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# Tim-3在自身免疫性疾病中的研究进展

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**摘要** 自身免疫性疾病是一系列由于免疫系统错误地攻击自身组织或器官引起的疾病, 与免疫细胞过度激活有关。T细胞免疫球蛋白及黏蛋白结构域分子-3(T cell immunoglobulin and mucin domain-containing protein-3, Tim-3)作为一种免疫检查点分子, 可以通过与不同的配体结合来调节免疫细胞的功能, 在自身免疫性疾病中发挥免疫调节的作用。该综述总结了Tim-3的结构和生物学功能、Tim-3与不同配体间的相互作用、Tim-3在自身免疫性疾病中的研究进展, 讨论了Tim-3作为靶点的免疫治疗前景, 为Tim-3在自身免疫性疾病中的应用提供新思路。

**关键词** Tim-3; 免疫检查点; 自身免疫性疾病; 生物标志物

# Research Progress of Tim-3 in Autoimmune Diseases

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**Abstract** Autoimmune diseases are a series of diseases caused by the immune system mistakenly attacking its own tissues or organs, which are related to the excessive activation of immune cells. Tim-3 (T cell immunoglobulin and mucin domain-containing protein-3) is an immune checkpoint molecule. It can regulate the function of immune cells by binding to different ligands, and play an immunomodulatory role in autoimmune diseases. This review summarizes the structure and biological function of Tim-3, the interaction between Tim-3 and different ligands, and the research progress of Tim-3 in autoimmune diseases. The prospect of Tim-3 as a target for immunotherapy is discussed, which provides new ideas for the application of Tim-3 in autoimmune diseases.

**Keywords** Tim-3; immune checkpoints; autoimmune disease; biomarker

自身免疫性疾病是一系列由于免疫系统未能区分“自我”和“非我”而错误地攻击自身组织或器官引起的疾病, 与免疫细胞过度激活而产生过量的炎症因子有关。过度的炎症反应会对正常组织造成进行性损害。因此免疫细胞的激活需要精细调控, 以实现免疫稳态, 免疫细胞既能有效地清除病原体, 又不会造成过度的炎症性损害。为此, 免疫细胞在其表面表达各种免疫检查点蛋白, 这些蛋白与其配体的结合可以激活细胞内负调控信号通路, 起到“刹车”的作用。

T细胞免疫球蛋白及黏蛋白结构域分子-3(T cell immunoglobulin and mucin domain-containing protein-3, Tim-3)作为免疫检查点分子, 最初被鉴定在产生干扰素-γ(interferon-γ, IFN-γ)的$CD4^+$和$CD8^+$T细胞上表达, 随后在多种免疫细胞[例如: 调节性T细胞(regulatory T cell, Treg)、髓系细胞、自然杀伤细胞和肥大细胞]上也检测到Tim-3的表达[1]。Tim-3通过与不同的配体结合来调节免疫细胞的功能, 在自身免疫性疾病中发挥免疫调节的作用。本文综述了Tim-3的结构和生物学功能、Tim-3与不同配体间的相互作用、Tim-3在自身免疫性疾病中的研究进展以及Tim-3作为靶点的免疫治疗前景, 为Tim-3在自身免疫性疾病中的应用提供新思路。

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## 1 Tim-3的结构和生物学功能

Tim-3是一种I型跨膜蛋白, 其一级结构由一个可变的免疫球蛋白结构域、一个胞外黏蛋白结构域、一个跨膜区、一个胞内区组成[2]。值得注意的是, 胞内区上5个保守酪氨酸残基的磷酸化在激活细胞内信号通路中起着至关重要的作用[3], 特别是Tyr256和Tyr263。当Tim-3没有与其配体结合的时候, 人类白细胞抗原B相关转录物3(human leukocyte antigen B-associated transcript 3, BAT3)结合到胞内区上, 募集具有活性催化形式的酪氨酸激酶LCK, 以促进Tim-3下游的阳性信号的激活, 帮助维持T细胞的激活状态[1]。相反, 当Tim-3与其配体结合时, 酪氨酸蛋白激酶ITK触发胞内区上Tyr256和Tyr263的磷酸化, 导致BAT3从Tim-3上解离, 发挥抑制信号转导功能[4]。在自身免疫的背景下, *BAT3*基因敲除的T细胞共抑制受体的表达水平增加, 表明这种前馈负调控是通过BAT3进行的[5]。

Tim-3不仅存在膜结合形式, 还能以可溶性形式存在。可溶性Tim-3(soluble Tim-3, sTim-3)相较于膜结合型Tim-3, 缺少黏蛋白结构域和跨膜区。sTim-3可以通过解整合素金属蛋白酶(a disintegrin and metalloprotease, ADAM)10/17切割膜结合型Tim-3而来[6]。sTim-3还有部分来源于脾细胞, 有研究发现*sTim-3* mRNA主要在脾细胞中表达, 且在脾细胞激活后, sTim-3 mRNA和蛋白的表达上调[7]。目前, 已有很多文献报道sTim-3可以作为多种疾病的生物标志物, 我们所在的研究团队已经证明sTim-3可以作为胃癌、病毒性肝炎、慢性肾脏病的生物标志物[8-10]。然而目前尚不清楚sTim-3的确切功能。推测sTim-3可能是一个诱饵受体, 与膜结合型Tim-3共同竞争与Tim-3配体的结合, 从而干扰膜结合型Tim-3发挥其抑制功能。然而有体外实验表明, sTim-3可以减少T细胞产生白细胞介素(interleukin, IL)-2[11]。有关sTim-3的生物学功能有待进一步的研究。

