TREM2在动脉粥样硬化中的双重作用与治疗潜力

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[摘 要] 触发髓样细胞表达的受体2(triggering receptor expressed on myeloid cells 2，TREM2)是一种关键的跨膜免疫受体，在动脉粥样硬化(atherosclerosis，AS)斑块髓系细胞(尤其是巨噬细胞)中呈特异性高表达。单细胞测序技术的演进已明确将TREM2高表达巨噬细胞界定为脂质相关巨噬细胞这一独特亚群。TREM2在AS演变过程中表现出阶段特异性的双向调控作用：在疾病早期，TREM2通过上调清道夫受体CD36促进胆固醇摄取，加速泡沫细胞形成与病变扩张；进入晚期，其保护效应凸显，通过增强巨噬细胞存活、驱动胆固醇逆转运及提升胞葬作用效率，有效抑制坏死核心扩大并维持斑块稳定。在分子机制层面，TREM2-DNAX激活蛋白12(DNAX-activating protein of 12 kD，DAP12)复合体经p38丝裂原活化蛋白激酶/过氧化物酶体增殖物激活受体γ(peroxisome proliferator-activated receptor gamma，PPARγ)轴上调CD36介导脂质摄取，而肝X受体(liver X receptor，LXR)缺陷可削弱其保护作用。线粒体活性氧(mitochondrial reactive oxygen species，mtROS)经信号转导及转录激活因子5(signal transducer and activator of transcription 5，STAT5)驱动巨噬细胞向促炎泡沫表型转化；铁死亡相关的线粒体功能障碍则促进晚期泡沫巨噬细胞死亡，加重斑块失稳。在临床转化方面，可溶性TREM2(soluble TREM2，sTREM2)水平与冠心病及心血管不良事件风险相关，提示其可作为反映斑块炎症与细胞损伤的潜在生物标志物，并可能提供超越高敏C反应蛋白的增量预测价值；TREM2激动剂(如AL002a)可重编程泡沫巨噬细胞、增强胞葬与坏死核心清除，从而提升斑块稳定性，展现出精准干预潜力。综上，TREM2在AS不同阶段呈现“双刃剑”特征，针对其阶段特异性的精准调控有望成为AS免疫治疗的新方向。

[关键词] 触发髓样细胞表达的受体2；动脉粥样硬化；脂质相关巨噬细胞；胞葬作用；单细胞测序

Dual role and therapeutic potential of TREM2 in atherosclerosis

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ABSTRACT Triggering receptor expressed on myeloid cells 2 (TREM2) is a key transmembrane immune receptor that is specifically highly expressed in myeloid cells, particularly macrophages, within atherosclerosis (AS) plaques. Advances in single-cell sequencing technology have clearly defined TREM2-high macrophages as a distinct subpopulation

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known as lipid-associated macrophages. TREM2 exhibits stage-specific bidirectional regulatory effects during the progression of AS. In the early stage of the disease, TREM2 promotes cholesterol uptake by upregulating the scavenger receptor CD36, thereby accelerating foam cell formation and lesion expansion. In the advanced stage, however, its protective effects become prominent: TREM2 enhances macrophage survival, drives reverse cholesterol transport, and improves efferocytosis efficiency, thereby effectively inhibiting necrotic core expansion and maintaining plaque stability. At the molecular level, the TREM2-DAP12 complex upregulates CD36-mediated lipid uptake through the p38 mitogen-activated protein kinase/peroxisome proliferator-activated receptor gamma (PPARγ) axis, whereas deficiency of liver X receptor (LXR) can weaken its protective effects. Mitochondrial reactive oxygen species (mtROS) drive the transition of macrophages toward a pro-inflammatory foam cell phenotype through signal transducer and activator of transcription 5 (STAT5). In addition, ferroptosis-related mitochondrial dysfunction promotes the death of advanced foam macrophages and aggravates plaque instability. In terms of clinical translation, soluble TREM2 (sTREM2) levels are associated with the risk of coronary heart disease and adverse cardiovascular events, suggesting that sTREM2 may serve as a potential biomarker reflecting plaque inflammation and cellular injury and may provide incremental predictive value beyond high-sensitivity C-reactive protein. TREM2 agonists, such as AL002a, can reprogram foam macrophages and enhance efferocytosis and necrotic core clearance, thereby improving plaque stability and showing potential for precision intervention. In summary, TREM2 shows a “double-edged sword” role at different stages of AS, and precise stage-specific modulation of TREM2 may represent a new direction for immunotherapy in AS.

