

DOI: 10.14188/j.1671-8852.2025.1134

文章编号 1671-8852(2026)08-1089-07

TREM-2 在脓毒症中的作用研究进展

张蓉 伍威 潘舟 严颜 张云龙 王慧娟 竹雪 潘明亮 李菁琦 闫一成 詹丽英
武汉大学人民医院重症医学科 湖北 武汉 430060

摘要 髓样细胞触发受体 2 (TREM-2) 是一种免疫球蛋白超家族的跨膜受体, 其在髓系细胞表面的表达对调节炎症反应和维持组织稳态至关重要。脓毒症 (Sepsis) 是感染引起的宿主反应失调, 导致危及生命的器官功能损害症候群。TREM-2 在脓毒症患者中表达水平升高, 并与病情严重程度呈负相关。TREM-2 可通过多种机制参与机体对脓毒症的调控, 包括促进细菌吞噬、介导病原体清除、协调 Toll 样受体 (TLR) 反应、抑制过度炎症、促进细胞存活和组织修复、调节免疫细胞功能状态以及维持器官稳态。本文综述了 TREM-2 在脓毒症中的作用及其作为治疗靶点的潜力, 为脓毒症靶向治疗提供理论依据。

关键词 脓毒症; 髓样细胞触发受体 2; 巨噬细胞; 炎症反应

中图分类号 R54

文献标志码 A

Research progress on the role of TREM-2 in sepsis

ZHANG Rong, WU Wei, PAN Zhou, YAN Yan, ZHANG Yunlong, WANG Huijuan, ZHU Xue,
PAN Mingliang, LI Jingqi, YAN Yicheng, ZHAN Liying

Department of Critical Care Medicine, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei, China

Abstract

Triggering receptor expressed on myeloid cells 2 (TREM-2), a transmembrane receptor of the immunoglobulin superfamily, plays a crucial role in regulating inflammatory responses and maintaining tissue homeostasis. Sepsis is a life-threatening syndrome characterized by dysregulated host responses to infection, leading to organ dysfunction. In sepsis patients, TREM-2 expression is upregulated, with higher levels negatively correlating with disease severity. TREM-2 modulates sepsis progression through multiple mechanisms, including enhancing bacterial phagocytosis and pathogen clearance, suppressing Toll-like receptor (TLR)-mediated inflammation, promoting cell survival and tissue repair, and regulating immune cell functional states. An emerging and critical insight is the context-dependent duality of TREM-2 signaling: although it is predominantly protective, recent studies suggest that under certain conditions it may exacerbate inflammatory injury, highlighting the complexity of its regulatory network. In conclusion, this review summarizes the role of TREM-2 in sepsis and highlights its potential as a therapeutic target, providing a theoretical basis for targeted sepsis therapies.

Key Words Sepsis; Triggering Receptor Expressed on Myeloid Cells 2; Macrophage; Inflammatory Response

课题来源: 新发突发与重大传染病防控国家科技重大专项 (编号: 2025ZD01902600); 国家自然科学基金面上项目 (编号: 82272226; 82572461); 国家自然科学基金青年项目 (编号: 82502662)。

作者简介: 张蓉, 女, 2001—, 医学硕士, 主要从事脓毒症急性肺损伤的基础研究, E-mail: 2024283020105@whu.edu.cn。

通信作者: 詹丽英, E-mail: zhanliying@whu.edu.cn。

脓毒症是一种由感染引发的致命性全身炎症反应综合征,常导致多器官功能障碍^[1],是全球主要的公共卫生负担,年死亡人数高达约 1 100 万^[2]。其高死亡率驱使人们不断探寻新的治疗靶点。髓样细胞触发受体-2(triggering receptor expressed on myeloid cells 2, TREM-2)作为一种关键的免疫调节受体^[3],在脓毒症中表达上调,且其水平与疾病严重程度呈负相关^[4-5]。这提示其在脓毒症病理过程中可能起保护作用。因此,深入探讨 TREM-2 在脓毒症中的作用对于开发脓毒症新疗法具有重要意义。本综述旨在总结 TREM-2 在脓毒症中的作用及其作为治疗靶点的潜力,为脓毒症靶向治疗提供理论依据。

1 TREM-2 概述

TREM 是髓系细胞表面表达的一类免疫球蛋白超家族(Ig-SF)受体,迄今发现至少 3 个 TREM 家族成员,按其被发现的顺序依次命名为 TREM-1、TREM-2、TREM-3 等^[6]。TREM-2 主要表达于树突状细胞、巨噬细胞等髓系细胞表面^[7],由一个用于识别配体(如细菌产物、脂蛋白等)的胞外 V 型免疫球蛋白结构域、跨膜区和一个缺乏信号基序的短胞质尾部构成^[8-9](图 1)。由于 TREM-2 的短胞质尾部缺乏信号传导和运输基序, TREM-2 在与配体结合后产生的跨膜信号传递需要 DNAX 活化蛋白 12(DNAX-activating protein of 12 kU, DAP12)参与^[10]。当配体与 TREM-2 结合后,跨膜区电荷相互作用会募集 DAP12,导致 DAP12 胞内段的免疫受体酪氨酸基序激活模体(immunoreceptor tyrosine-based activation motif, ITAM)磷酸化,进而招募并激活脾酪氨酸激酶(spleen tyrosine kinase, SYK)。SYK 的激活可启动下游包括 PI3K/AKT、PLC γ 和 ERK 在内的多条信号通路,最终调控细胞的吞噬、存活及炎症因子释放等生物学行为^[11-12]。

