生理学报 *Acta Physiologica Sinica*, June 25, 2021, 73(3): 501–508
DOI: 10.13294/j.aps.2021.0027 http://www.actaps.com.cn

综 述

细胞因子在动脉粥样硬化发病中的作用机制及相关治疗举措研究现状

李志明，王铭洁*

上海市小分子活性物质重点实验室，复旦大学基础医学院生理与病理生理学系，上海市高水平地方高校重点创新团队，上海 200032

摘 要：动脉粥样硬化是一种慢性炎症性疾病，开展细胞因子相关研究为动脉粥样硬化的预防和治疗提供了重要方向。细胞因子由不同类型的细胞产生，作用于一系列靶点，在动脉粥样硬化的发病和进展过程中起关键作用。本文概述了动脉粥样硬化有关的主要促炎和抗炎细胞因子及其作用机制，归纳了现阶段有关动脉粥样硬化细胞因子的针对性治疗措施，并对细胞因子在动脉粥样硬化防治方面的研究和治疗前景进行展望。

关键词：动脉粥样硬化；细胞因子；炎症信号；治疗措施
中图分类号：R33

Current studies of cytokines in the pathogenesis of atherosclerosis and its therapeutic measures

LI Zhi-Ming, WANG Ming-Jie*

Shanghai Key Laboratory of Bioactive Small Molecules, Department of Physiology and Pathophysiology, School of Basic Medical Sciences, Shanghai Key Innovation Team of High-Level Local Universities, Fudan University, Shanghai 200032, China

Abstract: Atherosclerosis is a chronic inflammatory disease. Cytokine-related research provides an important direction for the prevention and treatment of atherosclerosis. Cytokines, produced by different types of cells and acting on a range of targets, play a key role in the pathogenesis and progression of atherosclerosis. This review summarizes the main pro-inflammatory and anti-inflammatory cytokines related to atherosclerosis and their underlying mechanism. We also outline current anti-atherosclerosis treatments targeting cytokines. The research and treatment prospects of cytokines in the prevention and treatment of atherosclerosis are discussed briefly as well.

Key words: atherosclerosis; cytokines; inflammatory signal; therapy

动脉粥样硬化 (atherosclerosis, AS) 斑块破裂后急性血栓的形成是心血管疾病中脑梗死和急性心肌梗死的主要原因 [1]。有关 AS 的发病原因早期主要集中在脂质的积累 [2] 和平滑肌细胞在内膜下的增生 [3]。各种细胞和脂质的不断积累加速斑块生长，斑块不稳定最终破裂，导致急性冠状动脉综合征等临床急症。随着对内皮功能障碍的深入研究 [4, 5]，炎症在 AS 发生中所起的作用越来越引起研究人员的重视。

AS 被认为是一种慢性炎症性疾病 [6]，其发展过程中相关细胞可分泌产生细胞因子，参与炎症反应，在早期的内皮功能损伤和随后的斑块形成中均

Received 2020-08-15 Accepted 2020-12-24

Research from the corresponding author's laboratory was supported by a grant from the National Natural Science Foundation of China (No. 81970361).

*Corresponding author. Tel: +86-21-54237609-1; E-mail: mjwang@shmu.edu.cn

扮演重要的角色[7]。促炎性细胞因子可促进 AS 发生，如白细胞介素 1β (interleukin-1β, IL-1β)、白细胞介素 6 (interleukin-6, IL-6) 和肿瘤坏死因子 α (tumor necrosis factor-α, TNF-α)。抗炎性细胞因子可抑制 AS 发生，如白细胞介素 10 (interleukin-10, IL-10) 和转化生长因子 -β (transforming growth factor-β, TGF-β)。首先，从动物实验和临床试验中均能观察到在 AS 发生过程中，促炎性细胞因子表达升高[8]，抗炎性细胞因子表达下降[9]。其次，围绕促炎性细胞因子开展的早期研究也取得了一定的成果。与载脂蛋白 E (apolipoprotein E, ApoE) 单敲小鼠 ($ApoE^{-/-}$) 相比，TNF-α 和 ApoE 双基因敲除小鼠相对病斑面积下降约 50%[10]；IL-1β 和 ApoE 双基因敲除小鼠的 AS 斑块面积比 $ApoE^{-/-}$ 小鼠低 30%，促炎性细胞因子表达显著低于 $ApoE^{-/-}$ 小鼠[11]。以上研究提示，开展细胞因子相关的治疗有助于降低 AS 的发生率或减缓疾病的进程。

1 细胞因子与AS

越来越多的证据表明，下调促炎性细胞因子或上调抗炎性细胞因子能有效降低 AS 的发病几率。

1.1 促炎性细胞因子

主要促炎性细胞因子有 IL-1β、IL-6 和 TNF-α 等[7]。单核细胞趋化蛋白 1 (monocyte chemotactic protein-1, MCP-1)[12] 能促进白细胞与血管内皮细胞的黏附，诱导炎症性心血管疾病的发生，因此 MCP-1 也是一种重要的促炎性细胞因子。巨噬细胞迁移抑制因子 (macrophage migration inhibitory factor, MIF) 在趋化单核细胞功能方面与 MCP-1 相似，且能诱导内皮细胞表达趋化因子和黏附分子，并促进巨噬细胞对氧化型低密度脂蛋白 (oxidized low density lipoprotein, ox-LDL) 的吞噬和促炎性细胞因子的分泌[13, 14]。血小板衍化生长因子 (platelet-derived growth factor, PDGF) 也参与了 AS 的炎症过程。由巨噬细胞分泌的 PDGF 是一种强力的平滑肌细胞趋化剂和有丝分裂原，可促进平滑肌细胞发生表型转变[3]。白细胞介素 IL-18[15]、IL-12[16]、IL-21[17] 作为促炎性细胞因子也有报道。而 IL-1β 在众多促炎性细胞因子中起到中心作用[18]，不仅自身有强大的促炎能力，还能促进 IL-6、IL-18 的分泌，从而放大炎症反应。研究表明，IL-1β 能诱导细胞间黏附分子 1 (intercellular adhesion molecule-1, ICAM-1) 和血管细胞黏附分子 1 (vascular cell adhesion molecule-1, VCAM-1) 的表达，促进白细胞的迁移[19]。IL-1β 能诱导平滑肌细胞分泌 IL-6[12]，IL-6 刺激肝脏细胞产生纤维蛋白原和抑制纤维蛋白溶解，加速 AS 的发展进程 (表 1)。