KEY WORDS　triggering receptor expressed on myeloid cells 2; atherosclerosis; lipid-associated macrophages; efferocytosis; single-cell sequencing

动脉粥样硬化(atherosclerosis，AS)是一种由脂质驱动的慢性炎症性疾病，是全球范围内心血管事件(如心肌梗死、卒中等)发生的主要病理学基础[1-3]。其特征在于脂质在动脉内膜的异常沉积，并伴随大量免疫细胞(尤其是巨噬细胞)的浸润及向富含脂质的泡沫细胞的转化[4-5]。泡沫细胞的细胞命运(包括存活、凋亡或清除)直接决定动脉斑块的稳定性，进而影响其破裂风险[5-6]。

近十年，高分辨率生物学技术，尤其是单细胞RNA测序(single-cell RNA sequencing，scRNA-seq)，极大地拓展了对AS斑块微环境中细胞异质性的认知[3, 7-9]。这些研究共同揭示了一个独特的巨噬细胞亚群，该亚群高表达触发髓样细胞表达的受体2(triggering receptor expressed on myeloid cells 2，TREM2)，并与脂质代谢功能密切相关[7-8, 10-11](图1)。TREM2是一种I型跨膜免疫受体，主要表达于髓系细胞(如巨噬细胞、小胶质细胞和树突状细胞)[12-14]。TREM2通过与衔接蛋白DNAX激活蛋白12(DNAX-activating protein of 12 kD，DAP12)结合介导信号转导，参与调控细胞吞噬作用、脂质代谢、炎症反应及细胞存活等多种生物学过程[13, 15-16]。TREM2最初被确定为阿尔茨海默病及其他神经退行性变性疾病的关键风险因子[15, 17-18]。然而，近期的大量证据[14, 19-21]表明，TREM2及其下游信号通路在心血管疾病，如AS和高血压性心力衰竭的发生和发展中，发挥至关重要的调控作用。本综述旨在系统性整合TREM2在AS发病机制中的最新研究进展，重点探讨其在斑块不同发展阶段的动态功能、潜在的分子调控机制，以及其作为新型治疗靶点的临床转化潜力。尽管以他汀类药物和前蛋白转化酶枯草溶菌素9型(proprotein convertase subtilisin/kexin type 9，PCSK9)抑制剂为代表的强效降脂治疗已显著降低心血管事件风险，但仍有一定比例的患者面临以斑块炎症为核心的“残余炎症风险”[22]，这说明在传统降脂策略

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之外，针对斑块免疫-代谢微环境开发新型干预靶点的迫切需求[23]。在笔者看来，TREM2正是连接脂质代谢与免疫调控的关键候选靶点之一；理解其作用的关键，在于跳出“促病或保护”的二元判断，转而将其视为随病变阶段、脂质负荷与代谢状态而动态变化的“条件性”调控枢纽。

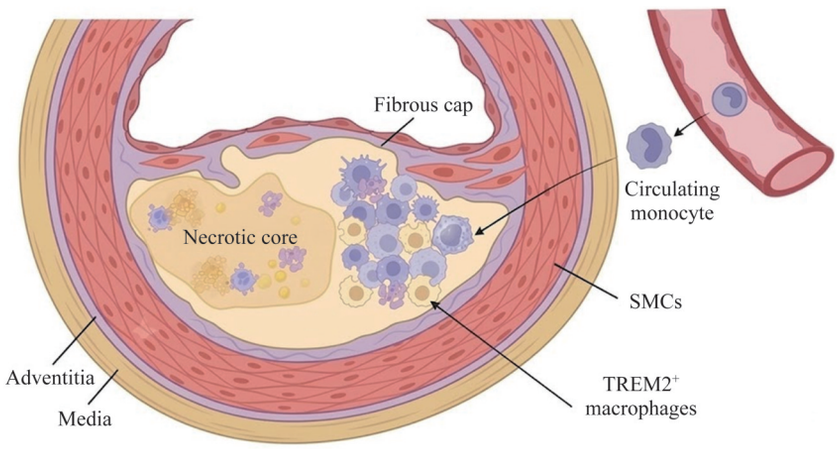

图1 AS斑块中TREM2$^+$巨噬细胞的细胞起源、空间定位及亚群特征

Figure 1 Cellular origin, spatial localization, and subset features of TREM2$^+$ macrophages in AS plaques