TREM-2 可被 ADAM 蛋白酶在 H157S158 肽键处剪切,产生可溶性形式的 TREM-2(soluble TREM-2, sTREM-2)^[13]。当受到细菌、干扰素 γ 或脂多糖的刺激时,ADAM 也可以进一步切割 TREM-2 的跨膜部分,使髓系细胞膜表面的 TREM-2 表达迅速下降,从而阻断 TREM-2 信号传导,间接发挥 TREM-2 抑制剂的作用^[14]。研究^[15]表明 sTREM-2 具有双重功能:一方面可通过激活

ERK1/2 和 PI3K-AKT 通路促进细胞存活。另一方面可作为脓毒症相关脑病等疾病的生物标志物,其水平与认知功能下降相关^[16]。在炎症状态下, sTREM-2 的产生会降低细胞 TREM-2 的表达,从而调节信号传导强度^[17]。

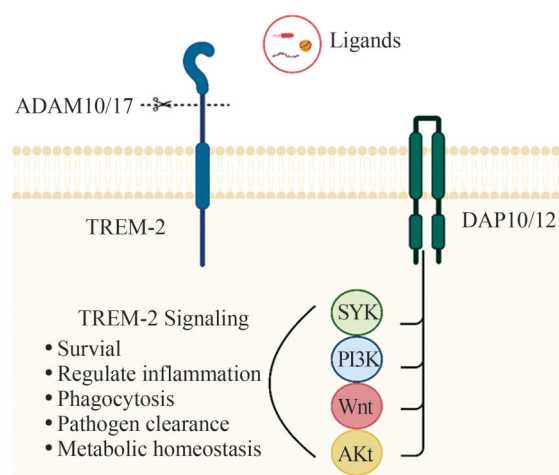


图 1 TREM-2 受体的结构示意图

注:本图展示了 TREM-2 受体的结构及其介导的信号转导通路。TREM-2 可通过 ADAM10/17 蛋白酶进行切割,并与接头蛋白 DAP10/12 相互作用,激活下游信号分子 SYK、PI3K、Wnt、AKT,进而调节炎症反应(Regulate inflammation)、吞噬作用(Phagocytosis)、病原体清除(Pathogen clearance)和代谢稳态(Metabolic homeostasis)等多种生物学过程。

2 TREM-2 调控脓毒症

2.1 增强病原体清除与维护组织完整性 作为巨噬细胞表面的吞噬受体, TREM-2 直接识别并介导对细菌、凋亡细胞及细胞碎片的吞噬,是启动免疫清除的第一道环节^[8]。研究^[18]表明 TREM-2 在不具有吞噬能力的细胞中过表达,可诱导细菌、脂蛋白和细胞碎片等的吞噬,比如在中国仓鼠卵巢细胞中 TREM-2 通过 TREM-2/DAP12 信号复合体招募并磷酸化 SYK,进而启动 PI3K/AKT 与 PKC 等下游通路,促进细菌的结合和吞噬。同样在具有吞噬作用的细胞中, TREM-2 表达缺失或减少也会减少凋亡细胞、细胞碎片、细菌等的吞噬^[19]。

这一介导病原体吞噬的过程不仅增强了吞噬体的成熟,更关键的是能激活 NADPH 氧化酶 2(NADPH oxidase 2, NOX2),促使吞噬体内产生活性氧(reactive oxygen species, ROS),直接杀伤如大肠杆菌、铜绿假单胞菌和鼠伤寒沙门氏菌等病原体^[20-21]。此外, TREM-2 通过稳定 β -连环蛋白(β -catenin),有效抑制由线粒体 ROS 驱动的 NLRP3 炎症小体活化和 caspase-1 介导的细胞焦亡,从而在

清除感染源的同时限制炎症性细胞死亡带来的二次损伤^[5, 20]。临床研究^[5]证明细菌性脓毒症患者TREM-2表达与NOX2浓度呈正相关,与caspase-1阳性单核细胞数量呈负相关,并且TREM-2浓度与脓毒症的严重程度呈负相关。

在组织修复层面,TREM-2与巨噬细胞集落刺激因子(colony-stimulating factor 1,CSF-1)信号协同,通过SYK-PI3K/AKT轴上调抗凋亡蛋白(如BCL-2)的表达,促进巨噬细胞在炎症环境中的存活^[22]。此外,TREM-2可激活Wnt/ β -catenin通路,促进Wnt蛋白分泌,抑制 β -catenin的降解,调控修复相关基因的表达,为组织再生创造有利的微环境^[23-24]。