1.2 抗炎性细胞因子

抗炎性细胞因子可抑制 AS 中斑块的形成。由平滑肌细胞、血管内皮细胞、单核细胞和 T 细胞产生的 TGF-β 是一种重要的抗炎性细胞因子。研究表明，TGF-β 在 $ApoE^{-/-}$ 小鼠体内过表达后，小鼠主

表 1. 动脉粥样硬化主要的促炎和抗炎性细胞因子

Table 1. Major pro-inflammatory and anti-inflammatory cytokines related to atherosclerosis

Cytokines	Pro/anti-inflammation	Effects in atherosclerosis progression
IL-1β	Promoting	Increase ICAM-1, VCAM-1 and IL-6 [12]
		Promote the migration of smooth muscle cells [19]
IL-6	Promoting	Induce endothelial cell dysfunction, vascular smooth muscle proliferation and migration [31]
		Induce the liver to produce fibrinogen, plasminogen activator inhibitor and C-reactive protein [27]
TNF-α	Promoting	Destroy the tight junctions between endothelial cells and promote the adhesion of monocytes to the surface of endothelial cells [32]
		Promote LDL to enter the subendothelial layer and accelerate the accumulation of lipids in the blood vessel wall [33]
MIF	Promoting	Promote the adhesion of monocytes to endothelial cells and the phagocytosis of ox-LDL by macrophages [13, 14]
IL-10	Suppressing	Decrease TNF-α, MCP-1 and ICAM-1 [21]
TGF-β	Suppressing	Inhibit plaque development and stabilize plaque [20]
IL-13	Suppressing	Increase the collagen content of plaques and increase the proportion of M2 macrophages [27]

MIF: macrophage migration inhibitory factor; TNF-α: tumor necrosis factor-α; TGF-β: transforming growth factor-β; LDL: low density lipoprotein; ox-LDL: oxidized LDL; ICAM-1: intercellular adhesion molecule-1; VCAM-1: vascular cell adhesion molecule-1; MCP-1: monocyte chemotactic protein-1.

动脉损伤面积和脂质积累减少，斑块的胶原成分增多，表现出抗炎和抗 AS 的特性 [20]。抗炎性细胞因子 IL-10 可降低促炎性细胞因子 TNF-α 和黏附分子 ICAM-1 的生成 [21]。

IL-10 和 TGF-β 都可由调节性 T 细胞分泌产生，IL-10 可以降低促炎性细胞因子和趋化因子表达升高引起的内皮细胞激活 [22]，促进巨噬细胞对低密度脂蛋白 (low density lipoprotein, LDL) 的摄取 [23]，抑制巨噬细胞释放基质金属蛋白酶，并诱导巨噬细胞向免疫中和特性的 M2 型转变 [21]。TGF-β 通过抑制 T 细胞的激活降低 *ApoE*$^{-/-}$ 小鼠 AS 的病变程度，从而增加 *ApoE*$^{-/-}$ 小鼠的斑块稳定性 [24]。IL-10 和 TGF-β 抑制促炎效应 T 细胞的增殖和促炎性细胞因子的分泌 [25]。IL-13 是辅助型 T 细胞 2 (T helper 2 cell, Th2) 分泌的抗炎性细胞因子，血浆中 IL-13 含量与肥胖老年人颈动脉内膜中层厚度呈负相关 [26]。IL-13 处理高脂饲喂的 LDL 受体基因敲除小鼠后，斑块内胶原含量显著增加，VCAM-1 表达降低，抗炎性的 M2 型巨噬细胞比例增高 [27]，表现出良好的稳定斑块效果 (表 1)。IL-4 也属于抗炎性细胞因子，相关研究提示 IL-4 可发挥抗 AS 效应 [28]。但也有研究表明 IL-4 能诱导氧化应激和加剧炎症反应 [29, 30]，因此还需要进一步的研究确定 IL-4 在 AS 中发挥的作用。

1.3 AS相关细胞因子参与的信号通路

由于 IL-1β 的促炎中心作用，对其产生机制的研究也是最深入的 [34, 35]。病原相关分子模式 (pathogen-associated molecular patterns, PAMPs)，如肺炎衣原体 (*Chlamydia pneumonia*) [36]、或危险物相关分子模式 (danger-associated molecular patterns, DAMPs)，如热激蛋白 (heat shock protein, HSP) [37]，与 Toll 样受体 (Toll-like receptor, TLR) 的胞外结构域结合后，可启动信号传导，促进 IL-1β 生成 (图 1)。激活的 TLR 与胞内的衔接蛋白——髓样分化因子 (myeloid differentiation factor 88, MyD88) 结合，后者招募丝苏氨酸激酶白介素 1 受体相关激酶 1 和 4 (IL-1 receptor-associated kinase 1 and 4, IRAK1 and IRAK4)，