After infiltrating the arterial intima, circulating monocytes differentiate into macrophages that highly express TREM2 within the lipid-rich microenvironment, giving rise to LAMs. This subset features high expression of lipid-metabolism genes (e.g., *ApoE, CD36*) and lysosome-related genes (e.g., *CTSD*, *LAMP1*), and is mainly localized to the border zone between the fibrous cap and the necrotic core. In parallel, vascular SMCs can also transdifferentiate into foam cells, some of which express TREM2 and contribute to plaque formation. AS: Atherosclerotic; SMCs: Smooth muscle cells; TREM2: Triggering receptor expressed on myeloid cells 2; *ApoE*: Apolipoprotein E; *CD36*: Cluster of differentiation 36; LAMs: Lipid-associated macrophages; *CTSD*: Cathepsin D; *LAMP1*: Lysosomal-associated membrane protein 1.

1 AS斑块中TREM2高表达巨噬细胞的鉴定与细胞起源

1.1 scRNA-seq定义的脂质相关巨噬细胞亚群

scRNA-seq技术显著革新了AS斑块内巨噬细胞的分类体系，有效地挑战了传统的M1/M2分类范式[24-25]。多项独立的高维单细胞组学研究[3, 7-9, 26]表明，在颈动脉斑块模型小鼠[如Ldlr$^{-/-}$和载脂蛋白E(apolipoprotein E，ApoE)$^{-/-}$]及颈动脉斑块人类样本中，均鉴定出一个特征性的巨噬细胞亚群，即TREM2高表达(TREM2^{hi})巨噬细胞。该亚群具有高度特异性，通常被界定为斑块脂质相关巨噬细胞或脂质相关巨噬细胞(lipid-associated macrophages，LAMs)，并展现出高度特异的转录组学特征[27-28](图1)。这些细胞富集了脂质代谢、吞噬/内吞、溶酶体功能及氧化磷酸化等关键生物学过程相关的基因程序[11, 27]。其基因特征与肥胖、非酒精性脂肪性肝炎和阿尔茨海默病中发现的疾病相关巨噬细胞高度相似，这说明TREM2在慢性代谢和炎症性疾病的发病机制中具有关键作用[15, 27-30]。最新的单细胞与空间转录组学综述[31]进一步整合了不同物种与不同病变阶段中AS斑块的细胞图谱，进一步强化了TREM2^{hi}泡沫巨噬细胞作为核心免疫-代谢节点的认识。

1.2 细胞起源的多样性

AS泡沫细胞的起源具有多样性。除来源于循环单核细胞分化而成的巨噬细胞外，血管平滑肌细胞(smooth muscle cell，SMC)亦可通过去分化机制转化为泡沫细胞[3, 32](图1)。研究[26]证实，在人颈动脉AS斑块中，存在表达TREM2的泡沫细胞亚群，以及纤维化通路显著上调的SMC衍生泡沫细胞。具体而言，有研究[1]明确指出，TREM2在SMCs和巨噬细胞中均可通过促进脂质摄取和流入，加剧泡沫细胞的形成过程。此外，单细胞空间转录组学分析揭示[33]，TREM2$^+$脂质处理型巨噬细胞定位于斑块的纤维帽与坏死核心的交界区域，这提示该亚群在维持斑块结

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构和稳定性方面可能发挥重要的空间定位和潜在功能作用(图1)。值得强调的是，TREM2并非巨噬细胞所特有：SMC去分化来源的泡沫细胞亦可表达TREM2，因此在解读斑块TREM2表达数据、评估其作为细胞身份标志或治疗靶点的价值时，必须充分考虑细胞起源的异质性，单纯以TREM2水平推断巨噬细胞功能可能产生偏倚。此外，目前LAMs的概念主要源自模型小鼠及肥胖、脂肪肝等代谢性疾病的研究[34]，其在不同血管床、不同病程及不同人群的颈/冠状动脉斑块中的保守性与功能权重，仍有待更大规模的单细胞与空间转录组学证据加以厘清。