2.2 负向调控过度炎症反应 脓毒症中失控的全身炎症反应是导致器官损伤的关键^[25]。TREM-2可以通过多种通路负向调节炎症反应。第一,在脂多糖的刺激下,TREM-2能通过其衔接蛋白DAP12的ITAM结构域募集对接蛋白3(docking protein 3,DOK3)。磷酸化的DOK3与Grb2-SOS1结合,负向调控Ras-ERK MAPK信号通路,从而抑制TNF- α 、IL-6等促炎因子^[22, 26]。第二,TREM-2信号能直接或间接抑制PI3K/AKT/I κ B kinase通路,减少NF- κ B的核转位,从转录源头遏制炎症风暴^[27]。第三,TREM-2还可诱导细胞因子信号抑制因子(suppressor of cytokine signaling,SOCS)家族蛋白的表达,通过JAK/STAT/SOCS通路反馈性抑制细胞因子信号,形成抗炎闭环^[28]。最后,TREM-2的缺失会导致感染模型中趋化因子(如CXCL1、CXCL2)水平升高,进而引起中性粒细胞过度浸润至组织,加重炎症损伤,这进一步体现了TREM-2在炎症细胞募集层面的全局调控作用^[29-30]。

2.3 桥接并调控适应性免疫应答 TREM-2通过调控抗原提呈细胞的功能,桥接固有免疫与适应性免疫。在树突状细胞中,TREM-2/DAP12信号通过SYK激活ERK-MAPK通路^[31],不仅促进细胞存活与成熟,更显著上调主要组织相容性复合体Ⅱ类(major histocompatibility complex Ⅱ,MHC Ⅱ)分子和共刺激分子CD86/CD40的表达^[32],从而极大地增强了树突状细胞向初始CD4⁺T细胞提呈抗原的能力^[33]。缺乏TREM-2将导致T细胞活化不足,削弱机体清除病原体的能力^[34-35]。研究^[34]发现,在MHV-A59小鼠模型中,敲除TREM-2基因的小鼠比野生型小鼠表现出更严重的肺损伤、更高的病毒负荷以及更低水平的细胞因子IFN- γ 、TNF- α 。更

为精准的是,TREM-2本身亦可在T细胞上表达,并通过与T细胞受体(T cell receptor,TCR)信号协作,促进ZAP70-STAT1/STAT4信号轴的激活,这有利于促炎的Th1型免疫应答的分化,增强IFN- γ 的产生,从而更有效地对抗细胞内病原体感染^[36]。这表明TREM-2通过多细胞、多途径协同,确保适应性免疫应答的适时、适度和有效。

3 TREM-2维持脓毒症器官代谢稳态

脓毒症导致的多器官功能衰竭是患者死亡的主要原因。除系统性免疫调节外,TREM-2通过在关键器官的组织巨噬细胞中特异性表达,参与维持局部稳态,对改善预后具有重要意义^[37-41]。

3.1 维持心脏代谢和功能 脓毒症会引起心肌细胞功能失调线粒体的积累,而游离线粒体和线粒体DNA(mitochondria DNA,mtDNA)会引起心脏损伤^[42]。并且,线粒体功能障碍与脓毒症预后不良直接相关^[43],因此维持心肌线粒体稳态对于脓毒症心肌病(sepsis-induced cardiomyopathy,SICM)至关重要。Mac1是一种常驻于心肌的巨噬细胞,可以通过吞噬和清除心肌细胞释放的功能失调的线粒体来恢复心肌线粒体稳态^[42, 44]。但如果Mac1缺乏TREM-2表达,其自我更新能力将会降低,进而导致受损线粒体在心肌中堆积,心脏组织炎症反应过度,心功能障碍加剧,死亡率升高^[37, 42]。研究^[37]报道,移植高表达TREM-2的巨噬细胞(TREM-2hi Mac1)可以改善心脏损伤、炎症及线粒体损伤,提升ATP水平并降低乳酸堆积,并且心包内注射TREM-2hi Mac1细胞可预防SICM的发生和发展。

3.2 协调肝脏细胞间代谢 脓毒症容易导致肝脏损伤,特别是在患者存在既往肝损伤病史的情况下^[45]。外泌体(exosome,Exos)是小的细胞外囊泡,可转移分子成分,如蛋白质、DNA和miRNAs等^[46],在内源性分子的递送中调节受体细胞的基因表达和相关的生理和病理生理过程^[47]。不表达TREM-2的巨噬细胞释放的外泌体会损伤肝细胞的线粒体结构和能量供应,进而加重非酒精性脂肪肝相关脓毒症^[48]。这可能与Exos含有的大量miR-106b-5p阻断线粒体融合蛋白2相关^[38, 49]。相反,肝巨噬细胞中TREM-2过表达可以通过改善肝脏能量供应来降低脓毒症死亡率^[39]。