目前主流的观点认为Tim-3是一种共抑制受体。然而有研究证明在短期T细胞受体(T cell receptor, TCR)刺激下, Tim-3在体外Jurkat细胞上的异位表达可以促进TCR信号转导[12]。Tim-3的表达与AKT-雷帕霉素机械靶蛋白(mechanistic target of rapamycin, mTOR)信号通路的增加有关, 这被认为是Tim-3共刺激的标志[13]。在结核分枝杆菌(*M. tuberculosis*)感染过程中, Tim-3似乎具有双重作用, 既介导了Galectin-9激活巨噬细胞以抑制细胞内细菌复制, 同时又抑制了Tim-3$^+$效应T细胞反应[1]。总之需要进一步的研究来阐明Tim-3在免疫细胞功能调节中是作为共抑制受体还是共刺激受体。值得注意的是, Tim-3及其配体结合的生物学影响在不同疾病之间甚至在同一疾病的不同阶段中可能会有差异。

## 2 Tim-3与配体的相互作用

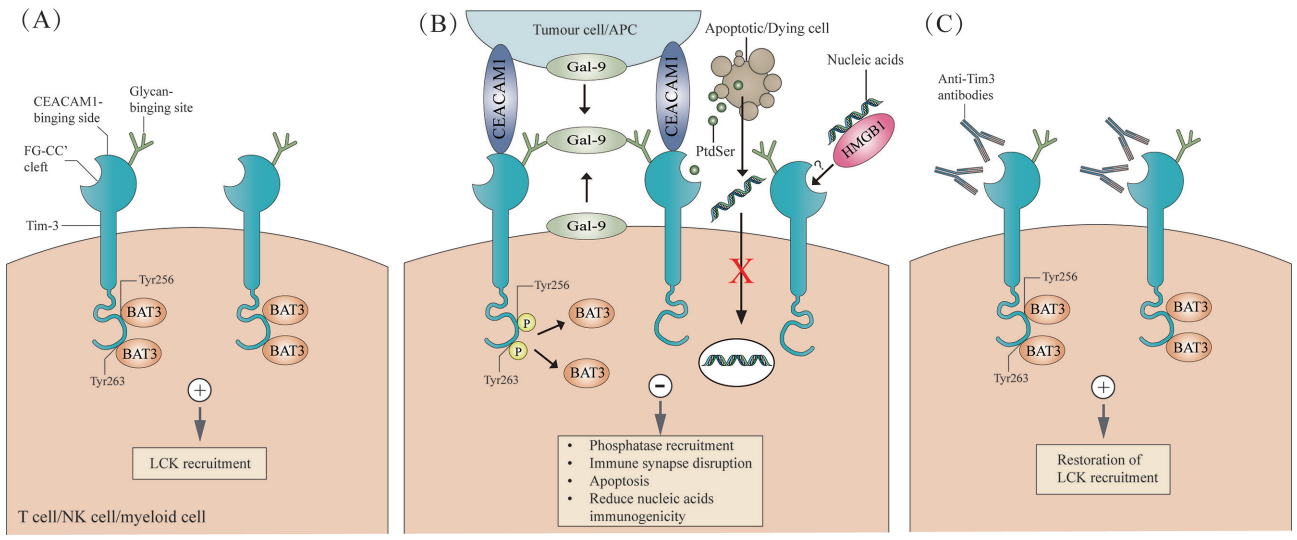
Tim-3与其配体的相互作用以正向或反向信号方式激活不同的下游通路, 从而参与调节自身免疫性疾病、慢性感染和癌症的免疫反应(图1)[1]。目前, 已发现Tim-3有以下4种配体: 半乳糖凝集素-9(Galectin-9, Gal-9)、高迁移率族蛋白B1(high mobility group box 1 protein, HMGB1)、磷脂酰丝氨酸(phosphatidylserine, PtdSer)、癌胚抗原相关细胞黏附分子1(carcinoembryonic antigen-related cell adhesion molecule 1, CEACAM1), 这些配体与Tim-3结合后有不同的作用机制(表1)。

### 2.1 Gal-9

Gal-9是一种可溶性C型凝集素, 由多种造血细胞广泛表达和分泌, 能与细胞表面蛋白上的碳水化合物部分结合。Gal-9能与Tim-3免疫球蛋白结构域上的碳水化合物基序结合, 驱动Tim-3在细胞表面上寡聚, 导致位于Tim-3胞内区上的Tyr256和Tyr263磷酸化。这个过程能促使BAT3从Tim-3的胞内区释放, 导致Tim-3$^+$T细胞钙离子内流和细胞死亡[16]。Tim-3$^+$Treg细胞与Tim-3$^-$Treg细胞相比有着更强的抑制功能, 阻断Tim-3-Gal-9途径降低了Treg细胞的抑制能力[24]。此外, Tim-3可以通过某种潜在机制上调Gal-9的表达, 在T细胞过度表达Tim-3的转基因小鼠中, CD11b$^+$髓系来源的抑制细胞表达Gal-9的数量显著增加[25]。Tim-3和Gal-9相互作用不都是引起免疫功能的抑制, 例如在结核分枝杆菌感染期间, 肺内CD4$^+$T细胞和CD8$^+$T细胞都表达Tim-3, 使这些T细胞能与在细胞表面表达Gal-9的巨噬细胞相互作用, 导致细菌增殖受到抑制[26]。