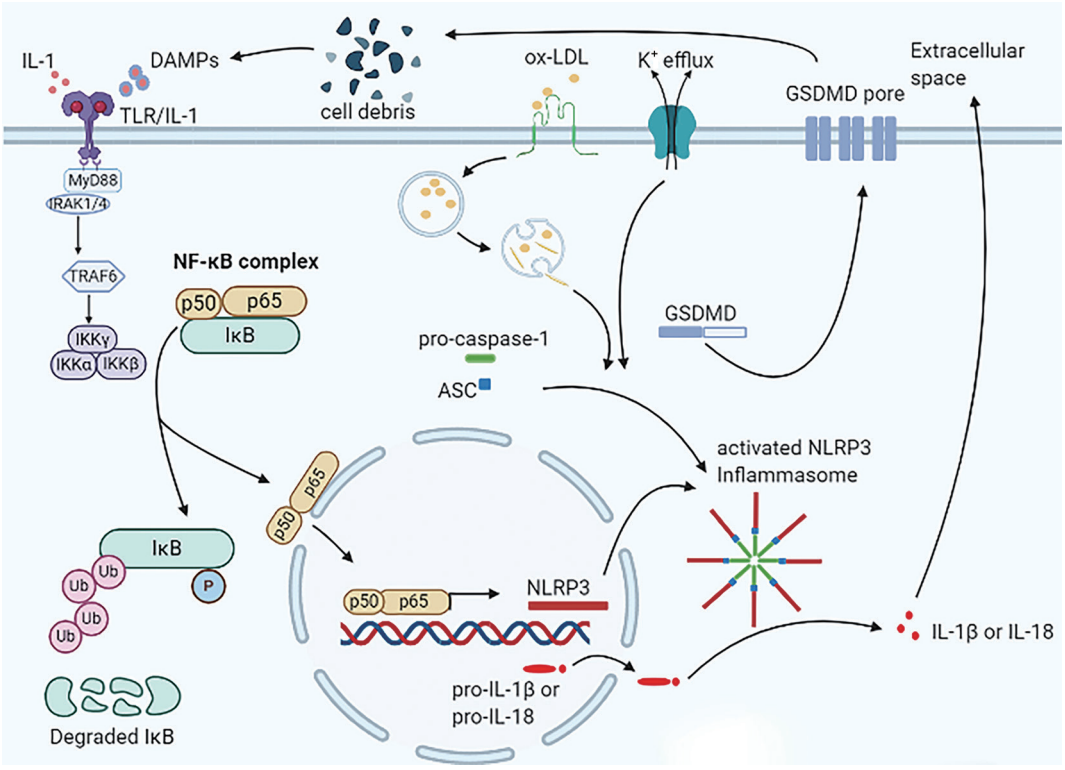

图 1. 促炎性细胞因子IL-1β的生成

Fig. 1. Production of pro-inflammatory cytokine IL-1β. DAMPs: danger-associated molecular patterns; TLR: Toll-like receptor; MyD88: myeloid differentiation factor 88; IRAK1/4: IL-1 receptor-associated kinase 1 and 4; TRAF6: tumor necrosis factor receptor-associated factor 6; IKK: inhibitor of nuclear factor kappaB kinase; NLRP3: nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain containing 3; ASC: apoptosis-associated speck-like protein containing a CARD; GSDMD: gasdermin D. This figure was created in BioRender.com.

并激活泛素连接酶肿瘤坏死因子受体相关因子 6 (tumor necrosis factor receptor-associated factor 6, TRAF6)。TRAF6 招募并激活核因子 κB 抑制蛋白 (inhibitor of nuclear factor κB, IκB) 的激酶复合体 (IκB kinase, IKK)，该复合体使 IκB 磷酸化后发生泛素化降解。由 p65 和 p50 两个基团组成的核因子 κB (nuclear factor κB, NF-κB) 被释放后转位进入细胞核，作用于顺式作用元件，转录出 pro-IL-1、pro-IL-18 和未活化的 NOD 样受体蛋白 3 (nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain containing 3, NLRP3) [38]。另一方面，多种途径如吞噬溶酶体破裂后形成的胆固醇结晶 [39]、K^+ 经 P2X7-ATP (purinergic 2X7-adenosine triphosphate) 通道外流导致胞内 K^+ 浓度降低 [40] 等都能激活 NLRP3 炎性小体。活化的 NLRP3 炎性小体与凋亡相关斑点样蛋白 (apoptosisassociated speck-like protein containing a CARD, ASC)、pro-Caspase-1 组成蛋白复合物。pro-Caspase-1 经蛋白复合物切割活化后将 pro-IL-1 和 pro-IL-18 分解成有促炎活性的成熟 IL-1β 和 IL-18，上述这两种促炎性细胞因子释放到胞外后引起炎症反应。此外，Caspase-1 切割消化道皮肤素 D (gasdermin D, GSDMD) 后形成的 GSDMD 低聚物可在细胞膜上形成“孔洞”，引起自身细胞完整性丧失，细胞裂解后释放的 DAMPs 又进一步引发免疫反应，加速病程进展 [35]。

IL-6 可识别并结合 IL-6 受体形成二元复合物，并与跨膜糖蛋白 gp130 形成三元复合物，引起下游酪氨酸激酶 JAK (Janus kinases) 和信号传导与转录激活因子 3 (signal transducer and activator of transcription 3, STAT3) 的激活，继而引起促炎相关基因的转录。抑制 IL-6/STAT3 通路可减轻 *ApoE*$^{-/-}$ 小鼠高脂饮食诱导的 AS 发生 [41, 42]。