3.3 精细调控肾上腺应激轴 TREM-2还参与对神经内分泌应激反应的精细调控。研究^[50]表明,

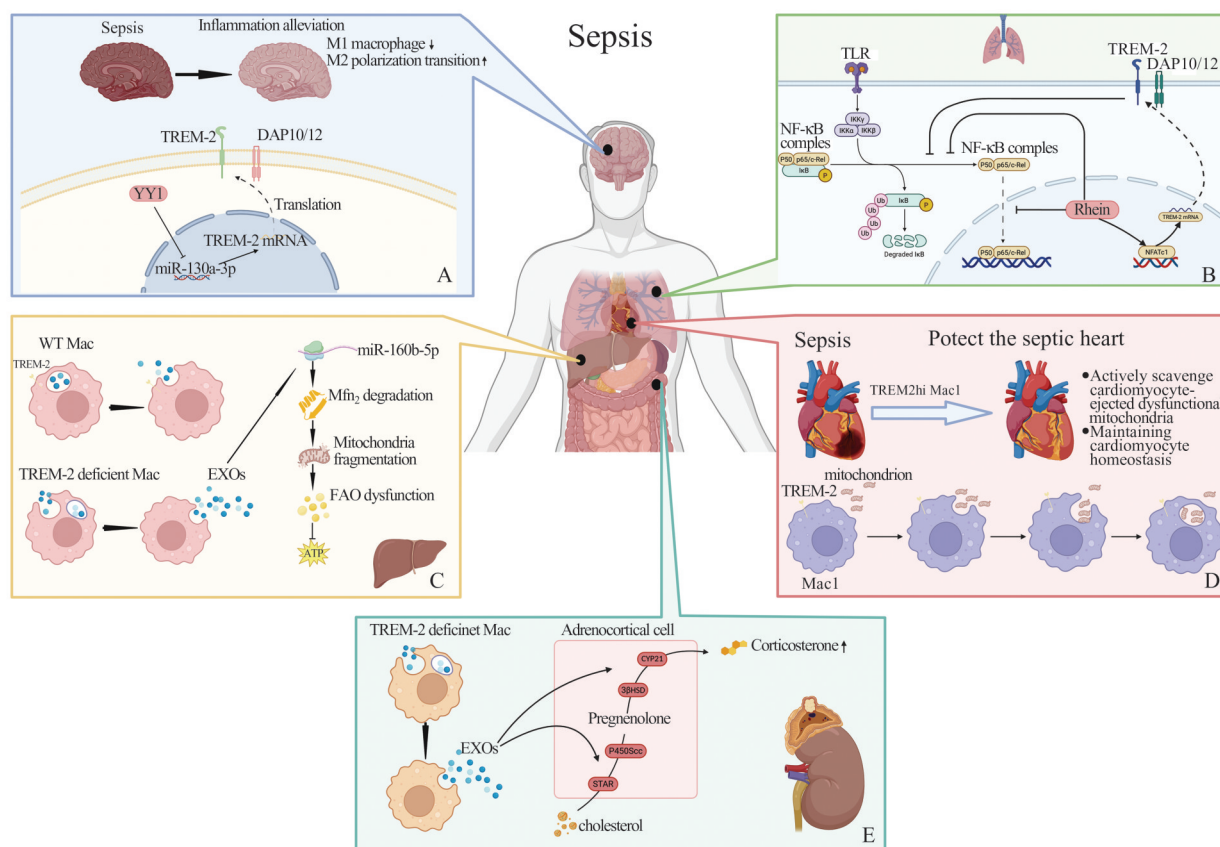
TREM-2 基因敲除的巨噬细胞能通过外泌体向肾上腺皮质细胞传递信号,促进类固醇生成酶的表达,导致皮质醇的过度合成。这种失控的免疫-肾上腺串扰可能增加死亡风险^[51],而正常的 TREM-2 功能则有助于限制过度的糖皮质激素反应,维持内环境稳定^[50, 52]。

3.4 调控脓毒症脑病,减轻脑部炎症 在脓毒症相关脑病中,M1 极化的小胶质细胞具有破坏性,会分泌促炎细胞因子^[53]。TREM-2 过表达可以抑制高糖低氧状态下小胶质细胞释放促炎因子,而 TREM-2 沉默可促进促炎因子释放^[54]。研究^[55]发现阴阳 1(Yin Yang 1, YY1)是一种多功能转录因子,可以通过抑制 miR-130a-3p 启动子的活性,上调 TREM-2 的表达,从而促进小胶质细胞 M2 极化,减轻炎症,在脓毒症的发展中起关键作用^[40, 56]。