### 2.2 HMGB1

HMGB1是一种高度保守的非组蛋白DNA结合蛋白, 主要存在于细胞核内, 但在细胞激活和死亡过程中可以转运到细胞质或细胞外[27]。细胞外HMGB1能与垂死细胞释放的DNA结合, 通过Toll样受体(toll-like receptors, TLRs)促进核酸感知, 激活巨噬细胞和其他免疫细胞, 表现为损伤相关分子模式(damage-




A: 在没有与其配体结合的情况下, Tim-3与BAT3相互作用并通过募集LCK来维持免疫细胞活化。B: Gal-9可以结合到肿瘤细胞的表面, 也可以由肿瘤细胞、抗原呈递细胞和其他细胞分泌, 或者由表达Tim-3的细胞以自分泌的方式分泌。其碳水化合物识别结构域结合到Tim-3上的聚糖结合位点。Gal-9具有两个碳水化合物识别结构域, 并且可以促进Tim-3的寡聚化, 从而潜在地促进其他Tim-3-配体复合物如CEACAM1-Tim-3的形成。此外, 从凋亡细胞释放的PtdSer可以结合Tim-3上的FG-CC'裂缝结合位点。在与Gal-9或CEACAM1结合时, Tim-3的胞内区上的Tyr256和Tyr263被磷酸化, 从而释放BAT3。这将破坏免疫突触形成和募集磷酸酶。最终, 细胞变得无反应性或凋亡, 这是由细胞内钙释放介导的。HMGB1与Tim-3结合将干扰垂死细胞的核酸进入DCs, 降低核酸的免疫原性, 然而具体的结合位置还不清楚。C: 抗Tim-3抗体通过干扰Tim-3与Tim-3的配体结合, 从而维持Tim-3-BAT3相互作用募集LCK维持免疫细胞活化。

A: in the absence of binding to its ligand, Tim-3 interacts with BAT3 and maintains immune cell activation by recruiting LCK. B: Gal-9 can be bound to the surface of tumor cells, secreted by tumor cells, antigen-presenting cells, and other cells, or secreted in an autocrine manner by Tim-3-expressing cells. Its carbohydrate recognition domain binds to the glycan binding site on Tim-3. Gal-9 possesses two carbohydrate recognition domains and can promote the oligomerization of Tim-3, thereby potentially facilitating the formation of other Tim-3-ligand complexes such as CEACAM1-Tim-3. In addition, PtdSer released from apoptotic cells can bind the FG-CC'cleft binding site on Tim-3. In combination with the Gal-9 or CEACAM1, Tyr256 and Tyr263 in the Tim-3 intracellular region are phosphorylated to release BAT3. This would disrupt immune synapse formation and recruitment of phosphatases. In the end, the cells become reactive or apoptosis, which is mediated by intracellular calcium release. The binding of HMGB1 and Tim-3 will interfere with the nucleic acid of dying cells into DCs and reduce the immunogenicity of nucleic acid, however, the specific binding site is not clear. C: anti-Tim-3 antibodies maintain the Tim-3-BAT3 interaction and recruit LCK to maintain immune cell activation by interfering with Tim-3 binding to its ligands.

**图1 Tim-3与其配体相互作用的模型(根据参考文献[1]修改)**

**Fig.1 Model of the interaction of Tim-3 with its ligand (modified from reference [1])**

associated molecular pattern, DAMP)[3]。HMGB1可以由肿瘤细胞分泌, 在肿瘤微环境中, Tim-3可以作为HMGB1的分子接收器, 阻碍核酸进入树突状细胞(dendritic cells, DCs), 从而降低垂死肿瘤细胞释放的核酸的免疫原性, 抑制针对肿瘤细胞的先天免疫反应[18]。这可能是影响DNA疫苗和化疗对治疗肿瘤的有效性的机制之一。目前HMGB1与Tim-3结合的具体位点仍不清楚, 但HMGB1与Tim-3的相互作用并不依赖于其他Tim-3的配体。

### 2.3 PtdSer

PtdSer是一种作为凋亡细胞表面标志的阴离子磷脂, 主要存在于真核细胞膜的内叶中。在细胞凋亡和融合过程中, 细胞表面的PtdSer会充当吞噬细胞受体的识别信号, 从而激发吞噬反应[28]。PtdSer结合到Tim-3免疫球蛋白结构域中FG和CC'环形成的口袋结构上[19], 与涉及氨基酸Asn119和Asp120的配位钙结合[29]。PtdSer与Tim-3的结合不会导致T细胞吞噬凋亡物质, 但对Tim-3$^+$DCs的抗原交叉呈递很重要[20]。最近有研究发现, 肿瘤浸润性自然杀伤(natural killer, NK)细胞中Tim-3的表达水平显著增加, 导致NK细胞的细胞毒作用被抑制, PtdSer与Tim-3的相互作用抑制下游AKT/mTORC1信号转导和损害NK细胞介导的肿瘤杀伤功能[30]。