IL-10 诱导产生细胞因子信号转导抑制分子 3 (suppressor of cytokine signaling-3, SOCS3)，SOCS3 可通过不同蛋白结构域抑制小鼠巨噬细胞 TNF-α 和过量一氧化氮 (nitric oxide, NO) 诱导的炎症反应 [43]。TGF-β 与受体结合后磷酸化 Smad2 和 Smad3 蛋白，再与 Smad4 形成能影响转录的 Smad 复合体。TGF-β 通过 Smad3 途径抑制平滑肌细胞诱导型一氧化氮合酶和 IL-6 的表达 [44]，但也有研究指出 TGF-β/Smad 信号通路参与了 ox-LDL 诱导的内皮细胞凋亡 [45]，因此有关 TGF-β 参与抗 AS 具体机制有待进一步探讨。

2 针对细胞因子的现有抗AS治疗策略

他汀类药物是针对 AS 的一线用药，可通过抑制羟甲基戊二酰辅酶 A 还原酶 (3-hydroxy-3-methyl-glutaryl coenzyme A reductase, HMG-CoA) 的活性减少胆固醇的合成，从而达到降低血脂的效果。他汀类药物还能减缓 AS 斑块的炎症进展 [46]。但他汀类药物也存在一些限制和不足 [47]，如 1%~10% 的患者服药后出现肌肉疼痛，以及他汀类药物难以逾越的 6% 规律，即他汀类药物用药量增加一倍，低密度脂蛋白胆固醇 (low-density lipoprotein cholesterol, LDL-C) 的水平仅仅降低 6%，而且用药产生的不良反应增加。除了降低血脂含量外，针对炎症，尤其是针对细胞因子开展的治疗也可以降低 AS 的发病率，因此这种新型的治疗策略日益受到重视。

2.1 针对炎症中心细胞因子——IL-1β的治疗措施

CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) 是一项评估有心肌梗死病史的患者在使用卡纳单抗 (Canakinumab) 后能否降低心血管疾病复发的双盲试验。卡纳单抗是一种能与 IL-1β 结合从而阻断其发挥作用的单克隆抗体。CANTOS 试验结果表明卡纳单抗可以在不影响血脂水平的情况下降低患者血浆中的 C 反应蛋白 (C-reactive protein, CRP) 和 IL-6 炎症标志物水平。与安慰剂组相比，每三个月皮下注射 150 mg 卡纳单抗可显著降低中风、心肌梗死等心血管疾病的死亡率 [48]，提示卡纳单抗可作为抗 AS 的潜在药物。但值得注意的是，这是在已有的他汀类药物降脂治疗基础上的追加给药效果，单纯使用卡纳单抗对 AS 的病程是否有效目前尚无临床数据。从针对 IL-1β 的 CANTOS 试验我们可以得出以下结论：卡纳单抗可以在他汀类药物降脂的基础上进一步降低心血管疾病的复发率和死亡率 [49]，从而为 AS 抗炎治疗的可行性提供了临床试验支持。降脂加抗炎的鸡尾酒疗法是否会成为未来临床应用的新趋势，值得关注和探讨。

在动物实验方面，*ApoE*$^{-/-}$ 鼠在造模同时每周给予两次 IL-1β 的抗体 XOMA052，能有效延缓 *ApoE*$^{-/-}$ 鼠的 AS 进程 [50]。开展 NLRP3 方面的研究表明，抑制 NLPR3 炎性小体后 IL-1β 分泌减少，AS 病症随之减轻 [51, 52]。内源性的 IL-1 受体抑制物 (interleukin-1 receptor antagonist, IL-1Ra) 是一种结构类似于 IL-1 的蛋白质，能与 IL-1β 竞争受体结合位点，从而负向调控 IL-1β，减少 AS 的发生 [53]，相关实验结果显示，*ApoE*$^{-/-}$ 背景的 IL-1Ra 杂合子比 *ApoE*$^{-/-}$

背景的野生型 IL-1Ra 小鼠病斑面积大 30% [54]。

2.2 针对其他促炎性细胞因子的治疗手段

IL-6 在感染和损伤的早期阶段由巨噬细胞和 T 淋巴细胞产生，是一种重要的促炎性细胞因子。IL-6 也是一种炎症生物标志物，其含量可反映机体的炎症水平。临床研究表明，不稳定型心绞痛患者血清中 IL-6 水平显著升高。相较于 IL-1β 和 TNF-α 而言，目前有关 IL-6 的抗炎性临床研究较少，且主要以 IL-6 的阻断剂托珠单抗 (tocilizumab) 为主。托珠单抗是一种可与 IL-6 竞争结合 IL-6 受体的单克隆抗体，可减少促炎性细胞因子 IL-6 与 IL-6 受体的结合，改善类风湿关节炎患者的血管内皮功能 [55]，从而减少此类患者 AS 的发生。但也有研究表明使用托珠单抗增加了血浆 LDL 的水平 [56]，因此单独使用托珠单抗的可行性不佳，而与他汀类药物联合应用是否能克服上述缺陷，有待进一步研究加以论证。

巨噬细胞分泌的 TNF-α 参与全身炎症反应，TNF-α 的相关治疗可减缓亚临床 AS 进程 [57]。目前有几种特异性阻断 TNF-α 的单抗，如阿达木单抗 (adalimumab)、英利昔单抗 (infliximab)、妥珠单抗 (certolizumab pegol)。依那西普 (etanercept) 是一种相较于 TNF 受体而言，与 TNF-α 有更高亲和力的 TNF-α 阻断剂类药物 [58]，已被美国食品药品监督管理局批准用于治疗类风湿性关节炎。以 TNF-α 升高为特征的类风湿性关节炎患者有发展成 AS 和相关心血管疾病的风险，因此依那西普有潜在的预防 AS 价值。TNF-α 阻断剂、普伐他汀、抗血小板聚集药物沙格雷酯三类药物联用后，在老年小鼠中取得更好的降低斑块面积和 ICAM-1 水平的效果 [59]。但也有研究表明阻断 TNF-α 后 LDL 受体基因敲除小鼠血浆中的炎症标志物水平降低，但斑块稳定性有下降的趋势 [60]，可能会增加心血管急性事件的发生率，因此还需进一步评估其生物效应。目前 TNF-α 阻断类治疗主要用于类风湿性关节炎和牛皮癣等自身免疫性疾病，是否能单独或联合运用于抗 AS 的治疗，尚缺乏直接的临床证据。

