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细胞因子参与动脉粥样硬化炎症反应的研究进展

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[摘要] 细胞因子在动脉粥样硬化(atherosclerosis, AS)的病理过程中发挥了重要作用,影响着AS相关心脑血管疾病的进展与预后。细胞因子主要包括C反应蛋白、白细胞介素、肿瘤坏死因子、趋化性细胞因子、基质金属蛋白酶等。这些细胞因子通过不同的作用靶点和机制促进或抑制AS过程中的炎症反应及斑块形成。全面掌握细胞因子在AS发生、发展全程中的作用有助于为AS寻找新的治疗靶点和药物。

[关键词] 细胞因子;动脉粥样硬化;炎症反应;研究进展
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Role of cytokines in atherosclerotic inflammation response: A review

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View from specialist: It is creative, and of certain scientific and educational value.

[ABSTRACT] Cytokines play an important role in the pathological process of atherosclerosis (AS), affecting the progression and prognosis of AS-related cerebrovascular diseases. Cytokines mainly include C-reactive protein, interleukin, tumor necrosis factor, chemotactic cytokines, matrix metalloproteinases, *etc*. These cytokines promote or inhibit the inflammatory response and plaque formation during AS process through different targets and mechanisms. A comprehensive understanding of the cytokines in the occurrence and development of AS is conducive to search for new therapeutic targets and drugs.

[KEYWORDS] Cytokines; Atherosclerosis; Inflammation response; Research progress

现代医学认为,大量细胞因子参与了动脉粥样硬化(atherosclerosis, AS)的发生、发展过程,导致血管内壁形态结构发生变化,损伤血管内皮,改变血流动力学,形成易损斑块,从而引发冠状动脉AS性心脏病、脑梗死等心脑血管疾病。

细胞因子是指参与细胞间信号传导的一类小蛋白调节物质,主要包括C反应蛋白、白细胞介素、肿瘤坏死因子、趋化性细胞因子、基质金属蛋白酶等。根据AS炎症反应过程中不同作用可分为促炎性因子(促AS)和抗炎性因子(抗AS)[1]。不过一些细胞因子功能尚未明确,需要根据周围环境来区分其在AS发生、发展过程中发挥的生物学功能[2,3]。此外,细胞因子引起血管内皮功能障碍,并伴有黏附分子和趋化因子的上调,从而促进免疫细胞(单核细胞,嗜中性粒细胞,淋巴细胞)迁移至AS部位发挥作用[4]。细胞因子还可促进平滑肌细胞(smooth muscle cell, SMC)的增殖和迁移来影响SMC的功能。在AS后期,促炎性细胞因子引起

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AS斑块的不稳定,各种细胞的凋亡和基质降解,从而加速斑块破裂和血栓形成[5]。以下就不同的细胞因子对于AS的影响及机制展开综述。

1 C反应蛋白(C-reaction protein, CRP)

CRP是一种急性时相反应蛋白,血液中的CRP主要由肝细胞合成,泡沫细胞产生的白介素-6也可诱导产生少量CRP[6,7]。损伤、炎症或感染的急性期均可使其生成增加,在炎症刺激后大部分CRP释放到血液循环中[8],其浓度可升高1 000倍以上。CRP与低密度脂蛋白(low density lipoprotein, LDL)结合并存在于AS斑块中,表明CRP参与了AS斑块形成的病理过程[9,10]。有研究指出,高敏CRP(hsCRP)作为一个敏感的循环炎症标志,可能成为冠心病的独立危险因素,用于预测未来的心血管事件[11,12],并可通过监测hsCRP指标以确定患者对治疗用药的信息反馈。

CRP通常被认为能增强炎症反应并促AS病理发展,其可能作用机制如下[13-16]:(1)参与炎症反应。沉积于AS局部病灶的CRP可诱发血管内皮细胞分泌趋化因子和黏附分子,使多种细胞积聚于局部病灶并分泌促炎症因子;(2)参与斑块形成。CRP增强LDL的调理素作用,促进巨噬细胞摄取经过修饰的LDL,增加泡沫细胞含量,从而参与AS斑块的形成;(3)促进血栓形成。CRP可以活化血管内皮细胞,促进其合成纤溶酶原激活物抑制剂-1和促凝因子。CRP还可增加单核细胞组织因子的表达和分泌,组织因子是外源性的凝血途径启动因子,通过凝血系统的激活促进形成血栓;(4)促进内皮功能障碍。CRP促使血小板、单核细胞和T淋巴细胞等黏附于内皮细胞,引起血管内皮细胞功能障碍;CRP还可介导补体活性并经由经典途径激活补体系统,诱发脂质沉积并损伤血管内皮;此外,CRP与氧化LDL结合后可激活单核-巨噬细胞,从而抑制内皮型一氧化氮合酶,减弱血管舒张功能,导致内皮功能障碍。

