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炎症在基于冠状动脉粥样硬化的急性冠脉综合征中的作用

赵　鹏，刘志强

新疆医科大学第一附属医院综合心脏内科，新疆　乌鲁木齐

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摘　要

急性冠脉综合征(ACS)是全球急性死亡的主要原因之一，虽然非动脉粥样硬化因素也可导致ACS，但ACS最常见的原因是动脉粥样硬化斑块破裂或糜烂，随后形成血栓。动脉粥样硬化是一种慢性炎症性疾病，其中免疫系统在其发展和进展中起着重要作用。炎症诱发的内皮功能障碍导致脂蛋白通透性增加及其内皮下积聚、白细胞募集和血小板活化，从而形成动脉粥样硬化。但在慢性炎症的情况下，巨噬细胞同时会对纤维帽产生分解代谢作用，导致薄帽纤维动脉粥样硬化，使斑块脆弱，若发生免疫和炎症功能障碍，免疫和炎症功能障碍，促动脉粥样硬化和抗动脉粥样硬化免疫网络的不平衡促进斑块从稳定状态转变为不稳定状态，并导致急性冠状动脉事件的发生。

关键词

急性冠脉综合征，冠状动脉粥样硬化，炎症

The Role of Inflammation in Acute Coronary Syndromes Based on Coronary Atherosclerosis

Peng Zhao, Zhiqiang Liu

Department of General Cardiology, The First Affiliated Hospital of Xinjiang Medical University, Urumqi Xinjiang

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Abstract

Acute coronary syndrome (ACS) is one of the leading causes of acute death worldwide. Although

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non-atherosclerotic factors can also cause ACS, the most common cause of ACS is the rupture or erosion of atherosclerotic plaques followed by the formation of blood clots. Atherosclerosis is a chronic inflammatory disease in which the immune system plays an important role in its development and progression. Inflammation induced endothelial dysfunction leads to increased permeability of lipoproteins and their subcutaneous accumulation, leukocyte recruitment and platelet activation, resulting in atherosclerosis. However, in the case of chronic inflammation, macrophages will also have catabolic effects on the fiber cap, leading to atherosclerosis of the thin cap fiber and making the plaque fragile. If immune and inflammatory dysfunction occurs, the imbalance of the pro-atherosclerosis and anti-atherosclerosis immune network promotes the plaque to change from a stable state to an unstable state and lead to acute coronary events.

Keywords

Acute Coronary Syndrome, Coronary Atherosclerosis, Inflammation

1. 引言

急性冠脉综合征(ACS)是指一种复杂的临床综合征，包括一系列疾病，包括不稳定型心绞痛、ST 段抬高型心肌梗死(STEMI)、非 ST 段抬高型心肌梗死(NSTEMI)以及猝死，常见的原因是动脉粥样硬化斑块破裂或糜烂，随后形成血栓。过去二十年来，临床和实验研究表明，动脉粥样硬化是一种低级别无菌炎症性疾病[1] [2]，其特征是免疫炎症功能失调，涉及免疫细胞(巨噬细胞、T 淋巴细胞和单核细胞)与血管细胞(内皮细胞、平滑肌细胞)之间的相互作用[3]。全身或局部炎症促进冠状动脉血栓形成。先天性免疫应答(巨噬细胞)和适应性免疫应答(T 淋巴细胞和 B 淋巴细胞、树突状细胞)都通过动脉粥样硬化、先天免疫和炎症之间的复杂相互作用导致 ACS 患者的动脉粥样硬化及其血栓并发症[2]，几十年来，斑块破裂一直主导着我们对 ACS 病理生理学的思考。然而，目前的证据表明，仅仅关注斑块破裂掩盖了可能需要不同管理策略的其他机制，因此 ACS 的发病机制可分为斑块破裂伴全身炎症、斑块破裂无全身炎症、斑块糜烂和 ACS 伴无冠状动脉血栓或狭窄[4]。其中 ACS 伴无冠状动脉血栓或狭窄及斑块破裂无全身炎症与本次探讨内容相关性不大，不进一步探讨。

2. 冠状动脉粥样硬化

在正常个体中，内皮具有抗炎和抗血栓形成特性，并通过血管扩张物质(如一氧化氮)和内皮衍生收缩物(如内皮素)之间的平衡来调节循环分子和血管张力的通透性[5]。内皮功能的主要调节剂是一氧化氮(NO)，它具有血管松弛，抗血栓形成，抗增殖和抗炎的特性[6]。然而，当内皮细胞被激活时，随着血管收缩、血栓形成、白细胞动员－迁移和血管平滑肌细胞增殖的促进，向动脉粥样硬化易感表型转变，这源于 NO 生物利用度受损[7]。而 NO 生物利用度受损导致保护性能的丧失、内皮接头的损伤以及对大分子的渗透性增加。这些变化导致含胆固醇脂蛋白的内皮下蓄积，从而引发低度炎症反应[7] [8]。

一些研究表明，低密度脂蛋白(LDL-C)与动脉粥样硬化之间存在密切关系[9] [10]。LDL-C 是一种非均相分子，负责不溶性胆固醇的转运，已经发现了四种 LDL 类别，其中小密度 LDL-C (sdLDL-C)是最易致动脉粥样硬化的。低密度脂蛋白颗粒进入内皮下目前不再被视为被动过程，它们的转吞作用取决于小