2.3 针对抗炎性细胞因子的治疗策略

与下调促炎性细胞因子的思路相似，通过上调抗炎性细胞因子从而缓解 AS，在动物实验中也取得了一定的成功。

过表达 TGF-β 限制和稳定了 *ApoE*$^{-/-}$ 小鼠的 AS 斑块 [20]。最近的一项研究表明，借助纳米颗粒把抗炎性细胞因子 IL-10 运输到特定部位可发挥抗炎继而减轻 AS 的作用 [61]。过表达巨噬细胞来源的 IL-10 可通过促进巨噬细胞胆固醇的外排，降低病变部位的胆固醇积累，减少炎症和抑制 AS [62]。而在家兔 AS 模型中，增高 IL-10 表达对 AS 病变斑块的大小、黏附分子或致 AS 细胞因子的表达均无显著影响 [63]，提示种属来源和饮食结构可能影响抗炎性细胞因子治疗的效果。

本研究组长期从事中药来源小分子活性物质的基础与转化研究。大蒜中的活性物质硫化氢 (hydrogen sulfide, H_2S) 是一种新型的气体信号分子，在 AS 动物模型中表现出良好的抗炎特性，外源性 H_2S 供体 NaHS 可减缓小鼠 AS 发展，稳定斑块，并呈现一定程度的剂量依赖性 [64]。Moore 研究团队报道，一种新型 H_2S 供体 FW1256 可通过抑制细菌脂多糖诱导的 IκB 磷酸化和 p65 基团入核，减少巨噬细胞释放促炎性的 IL-1β、TNF-α 和 IL-6 [65]。本研究组近期对另一种中药单体益母草碱 (leonurine) 的研究表明，益母草碱可通过抑制 NF-κB 相关分子的过度表达下调颈动脉串联狭窄合并西方饮食所致不稳定斑块小鼠模型血液和组织中的 IL-6、黏附分子的表达，从而具有抗 AS、稳定斑块的作用 [66]。以上研究提示中药来源小分子活性物质具有良好的抗炎性细胞因子的效果。

针对抗炎性细胞因子的相关研究目前仅停留在动物实验水平，人群疗效如何尚未可知。本研究组正在进行的益母草碱一期临床实验提示药物安全性佳，将通过随后的二期临床实验对人群疗效进行评估。

3 针对细胞因子的抗AS治疗策略的不足和展望

已有的研究提示，目前针对细胞因子开展的抗 AS 治疗策略存在不足之处，因为细胞因子除了参与 AS 的进程，也在其他免疫调节中发挥作用，人为降低或阻断其发挥作用的途径可能增加机体感染的几率。有研究提示抗促炎性细胞因子的治疗可能增加罹患癌症的风险 [53]。因此，针对细胞因子开展的抗 AS 治疗策略还需要进一步的评估和优化。

首先，全身拮抗促炎性细胞因子或增强抗炎性细胞因子的疗法有待改进。今年发表在 *Biomaterials* 上的一篇文章提示病变局部抗炎策略的良好前景。该研究借助纳米载体将抗炎性的 IL-10 运送到病变部位并实现长效释放。该策略在不影响总体免疫水平的基础上减少了 AS 的发生 [61]。此项研究为未来靶向治疗 AS 带来更多的参考和依据。运用类似的

方法进行病变局部抗促炎性细胞因子的治疗，应能获得类似的疗效。

其次，深入研究各类细胞因子在 AS 疾病发生和发展过程中的共同及差异性作用机制，将有助于开发出更具特异性的药物作用靶点，同时也可避免直接作用于细胞因子层面而并存的副作用。

参考文献

1 Williams JW, Huang LH, Randolph GJ. Cytokine circuits in cardiovascular disease. Immunity 2019; 50(4): 941–954.

2 Moore KJ, Koplev S, Fisher EA, Tabas I, Bjorkegren JLM, Doran AC, Kovacic JC. Macrophage trafficking, inflammatory resolution, and genomics in atherosclerosis: JACC macrophage in CVD Series (Part 2). J Am Coll Cardiol 2018; 72(18): 2181–2197.

3 Basatemur GL, Jorgensen HF, Clarke MCH, Bennett MR, Mallat Z. Vascular smooth muscle cells in atherosclerosis. Nat Rev Cardiol 2019; 16(12): 727–744.

4 Gimbrone MA Jr, Garcia-Cardena G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circ Res 2016; 118(4): 620–636.

5 Lu JX, Guo C, Ou WS, Jing Y, Niu HF, Song P, Li QZ, Liu Z, Xu J, Li P, Zhu ML, Yin YL. Citronellal prevents endothelial dysfunction and atherosclerosis in rats. J Cell Biochem 2019; 120(3): 3790–3800.

6 Bäck M, Yurdagul A, Tabas I, Öörni K, Kovanen PT. Inflammation and its resolution in atherosclerosis: mediators and therapeutic opportunities. Nat Rev Cardiol 2019; 16(7): 389–406.

7 Tousoulis D, Oikonomou E, Economou EK, Crea F, Kaski JC. Inflammatory cytokines in atherosclerosis: current therapeutic approaches. Eur Heart J 2016; 37(22): 1723–1732.