### 2.4 CEACAM1

CEACAM1是一种单次的I型跨膜蛋白, 主要作为细胞外信号的转导蛋白发挥作用[31]。CEACAM1广泛表达于多种免疫细胞表面, 例如T细胞、树突状细胞、单核细胞和巨噬细胞。CEACAM1通过其N-端结构域和Tim-3上的FC和CC'环与Tim-3形成异二聚体复合物。Tim-3-CEACAM1轴通过促进

表1 Tim-3及其配体的结构特点和作用机制

Table 1 Structural features and mechanism of action of Tim-3 and its ligands

| 受体/配体 Acceptor/ligands | 结构特点 Structural features | 结合位点 Binding site | 作用机制 Mechanisms of action | 参考文献 References |
|---|---|---|---|---|
| Tim-3 | A type I transmembrane protein composed of a variable immunoglobulin structural domain, an extracellular mucin structural domain, a transmembrane region, and an intracellular region | — | The main molecular mechanism of action is direct inhibition of Th1 cells activation after binding to ligands | [2,14] |
| Gal-9 | Two N-terminal carbohydrate-recognizing regions and a C-terminal tail region linked by a linker peptide in a two-structure domain protein | Carbohydrate motifs | Binding leads to phosphorylation of Tyr256 and Tyr263 located on the cytoplasmic tail region of Tim-3, contributing to the release of BAT3, leading to calcium in-flow and cell death in Tim-3$^+$T cells and mediating the inhibitory function of Tim-3 | [15-16] |
| HMGB1 | A single-chain polypeptide containing 215 amino acid residues, rich in lysine at the N-terminus and aspartate and glutamate at the C-terminus, with an HMG-box structural domain | Not clear yet | Binding to Tim-3 hinders the entry of nucleic acids into DCs, thereby reducing the immunogenicity of nucleic acids released by dying tumor cells and inhibiting the innate immune response against tumor cells | [17-18] |
| PtdSer | A phospholipid molecule comprising a phosphate group, a serine residue and a glycerol backbone | FG-CC' cleft | Binding to Tim-3 to promote antigen cross-presentation in DCs cells and facilitates clearance of apoptotic cells *in vivo* | [19-21] |
| CEACAM1 | Transmembrane protein with an N-terminal V-type Ig-like structural domain, three C2-type Ig-like structural domains, an ITIM motif, and a calmodulin binding site in the cytoplasmic region | FG-CC' cleft | Binding to Tim-3 leads to phosphorylation of Tyr256 and Tyr263 located on the cytoplasmic tail region of Tim-3, contributing to the release of BAT3, which inhibits *cis*- or *trans*-immunoreactivity of T cells and myeloid cells, thus mediating the inhibitory function of Tim-3 | [22-23] |

"–"表示此处不适用。

"–" indicates that it is not applicable here.

BAT3的释放而抑制T细胞和髓系细胞的顺式或反式免疫反应, 从而介导Tim-3的抑制功能, 阻断TCR信号通路, 使T细胞发挥免疫抑制作用[23]。CEACAM1还被发现能够在细胞内结合Tim-3, 这似乎对Tim-3成熟很重要, 因为在小鼠结肠炎模型中, 缺乏表达CEACAM1的T细胞表现出Tim-3的表达水平降低, 恢复CEACAM1的表达后Tim-3的表达水平也随之恢复[23]。CEACAM1与Tim-3的顺式相互作用增强了成熟Tim-3在细胞表面的稳定性, 与Tim-3的顺式和反式相互作用均介导Tim-3的抑制作用[1]。

## 3 Tim-3在自身免疫性疾病中的研究

目前Tim-3主要在4种自身免疫性疾病中研究较多, 分别为类风湿性关节炎(rheumatoid arthritis, RA)、系统性红斑狼疮(systemic lupus erythematosus, SLE)、多发性硬化症(multiple sclerosis, MS)和炎症性肠病(inflammatory bowel disease, IBD), 研究中所使用的干预方法或试剂主要有以下三种: 一是注射外源Tim-3的配体, 从而增强Tim-3配体轴; 二是加入抗Tim-3抗体来阻断Tim-3受体与其他配体间的相互作用; 三是使用siRNA来抑制Tim-3的表达(表2)。下面将展开叙述Tim-3在不同自身免疫性疾病中的研究。

### 3.1 Tim-3在类风湿性关节炎中的研究

RA是一种以滑膜细胞增殖和炎症失控为特征的慢性全身性炎症性疾病, 可导致不可逆的关节破坏, 关节功能丧失、残疾[32]。参与先天性和适应性免疫系统的细胞驱动RA中发生过度免疫反应, Tim-3可能通过影响免疫细胞功能在RA进展中起作用。LEE等[33]发现RA患者外周血单个核细胞(peripheral blood mononuclear cell, PBMC)的*Tim-3* mRNA表达与疾病活动性评分28(disease activity score 28, DAS28)呈负相关。LIU等[34]发现与健康对照组相比, RA外周血CD4$^+$T、CD8$^+$T、NKT细胞、单核细胞上Tim-3的