2 TREM2在AS进展中的阶段性作用

TREM2的功能并非恒定不变，而是展现出显著的阶段特异性，在AS的早期与晚期表现出截然相反的作用，这构成了其作为潜在治疗靶点的复杂性基础[21, 35-36]。

2.1 早期阶段：促AS作用

在AS的起始阶段，TREM2的表达水平与脂质积累和病变扩大呈正相关。TREM2通过调控胆固醇摄取，促进泡沫细胞形成(图2)。ApoE$^{-/-}$模型小鼠在高脂饮食喂养下，TREM2阳性泡沫细胞在主动脉斑块中的密度随疾病进程递增[1]。进一步的遗传学证据表明，TREM2$^{-/-}$/ApoE$^{-/-}$双敲除小鼠在高脂饮食干预后，AS病变面积、泡沫细胞数量和脂质负荷均显著降低[1]。这种促AS作用的机制在于TREM2能够上调清道夫受体CD36的表达，从而增强巨噬细胞对氧化低密度脂蛋白(oxidized low-density lipoprotein，oxLDL)的摄取能力[1, 4](图2)。在分子机制层面，TREM2通过调节关键的核受体信号通路介导其促AS功能。具体而言，TREM2抑制p38丝裂原活化蛋白激酶(p38 mitogen-activated protein kinase，p38 MAPK)的磷酸化水平，进而激活过氧化物酶体增殖物激活受体γ(peroxisome proliferator-activated receptor gamma，PPARγ)的核转录活性，最终驱动CD36的转录表达[1, 37](图2)。