8 Ghanim H, Green K, Abuaysheh S, Patel R, Batra M, Chaudhuri A, Makdissi A, Kuhadiya ND, Dandona P. Ezetimibe and simvastatin combination inhibits and reverses the proinflammatory and pro-atherogenic effects of cream in obese patients. Atherosclerosis 2017; 263: 278–286.

9 Vila-Caballer M, Gonzalez-Granado JM, Zorita V, Abu Nabah YN, Silvestre-Roig C, Del Monte-Monge A, Molina-Sanchez P, Ait-Oufella H, Andres-Manzano MJ, Sanz MJ, Weber C, Kremer L, Gutierrez J, Mallat Z, Andres V. Disruption of the CCL1-CCR8 axis inhibits vascular Treg recruitment and function and promotes atherosclerosis in mice. J Mol Cell Cardiol 2019; 132: 154–163.

10 Branen L, Hovgaard L, Nitulescu M, Bengtsson E, Nilsson J, Jovinge S. Inhibition of tumor necrosis factor-alpha reduces atherosclerosis in apolipoprotein E knockout mice. Arterioscler Thromb Vasc Biol 2004; 24(11): 2137–2142.

11 Kirii H, Niwa T, Yamada Y, Wada H, Saito K, Iwakura Y, Asano M, Moriwaki H, Seishima M. Lack of interleukin-1beta decreases the severity of atherosclerosis in ApoE-deficient mice. Arterioscler Thromb Vasc Biol 2003; 23(4): 656–660.

12 Libby P. Interleukin-1 beta as a target for atherosclerosis therapy: biological basis of CANTOS and beyond. J Am Coll Cardiol 2017; 70(18): 2278–2289.

13 Asare Y, Schmitt M, Bernhagen J. The vascular biology of macrophage migration inhibitory factor (MIF). Expression and effects in inflammation, atherogenesis and angiogenesis. Thromb Haemost 2013; 109(3): 391–398.

14 Schmitz C, Noels H, El Bounkari O, Straussfeld E, Megens RTA, Sternkopf M, Alampour-Rajabi S, Krammer C, Tilstam PV, Gerdes N, Burger C, Kapurniotu A, Bucala R, Jankowski J, Weber C, Bernhagen J. Mif-deficiency favors an atheroprotective autoantibody phenotype in atherosclerosis. FASEB J 2018; 32(8): 4428–4443.

15 Durpes MC, Morin C, Paquin-Veillet J, Beland R, Pare M, Guimond MO, Rekhter M, King GL, Geraldes P. PKC-beta activation inhibits IL-18-binding protein causing endothelial dysfunction and diabetic atherosclerosis. Cardiovasc Res 2015; 106(2): 303–313.

16 Ye J, Wang Y, Wang Z, Liu L, Yang Z, Wang M, Xu Y, Ye D, Zhang J, Lin Y, Ji Q, Wan J. Roles and mechanisms of interleukin-12 family members in cardiovascular diseases: opportunities and challenges. Front Pharmacol 2020; 11: 129.

17 Li Y, To K, Kanellakis P, Hosseini H, Deswaerte V, Tipping P, Smyth MJ, Toh BH, Bobik A, Kyaw T. $CD4^+$ natural killer T cells potently augment aortic root atherosclerosis by perforin- and granzyme B-dependent cytotoxicity. Circ Res 2015; 116(2): 245–254.

18 Back M, Hansson GK. Anti-inflammatory therapies for atherosclerosis. Nat Rev Cardiol 2015; 12(4): 199–211.

19 Eun SY, Ko YS, Park SW, Chang KC, Kim HJ. IL-1beta enhances vascular smooth muscle cell proliferation and migration via P2Y2 receptor-mediated RAGE expression and HMGB1 release. Vascul Pharmacol 2015; 72: 108–117.

20 Frutkin AD, Otsuka G, Stempien-Otero A, Sesti C, Du L, Jaffe M, Dichek HL, Pennington CJ, Edwards DR, Nieves-Cintron M, Minter D, Preusch M, Hu JH, Marie JC, Dichek DA. TGF-[beta]1 limits plaque growth, stabilizes plaque structure, and prevents aortic dilation in apolipoprotein E-null mice. Arterioscler Thromb Vasc Biol 2009; 29(9): 1251–1257.

21 Han X, Boisvert WA. Interleukin-10 protects against atherosclerosis by modulating multiple atherogenic macrophage function. Thromb Haemost 2015; 113(3): 505–512.

22 Li X, Fang P, Sun Y, Shao Y, Yang WY, Jiang X, Wang H, Yang X. Anti-inflammatory cytokines IL-35 and IL-10 block atherogenic lysophosphatidylcholine-induced, mitochondrial

ROS-mediated innate immune activation, but spare innate immune memory signature in endothelial cells. Redox Biol 2020; 28: 101373.

23 Lucero D, Islam P, Freeman LA, Jin X, Pryor M, Tang J, Kruth HS, Remaley AT. Interleukin 10 promotes macrophage uptake of HDL and LDL by stimulating fluid-phase endocytosis. Biochim Biophys Acta Mol Cell Biol Lipids 2020; 1865(2): 158537.

24 Robertson AK, Rudling M, Zhou X, Gorelik L, Flavell RA, Hansson GK. Disruption of TGF-beta signaling in T cells accelerates atherosclerosis. J Clin Invest 2003; 112(9): 1342–1350.

25 Ou HX, Guo BB, Liu Q, Li YK, Yang Z, Feng WJ, Mo ZC. Regulatory T cells as a new therapeutic target for atherosclerosis. Acta Pharmacol Sin 2018; 39(8): 1249–1258.