**表2 Tim-3在自身免疫性疾病中的研究**

**Table 2 Tim-3 in autoimmune diseases**

| 疾病 Diseases | 干预措施 Interventions | 细胞 Cells | 配体 Ligand | 研究发现 Research findings | 参考文献 References |
|---|---|---|---|---|---|
| RA | — | PBMC, Treg | — | *Tim-3* mRNA expression and percentage of Tim-3$^+$ cells in PBMC negatively correlate with DAS28. Decreased Tim-3 expression in Treg cells exacerbates inflammation | [33-34,36] |
| | Inject exogenous Gal-9 | Osteoclast | Gal-9 | Gal-9 significantly inhibits osteoclastogenesis and markedly inhibits bone destruction | [37] |
| | — | Neutrophil | CEACAM1 | CEACAM1 is highly expressed on peripheral blood neutrophils and is associated with rheumatoid inflammation | [38] |
| | Inhibition of Tim-3 expression using siRNA | FLS | — | Tim-3 silencing decreases the viability of FLS and attenuates the LPS-induced inflammatory reaction | [39] |
| | Add neutralizing Tim-3 antibody | — | — | sTim-3 levels are elevated and correlate with pro-inflammatory markers and disease activity; add neutralizing Tim-3 antibody promotes IFN-γ and MCP-1 secretion | [41-45] |
| SLE | — | PBMC | Gal-9 | The mRNA expression level of *Gal-9* is increased in PBMC of SLE patients | [48] |
| | Add anti-human Gal-9 antibody | Th1, Th2, Th17 | Gal-9 | Significantly inhibited the release of Th1, Th2, and Th17-derived cytokines in SLE patients | [49] |
| | — | monocyte, NK, CD4$^+$T, Treg | — | Tim-3 expression was increased on T cells, monocytes, and NK cells and correlated with anti-dsDNA antibody levels and SLEDAI. Significant reduction of Tim-3 expression in CD4$^+$T and Treg ameliorates lupus nephritis | [50-52,54] |
| | Experiments using Gal-9 gene-deficient mice | Macrophage | Gal-9 | Gal-9 is required for the induction and development of lupus nephritis and arthritis | [53] |
| | Add reorganized sTim-3 | — | PtdSer | sTim-3 levels were significantly elevated, and sTim-3 levels were positively correlated with anti-dsDNA antibody and SLEDAI, and negatively correlated with C3 and C4; add sTim-3 significantly inhibited efferocytosis | [55-58] |
| MS | — | PBMC, macrophage, CD4$^+$T | — | *Tim-3* mRNA activity is associated with high expression of IFN-γ and TNF-α. Tim-3 inhibits CD4$^+$T cell activation by affecting autoantigen presentation | [62,68] |
| | Inhibition of Tim-3 expression using siRNA | T | — | Promotes T cell proliferation and IFN-γ production | [63] |
| | Add anti-human Tim-3 monoclonal antibody | T, CD4$^+$T | Gal-9 | Reduces T cell apoptosis and promotes IFN-γ and IL-17 release | [64-65] |
| | — | CD4$^+$T, CD8$^+$T | CEACAM1 | Decreased Tim-3 and CEACAM1 expression leads to increased autoreactive T cells and CNS inflammation | [66-67] |
| | Add anti-IL-6 antibody | CD4$^+$T, CD8$^+$T | — | Increased Tim-3 expression on CD4$^+$T, CD8$^+$T and increased peripheral immunosuppressive response | [69] |
| IBD | — | Treg, Th17, Th1 | Gal-9 | The downregulation of Tim-3 and Gal-9 is associated with enhanced inflammation in Th17 effector cells and reduced Treg cell function, and the reactivity of Th1 cells is significantly reduced | [73] |
| | — | PBMC, Th, macrophage | — | Tim-3 expression was significantly reduced, and the response to exogenous Gal-9 was reduced. Tim-3 on macrophages inhibits neutrophil recruitment and necrotic apoptosis and promotes intestinal homeostasis | [74-75,77-78] |
| | Add recombinant mouse Tim-3 extracellular structural domains | CD4$^+$T | — | Increased Tim-3 expression on CD4$^+$T cells and decreased Treg cells exacerbated colitis | [76] |
| | Transplantation of stem cells with mutations in the *Tim-3* gene | — | — | Tim-3 is barely expressed on immune cells in the intestinal mucosa of patients who have received transplants, leading to the development of fulminant IBD | [79] |

RA: 类风湿性关节炎; SLE: 系统性红斑狼疮; MS: 多发性硬化症; IBD: 炎症性肠病; DAS28: 疾病活动性评分28; FLS: 成纤维细胞样滑膜细胞; SLEDAI: 系统性红斑狼疮疾病活动指数; CNS: 中枢神经系统。“–”表示此处并未涉及或不适用。

RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; MS: multiple sclerosis; IBD: inflammatory bowel disease; DAS28: disease activity score 28; FLS: fibroblast-like synoviocytes; SLEDAI: systemic lupus erythematosus disease activity index; CNS: central nervous system. “–” indicates that it is not addressed here or is not applicable.