泡、清除受体 B1 (SR-B1)-胞质分裂作用因子 4 (DOCK4)以及激活素受体样激酶 1 (ALK1) [11]。一旦进入内皮下空间，LDL-C 就会在大型复合物中发生氧化和聚集。此外，在炎症环境中，脂蛋白代谢从大中型 LDL-C 转变为对肝脏特异性 LDL-C 受体亲和力较低的小而致密的 sdLDL-C [12]。一旦进入内皮下间隙，招募的单核细胞分化成巨噬细胞，然后极化，采用不同的功能表型，以响应其微环境[13]。T 淋巴细胞将这些细胞激活为促炎 M1 巨噬细胞，这些巨噬细胞可细化参与动脉粥样硬化进展的促炎细胞因子(白细胞介素 IL-1α、IL-1β、IL-6、IL-12、IL-15、IL-18 和肿瘤坏死因子(TNF-α)，或替代抗炎 M2 巨噬细胞，其分泌抗炎细胞因子(IL-4、IL-10、IL-13 和转化生长因子(TGF-β)，这些巨噬细胞因子在炎症和斑块愈合的消退中起关键作用[14] [15] [16] [17] [18]。一些白细胞介素(IL-1β、IL-6 和 IL-12)控制 CRP 的肝脏生成，CRP 是心血管疾病风险最确定的炎症生物标志物[19] [20] [21] [22]。虽然巨噬细胞是细胞因子的主要来源，但其他细胞，如淋巴细胞、内皮细胞和多形核白细胞也有助于它们的产生。免疫系统的大多数成分可以根据炎症环境产生促炎或抗炎的可溶性因子和细胞，而这些炎症相关可溶性因子和细胞在动脉粥样硬化中起到了关键的作用[23] [24]。

3. 斑块破裂伴全身炎症

通过生物标志物 c 反应蛋白的评估，一些研究表明 ACS 存在全身性炎症[25]。其中粥样斑块纤维帽的破裂中巨噬细胞可能扮演了重要角色：一些酶(包括基质金属蛋白酶(MMPs)和某些组织蛋白酶)会被巨噬细胞被激活的时候合成，而这些酶会对所有细胞外基质进行降解。转录、翻译、酶原前体的激活以及与一些内源性抑制剂如基质金属蛋白酶组织抑制剂(TIMPS)或胱抑素的平衡。所以若这些活化的蛋白酶增多或者其抑制剂的减少都可以加快粥样斑块细胞外基质的分解[26]。

适应性免疫在冠状动脉斑块不稳定时也出现改变[27]。此时 ACS 患者的 CD4+T 细胞数量上升，所表现的特点是细胞表面的共刺激分子 CD28 表达降低，而 CD28 在决定 T 细胞识别抗原的结果中起到了枢纽作用[28]。此外，ACS 还明显干扰了循环中另外两类 T 细胞的数目，包括 17 型辅助 T 细胞(Th17)及 CD4CD25 调节性 T 细胞(Treg)。但是，一些动物的基础研究支持了 IL-17 的促动脉粥样硬化作用，这导致了白细胞介素-17 (IL-17)在动脉粥样硬化中的作用仍然存在不同意见，但在动脉斑块中被激活的 Th17 细胞可促进厚胶原蛋白纤维的产生，可能会因此提高动脉斑块的稳固性[29] [30]。Treg (包括抗原呈递细胞和效应 T 细胞)一般对于维持参与适应性免疫的细胞的稳态起正向作用，Treg 通过抑制或释放抗炎细胞因子，如 IL-10 或 TGF-β1，介导此类调节作用[31]。在与稳定型心绞痛患者和健康对照中，ACS 患者循环 Treg 的数量和抑制功能是较低的[27]。这些都导致 T 细胞失调的分子机制在 ACS 患者体内仍有这诸多疑云与矛盾。而最近刺激 T 细胞抗原受体(TCR)在辅助性 T 细胞亚群分化中扮演的角色越来越受到大家的重视。目前在 ACS 中观察到的参与上游 TCR 信号调节的蛋白活性改变，如 CD31 和 PTPN22，也可能调节 T 细胞功能[32] [33]。

4. 斑块糜烂

斑块糜烂是冠状动脉粥样硬化血栓形成的第二常见原因，仅次于斑块破裂，约占 ST 段抬高病例的 30%和非 ST 段抬高型心肌梗死的 50% [34]。糜烂的特征是去内皮化，而不是纤维帽破坏[35] [36]。虽然侵蚀斑块的典型微观结构特征尚未完全阐明，但公认的特征是斑块上没有内皮，斑块具有较厚的纤维帽、更小的脂质和坏死核心、更丰富的血管平滑肌细胞，但与破裂斑块相比，巨噬细胞更少，炎症更少[37]。机理观察表明，这些斑块干扰流动，导致 Toll 样受体 2 (TLR2)活化、中性粒细胞募集以及随后去内皮化的促进。这使得流动的血液与斑块胶原蛋白接触，从而形成富含中性粒细胞的血栓[38]。中性粒细胞胞外陷阱(Neutrophil extracellular traps, NETS)与斑块侵蚀并发血栓形成尤其相关[38]。这些由去致密染色质形式的 DNA 链组成的陷阱被活化或死亡的中性粒细胞释放，并定位于血液和病变动脉的内膜表面[39]。在

这里，它们形成纤维蛋白样碱基，用于血小板粘附、活化和聚集；促进血栓前分子的积累，包括血管性血友病因子(vWF)和纤维蛋白原；并促进红细胞粘附。这些都有助于血栓形成[39]。

5. 结论

虽然传统危险因素在冠状动脉疾病中仍占有重要地位，越来越多的证据强调了局部和全身炎症在动脉粥样硬化及其并发症的所有阶段的重要性。然而，许多针对临床前研究中涉及的炎症途径的实验性疗法未能在临床试验中显示出积极的结果，这突出表明炎症在动脉粥样硬化中的作用是复杂的，并涉及多种炎症途径，目前远未完全了解。所以，冠状动脉疾病与炎症关系需要我们进一步探索，剖析出两者之间的作用途径，寻找相应的干预方案，使患者可以得到进一步的获利。

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