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Association between the pathogenesis and development of sepsis and *TIM* gene family

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Abstract: Sepsis is a life-threatening organ dysfunction caused by a series of uncontrolled reactions of the host to infection, trauma, and other factors. In recent years, research has found that various pathological and physiological changes such as inflammation, immune dysfunction, cell apoptosis, autophagy, and coagulation dysfunction are involved in the occurrence and development of sepsis. The proteins encoded by T cell immunoglobulin mucin (TIM) may be potential targets for early diagnosis, immunotherapy, and prognostic evaluation of sepsis. This article provides an overview of the pathogenesis of sepsis and its association with the mucin gene family, in order to provide new ideas for the diagnosis and treatment of sepsis.

Keywords: Sepsis; T cell immunoglobulin mucin; Mucin; T cells; Immunoglobulin

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Sepsis is a complex inflammatory imbalance response of the body to infection, trauma, and other factors, leading to life-threatening organ dysfunction [1]. Some cases progress to septic shock, with high incidence and mortality rates and poor prognosis. According to a systematic epidemiological survey, 33.6% of ICU patients in mainland China were diagnosed with sepsis, and the overall mortality rate of sepsis (28-30 days or during hospitalization) was 29.0% (95% CI: 25.3%-32.8%), with the overall mortality rates of septic shock and severe sepsis (28-30 days or during hospitalization) being 37.3% (95%CI: 28.6% - 46.0%) and 31.1% (95%CI: 25.3% - 36.9%), respectively [2]. Therefore, early diagnosis and treatment of sepsis are crucial for patient prognosis. Research in recent years has found that members of the T cell immunoglobulin and mucin domain (*TIM*) gene family may be involved in the inflammatory response and immune regulation process of sepsis [3-5]. This article reviews the pathogenesis of sepsis and its association with the *TIM* gene family, in order to provide new ideas for the research on the diagnosis and treatment of sepsis.

1 Sepsis

Sepsis is one of the most common critical diseases encountered in clinical practice and represents a major challenge in modern medicine. Currently, antibiotics, fluid resuscitation, and organ system support are still the primary therapeutic strategies for sepsis. The pathogenesis of sepsis is complex, and to better explore new approaches for its diagnosis and treatment, it is essential to conduct in-depth studies on its mechanisms. Recent studies have focused on pathological processes such as inflammation imbalance, immune dysfunction, autophagy, genetic polymorphisms, and coagulation abnormalities [6-7], which provide a theoretical basis for the clinical prevention and treatment of sepsis.

1.1 Disruption of the pro-inflammatory and anti-inflammatory balance

Sepsis initially manifests as a hyper-inflammatory phase, followed by an anti-inflammatory or immunosuppressive phase. The imbalance between pro-inflammatory and anti-inflammatory responses plays a crucial role in the pathogenesis and progression of sepsis [8]. In the early stages of sepsis, infection triggers the release of numerous pro-inflammatory cytokines, primarily tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-1, and IL-6. Although the formation of these cytokines helps the host eliminate pathogenic microorganisms, the pro-inflammatory response can lead to a cytokine storm, resulting in the excessive release of pro-inflammatory factors, which causes fever, increased vascular permeability, and tissue damage. This is a major reason for the high early mortality in sepsis patients.

In the later stages of sepsis, laboratory tests show that, while pro-inflammatory mediators such as C-reactive protein (CRP) and IL-1β continue to be expressed, various endogenous anti-inflammatory responses are activated, generating anti-inflammatory cytokines such as transforming growth factor-β (TGF-β), IL-4, IL-10, and IL-13. These anti-inflammatory cytokines aim to reduce excessive inflammatory responses and protect normal cells from inflammatory damage. These anti-inflammatory cytokines work to mitigate excessive inflammation and protect healthy cells from inflammatory damage. However, this ultimately leads to the depletion of pro-inflammatory mediators and an increase in the proportion of anti-inflammatory mediators, causing an imbalance between

pro-inflammatory and anti-inflammatory responses. At this stage, the host enters an immunosuppressive state with reduced resistance to external pathogens, increasing susceptibility to opportunistic infections, and ultimately leading to multiple organ dysfunction syndrome [7].