表达水平增加, PBMC中Tim-3$^+$细胞百分比与DAS28和肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)水平呈负相关, 在对治疗有反应的患者中, CD3$^+$T细胞上Tim-3的表达水平进一步增加。滑液中的T细胞中显示出比外周血中更高的Tim-3表达水平[35]。进一步的研究发现, RA患者的CD4$^+$CD25$^+$Foxp3$^+$ Treg细胞中Tim-3表达水平降低, 其功能低于健康对照组的Treg细胞, 导致PBMC分泌更多的IFN-γ和TNF-α, 加重炎症的恶化[36]。这提示Tim-3可能通过对多种T细胞亚群的负性调节参与RA的发生发展。

MORIYAMA等[37]发现Tim-3在体内和体外破骨细胞中均有表达, 当将半乳糖凝集素-9注射到患有类固醇诱导的关节炎的大鼠中时, 外源性Gal-9显著抑制破骨细胞生成, 观察到骨破坏的显著抑制。这表明通过调控Tim-3/Gal-9系统可以有效地改善类风湿关节炎的炎症性骨破坏。MATSUMOTO等[38]发现与健康对照组相比, RA患者外周血中性粒细胞上CEACAM1的表达水平更高, 与RA炎症严重程度相关, 这提示了Tim-3配体轴调控效应细胞的多样性。

上述的研究均表明Tim-3表达水平高与RA疾病严重程度较低有关, 但也有例外, WU等[39]发现与健康对照组相比, RA患者的成纤维细胞样滑膜细胞(fibroblast-like synoviocytes, FLS)中Tim-3表达水平增加, *Tim-3*基因沉默降低了FLS的活性, 并减弱了LPS诱导的炎症反应, 说明Tim-3在不同细胞中调控RA进展的机制不一样。

目前已有大量文献报道sTim-3在RA患者中升高[40-44]。血清sTim-3水平升高与特定ACPA状态下RA患者的促炎标志物和疾病活动度相关[41]。SKEJOE等[44]发现RA患者的sTim-3水平升高与早期RA的疾病活动相关, 加入Tim-3中和抗体可以促进RA患者的SFMC分泌IFN-γ和MCP-1, 加重患者炎症反应, 说明Tim-3在RA患者中上调, 但不足以控制炎症。最新的研究发现在RA伴非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)患者中, 血清Gal-9和sTim-3的水平升高且与NAFLD严重程度呈正相关[45]。sTim-3可以作为评估RA疾病活动性和进展的生物标志物, 有关Tim-3与其配体的信号通路在RA发病机制中的作用及其对不同药物治疗的反应还需进一步的研究。

### 3.2 Tim-3在系统性红斑狼疮中的研究

SLE是一种可以累及全身多个系统、多脏器的慢性自身免疫性疾病[46]。主要的病理特征包括B和T细胞的异常激活, 导致自身抗体的过度产生和免疫复合体的沉积。其病理生理学特点是免疫自我耐受性丧失, 淋巴细胞异常活化, 炎症因子和致病自身抗体大量分泌。虽然SLE的病因和发病机制尚未被完全阐明, 但一个中心的病理因素是细胞免疫和体液免疫平衡的紊乱, 以及T细胞亚群功能障碍的持续性炎症[47]。

早期临床观察报告在SLE患者的PBMC中发现*GaL-9* mRNA表达水平升高[48]。随后的研究证实CD4$^+$T细胞、CD8$^+$T细胞、CD56$^+$T细胞上Tim-3和Gal-9的表达水平均高于健康对照组, Tim-3和Gal-9的表达水平与系统性红斑狼疮疾病活动指数(systemic lupus erythematosus disease activity index, SLEDAI)评分密切相关[49]。此外, Gal-9阻断抗体显著抑制SLE患者中辅助性T细胞(helper T cells, Th)1衍生细胞因子(IL-2、IFN-γ和TNF-α)、Th2衍生细胞因子(IL-4、IL-10)、Th17衍生细胞因子(IL-17A)以及促炎因子(IL-6)的释放, 表明Tim-3-Gal-9通路可能参与了SLE的发生与发展。SONG等[50]发现活动期SLE患者CD3$^+$CD4$^+$T细胞比例低于稳定期SLE患者, 而CD3$^+$CD4$^+$Tim-3$^+$T细胞比例高于稳定期SLE患者。这说明检测T细胞上Tim-3的表达水平有利于评估SLE疾病活动性。除了T细胞以外, Tim-3还通过在其他免疫细胞上表达来参与SLE的发展。MIKOLAJCZYK等[51]发现在SLE患者的单核细胞中, Tim-3的表达水平显著增加, 特别是在CD16$^+$单核细胞亚群中, Tim-3在单核细胞上的表达水平增加可能与SLE患者中凋亡细胞的清除出现障碍有关, 这可能导致炎症反应和自身免疫反应的增强。此外, SLE患者外周血中Tim-3$^+$PD-1$^+$NK细胞显著增多, Tim-3$^+$PD-1$^+$NK细胞升高与血沉、CRP、抗dsDNA抗体、SLE疾病活动指数及临床特征相关, SLE患者经治疗后Tim-3$^+$PD-1$^+$NK细胞显著减少[52]。

狼疮性肾炎是SLE的严重并发症, 是SLE发病率和死亡率的重要驱动因素。ZEGGAR等[53]发现Gal-9是SLE小鼠模型中狼疮性肾炎和关节炎的诱导和发展所必需的, Gal-9缺陷通过靶向活化的巨噬细胞而有益于治疗SLE中的肾炎和关节炎。GAO等[54]发现在用雷帕霉素处理的小鼠中, CD4$^+$T细胞和Treg细胞中Tim-3的表达水平显著降低, CTLA-4、IL-10、TGF-β1的表达水平增加, 从而改善MRL/lpr小鼠模