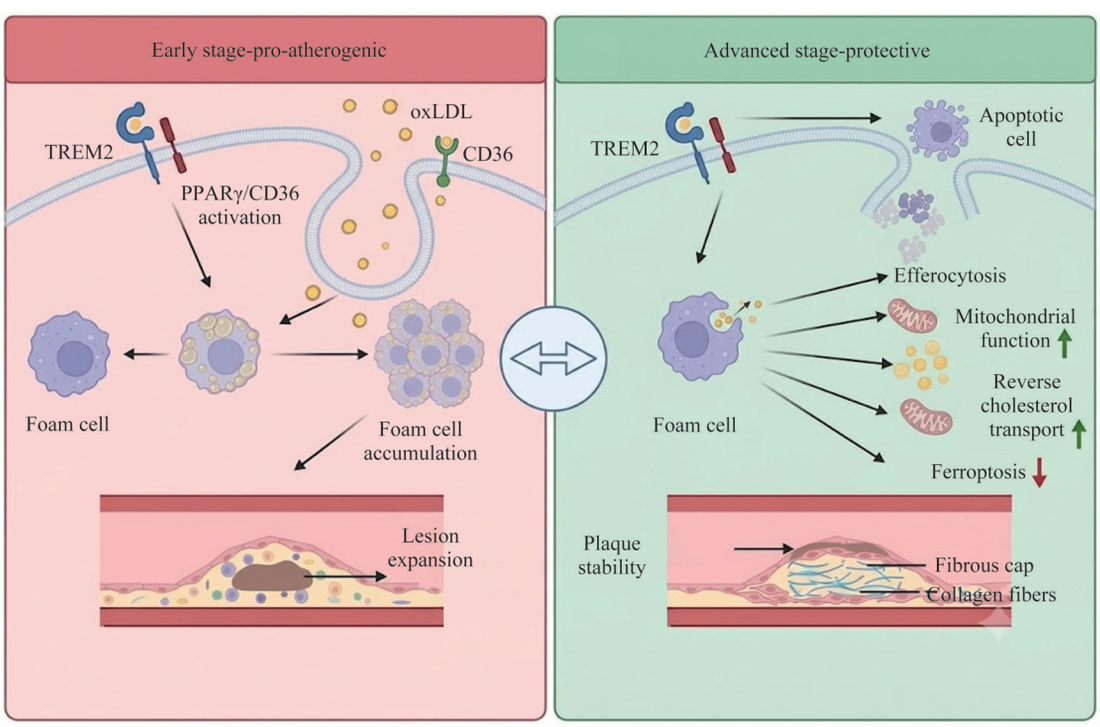

图2　TREM2在AS不同阶段的动态功能转换

Figure 2　Dynamic functional switch of TREM2 across different stages of AS

Left panel (early stage, pro-atherogenic): through activation of the PPARγ/CD36 signaling pathway, TREM2 promotes macrophage uptake of oxLDL, leading to foam cell formation and accumulation and ultimately expanding the lesion area. Right panel (advanced stage, protective): By enhancing efferocytosis, promoting reverse cholesterol transport, improving mitochondrial function, and suppressing ferroptosis, TREM2 reduces the necrotic core, thickens the fibrous cap, and increases collagen deposition, thereby maintaining plaque stability. PPARγ: Peroxisome proliferator-activated receptor gamma; oxLDL: Oxidized low-density lipoprotein.

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2.2 晚期阶段：维持斑块稳定性的保护作用

进入疾病晚期，AS的主要风险由病变扩大演变为斑块破裂。此时TREM2的作用机制转变为保护性/抗AS特性，主要通过维持巨噬细胞生存和促进死亡细胞清除实现[2, 21, 35](图2)。

胞葬作用是巨噬细胞清除凋亡细胞的关键机制。胞葬作用障碍会导致凋亡细胞在斑块内堆积，形成易于破裂的坏死核心，这是晚期AS的主要特征之一[6]。研究[2, 14, 38]已证实TREM2对巨噬细胞的胞葬能力具有关键调节作用。具体而言，TREM2通过调控巨噬细胞的胞葬功能及脂质负荷细胞的生存，有效控制斑块坏死程度，从而发挥限制坏死核心形成的功能，维持斑块稳定性[2]。缺乏TREM2的巨噬细胞表现为胆固醇流出相关分子上调受损，进而导致细胞增殖和存活能力下降[4]。尽管TREM2激动剂(如AL002a抗体)可能通过增加巨噬细胞数量和存活率导致斑块面积轻微增大，但其显著改善了斑块的稳定性特征，体现在坏死核心缩小、纤维帽增厚和胶原沉积增加等方面[39-40](图2)。晚期AS中泡沫细胞的死亡涉及多种途径，其中铁死亡是坏死核心形成的关键决定因素[41]。研究[41]发现，TREM2低表达(TREM2^{low})的泡沫细胞呈现出低水平氧化磷酸化的代谢表型，从而导致对铁死亡的敏感性显著增加。因此，维持TREM2的稳态表达可能通过保障线粒体功能，间接赋予泡沫细胞抵抗铁死亡的能力[41](图2)。如何统一TREM2在早期“促进泡沫化”与晚期“维持稳定”这一看似矛盾的双重表型，是理解其病理作用的核心问题。笔者认为，二者并非源自彼此独立的机制，而更可能是同一“脂质摄取-存活-胞葬”功能程序在不同病变微环境下输出的净效应：在脂质供应充足而凋亡负荷较低的早期，TREM2介导的脂质摄取占据主导，表现为促AS；而当晚期凋亡细胞与坏死核心不断累积时，其维持巨噬细胞存活、增强胞葬并促进胆固醇逆转运的作用更具决定意义，从而转为保护[42]。这一阶段的功能转换，与巨噬细胞在AS不同阶段表型可塑性的整体规律相吻合[43]。由此推论，既往研究结论的分歧在很大程度上可能源于所取病变阶段、脂质负荷及模型体系的差异，而非TREM2作用方向的根本对立。