3.5 抑制 NF- κ B 活化,减轻急性肺损伤 脓毒症

相关的急性肺损伤(acute lung injury, ALI)的病理生理机制与巨噬细胞密切相关。在急性炎症期,M1 型巨噬细胞通过激活 NF- κ B 信号通路,产生高水平细胞内 ROS,在清除病原体的同时引发组织损伤^[57-58]。进入增殖期后,巨噬细胞发生由 M1 型向 M2 型的极化转变。至纤维化期(或修复期),M2 型巨噬细胞主导组织修复和纤维化过程^[59-60]。研究^[61]表明,早期巨噬细胞发生 M2 极化可以降低 ALI/ARDS 死亡率和改善预后。大黄酸是多种中药(包括大黄、芦荟和番泻叶)的成分之一,具有较强的抗炎、抗肿瘤、抗纤维化、抗氧化等作用^[62-63]。研究^[41]发现,大黄酸可通过激活 TREM-2 上游转录因子 NFATc1 并与之相互作用,促进 TREM-2 的表达,进而抑制 NF- κ B 的易位和活化,最终抑制巨噬细胞的 M1 极化,减轻 ALI/ARDS 后的肺部炎症。

REM-2 维持器官代谢稳态作用示意图见图 2。



A. TREM-2 在脓毒症脑病中的作用:YY1 可通过抑制 miR-130a-3p 启动子的活性,上调 TREM-2 的表达,从而促进小胶质细胞 M2 极化,减轻炎症;B. TREM-2 在脓毒症急性肺损伤中的作用:大黄酸通过激活 TREM-2 上游转录因子 NFATc1 并与之相互作用,促进 TREM-2 的表达,进而抑制 NF- κ B 的易位和活化,最终抑制巨噬细胞的 M1 极化,从而减轻肺部炎症;C. TREM-2 在脓毒症肝损伤中的作用:TREM-2 过表达可以减少外泌体的释放,进而减少其对肝细胞的线粒体结构和能量供应的损伤;D. TREM-2 在脓毒症心肌病中的作用:TREM-2 高表达可促进巨噬细胞通过吞噬和清除心肌细胞释放的功能失调的线粒体来恢复心肌线粒体稳态;E. TREM-2 在脓毒症肾上腺激素分泌中的作用:TREM-2 通过巨噬细胞来源的外泌体抑制肾上腺皮质细胞生成类固醇,维持机体稳态。

图 2 TREM-2 维持器官代谢稳态的作用示意图

4 小结与展望

本综述系统阐述了TREM-2在脓毒症复杂病理过程中的多重调控作用。现有研究表明,TREM-2通过促进病原体清除^[8]、抑制过度炎症^[26]、协调组织修复^[23-24]、桥接适应性免疫^[36]以及维持多器官功能稳态^[37-41]等多重途径,在脓毒症中发挥着重要的保护作用。从分子机制来看,TREM-2/DAP12信号轴及其下游的SYK、PI3K/AKT、ERK等通路构成其功能执行的核心基础^[11-12],而其可溶形式sTREM-2则作为重要的调节分子和生物标志物^[16-17],进一步丰富了TREM-2的调控网络。

然而,这一领域仍存在亟待解决的关键问题:尽管大量证据支持TREM-2的积极作用,但最新研究发现其功能可能具有条件依赖性,甚至在某些情况下产生有害效应。例如,一项研究^[64]发现TREM2缺失反而可以提高脓毒症小鼠的存活率,减轻炎症和器官损伤。该研究发现TREM-2能够直接结合磷酸酶SHP-1的PTPase结构域,促使SHP-1募集并抑制Bruton酪氨酸激酶(Bruton's tyrosine kinase,BTK)的磷酸化,从而阻断脂肪酸氧化(fatty acid oxidation,FAO)反应,导致促炎细胞因子释放增加和炎症介导的器官损伤加剧^[64]。这看似矛盾的结果提示,TREM-2在脓毒症中的最终效应可能并非单一方向,而是受到病原体类型、感染阶段、细胞类型及组织微环境等多因素精细调控。例如,在感染早期或特定病原体作用下,TREM-2可能主要发挥清除病原体和启动保护性免疫的作用;而在持续或过度炎症状态下,其信号可能通过某些通路(如上述SHP-1/BTK/FAO轴)间接促进炎症损伤。因此,更加深入地阐明TREM-2精准调控脓毒症的机制将成为未来研究的重点方向。

基于TREM-2在免疫调节与器官保护中的作用,靶向TREM-2无疑为脓毒症治疗提供了极具潜力的新策略。未来的研究应当深入解析其双向调节机制,明确其在各类免疫细胞及实质细胞中的特异性功能,并积极推动靶向治疗的转化研究,通过开发针对脓毒症的TREM-2特异性调节剂,实现对脓毒症的精准治疗,为应对这一全球健康挑战开辟新的途径。



开放科学(资源服务)标识码(OSID):