1.2 Immune dysfunction

Various types of immune cells, including neutrophils, macrophages, B cells, and T cells, collaborate in the development and progression of sepsis [8]. Studies have shown that these immune cells can be activated through different signaling pathways in septic mice, playing a crucial role in both innate and adaptive immunity during sepsis [9]. Innate immunity involves monocytes, macrophages, dendritic cells, granulocytes, and natural killer cells. In the early stages of sepsis, innate immunity begins to function. When an infection occurs, a large number of mature neutrophils are recruited to the site of infection to provide early defense. However, as sepsis progresses, neutrophil migration capacity decreases, and apoptosis increases, leading to a decline in the functionality of the innate immune system [10]. Macrophage activation is essential in the development of septic shock. Endotoxins (LPS) from Gram-negative bacterial infections can activate macrophages, triggering the release of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6, thereby causing systemic inflammation. Macrophages exist in two activation states, M1 and M2. The M1 phenotype primarily exerts pro-inflammatory effects, whereas M2 exerts anti-inflammatory effects. In the early stages of sepsis, M1 is activated and plays a key role. However, in the later stages of sepsis, M1 apoptosis increases, and M2 polarization rises, contributing to the immune suppression seen in late-stage sepsis and subsequent secondary infections [9,11]. In sepsis, dendritic cell maturation and activation are suppressed, which impairs the process of antigen presentation and the promotion of inflammatory responses. This immunosuppressive effect of dendritic cell dysfunction is particularly evident in the later stages of sepsis [12].

T lymphocytes and B lymphocytes are crucial for acquired immunity. $CD4^+$ T cells assist $CD8^+$ T cells in cellular immunity and also support B cells in humoral immunity. Upon activation, $CD4^+$ T cells differentiate into different subgroups, such as Th1, Th2, Th17, and Treg cells. The Th2 subgroup mainly secretes anti-inflammatory cytokines, while Th1 cells predominantly produce pro-inflammatory cytokines [13]. The Th1/Th2 imbalance has been closely associated with sepsis progression [14]. Late-stage sepsis is more likely to be dominated by a Th2-driven immunosuppressive phase [15]. Persistent immunosuppression is a major cause of sepsis-related mortality [16]. Th17 cells represent a pro-inflammatory subset, while Treg cells promote anti-inflammatory actions. Studies have shown that Tregs can inhibit immune responses of other T cell subsets. During sepsis, the proportion of helper T lymphocyte subsets becomes imbalanced, and Treg differentiation increases, leading to a Th17/Treg imbalance. This imbalance plays a significant role in inflammatory diseases such as sepsis and rheumatoid arthritis [17], and it is a key mechanism that promotes immune paralysis during the later stages of sepsis. When pathogens invade the body, B lymphocytes produce a variety of antibodies involved in humoral immunity. The interaction between antibodies and antigens can block the interaction of viruses or microbial toxins with host cells, thereby inactivating them. It can also tag the invading pathogens for destruction by phagocytic cells. However, in septic patients, B cells are reduced, and the surviving B cells are mainly of a subtype with low antigen-presenting capacity, as well as poor activity and proliferative ability. Furthermore, the occurrence of septic shock is also associated with regulatory B cells, which exert immune - suppressive effects through multiple pathways [9].

1.3 Macrophage autophagy

Macrophage autophagy is closely related to inflammation and immunity. In sepsis, enhanced autophagy can exert protective effects by negatively regulating abnormal macrophage activation, modulating macrophage polarization phenotype, reducing inflammasome activation and inflammatory factor release, and influencing macrophage apoptosis. However, excessive autophagy may lead to autophagic cell death, further exacerbating the inflammatory response [18].

The changes in various inflammation and immune responses are closely associated with the development of sepsis. It is now known that the *TIM* gene family may be closely related to the occurrence and development of sepsis and is an important regulator of immune responses.

2 *TIM* gene family

Currently, eight *TIM* genes (*TIM*-1 to *TIM*-8) have been discovered on mouse chromosome 11B1.1, and three *TIM* genes (*TIM*-1, *TIM*-3, and *TIM*-4) have been identified on human chromosome 5q33.2 [19]. The mouse *TIM*-1, *TIM*-3, and *TIM*-4 genes are homologous to their human counterparts and encode similar type I transmembrane proteins (*TIM*-1, *TIM*-3, and *TIM*-4). Increasing evidence suggests that TIM proteins are expressed on various immune cells and play diverse roles [20]. Studies have shown that *TIM*-1, *TIM*-3, and *TIM*-4 are pattern recognition receptors that specifically recognize phosphatidylserine exposed on the surface of apoptotic cells [21]. phosphatidylserine is typically located on the inner leaflet of the plasma membrane, but during apoptosis, it is redistributed and exposed on the outer membrane. The recognition of apoptotic cells is a critical part of maintaining tissue homeostasis and immune regulation, and the phosphatidylserine on apoptotic cells serves as a key signal to trigger phagocytosis. *TIM*-1, *TIM*-3, and *TIM*-4 can all recognize phosphatidylserine [22-23]. However, their molecular structures and expressions differ, indicating that these three proteins have distinct effects in regulating immune responses.