3 TREM2功能的分子调控机制与信号转导通路

TREM2的功能受控于复杂的免疫和代谢信号网络，其调控机制对于理解其在疾病中的作用至关重要。

3.1 TREM2与炎症-代谢的交互作用

作为一种重要的脂质感应受体，TREM2的功能与细胞脂质代谢状态存在高度关联[15]。肝X受体(liver X receptor，LXR)转录因子在泡沫细胞中激活后具有显著的抗炎效应。研究[44]显示，髓系LXR缺陷显著加速AS进程。尽管TREM2^{+}泡沫细胞数量有所增加，但其却丧失了*TREM2*基因表达模块特征(包括吞噬功能和胆固醇流出基因表达)，并转变为促炎和增殖表型[44](图3，通路A)。这提示LXR是促进*TREM2*基因表达及抑制泡沫细胞炎症反应的关键调控因子。PPARγ信号通路在TREM2介导的泡沫细胞形成中发挥重要作用[1](图3，通路A)。此外，研究[37]发现某些天然药物(如“活血通络片”)能够通过激活PPARγ信号通路，上调TREM2^{+}巨噬细胞的数量，进而增强胞葬作用，有效延缓AS进展(图3，通路A)。

3.2 细胞死亡和炎症途径的调控

TREM2亦参与调控与动脉斑块稳定性密切相关的细胞死亡和炎症信号：oxLDL诱导的线粒体活性氧(mitochondrial reactive oxygen species，mtROS)是驱动泡沫细胞形成的重要因素。mtROS能够激活信号转导及转录激活因子5(signal transducer and activator of transcription 5，STAT5)，STAT5的活化抑制了三羧酸循环活性，并促进巨噬细胞向TREM2^{hi}Gpnmb^{hi}[即高表达TREM2与糖蛋白非转移性黑色素瘤蛋白B(glycoprotein non-metastatic melanoma protein B，Gpnmb)]的泡沫细胞表型转化[45](图3，通路B)。对STAT5的抑制可有效阻断这一过程。克隆性造血(clonal hematopoiesis，CH)通过激活白细胞介素-1(interleukin-1，IL-1)信号通路加剧AS，导致包括TREM2在内的吞噬受体降解，从而显著增加斑块不稳定性[39, 46](图3，通路C)。然而，使用TREM2激动剂抗体可显著增加纤维帽厚度，有效逆转CH所驱动的斑块不稳定性[39]。此外，京尼平苷可通过抑制TREM2/哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin，mTOR)信号轴，提升巨噬细胞自噬水平，从而抑制AS的进一步发展[47](图3，通路C)。

3.3 跨疾病模型的TREM2功能保守性

TREM2的功能特性在多种疾病环境中表现出高度保守性，其核心作用均围绕脂质处理、炎症反应和细胞吞噬作用展开[13, 15, 30](图3)。例如，在腹主动脉中，scRNA-seq技术同样鉴定了TREM2^{+}巨噬细胞亚群，并确证其是动脉损伤过程的关键介质[48]。类似地，在射血分数保留型心力衰竭模型中，TREM2亦发挥保护作用，TREM2的缺失会加剧心脏肥大和舒

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张功能障碍。其机制在于，缺乏TREM2的巨噬细胞在促血管生成基因表达上存在缺陷，且伴随促炎性细胞因子表达量的增加[20-21]。综合多种器官系统的研究[49]证据来看，TREM2$^+$巨噬细胞在不同疾病的发生与进展中均发挥关键的免疫-代谢调控作用，提示其有望成为多种疾病的通用治疗靶点。综观上述调控网络，笔者倾向于将TREM2视为一个整合脂质信号(LXR/PPARγ)与炎症-存活信号(STAT5、IL-1、mTOR)的免疫-代谢检查点：作为脂质感应受体，TREM2将细胞外脂质负荷“翻译”为下游的代谢重塑与存活信号[50]，这也解释了为何其功能高度依赖局部脂质与代谢环境。但需要清醒认识到，现有机制证据多来自小鼠模型与体外实验，相关通路在人类斑块中的权重、时序及可干预性仍缺乏系统验证，这是将上述网络转化为治疗策略前必须跨越的关键鸿沟。