参考文献

- [1] SRZIC I, NESEK ADAM V, TUNJIC PEJAK D. Sepsis definition: What's new in the treatment guidelines [J]. *Acta Clin Croat*, 2022, 61(Suppl 1): 67-72.
- [2] RUDD K E, JOHNSON S C, AGESA K M, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: Analysis for the Global Burden of Disease Study[J]. *Lancet*, 2020, 395(10219): 200-211.
- [3] SU P, ZHANG J B, WU J X, et al. TREM2 expression on the microglia resolved lead exposure-induced neuroinflammation by promoting anti-inflammatory activities[J]. *Ecotoxicol Environ Saf*, 2023, 260: 115058.
- [4] CHEN Q X, ZHANG K, JIN Y, et al. Triggering receptor expressed on myeloid cells-2 protects against polymicrobial sepsis by enhancing bacterial clearance [J]. *Am J Respir Crit Care Med*, 2013, 188(2): 201-212.
- [5] YANG S Y, YANG Y, WANG F F, et al. TREM2 dictates antibacterial defense and viability of bone marrow-derived macrophages during bacterial infection [J]. *Am J Respir Cell Mol Biol*, 2021, 65(2): 176-188.
- [6] SINGH H, RAI V, NOOTI S K, et al. Novel ligands and modulators of triggering receptor expressed on myeloid cells receptor family: 2015-2020 updates[J]. *Expert Opin Ther Pat*, 2021, 31(6): 549-561.
- [7] ULLAND T K, COLONNA M. TREM2: A key player in microglial biology and Alzheimer disease[J]. *Nat Rev Neurol*, 2018, 14(11): 667-675.
- [8] DECZKOWSKA A, WEINER A, AMIT I. The physiology, pathology, and potential therapeutic applications of the TREM2 signaling pathway[J]. *Cell*, 2020, 181(6): 1207-1217.
- [9] KOBER D L, BRETT T J. TREM2-ligand interactions in health and disease[J]. *J Mol Biol*, 2017, 429(11): 1607-1629.
- [10] HAURE-MIRANDE J V, AUDRAIN M, EHRLICH M E, et al. Microglial TYROBP/DAP12 in Alzheimer's disease: Transduction of physiological and pathological signals across TREM2[J]. *Mol Neurodegener*, 2022, 17(1): 55.
- [11] KONISHI H, KIYAMA H. Microglial TREM2/DAP12 signaling: A double-edged sword in neural diseases[J]. *Front Cell Neurosci*, 2018, 12: 206.
- [12] GRATUZE M, LEYNS C E G, HOLTZMAN D M. New insights into the role of TREM2 in Alzheimer's disease[J]. *Mol Neurodegener*, 2018, 13(1): 66.
- [13] FILIPELLO F, GOLDSBURY C, YOU S F, et al. Soluble TREM2: Innocent bystander or active player in neurological diseases? [J]. *Neurobiol Dis*, 2022, 165: 105630.
- [14] FEUERBACH D, SCHINDLER P, BARSKE C, et