2.1 TIM-1

A clinical study showed that plasma TIM-1 levels are elevated in septic patients compared to non-septic patients, with higher levels in patients with septic shock. Furthermore, septic patients with higher plasma TIM-1 levels had a lower survival rate [3]. This suggests that TIM-1 may participate in the inflammatory development and immune regulation process in sepsis, and may have certain research value in sepsis diagnosis and prognosis evaluation.

Recent studies have found that TIM-1 is expressed on the surface of various immune cells, including activated T cells (primarily Th2 cells), mast cells, natural killer cells, dendritic cells, and B cells [24]. TIM-1 widely regulates both innate and adaptive immune systems [25]. TIM-1 is a co-stimulatory factor for T cell activation. After the activation of $CD4^+$ T cells, TIM-1 is expressed on Th2 cells and promotes Th2 immunity by enhancing the production of Th2 cytokine IL-4. It is not expressed on Th1 cells. TIM-1 can also shift the balance between Th1 and Th2 immunity towards a Th2 response by interacting with its ligands, promoting Th2 immunity [26]. This regulatory effect of TIM-1 on Th1/Th2 balance may be the mechanism through which TIM-1 participates in the inflammation reactions and immune regulation in sepsis. Therefore, TIM-1 may serve as a novel drug target for diseases with Th1/Th2 imbalance, such as sepsis. TIM-1 may also serve as a clinical marker for sepsis, playing a role in early diagnosis and intervention.

In addition, TIM-1 plays an important role in regulating Treg cell function. Studies have confirmed that activation of TIM-1 can reduce the expression of certain cell molecules, such as Foxp3, in Treg cells, impairing their function and reducing the conversion of other cells into Tregs. This leads to an immune imbalance between Th17 and Treg cells, affecting the levels of inflammatory factors [27] and ultimately resulting in immune dysregulation, thereby contributing to the development of sepsis and affecting its outcome and prognosis.

Since TIM-1 is a receptor for PS, cells expressing TIM-1 can bind to and/or engulf apoptotic cells that express PS, mediating the clearance of apoptotic cells and thus participating in the body's immune response.

2.2 TIM-3

TIM-3 is also a member of the *TIM* gene family. A large number of experimental data supports TIM-3 as an immune checkpoint, and targeting TIM-3 is a promising immune therapeutic approach. Recent research has found that TIM-3 plays an important role not only in chronic viral infections and cancer [28] but also in sepsis, where it plays a critical role in the immune functions of sepsis monocytes, macrophages and T lymphocytes [29]. Specifically, blocking the TIM-3 pathway can exacerbate the pro-inflammatory macrophage response and lymphocyte apoptosis induced in the early stages of sepsis. However, in the later stages of sepsis, co-culturing TIM-3-deficient macrophages with T cells induces a shift towards a Th2 response, which promotes immune suppression during the later stages of sepsis [5].

During acute sepsis, TIM-3 expression on macrophages is upregulated, significantly inhibiting the production of pro-inflammatory cytokines mediated by Toll-like receptors (TLRs), thus alleviating the inflammatory response [30]. Numerous studies have proven the important role of TLRs in the pathogenesis of sepsis [31]. The negative regulation of TLR by TIM-3 helps prevent excessive inflammation during the acute phase of sepsis and mitigates the disease, suggesting that this pathway may become a new target for sepsis therapy. Furthermore, clinical studies have found that TIM-3 expression on $CD4^+$ T cells is increased in septic patients, and its levels correlate with the severity of immune suppression in these patients. In septic mice, inhibiting TIM-3 expression reduced the mortality rate associated with septic immunosuppression [32]. Studies also found that during early sepsis induced by cecal ligation and puncture, TIM-3 expression increased in $CD8^+$ T cells in the spleen, and blocking TIM-3 with anti-TIM-3 antibodies reduced inflammation and lymphocyte apoptosis, as well as alleviated sepsis severity [33]. Moreover, inhibiting TIM-3 expression can control the excessive activation of natural killer T cells in septic patients, thus alleviating the inflammatory cytokine cascade triggered by NKT cells, which otherwise leads to poor prognosis in sepsis patients. This helps maintains immune homeostasis and improves prognosis [34]. Therefore, targeting TIM-3 expression may provide a novel approach for immunotherapy in sepsis.