型中的狼疮性肾炎。以上表明Tim-3及其配体的信号通路可以作为狼疮性肾炎治疗的靶点，还需更深入的研究来阐明其中的机制。

目前已有大量研究发现SLE患者血清sTim-3水平显著高于健康对照组[55-57]，活动期SLE患者血清sTim-3水平更高，sTim-3水平与抗dsDNA抗体、SLEDAI评分、血沉、尿白蛋白呈正相关，与C3和C4呈负相关[57]。ZHAO等[58]验证了Tim-3作为PtdSer的受体启动凋亡细胞的吞噬，用sTim-3处理显著抑制了Tim-3启动的吞噬凋亡细胞的作用。然而，sTim-3在SLE中的具体作用仍不明确，这将成为未来研究的热点。

### 3.3 Tim-3在多发性硬化症中的研究

MS是一种以中枢神经系统脱髓鞘为特征的自身免疫性疾病，其特点是病灶扩散、缓解和复发交替出现，病程缓慢进行。虽然MS发生的具体原因仍不清楚，但环境因素和遗传多态性被认为是其发展的原因[59]。MS患者的脑脊液中富含Th1和Th17细胞，能分泌大量促炎因子如IFN-γ、IL-1和IL-17，提示Th1细胞驱动的炎症参与了中枢神经系统的免疫病理过程[60]。Tim-3作为表达于Th1细胞上的免疫检查点，若出现功能障碍，导致自身反应性T细胞的过度炎症反应，可能会导致MS的发生[61]。

早期的研究表明Th1细胞中Tim-3的功能障碍介导了MS的炎症损伤，活动期MS患者脑脊液(cerebral spinal fluid, CSF) PBMC中*Tim-3* mRNA的活性与IFN-γ和TNF-α的高表达密切相关[62]。这提示*Tim-3* mRNA可以作为评估MS疾病活动性和进展的生物标志物。KOGUCHI等[63]发现MS患者CSF中的T细胞分泌的IFN-γ显著高于对照组，而Tim-3的表达水平明显低于对照组，使用siRNA抑制Tim-3的表达可促进T细胞增殖和IFN-γ的产生。另一个研究中使用抗人Tim-3单抗阻断CSF中$CD4^+$T细胞上的Tim-3受体，可以显著增强健康受试者的IFN-γ分泌，但在未经治疗的MS患者中没有效果，证明了MS患者CSF的T细胞中Tim-3的免疫调节功能存在缺陷[64]。这表明用于治疗MS的方法可能部分通过恢复Tim-3免疫调节功能而起作用。

SARESELLA等[65]发现T细胞上Tim-3和Gal-9的表达水平在良性MS患者中增加，而在原发进展型MS患者中减少。用特异性单抗阻断Tim-3与Gal-9的相互作用可以减少T细胞的凋亡，并促进促炎因子IFN-γ和IL-17的释放，说明Tim-3-Gal-9通路参与了MS疾病的发展。PIANCONE等[66]发现原发进展型MS患者外周血$CD4^+$T细胞和$CD8^+$T细胞中Tim-3和CEACAM-1的表达水平下降，而BAT3的表达水平增加。这种改变可能会导致自身反应性T细胞的凋亡减少，并加剧中枢神经系统炎症。除了在T细胞上发挥作用外，Tim-3-CEACAM-1轴还可能通过诱导致病B细胞聚集来参与中枢神经系统的炎性损伤过程[67]。CEACAM1已成为MS发病机制中临床上高度关注的靶点，并为治疗MS开辟了新的治疗途径。

实验性自身免疫性脑脊髓炎(experimental autoimmune encephalomyelitis, EAE)小鼠是研究MS的重要实验动物模型，可以帮助探索疾病的复杂性并开发新的治疗策略。TANG等[68]发现EAE小鼠模型中Tim-3通过STAT1/CIITA途径抑制MHC-II在巨噬细胞中的表达，从而抑制MHC-II介导的自身抗原呈递和$CD4^+$T细胞活化，调节Tim-3-MHC-II信号通路有望为MS的治疗提供新的解决方案。此外，DEMA等[69]在EAE小鼠中使用抗IL-6抗体阻断IL-6信号转导，发现外周免疫抑制应答增加，$CD4^+$T细胞和$CD8^+$T细胞上Tim-3的表达水平增加，认为IL-6抑制剂可以作为MS患者的治疗靶点。Tim-3如何影响MS患者的治疗效果有待进一步的研究。

### 3.4 Tim-3 在炎症性肠病中的研究

IBD是一组慢性炎症性疾病，主要有两种类型：溃疡性结肠炎(ulcerative colitis, UC)和克罗恩病(Crohn's disease, CD)[70]。UC表现为从直肠延伸至结肠的黏膜连续性炎症，CD可以影响整个消化道，表现为跨肠道的跳跃性病变[71]。IBD的免疫特征是先天性和适应性免疫系统异常反应的结果[72]，免疫检查点分子可能参与IBD的发生与发展。