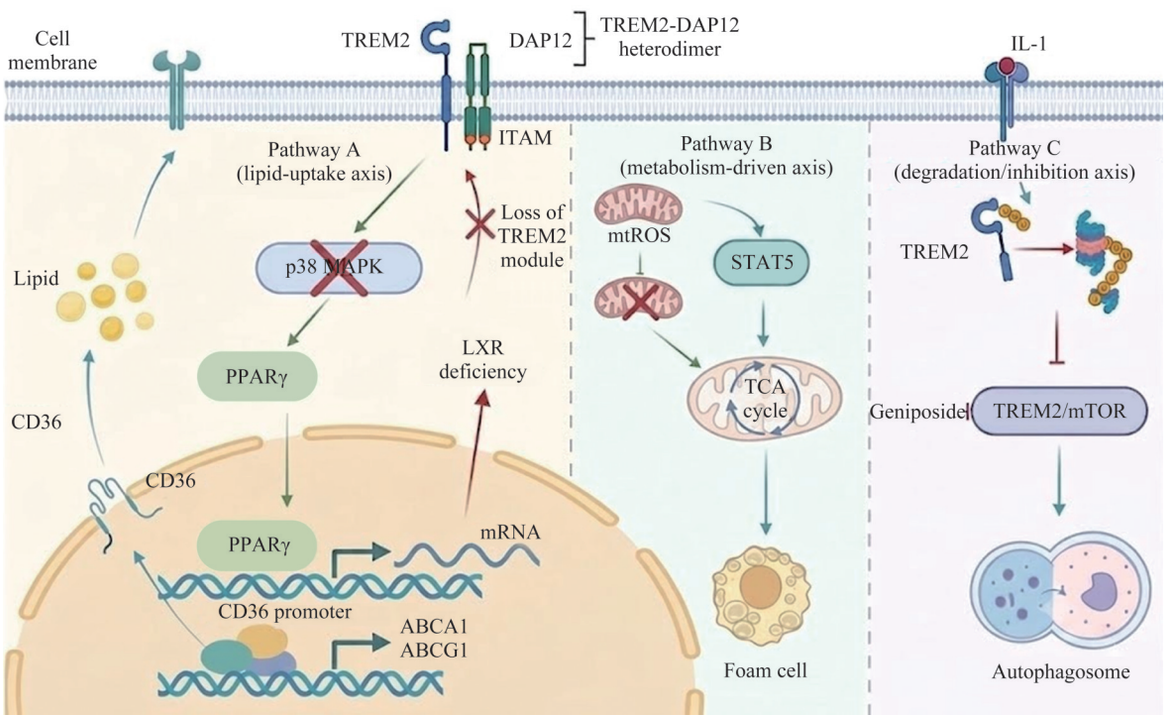

图3　TREM2介导的分子调控与信号转导网络

Figure 3　TREM2-mediated molecular regulation and signal transduction network

Pathway A (lipid-uptake axis): TREM2-DAP12 heterodimer inhibits p38 MAPK phosphorylation, activates PPARγ nuclear transcriptional activity, and enhances CD36 promoter activity, thereby promoting lipid uptake and foam cell formation; LXR deficiency leads to loss of the TREM2 functional module. Pathway B (metabolism-driven axis): mtROS activates STAT5 and suppresses TCA cycle activity, inducing the phenotypic conversion toward TREM2^{hi} foam cells. Pathway C (degradation/inhibition axis): IL-1 signaling downregulates TREM2 by promoting its degradation, whereas geniposide enhances macrophage autophagy by inhibiting the TREM2/mTOR axis to exert a protective effect. DAP12: DNAX-activating protein of 12 kD; MAPK: Mitogen-activated protein kinase; LXR: Liver X receptor; mtROS: Mitochondrial reactive oxygen species; STAT5: Signal transducer and activator of transcription 5; TCA: Tricarboxylic acid (cycle); IL-1: Interleukin-1; mTOR: Mammalian target of rapamycin; ABCA1: ATP-binding cassette subfamily A member 1; ABCG1: ATP-binding cassette subfamily G member 1; mRNA: Messenger RNA.