Additionally, since phosphatidylserine is a ligand for TIM-3, the interaction between TIM-3 and phosphatidylserine mediates the phagocytosis of apoptotic bodies [23] and promotes cross-presentation by dendritic cells, enhancing the phagocytosis of apoptotic cells and cross-presenting antigens. This, in turn, regulates immune cells and pathogenic pathways [28].

2.3 TIM-4

The expression of *TIM*-4 gene was significantly upregulated in peritoneal macrophages from septic mice following activation. TIM-4 can attenuate the development of endotoxin-induced sepsis in mice, and this process may be mediated by negative regulation of macrophage function [4], suggesting that TIM-4 holds significant potential as a therapeutic target for immune modulation in sepsis.

TIM-4 is a phosphatidylserine receptor [35], which is expressed on antigen-presenting cells such as macrophages and mature dendritic cells, and is involved in the recognition and clearance of apoptotic cells. Moreover, studies have shown that TIM-4 is expressed on various other immune cells. One of its most important functions is its expression on macrophages, where TIM-4 interacts with its ligand, phosphatidylserine, to mediate its effects. This interaction allows TIM-4-expressing macrophages not only to recognize apoptotic cells but also to activate various immune cells, including T cells,

by recognizing different densities of PS. When pathogens enter the body, phagocytic cells expressing high levels of TIM-4 rapidly recognize PS and engulf apoptotic cells or antigen-specific T cells, thereby clearing apoptotic cells or reducing the number of antigen-specific T cells in the periphery. This process helps regulate immunity by balancing the number and ratio of antigen-specific T cells and memory T cells, ultimately inducing immune tolerance [36]. Studies have found that after endotoxin stimulation, TIM-4 expression is upregulated on the surface of activated macrophages in mice. The increased expression of TIM-4 inhibits the production of NO and cytokines (TNF-α, IL-1β, IL-6, and IFN-β) by macrophages, thereby alleviating the occurrence of endotoxin-induced septic shock in the early stages of sepsis [37]. However, in the late stages of sepsis, the expression of TIM-4 in peripheral blood monocytes/macrophages is significantly decreased, leading to macrophage dysfunction, loss of phagocytic ability, and an immunosuppressive state. Secondary infections become the leading cause of death in late-stage sepsis patients. This suggests that TIM-4 plays an important role as a target for immune modulation therapy in sepsis.

TIM-1, a natural ligand of TIM-4, is expressed on activated macrophages or mature dendritic cells, and the increased expression of TIM-4 on these cells can bind to TIM-1 expressed on the surface of activated T cells. This binding induces phosphorylation of TIM-1, activating a series of signaling pathways that ultimately regulate T cell proliferation and balance Th1/Th2 cell differentiation [38]. Thus, TIM-4 contributes to the maintenance of immune homeostasis in sepsis and is involved in the development and progression of sepsis. Furthermore, research has shown that TIM-4 can also bind to TIM-3 on the surface of Th1 cells, inducing Th1 cell apoptosis [39]. This promotes an immune suppressive phase dominated by Th2 cells in sepsis patients, accelerating their mortality. Therefore, the TIM gene family members and their interactions play a significant role in the development of sepsis, and understanding these interactions is crucial for early diagnosis and prognosis-based treatment of sepsis.

The pathogenesis of sepsis is complex, involving mechanisms such as the inflammatory cascade, excessive oxidation, immune cell dysregulation, coagulopathy, and fibrinolysis, all of which interact to form a complex pathogenic network in sepsis. Among these, inflammation and immune system damage remain the most critical factors for sepsis patients. The TIM gene family is widely involved in immune responses and offers new insights and methods for immunotherapy in sepsis and other immune-related diseases. It is hoped that *TIM* genes and their proteins will become important indicators for the diagnosis, severity assessment, and prognosis of sepsis, and serve as potential targets for molecular or gene-targeted therapies in sepsis. However, the clinical application of the *TIM* gene family and its proteins requires further experimental and clinical research.