2 白细胞介素(interleukin, IL)

简称白介素,是一种多肽,在免疫调节及炎症反应过程中具有重要的作用,并与心脑血管疾病关系密切。

2.1 IL-1β

IL-1通常是膜结合的,主要在局部而非全身产生影响。IL-1β是循环的IL-1的主要形式,被认为是促炎性细胞因子,主要由巨噬细胞、中性粒细胞和内皮细胞产生,通过炎症小体的组装介导caspase-1的激活[17],从而调控炎症反应[18]。胆固醇可诱导炎性晶体沉积于斑块的坏死核中,所以IL-1β含量增加与动脉壁中胆固醇蓄积导致的促炎作用之间存在密切联系[19]。

目前已有临床研究证明抑制IL-1β表达可治疗多种慢性炎症性疾病,表明IL-1β具有作为AS抗炎治疗靶点的临床潜力[20]。其中卡那奴单抗(一种人源IL-1β特异性单克隆抗体)的临床结果提示,该药可显著降低CRP、IL-6、胆固醇和甘油三酸酯含量,减少急性心血管事件[21-24]。总之,IL-1β特异性单克隆抗体表现出有效的抗炎作用,可预防心血管疾病。

2.2 IL-6

又称前炎症细胞因子,主要由巨噬细胞和内皮细胞产生,也可通过刺激肝细胞产生。是一种作用广泛的免疫细胞激活剂和细胞因子,参与先天性和适应性免疫反应,可调节急、慢性炎症,并发挥抗感染及影响造血作用[25,26]。

据报道,冠心病患者血液中IL-6水平显著高于健康人,且疾病严重性与IL-6表达含量成正相关[27]。此外,斑块破裂的情况下,IL-6水平明显升高[28]。因此,IL-6可能成为预测AS斑块易损性的潜在标志物。

IL-6对于动脉粥样斑块的形成也起着十分重要的作用,可能的机制有[29-31]:(1)增强其他炎性细胞因子的表达,激活巨噬细胞分泌单核细胞趋化蛋白,诱导白细胞、中性粒细胞、单核细胞等在血管中黏附和聚集,增强内皮细胞的炎症反应;(2)诱导血小板源性生长因子,促进血管平滑肌细胞(vascular smooth muscle cell, VSMC)增殖并导致血管重构,使斑块面积增大并趋于不稳定,进而加快AS进展;(3)诱导肝细胞产生纤维蛋白原和纤溶酶原激活物抑制剂,导致机体纤溶功能低下,同时促进血小板聚集和血栓形成。

2.3 IL-10

是由Th2细胞产生的一种抗炎因子,可抑制巨噬细胞释放的炎症介质,并能促进其他抗炎因子(如IL-2和重组人干扰素)的分泌,对于AS斑块的形成及稳定具有保护作用。IL-10对炎症的抑制作用主要表现在[32,33]:(1)抑制Th1和自然杀伤细胞的活性,抑制T淋巴细胞调亡;(2)减少单核细胞表面的主要组织相容性复合物Ⅱ类分子表达量,降低单核细胞的抗原呈递能力;(3)减少IL-1、IL-6、IL-8和肿瘤坏死因子-α(TNF-α)等炎性因子的分泌,抑制炎性反应,减轻炎症对血管的损伤。

2.4 IL-17

主要是由CD4$^+$T细胞、辅助T细胞17产生，在AS及其并发症的病变过程中有重要作用。IL-17与受体IL-17R结合后激活下游炎性因子，如促分裂原活化蛋白激酶、核因子-κB等，诱导受体细胞分泌更多炎性因子，如CRP、IL-1、IL-6、基质金属蛋白酶等，并募集巨噬细胞、中性粒细胞、T淋巴细胞等免疫细胞至局部斑块病灶处。抑制IL-17，阻止斑块增大，缓解患者临床症状[34]。