26 Boccardi V, Paolacci L, Croce MF, Baroni M, Ercolani S, Cecchetti R, Villa A, Mecocci P. Lower serum levels of IL-13 is associated with increased carotid intima-media thickness in old age subjects. Aging Clin Exp Res 2020; 32(7): 1289–1294.

27 Cardilo-Reis L, Gruber S, Schreier SM, Drechsler M, Papac-Milicevic N, Weber C, Wagner O, Stangl H, Soehnlein O, Binder CJ. Interleukin-13 protects from atherosclerosis and modulates plaque composition by skewing the macrophage phenotype. EMBO Mol Med 2012; 4(10): 1072–1086.

28 Grehan JF, Levay-Young BK, Fogelson JL, Francois-Bongarcon V, Benson BA, Dalmasso AP. IL-4 and IL-13 induce protection of porcine endothelial cells from killing by human complement and from apoptosis through activation of a phosphatidylinositide 3-kinase/Akt pathway. J Immunol 2005; 175(3): 1903–1910.

29 Lee YW, Kim PH, Lee WH, Hirani AA. Interleukin-4, oxidative stress, vascular inflammation and atherosclerosis. Biomol Ther (Seoul) 2010; 18(2): 135–144.

30 Davenport P, Tipping PG. The role of interleukin-4 and interleukin-12 in the progression of atherosclerosis in apolipoprotein E-deficient mice. Am J Pathol 2003; 163(3): 1117–1125.

31 Schuett H, Luchtefeld M, Grothusen C, Grote K, Schieffer B. How much is too much? Interleukin-6 and its signalling in atherosclerosis. Thromb Haemost 2009; 102(2): 215–222.

32 Deng X, Zhang J, Liu Y, Chen L, Yu C. TNF-alpha regulates the proteolytic degradation of ST6Gal-1 and endothelial cell-cell junctions through upregulating expression of BACE1. Sci Rep 2017; 7: 40256.

33 Zhang Y, Yang X, Bian F, Wu P, Xing S, Xu G, Li W, Chi J, Ouyang C, Zheng T, Wu D, Zhang Y, Li Y, Jin S. TNF-alpha promotes early atherosclerosis by increasing transcytosis of LDL across endothelial cells: crosstalk between NF-kappaB and PPAR-gamma. J Mol Cell Cardiol 2014; 72: 85–94.

34 Zimmer S, Grebe A, Latz E. Danger signaling in atherosclerosis. Circ Res 2015; 116(2): 323–340.

35 Grebe A, Hoss F, Latz E. NLRP3 inflammasome and the IL-1 pathway in atherosclerosis. Circ Res 2018; 122(12): 1722–1740.

36 Tumurkhuu G, Dagvadorj J, Porritt RA, Crother TR, Shimada K, Tarling EJ, Erbay E, Arditi M, Chen S. Chlamydia pneumoniae hijacks a host autoregulatory IL-1beta loop to drive foam cell formation and accelerate atherosclerosis. Cell Metab 2018; 28(3): 432–448.e4.

37 Roh JS, Sohn DH. Damage-associated molecular patterns in inflammatory diseases. Immune Netw 2018; 18(4): e27.

38 Koushki K, Shahbaz SK, Mashayekhi K, Sadeghi M, Zayeri ZD, Taba MY, Banach M, Al-Rasadi K, Johnston TP, Sahebkar A. Anti-inflammatory action of statins in cardiovascular disease: the role of inflammasome and toll-like receptor pathways. Clin Rev Allergy Immunol 2021; 60(2): 175–199.

39 Martínez GJ, Celermajer DS, Patel S. The NLRP3 inflammasome and the emerging role of colchicine to inhibit atherosclerosis-associated inflammation. Atherosclerosis 2018; 269: 262–271.

40 Di Virgilio F, Dal Ben D, Sarti AC, Giuliani AL, Falzoni S. The P2X7 receptor in infection and inflammation. Immunity 2017; 47(1): 15–31.

41 Tedgui A, Mallat Z. Cytokines in atherosclerosis: pathogenic and regulatory pathways. Physiol Rev 2006; 86(2): 515–581.

42 Luo P, Shi W, Wang Y, Ma H, Liu T, Yan D, Huo S, Guo J, Wang M, Li C, Lin J, Zhang C, Li S, Lv J, Lin L. Raloxifene inhibits IL-6/STAT3 signaling pathway and protects against high-fat-induced atherosclerosis in $ApoE^{(-/-)}$ mice. Life Sci 2020; 261: 118304.

43 Qasimi P, Ming-Lum A, Ghanipour A, Ong CJ, Cox ME, Ihle J, Cacalano N, Yoshimura A, Mui AL. Divergent mechanisms utilized by SOCS3 to mediate interleukin-10 inhibition of tumor necrosis factor alpha and nitric oxide production by macrophages. J Biol Chem 2006; 281(10): 6316–6324.

44 Feinberg MW, Watanabe M, Lebedeva MA, Depina AS, Hanai J, Mammoto T, Frederick JP, Wang XF, Sukhatme VP, Jain MK. Transforming growth factor-beta1 inhibition of vascular smooth muscle cell activation is mediated via Smad3. J Biol Chem 2004; 279(16): 16388–16393.

45 Yin J, Hou X, Yang S. MicroRNA-338-3p promotes ox-LDL-induced endothelial cell injury through targeting BAMBI and activating TGF-beta/Smad pathway. J Cell Physiol 2019; 234(7): 11577–11586.

46 Pirro M, Simental-Mendía LE, Bianconi V, Watts GF, Banach M, Sahebkar A. Effect of statin therapy on arterial wall

inflammation based on 18F-FDG PET/CT: a systematic review and meta-analysis of interventional studies. J Clin Med 2019; 8(1): 118.

