboembolism and Atherosclerosis

After thromboembolism, the immune system is strongly activated, leading to the production of inflammatory cytokines and chemokines, and recruiting neutrophils and monocytes in the infarct area. Studies have shown that the absence of *TREM-1* can limit the recruitment of white blood cells And improve the heart function and survival rate of mice or pigs. In addition, *sTREM-1* was found in the plasma of patients with acute myocardial infarction, and its concentration is an independent predictor of death [24]. In addition, chronic inflammation, abnormal immune response and interference with key enzymes related to lipid metabolism are characteristic of atherosclerosis. In addition to targeting lipid metabolism disorders, in recent years, many international scholars believe that therapeutic regulation of chronic inflammation and immune system response is very promising for the treatment of atherosclerosis. Studies have shown that *TREM-1* can aggravate atherosclerosis. Hardening to promote cardiovascular disease [25].Dyslipidemia induces the surface expression of *TREM-1* on bone marrow cells, and then cooperates with *TREM-1* to enhance monocytes, promote atherosclerotic cytokine production and foam cell formation [26].

3.3 Autoimmune disease

Autoimmune diseases are a family of chronic systemic inflammatory diseases characterized by disorders of the immune system, which ultimately lead to the destruction of tolerance to self-antigens. Fine-tuning the immune response is essential to prevent excessive inflammation and tissue damage in autoimmune diseases.ShengGao et al. found that blocking *TREM-1* may be a new therapeutic target for autoimmune diseases without compromising the host's defense against microorganisms. *TREM-1* expression is dysregulated in inflammatory autoimmune diseases [15].Iman H. et al. found that *sTREM-1* level may be another useful marker of systemic lupus erythematosus activity, and emphasized its importance for patients with NPLE [27]. In addition, studies have also shown that *TREM-1* is induced by macrophages in human gouty arthritis and is related to human gout inflammation. Although its predictive effect on gout inflammation remains to be clarified, targeting *TREM-1* may have an inhibitory effect on gout inflammation [28]. Therefore, blocking *TREM-1* may be a new therapeutic target for autoimmune diseases without compromising the host's defenses against microorganisms.

3.4 Tumor

Maria Carla Bosco et al. found that high TREM-1 expression and increased soluble TREM-1 concentration in macrophages infiltrating human tumors are associated with aggressive tumor behavior and recurrence, and are independent predictors of poor patient survival. [29].Gotts et al. found that TREM-1 is expressed in hepatocellular carcinoma cells and significantly promotes tumor progression [30].Zhihong Yuan et al. determined for the first time the relationship between tumor COX-2 induction, PGE2 production and TREM-1 expression in macrophages in the tumor

microenvironment, and suggested that TREM-1 may be a new target for tumor immune regulation [31]. Leslie Saurer and others recently found that TREM-1 promotes intestinal tumors [32].

4. Conclusion

So far, due to its inflammation amplification effect, TREM-1 has not only become a research hotspot in infectious inflammatory diseases, but also has increasingly highlighted an important role in non-infectious inflammatory diseases. It has been recognized by many scholars and has good prospects. However, the mechanism of TREM-1 in infectious inflammatory diseases is still unclear, and more clinical studies and experimental verification are still needed.

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