3 TNF-α

主要由单核-巨噬细胞、T淋巴细胞、内皮细胞及SMC等产生，是一种具有多重生物学功能的细胞因子，促进AS的病理过程，增加心脑血管疾病的危害性。AS斑块包含TNF-α，且血浆中TNF-α水平与不良心血管事件的发生率密切相关，TNF-α基因敲除可有效降低高脂肪饮食小鼠的AS发生率[35,36]，积极抗TNF-α可减少意外心血管事件发生[37]。

TNF-α参与AS斑块形成的可能机制有[38,39]：(1)内皮细胞损伤。TNF-α增加内皮细胞通透性，使脂质穿透血管内膜的能力加强，参与AS斑块形成；(2)抑制纤溶，促进凝血；(3)促进SMC的增生和基质金属蛋白酶的表达。

4 趋化性细胞因子

趋化性细胞因子是一类具有募集、活化特定白细胞功能的小分子蛋白质，可分为α、β、γ及CX3C四个亚族。单核细胞趋化蛋白-1(monocyte chemotactic protein 1，MCP-1)是β亚族的代表，主要来源于巨噬细胞源性的泡沫细胞。MCP-1与其受体结合后，促进白细胞迁移到炎症病变处，进而激活单核/巨噬细胞并使其牢固黏附于活化的内皮细胞表面[40]。MCP-1加速小鼠AS的进展[41]，若使MCP-1缺失则可阻止巨噬细胞的募集和AS的形成而不影响脂蛋白代谢，提示干预MCP-1或可抑制AS病理进展[41,42]。

5 基质金属蛋白酶(matrix metalloproteinases，MMPs)

可由巨噬细胞分泌而来，活化和转录过程受细胞因子的调控，主要作用是降解细胞基质，是AS斑块趋向不稳定型的主要原因之一[43,44]。MMPs可通过活化血小板、损伤血管内膜等机制导致硬化斑块破裂，与斑块的易损性密切相关[45]，在AS斑块中的脆弱区域发现MMP活性增加[46]。

MMP-9是其中最重要的一种，也称为明胶酶B，主要由活化的巨噬细胞和VSMC产生。大量的MMP-9可过度降解细胞外基质，导致AS斑块纤维帽变薄，继而增加斑块的易破裂性[47]。抑制MMP-9的表达可减缓AS病理发展，并减少巨噬细胞浸润和胶原沉积[48]。临床研究表明，AS易损斑块中MMP-9含量与非易损斑块及正常组相比明显偏高，因此推测MMP-9表达量与AS斑块易损性呈正相关[49]。MMP-9可用于预测AS斑块易损性[50]。

MMP-2是促进斑块形成后细胞外基质降解的关键酶之一，并促进VSMC的增殖和迁移[51]，被认为是血管重构的独立危险因素。当血管内皮受损时，单核-巨噬细胞和内皮细胞分泌MMP-2，降解内皮细胞基底膜，降低血管内皮的防御能力。抑制MMP-2表达可增强载脂蛋白E敲除小鼠的斑块稳定性，可能机制是通过积聚SMC以发挥稳定斑块的作用[52]。

6 结语及展望

细胞因子在AS过程中具有调控炎症反应的关键作用，针对细胞因子及其信号传导途径或可抑制斑块形成，减缓AS病理过程，从而降低其相关的心脑血管疾病发生率。但是目前将抑制细胞因子的药物用于AS治疗仍存在以下问题和挑战。第一，部分细胞因子的作用存在两面性，对斑块的促进或抑制作用取决于AS的不同时期，所以药物研发和使用具有矛盾性；第二，某些细胞因子的生物学功能尚未完全阐释清楚，贸然抑制或者促进其表达量，可能会增加临床试验受试者的风险；第三，人体是一个非常复杂的结构，抑制某种细胞因子或许可以减缓AS进展，但与此同时亦可能影响其他脏器功能。

总之，针对细胞因子研发治疗AS的药物具有广阔的应用前景，但是在研究过程中需要十分谨慎且全面。

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