- al. ADAM17 is the main sheddase for the generation of human triggering receptor expressed in myeloid cells (hTREM2) ectodomain and cleaves TREM2 after Histidine 157[J]. *Neurosci Lett*, 2017, 660: 109-114.
- [15] WU K Y, BYERS D E, JIN X H, et al. TREM-2 promotes macrophage survival and lung disease after respiratory viral infection[J]. *J Exp Med*, 2015, 212(5): 681-697.
- [16] ORHUN G, ESEN F, YILMAZ V, et al. Elevated sTREM2 and NFL levels in patients with sepsis associated encephalopathy[J]. *Int J Neurosci*, 2023, 133(3): 327-333.
- [17] HOLTZMAN M J, BYERS D E, ALEXANDER-BRETT J, et al. The role of airway epithelial cells and innate immune cells in chronic respiratory disease[J]. *Nat Rev Immunol*, 2014, 14(10): 686-698.
- [18] WANG S T, SUDAN R, PENG V, et al. TREM2 drives microglia response to amyloid- β *via* SYK-dependent and-independent pathways[J]. *Cell*, 2022, 185(22): 4153-4169. e19.
- [19] KLEINBERGER G, BRENDEN M, MRACSKO E, et al. The FTD-like syndrome causing TREM2 T66M mutation impairs microglia function, brain perfusion, and glucose metabolism[J]. *EMBO J*, 2017, 36(13): 1837-1853.
- [20] WANG Y, CAO C, ZHU Y T, et al. TREM2/ β -catenin attenuates NLRP3 inflammasome-mediated macrophage pyroptosis to promote bacterial clearance of pyogenic bacteria[J]. *Cell Death Dis*, 2022, 13(9): 771.
- [21] HU L F, LIU J, PENG J, et al. TREM2 alleviates neuroinflammation by maintaining cellular metabolic homeostasis and mitophagy activity during early inflammation[J]. *Diseases*, 2025, 13(2): 60.
- [22] ZHOU Y S, YU G R, LI H. Hancinone possesses potentials on increasing the ability of HMC3 cells to phagocytosis of A β 1-42 *via* TREM2/Syk/PI3K/AKT/mTOR signaling pathway[J]. *PLoS One*, 2025, 20(5): e0324202.
- [23] PERUGORRIA M J, OLAIZOLA P, LABIANO I, et al. Wnt- β -catenin signalling in liver development, health and disease[J]. *Nat Rev Gastroenterol Hepatol*, 2019, 16(2): 121-136.
- [24] ZHENG H H, JIA L, LIU C C, et al. TREM2 promotes microglial survival by activating Wnt/ β -catenin pathway[J]. *J Neurosci*, 2017, 37(7): 1772-1784.
- [25] SINGER M, DEUTSCHMAN C S, SEYMOUR C W, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3)[J]. *JAMA*, 2016, 315(8): 801-810.
- [26] COLONNA M. The biology of TREM receptors[J]. *Nat Rev Immunol*, 2023, 23(9): 580-594.
- [27] LI C X, ZHAO B, LIN C Z, et al. TREM2 inhibits inflammatory responses in mouse microglia by suppressing the PI3K/NF- κ B signaling[J]. *Cell Biol Int*, 2019, 43(4): 360-372.
- [28] RUGANZU J B, ZHENG Q Z, WU X Y, et al. TREM2 overexpression rescues cognitive deficits in APP/PS1 transgenic mice by reducing neuroinflammation *via* the JAK/STAT/SOCS signaling pathway[J]. *Exp Neurol*, 2021, 336: 113506.
- [29] IIZASA E, CHUMA Y, UEMATSU T, et al. TREM2 is a receptor for non-glycosylated mycolic acids of mycobacteria that limits anti-mycobacterial macrophage activation[J]. *Nat Commun*, 2021, 12(1): 2299.
- [30] LI D D, PAN L Y, CHEN M J, et al. TREM2 protects against LPS-induced murine acute lung injury through suppressing macrophage ferroptosis[J]. *Int Immunopharmacol*, 2025, 150: 114247.
- [31] SHU J X, LIANG J B, ZENG L D, et al. TREM2 drives neutrophil extracellular traps-induced dendritic cell maturation and contributes to lupus progression[J]. *Adv Sci*, 2025: e08938.
- [32] GALLO C, MANZO E, BARRA G, et al. Sulfavant A as the first synthetic TREM2 ligand discloses a homeostatic response of dendritic cells after receptor engagement[J]. *Cell Mol Life Sci*, 2022, 79(7): 369.
- [33] ZHENG J Y, WANG L X, ZHAO S Y, et al. TREM2 mediates MHC II-associated CD4⁺T-cell response against gliomas[J]. *Neuro Oncol*, 2024, 26(5): 811-825.
- [34] WU Y J, WANG M N, YIN H, et al. TREM-2 is a sensor and activator of T cell response in SARS-CoV-2 infection[J]. *Sci Adv*, 2021, 7(50): eabi6802.
- [35] PROVERA A, RAMAVATH N N, GADIPUDI L L, et al. Role of the co-stimulatory molecule inducible T-cell co-stimulator ligand (ICOSL) in the progression of experimental metabolic dysfunction-associated steatohepatitis[J]. *Front Immunol*, 2023, 14: 1290391.
- [36] WU Y J, WU M H, MING S Q, et al. TREM-2 promotes Th1 responses by interacting with the CD3 ζ -ZAP70 complex following *Mycobacterium tuberculosis* infection[J]. *J Clin Invest*, 2021, 131(17): e137407.
- [37] ZHANG K, WANG Y, CHEN S Y, et al. TREM2 (hi) resident macrophages protect the septic heart by maintaining cardiomyocyte homeostasis[J]. *Nat Metab*, 2023, 5(1): 129-146.
- [38] HERNÁNDEZ-ALVAREZ M I, SEBASTIÁN D, VIVES S, et al. Deficient endoplasmic reticulum-mitochondrial phosphatidylserine transfer causes liver disease[J]. *Cell*, 2019, 177(4): 881-895. e17.