Conflict of interest None

Reference

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·研究进展·

脓毒症发生发展机制与 *TIM* 基因家族的关联

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摘要：脓毒症是由机体对感染、创伤等的一系列失控反应引起的危及生命的器官功能障碍。近年来研究发现炎症反应、免疫功能紊乱、细胞凋亡、细胞自噬、凝血功能障碍等多种病理生理改变参与脓毒症的发生及发展，而人 T 细胞免疫球蛋白和黏蛋白结构域（T cell immunoglobulin mucin，TIM）蛋白及其单抗可能是脓毒症早期诊断、免疫治疗及预后评估的潜在靶点。本文对脓毒症的发病机制及其与黏蛋白基因家族之间的关联进行概述，以期为脓毒症诊断与治疗的研究提供新的思路。

关键词：脓毒症；T 细胞免疫球蛋白和黏蛋白结构域；黏蛋白；T 细胞；免疫球蛋白
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Association between the pathogenesis and development of sepsis and *TIM* gene family

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Abstract: Sepsis is a life-threatening organ dysfunction caused by a series of uncontrolled reactions of the host to infection, trauma, and other factors. In recent years, research has found that various pathological and physiological changes such as inflammation, immune dysfunction, cell apoptosis, autophagy, and coagulation dysfunction are involved in the occurrence and development of sepsis. The proteins encoded by T cell immunoglobulin mucin (TIM) may be potential targets for early diagnosis, immunotherapy, and prognostic evaluation of sepsis. This article provides an overview of the pathogenesis of sepsis and its association with the mucin gene family, in order to provide new ideas for the diagnosis and treatment of sepsis.

Keywords: Sepsis; T cell immunoglobulin mucin; Mucin; T cells; Immunoglobulin
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脓毒症是机体对感染、创伤等产生的一种复杂的炎症失调反应，继而导致威胁生命的器官功能障碍[1]，部分会发展为脓毒性休克，发病率和死亡率均高，预后差；据一项系统流行病学调查显示，中国大陆 ICU 的患者中有 33.6%被诊断为脓毒症，合并脓毒症（28~30 d 或住院期间）的总死亡率为29.0%（95%*CI*：25.3%~32.8%），感染性休克和严重脓毒症的总死亡率（28~30 d 或住院期间）分别为 37.3%（95%*CI*：28.6%~46.0%）和 31.1%（95%*CI*：25.3%~36.9%）[2]。因此，早期诊断和治疗脓毒症对患者预后十分重要。近年的研究发现，T 细胞免疫球蛋白和黏蛋白结构域（*TIM*）基因家族成员可能参与脓毒症的炎症反应及免疫调控过程[3-5]。本文对脓毒症的发病机制及其与 *TIM* 基因家族之间的关联进行综述，以期为脓毒症的诊断与治疗提供新的思路。

1　脓毒症

脓毒症是临床常见的重症疾病之一，是现代医学面临的一大疑难问题。目前，抗生素、液体复苏和器官系统支持等仍是临床治疗脓毒症的主要手段。脓毒症发病机制复杂，为了更好地探讨脓毒症的诊疗新思路，对脓毒症发病机制进行深入研究十分必要。近年来的研究涉及到炎症反应失衡、免疫功能紊乱[6]、细胞自噬、基因多态性、凝血功能障碍等病理生理过程[7]，为脓毒症临床防治提供了理论依据。

1.1　促炎-抗炎平衡失调　脓毒症发病初为高炎症期，随后为抗炎或免疫抑制期，促炎与抗炎反应的失衡是脓毒症发生、发展的关键[8]。脓毒症早期感染导致大量促炎细胞因子释放，主要有肿瘤坏死因子（TNF）-α、干扰素（IFN）-γ、白细胞介

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素(IL)-1、IL-6 等,此阶段的形成虽然有助于机体清除病原微生物,但促炎反应可引起炎症因子风暴,即各种促炎因子大量释放导致机体出现发热、血管通透性增加、组织损伤等一系列损伤,这是脓毒症患者早期死亡率较高的原因;而到脓毒症后期实验室检查可以发现,在 C 反应蛋白(CRP)、IL-1β 等促炎介质持续表达的同时,机体还会发生各种内源性抗炎反应,并生成转化生长因子-β(TGF-β)、IL-4、IL-10、IL-13 等抗炎细胞因子,其目的是减缓过度炎症反应,保护正常细胞不受炎症破坏,但最终将会导致机体促炎介质的耗竭以及抗炎介质的比例上升,发生促炎-抗炎平衡失调,此时机体以免疫抑制状态为主,对外界抵抗力低下,易发生各种机会性感染,最终将发生多器官功能障碍综合征(MODS)[7]。