4 转化应用与治疗前景

4.1 可溶性TREM2作为生物标志物

TREM2膜受体经蛋白水解过程释出可溶性TREM2(soluble TREM2，sTREM2)，随后释放至血液和脑脊液中[15]。在心血管领域，sTREM2的血清水平与冠心病发病具有独立相关性[51]。一项针对冠状AS患者的前瞻性队列研究[52]揭示，高水平的血清sTREM2可预示心血管死亡风险的增加，提示sTREM2可能是反映斑块破裂风险的潜在替代生物学

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标志物。这表明sTREM2水平能够有效表征斑块内部炎症与细胞损伤的程度，并具有超越传统炎症指标[如高敏C反应蛋白(high-sensitivity C-reactive protein，hs-CRP)]的临床诊断与预后评估价值[51]。

4.2 靶向TREM2的治疗策略

鉴于TREM2在AS进展过程中发挥的复杂且阶段性作用，精准调节其活性是未来治疗策略开发的关键[10, 21]。由于TREM2在晚期斑块中主要介导稳定化效应，激活TREM2是一种具有潜力的治疗策略。TREM2激动剂抗体(如AL002a)在模型小鼠实验中，通过促进泡沫细胞的存活、增强胆固醇流出及诱导胶原沉积，显著增强了斑块的稳定性[14, 39-40]。此外，激动剂干预还能够逆转高胆固醇驱动的AS模型中吞噬受损现象和斑块不稳定性[39]。

在疾病早期阶段，若治疗目标旨在抑制泡沫细胞的病理形成，则抑制TREM2可能提供治疗优势[1]。例如，研究[53]证据表明，艾塞那肽-4(胰高血糖素样肽-1受体激动剂)可通过抑制巨噬细胞TREM2表达，从而有效减轻oxLDL诱导的泡沫细胞形成和炎症反应。

新型纳米免疫疗法通过干扰小RNA靶向炎症因子干扰素调节因子5，成功地提升了巨噬细胞(特别是$CD11c^{+}$和$Trem2^{hi}$亚群)的胞葬功能，显著减少了坏死核心面积，增强了斑块的整体稳定性[6]。这证实了$Trem2^{hi}$巨噬细胞是进行细胞功能重编程的有效靶点。

肠道微生物组代谢产物，例如细菌脂二肽(S/G lipids)，已被证明能够调节髓系细胞TREM2的表达，进而影响全身炎症反应。这为通过调节微生物组来间接干预和调节TREM2功能提供了新的研究方向[54]。综合来看，靶向TREM2的核心难点在于其作用的“时相依赖性”：晚期激活TREM2有助于稳定斑块，早期过度激活却可能加剧脂质蓄积，而临床上对患者所处斑块阶段尚缺乏成熟的精准分层手段[55]。笔者认为，未来更现实的方向并非笼统地“激活”或“抑制”TREM2，而是借助斑块靶向纳米递送、细胞亚群特异性调控等策略实现时空可控的精准干预，并以sTREM2等循环标志物辅助识别潜在获益人群，从而将“生物标志物指导下的分层治疗”与TREM2精准调控有机结合。

5 结 语

TREM2是AS病理学中的一个核心枢纽，尤其是在调控脂质代谢和巨噬细胞命运方面发挥阶段依赖性的双重作用。scRNA-seq的突破性应用不仅识别了$TREM2^{hi}$巨噬细胞/LAMs这一关键亚群，更揭示了其在早期促泡沫化与晚期促稳定化之间的微妙平衡。

针对TREM2的治疗需要克服其双重性。理想的策略是开发能够阶段特异性或细胞亚群特异性地激活TREM2保护功能(胞葬作用、存活)而非其促脂质摄取功能的药物。尽管TREM2功能已知，但其内源性配体和下游信号网络的详细机制仍有待阐明[12, 14]。

例如，全面阐明TREM2与LXR/PPARγ、STAT5等信号通路，以及铁死亡/自噬等过程中的相互作用机制，将为设计更具靶向性的药物奠定基础。sTREM2作为预测心血管风险的潜在生物标志物，其预警和诊断价值尚需通过更大规模、多中心的前瞻性临床队列研究进行验证。与此同时，实现TREM2激动剂(如特异性抗体疗法)从临床前模型到人体试验的安全高效临床转化，是实现靶向AS免疫调控策略的关键环节。

综上所述，通过全面阐释TREM2的生物学功能及其在AS进展中的精细调控机制，研究人员有望设计出针对斑块微环境的精准免疫疗法，从而实质性降低心血管疾病的发生率和致死率。

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