47 Ramkumar S, Raghunath A, Raghunath S. Statin therapy: review of safety and potential side effects. Acta Cardiol Sin 2016; 32(6): 631–639.

48 Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ, Group CT. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017; 377(12): 1119–1131.

49 Ridker PM, Libby P, MacFadyen JG, Thuren T, Ballantyne C, Fonseca F, Koenig W, Shimokawa H, Everett BM, Glynn RJ. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). Eur Heart J 2018; 39(38): 3499–3507.

50 Bhaskar V, Yin J, Mirza AM, Phan D, Vanegas S, Issafras H, Michelson K, Hunter JJ, Kantak SS. Monoclonal antibodies targeting IL-1 beta reduce biomarkers of atherosclerosis in vitro and inhibit atherosclerotic plaque formation in apolipoprotein E-deficient mice. Atherosclerosis 2011; 216(2): 313–320.

51 Abderrazak A, Couchie D, Mahmood DF, Elhage R, Vindis C, Laffargue M, Mateo V, Buchele B, Ayala MR, El Gaafary M, Syrovets T, Slimane MN, Friguet B, Fulop T, Simmet T, El Hadri K, Rouis M. Anti-inflammatory and antiatherogenic effects of the NLRP3 inflammasome inhibitor arglabin in $ApoE_2$.Ki mice fed a high-fat diet. Circulation 2015; 131(12): 1061–1070.

52 van der Heijden T, Kritikou E, Venema W, van Duijn J, van Santbrink PJ, Slutter B, Foks AC, Bot I, Kuiper J. NLRP3 inflammasome inhibition by MCC950 reduces atherosclerotic lesion development in apolipoprotein E-deficient mice-brief report. Arterioscler Thromb Vasc Biol 2017; 37(8): 1457–1461.

53 Ridker PM. Anticytokine agents: targeting interleukin signaling pathways for the treatment of atherothrombosis. Circ Res 2019; 124(3): 437–450.

54 Isoda K, Sawada S, Ishigami N, Matsuki T, Miyazaki K, Kusuhara M, Iwakura Y, Ohsuzu F. Lack of interleukin-1 receptor antagonist modulates plaque composition in apolipoprotein E-deficient mice. Arterioscler Thromb Vasc Biol 2004; 24(6): 1068–1073.

55 Protogerou AD, Zampeli E, Fragiadaki K, Stamatelopoulos K, Papamichael C, Sfikakis PP. A pilot study of endothelial dysfunction and aortic stiffness after interleukin-6 receptor inhibition in rheumatoid arthritis. Atherosclerosis 2011; 219(2): 734–736.

56 Kim SC, Solomon DH, Rogers JR, Gale S, Klearman M, Sarsour K, Schneeweiss S. Cardiovascular safety of tocilizumab versus tumor necrosis factor inhibitors in patients with rheumatoid arthritis: a multi-database cohort study. Arthritis Rheumatol 2017; 69(6): 1154–1164.

57 Tam LS, Kitas GD, Gonzalez-Gay MA. Can suppression of inflammation by anti-TNF prevent progression of subclinical atherosclerosis in inflammatory arthritis? Rheumatology (Oxford) 2014; 53(6): 1108–1119.

58 Piaserico S, Osto E, Famoso G, Zanetti I, Gregori D, Poretto A, Iliceto S, Peserico A, Tona F. Treatment with tumor necrosis factor inhibitors restores coronary microvascular function in young patients with severe psoriasis. Atherosclerosis 2016; 251: 25–30.

59 Park KY, Heo TH. Critical role of TNF inhibition in combination therapy for elderly mice with atherosclerosis. Cardiovasc Ther 2017; 35(6). doi: 10.1111/1755-5922.12280.

60 Oberoi R, Vlacil AK, Schuett J, Schosser F, Schuett H, Tietge UJF, Schieffer B, Grote K. Anti-tumor necrosis factor-alpha therapy increases plaque burden in a mouse model of experimental atherosclerosis. Atherosclerosis 2018; 277: 80–89.

61 Kim M, Sahu A, Hwang Y, Kim GB, Nam GH, Kim IS, Chan Kwon I, Tae G. Targeted delivery of anti-inflammatory cytokine by nanocarrier reduces atherosclerosis in Apo $E^{-/-}$ mice. Biomaterials 2020; 226: 119550.

62 Han X, Kitamoto S, Wang H, Boisvert WA. Interleukin-10 overexpression in macrophages suppresses atherosclerosis in hyperlipidemic mice. FASEB J 2010; 24(8): 2869–2880.

63 Du L, Dronadula N, Tanaka S, Dichek DA. Helper-dependent adenoviral vector achieves prolonged, stable expression of interleukin-10 in rabbit carotid arteries but does not limit early atherogenesis. Hum Gene Ther 2011; 22(8): 959–968.

64 Xiong Q, Wang Z, Yu Y, Wen Y, Suguro R, Mao Y, Zhu YZ. Hydrogen sulfide stabilizes atherosclerotic plaques in apolipoprotein E knockout mice. Pharmacol Res 2019; 144: 90–98.

65 Huang CW, Feng W, Peh MT, Peh K, Dymock BW, Moore PK. A novel slow-releasing hydrogen sulfide donor, FW1256, exerts anti-inflammatory effects in mouse macrophages and *in vivo*. Pharmacol Res 2016; 113(Pt A): 533–546.

66 Ning K, Wang MJ, Lin G, Zhang YL, Li MY, Yang BF, Chen Y, Huang Y, Li ZM, Huang YJ, Zhu L, Liang K, Yu B, Zhu YZ, Zhu YC. eNOS-nitric oxide system contributes to a novel antiatherogenic effect of leonurine via inflammation inhibition and plaque stabilization. J Pharmacol Exp Ther 2020; 373(3): 463–475.