1.2　*免疫功能紊乱*　不同类型的免疫细胞,如中性粒细胞、巨噬细胞、B 细胞和 T 细胞,在脓毒症的发生发展过程中发挥协同作用[8]。研究发现,以上各种免疫细胞可以通过不同的信号通路在脓毒症小鼠中被激活,对机体脓毒症期间的先天和适应性免疫功能发挥至关重要的作用[9]。固有免疫主要由单核/巨噬细胞、树突状细胞、粒细胞、自然杀伤细胞等参与。在脓毒症早期,固有免疫即开始发挥作用,当机体出现感染时,血液中大量成熟的中性粒细胞首先聚集在感染部位发挥早期防御作用。但随着脓毒症的进展,中性粒细胞迁移能力减弱且凋亡逐渐增加,机体的固有免疫系统功能下降[10]。巨噬细胞的活化在脓毒性休克的发展中必不可少,革兰阴性菌感染引起的内毒素可以激活巨噬细胞产生一系列促炎细胞因子,如 TNF-α、IL-1、IL-6 等,从而导致全身性炎症;巨噬细胞具有 M1、M2 两种激活状态,M1 亚型主要发挥促炎作用,而 M2 亚型发挥抗炎作用,在脓毒症早期 M1 被激活并发挥作用,而到脓毒症后期 M1 细胞凋亡增加、M2 亚型极化增加,其与脓毒症后期发生免疫抑制从而引起继发感染相关[9,11]。脓毒症时树突状细胞的成熟与活化受抑制,导致成熟树实状细胞呈递抗原并促进炎症反应的过程受抑制,在脓毒症后期免疫抑制发挥一定作用[12]。而参与获得性免疫的细胞主要为 T 淋巴细胞和 B 淋巴细胞,其中,$CD4^+$T 淋巴细胞不仅可以辅助 $CD8^+$T 淋巴细胞参与机体细胞免疫,同时也可以辅助 B 淋巴细胞参与体液免疫,$CD4^+$T 细胞激活后可分化为 Th1、Th2、Th17、Treg 等不同的亚群,其中 Th2 亚群主要分泌抗炎因子,而 Th1 细胞则主要分泌促炎因子,Th1、Th2 细胞各自分泌细胞因子可以促进自身增殖并相互抑制对方增殖,从而维持相对平衡[13]。研究发现,Th1/Th2 细胞失衡与机体脓毒症的发展密切相关[14],脓毒症患者后期更倾向于由 Th2 主导的免疫抑制阶段[15],而持续处于免疫抑制状态则是脓毒症患者死亡的主要原因[16]。另外,Th17 细胞代表促炎亚群,而 Tregs 细胞促进抗炎作用,研究表明,Tregs 可抑制其他 T 细胞亚群的免疫反应,脓毒症时辅助性 T 淋巴细胞亚群比例失衡且 Tregs 分化增加,导致 Th17 和 Tregs 失衡,这在脓毒症和类风湿性关节炎等炎症性疾病中发挥重要作用[17],是最终促进脓毒症后期发生免疫麻痹的重要机制。而当病原体侵入机体后,机体的 B 淋巴细胞会产生一系列抗体参与体液免疫,抗体和抗原的相互作用可以阻断病毒或微生物毒素与宿主细胞的相互作用而使其失活,还可以标记入侵的病原体以供吞噬细胞破坏,但脓毒症患者 B 细胞减少,存活的 B 细胞主要为一种抗原呈递能力及活性和增殖能力均较低的亚型 B 细胞;此外,脓毒性休克的发生与调节 B 细胞亦有关,其可通过多种途径发挥免疫抑制效应[9]。

1.3　*巨噬细胞自噬*　巨噬细胞自噬与炎症和免疫密切相关,脓毒症中自噬增强可通过负性调节异常的巨噬细胞活化、调节巨噬细胞极化表型、减少炎性小体的活化和炎性因子的释放、影响巨噬细胞凋亡等发挥保护作用,但过度的自噬也可能导致其自噬性死亡,进一步加剧炎症反应[18]。

以上各种炎症与免疫反应的变化与脓毒症发生发展密不可分,现已知道 *TIM* 基因蛋白家族或许与脓毒症的发生发展之间存在紧密联系,是免疫反应的重要调节因子。

2　*TIM* 基因家族

目前已发现小鼠 11B1.1 染色体上的 8 个 *TIM* 基因(*TIM*-1~8),人类 5q33.2 染色体上的 3 个基因(*TIM*-1、*TIM*-3、*TIM*-4)[19],且小鼠与人类 *TIM*-1、*TIM*-3、*TIM*-4 基因同源,编码相似的Ⅰ型细胞表面跨膜蛋白(TIM-1、TIM-3、TIM-4)。越来越多的证据表明,TIM 蛋白在多种免疫细胞上表达且发挥各种作用[20]。研究显示,TIM-1、TIM-3 和 TIM-4 是同一种模式识别受体,可以特异性地识别暴露在凋亡细胞表面的磷脂酰丝氨酸(PS)[21]。PS 通常定位于质膜的内叶,但当细胞凋亡时,它被重新分布并暴露在外膜上,对凋亡细胞的识别是维持组织稳态和免疫调节过程中的重要组成部分,而凋亡细胞上的 PS 是触发细胞吞噬的关键信号,TIM-1、TIM-3 和 TIM-4 都能识别 PS[22-23],但其分子结构与表达不同,表明此 3 种蛋白在调节免疫应答具有不同的效应。