- [39] HOU J C, ZHANG J, CUI P, et al. TREM2 sustains macrophage-hepatocyte metabolic coordination in nonalcoholic fatty liver disease and sepsis[J]. J Clin Invest, 2021, 131(4): e135197.
- [40] VERHEUL T C J, VAN HIJFTE L, PERENTHAL-ER E, et al. The why of YY1: Mechanisms of transcriptional regulation by Yin Yang 1[J]. Front Cell Dev Biol, 2020, 8: 592164.
- [41] LI X, XIAO C, YUAN J, et al. Rhein-attenuates LPS-induced acute lung injury *via* targeting NFATc1/Trem2 axis[J]. Inflamm Res, 2023, 72(6): 1237-1255.
- [42] LIM G B. Cardiac-resident macrophages protect against sepsis-induced cardiomyopathy[J]. Nat Rev Cardiol, 2023, 20(3): 141.
- [43] PINTO B B, DYSON A, UMBRELLO M, et al. Improved survival in a long-term rat model of sepsis is associated with reduced mitochondrial calcium uptake despite increased energetic demand[J]. Crit Care Med, 2017, 45(8): e840-e848.
- [44] NICOLÁS-ÁVILA J Á, HIDALGO A. TREM2(+) macrophages are guardians of the heart[J]. Nat Metab, 2023, 5(1): 13-15.
- [45] STRNAD P, TACKE F, KOCH A, et al. Liver: Guardian, modifier and target of sepsis[J]. Nat Rev Gastroenterol Hepatol, 2017, 14(1): 55-66.
- [46] JEPPESEN D K, FENIX A M, FRANKLIN J L, et al. Reassessment of exosome composition[J]. Cell, 2019, 177(2): 428-445. e18.
- [47] TERRASINI N, LIONETTI V. Exosomes in critical illness[J]. Crit Care Med, 2017, 45(6): 1054-1060.
- [48] YING W, RIOPEL M, BANDYOPADHYAY G, et al. Adipose tissue macrophage-derived exosomal miRNAs can modulate *in vivo* and *in vitro* insulin sensitivity [J]. Cell, 2017, 171(2): 372-384. e12.
- [49] LIU Y J, LIU L J, ZHANG J. Protective role of matrine in sepsis-associated cardiac dysfunction through regulating the lncRNA PTENP1/miR-106b-5p axis[J]. Biomed Pharmacother, 2021, 134: 111112.
- [50] YE H, ZHAI Q, FANG P, et al. Triggering receptor expressed on myeloid Cells-2 (TREM2) inhibits steroidogenesis in adrenocortical cell by macrophage-derived exosomes in lipopolysaccharide-induced septic shock[J]. Mol Cell Endocrinol, 2021, 525: 111178.
- [51] VAIDYA A, FINDLING J, BANCOS I. Adrenal insufficiency in adults: A review[J]. JAMA, 2025, 334(8): 714-725.
- [52] XU Y Z, PATTERSON M T, DOLFIB, et al. Adrenal gland macrophages regulate glucocorticoid production through TREM2 and TGF- β [J]. JCI Insight, 2024, 9(14): e174746.
- [53] GAO Q Z, HERNANDES M S. Sepsis-associated encephalopathy and blood-brain barrier dysfunction[J]. Inflammation, 2021, 44(6): 2143-2150.
- [54] ZHANG J W, LIU Y, ZHENG Y L, et al. TREM-2-p38 MAPK signaling regulates neuroinflammation during chronic cerebral hypoperfusion combined with diabetes mellitus[J]. J Neuroinflammation, 2020, 17(1): 2.
- [55] WU S R, WANG H M, LI Y J, et al. Transcription factor YY1 promotes cell proliferation by directly activating the pentose phosphate pathway[J]. Cancer Res, 2018, 78(16): 4549-4562.
- [56] PENG L S, XU Y, WANG Q S. YY1 promotes microglia M2 polarization through the miR-130a-3p/TREM-2 axis to alleviate sepsis-associated encephalopathy[J]. Shock, 2022, 58(2): 128-136.
- [57] ZHOU F, MEI J T, HAN X G, et al. Kinsenoside attenuates osteoarthritis by repolarizing macrophages through inactivating NF- κ B/MAPK signaling and protecting chondrocytes[J]. Acta Pharm Sin B, 2019, 9(5): 973-985.
- [58] XU Y, SHEN J, RAN Z H. Emerging views of mitophagy in immunity and autoimmune diseases[J]. Autophagy, 2020, 16(1): 3-17.
- [59] ZHANG L, WANG Y, WU G R, et al. Macrophages: Friend or foe in idiopathic pulmonary fibrosis? [J]. Respir Res, 2018, 19(1): 170.
- [60] WITHEREL C E, ABEBAYEHU D, BARKER T H, et al. Macrophage and fibroblast interactions in biomaterial-mediated fibrosis[J]. Adv Healthc Mater, 2019, 8(4): 1801451.
- [61] LEE J W, CHUN W, LEE H J, et al. The role of macrophages in the development of acute and chronic inflammatory lung diseases[J]. Cells, 2021, 10(4): 897.
- [62] HE Y Q, ZHOU C C, YU L Y, et al. Natural product derived phytochemicals in managing acute lung injury by multiple mechanisms[J]. Pharmacol Res, 2021, 163: 105224.
- [63] ZHOU Y Y, GAO C F, VONG C T, et al. Rhein regulates redox-mediated activation of NLRP3 inflammasomes in intestinal inflammation through macrophage-activated crosstalk[J]. Br J Pharmacol, 2022, 179(9): 1978-1997.
- [64] MING S Q, LI X Y, XIAO Q, et al. TREM2 aggravates sepsis by inhibiting fatty acid oxidation *via* the SHP1/BTK axis[J]. J Clin Invest, 2024, 135(1): e159400.