SHI等[73]在UC患者中观察到Tim-3和Gal-9表达减少，与Th17效应细胞炎症反应增强和Treg细胞功能减弱有关，并且Th1细胞的反应性显著降低。此外，UC患者的单核细胞表现出较低的Tim-3表达以及对外源性Gal-9的反应降低，并且UC患者的粪便细菌可以显著抑制单核细胞Tim-3的表达[74]。MORIMOTO等[75]发现CD患者的肠黏膜组织上分离的Th细胞和PBMC上的Tim-3表达水平明显低于健康对照组，这可能为慢性炎性疾病相关炎症的消退提供线索。

在小鼠结肠炎模型中，阻断Tim-3通路导致$Tim\text{-}3^+CD4^+$T细胞增加，Treg细胞减少，加重了结肠炎，表

明Tim-3通路高度参与IBD负调控[76]。进一步的研究发现, Tim-3信号转导抑制IRF3的磷酸化, IRF3可以调节巨噬细胞极化, 从而抑制巨噬细胞的M1极化, 促进了结肠炎的肠道稳态[77]。此外, 巨噬细胞上的Tim-3通过抑制中性粒细胞的募集和坏死性凋亡, 从而保护肠黏膜屏障并维持结肠炎的肠道内稳态[78]。

最近BALDRICH等[79]报道了一例异基因干细胞移植患者, 由于干细胞供体中*Tim-3*基因突变, 该患者肠黏膜的免疫细胞上几乎不表达Tim-3, 导致其发生了暴发性IBD。这些研究结果进一步强调了Tim-3在维持肠道免疫平衡和预防炎症性肠病中的重要性。

## 4 Tim-3作为靶点的免疫治疗前景

免疫治疗是通过调节机体自身的免疫功能来治疗疾病, 目前Tim-3作为免疫检查点分子在肿瘤免疫治疗中备受关注。已有研究证实了通过阻断Tim-3通路来刺激炎性小体从而激发抗肿瘤免疫的可能性[80]。然而有研究发现在肺腺癌小鼠中阻断PD-1后其他免疫检查点分子(包括Tim-3)的表达水平上调[81]。这可能是一种补偿机制, 提示单一免疫检查点抑制剂的效果可能不佳。目前临床上更多的是联合不同免疫检测点抑制剂来治疗肿瘤, 使用较多的是抗PD-1单抗联合抗Tim-3单抗用药。研究表明, 同时靶向Tim-3和PD-1比单独靶向任一途径更有效[82]。双特异性抗体与单克隆抗体联合治疗具有相同的靶点, 但作用机制不同。双特异性抗体可以结合两种抗原并增加抗肿瘤效果[83], 目前已成为研究的热点。值得注意的是, 由于Tim-3在多种免疫细胞上表达并在免疫调节中发挥不同的作用, 因此需要关注抗Tim-3单克隆抗体在治疗疾病过程中的靶向性和脱靶效应。

目前在自身免疫性疾病领域, 大多数临床研究集中在利用Tim-3作为生物标志物来评估疾病的严重程度和预后, 但利用Tim-3作为免疫治疗靶点的临床研究却很少。利用Tim-3作为靶点治疗自身免疫性疾病的通用思路是增强或重塑Tim-3与其配体的通路, 改变机体的免疫以恢复其对自身抗原的耐受性。这可以通过增加Tim-3或其配体的表达来实现。在不改变机体基因表达的情况下, 可以通过ADAM10/17抑制剂来实现Tim-3在免疫细胞上的表达水平增加。因为ADAM10/17抑制剂可以防止Tim-3从细胞表面脱落, 间接增加了Tim-3在细胞表面的表达[84]。还可以通过注射Tim-3的配体来增强Tim-3介导的免疫功能。Gal-9的治疗性给药可以帮助治疗SLE[85], 但和前面讨论的ADAM10/17抑制剂一样, 这不仅会影响Tim-3的通路, 还可能会参与其他信号通路, 因此要关注可能会出现的脱靶效应。总之, 利用Tim-3作为靶点治疗自身免疫性疾病需要更全面的机制研究和更多临床前数据, 为其临床应用提供坚实的基础。

## 5 总结与展望

Tim-3作为一种免疫检查点分子, 已被证实在多种免疫细胞(T细胞、NK细胞、髓系细胞)上表达。目前已发现Tim-3有以下4种配体: Gal-9、HMGB1、PtdSer和CEACAM1。在与其配体结合后, Tim-3通过胞内区上的磷酸化反应触发调节免疫细胞功能的下游信号转导途径。Tim-3-配体轴通过调节各种T细胞亚群和先天免疫细胞的活性, 在一系列自身免疫性疾病如RA、SLE、MS和IBD的发病机制中起作用。Tim-3及其配体信号转导途径的免疫功能可受到不同疾病状态和治疗策略的影响, 根据Tim-3的表达水平设计个体化治疗方案将有利于患者的预后。目前大量研究集中在Tim-3作为生物标志物来评估自身免疫性疾病的严重程度和预后, 但利用Tim-3作为自身免疫性疾病的治疗靶点已成为研究热点。尽管关于Tim-3在不同细胞类型和疾病中发挥作用的通路仍需要研究, 但Tim-3作为多种人类疾病药物靶点的潜力将继续推动对其生物学的进一步研究。

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