2.1　*TIM-1*　研究显示,血浆 TIM-1 水平在脓毒症患者较非脓毒症患者升高,在脓毒性休克患者中更高,并且血浆 TIM-1 水平更高的同一阶段的脓毒症患者生存率更低[3]。由此可见,TIM-1 可能参与脓毒症的炎症发展及免疫调控过程,并在脓毒症诊断及预后评估中有一定的研究价值。近年来研究发现,TIM-1 表达在多种免疫细胞表面,包括被激活的 T 细胞(优先是 Th2 细胞)、肥大细胞、自然杀伤细胞、树突状细胞和 B 细胞[24],广泛地调节机体先天免疫及适应性免疫系统[25]。而 TIM-1 是 T 细胞活化的协同刺激因子,在 $CD4^+$T 细胞活化后,TIM-1 表达于 Th2 细胞中,对 Th2 免疫具有促进作用[20],增强 Th2 细胞因子 IL-4 的产生,而在 Th1 细胞中不表达,TIM-1 还可以通过与其配体的相互作用调节肥大细胞的分泌,使 Th1 与 Th2 之间的平衡向 Th2 免疫偏移,对 Th2 免疫具有促进作用[26],以上 TIM-1 分子对 Th1/Th2 平衡的调节作用可能是 TIM-1 参与脓毒症的炎症反应与免疫调控的机制。因此,TIM-1 可能成为新的药物靶点用来治疗 Th1/Th2 失衡为机制的疾病,比如脓毒症;同时,TIM-1 可能成为脓毒症的临床指标,对脓毒症患者的早期诊断与干预以及预测预后发挥价值。

另外,TIM-1 在调节 Treg 细胞功能中也有重要作用,研究证实,TIM-1 的激活能降低 Treg 细胞中某些细胞因子的表达

及其功能，并且减少相应细胞向 Treg 细胞转化，导致 Th17/Treg 的免疫失衡而影响炎症因子水平[27]，最终造成免疫紊乱，从而参与脓毒症发生发展，并影响脓毒症转归及预后。

由于 TIM-1 是 PS 的受体，表达 TIM-1 的细胞可以结合和/或吞噬表达 PS 的凋亡细胞，介导凋亡细胞的清除，从而参与机体免疫应答。

2.2　TIM-3　TIM-3 蛋白亦是 *TIM* 基因家族编码蛋白中的一员，大量实验数据支持 TIM-3 作为免疫检查点，靶向 TIM-3 是很有前景的一种免疫治疗方法。近年来研究发现，TIM-3 不仅在慢性病毒感染和肿瘤中起重要作用[28]，在脓毒症中亦发挥重要作用，对脓毒症单核细胞、巨噬细胞、T 淋巴细胞免疫功能发挥重要作用[29]。具体来说，阻断 TIM-3 通路可以加重脓毒症早期诱导的促炎巨噬细胞反应和淋巴细胞凋亡，但在脓毒症晚期 T 细胞与 TIM-3 敲低的巨噬细胞共培养导致了偏向的 Th2 反应，即导致机体向抗炎反应的转变，从而促进脓毒症晚期的免疫抑制[5]。在急性脓毒症期间巨噬细胞上的 TIM-3 上调，显著抑制 Toll 样模式识别受体（Toll-like receptor，TLR）介导的促炎细胞因子的产生，而减轻炎症反应[30]。许多研究已经证明了 TLR 在脓毒症发病机制中的重要作用[31]，TIM-3 对 TLR 的这种负调控作用有助于预防脓毒症急性期过度的炎症反应并减轻脓毒症，提示该作用通路可能成为干预脓毒症治疗的新靶点。另有临床研究发现脓毒症患者 $CD4^+$T 细胞上的 TIM-3 表达升高，其比例与脓毒症患者免疫抑制的严重程度有关，脓毒性免疫抑制患者 $CD4^+$T 细胞上 TIM-3 的表达升高，而通过抑制 TIM-3 的表达可降低脓毒性免疫抑制小鼠的死亡率[32]。另有研究发现，盲肠结扎穿孔术诱导的早期脓毒症小鼠，小鼠脾 $CD8^+$T 细胞中 TIM-3 表达升高，而用抗 TIM-3 抗体阻断 TIM-3 的表达可降低脓毒症小鼠的炎症反应和淋巴细胞凋亡，还可以减轻脓毒症的严重程度[33]。另外，研究发现通过抑制 TIM-3 的表达可以控制脓毒症患者 NKT 细胞的过度激活，从而减轻 NKT 细胞引发的炎症细胞因子级联反应导致脓毒症患者的不良预后，维持脓毒症患者免疫稳态，改善预后[34]。因此，抑制 TIM-3 的表达可能是一个脓毒症免疫治疗的新靶点。

其次，PS 作为 TIM-3 的配体，TIM-3 和 PS 的相互作用有助于介导凋亡小体的吞噬[23]，且可促进树突状细胞的交叉呈递，促进细胞凋亡的吞噬，增强交叉抗原呈递，从而调节免疫细胞和致病途径[28]。

2.3　TIM-4　脓毒症小鼠腹腔巨噬细胞激活后 *TIM*-4 基因表达明显上调，TIM-4 可减缓内毒素诱导的小鼠脓毒症的发生，并且此过程可能是负性调控巨噬细胞功能实现的[4]，提示 TIM-4 可作为脓毒症免疫调节治疗靶点的重要价值。

TIM-4 是一种 PS 受体[35]，除表达在抗原提呈细胞如巨噬细胞和成熟树突状细胞上参与凋亡细胞的识别和清除作用外，其在其他多种免疫细胞上表达，其中，TIM-4 最重要的功能之一是在巨噬细胞中表达，TIM-4 与其配体 PS 结合发挥作用，使表达 TIM-4 的巨噬细胞不仅可以识别凋亡细胞，还可以通过识别不同密度的 PS 使包括 T 细胞在内的各种免疫细胞激活，当病原体进入机体后，机体通过高表达 TIM-4 的吞噬细胞快速识别 PS 并吞噬凋亡细胞或抗原特异性 T 细胞，使凋亡细胞清除或导致进入外周的抗原特异性 T 细胞减少，从而通过平衡抗原特异性 T 细胞和记忆性 T 细胞的数量和比例来调节免疫[36]，最终诱导免疫耐受。研究发现，内毒素刺激小鼠巨噬细胞活化后其表面的 TIM-4 表达上调，表达上调的 TIM-4 抑制巨噬细胞产生 NO 及细胞因子（TNF-α、IL-1B、IL-6 和 IFN-β），从而减轻脓毒症早期内毒素诱导的脓毒性休克的发生[37]；而到了脓毒症晚期，外周血单核/巨噬细胞中 TIM-4 的表达显著降低，导致巨噬细胞瘫痪、吞噬功能丧失和免疫抑制状态，继发感染成为晚期脓毒症患者死亡的主要原因，由此提示 TIM-4 可作为脓毒症免疫调节治疗靶点的重要价值。

TIM-1 是 TIM-4 的天然配体，TIM-4 在活化的巨噬细胞或成熟的树突状细胞上的表达增加，而这些细胞上的 TIM-4 可以与活化 T 细胞表面表达的 TIM-1 结合，从而诱导 TIM-1 磷酸化，激活一系列信号通路，最终调控 T 细胞的增殖，调节 Th1/Th2 细胞平衡[38]，从而维持脓毒症的免疫自稳机制，从而参与脓毒症的发生发展过程。研究表明，TIM-4 还可通过与 Th1 细胞表面的 TIM-3 结合，诱导 Th1 细胞凋亡[39]，使脓毒症患者处于由 Th2 主导的免疫抑制阶段，从而加速脓毒症患者的死亡。由此可见，*TIM* 基因家族成员及其之间的相互作用在脓毒症的发生发展中起作用，对脓毒症的早期诊断及预后治疗有重要的意义。

脓毒症发病机制复杂，包括炎症瀑布、过度氧化、免疫细胞紊乱、凝血及纤溶系统异常等多种机制，其间相互作用形成脓毒症复杂的致病网络。其中，炎症及免疫系统对脓毒症患者的损害仍是最重要的，*TIM* 基因家族广泛参与免疫应答过程，为脓毒症等多种疾病的免疫相关治疗提供新的思路和方法。期望 *TIM* 基因及其蛋白能成为脓毒症疾病诊断、病情严重程度及预后评估的重要指标，并成为脓毒症分子靶向治疗或基因靶向治疗的潜在靶点，但 *TIM* 基因家族及其蛋白应用于临床，还需要更多的实验与临床研究。

利益冲突　无

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