·综述·

冠状动脉粥样硬化斑块愈合的研究进展

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【摘 要】 动脉粥样硬化斑块破裂后的愈合过程对临床结果意义重大,良好的斑块愈合可以阻止血栓的进一步发展,避免急性心血管事件的发生,但反复的斑块愈合也被认为可加重斑块负荷,引起血管慢性狭窄。随着腔内影像技术的发展,对斑块愈合的研究愈加深入,许多针对斑块愈合的治疗方法也在实施或研究中。

【关键词】 冠状动脉粥样硬化;斑块愈合;光学相干断层显像
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Research progress of coronary atherosclerotic plaque healing

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【Abstract】 The atherosclerotic plaque healing process after plaque rupture is of great significance to clinical results. Plaque healing can prevent the further development of thrombus and avoid the occurrence of acute cardiovascular events. However, repeated plaque healing can also cause chronic vascular stenosis. Plaque healing can be divided into three stages: thrombolysis, granulation tissue formation and vascular re-endothelialization, which are also affected by various local and systemic factors. With the development of new imaging techniques, the research on plaque healing is getting deeper, and many treatments for plaque healing are being used or studied.

【Key words】 coronary atherosclerosis;plaque healing;optical coherence tomography
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过去半个世纪,对动脉粥样硬化(atherosclerosis,AS)斑块的研究一直聚焦在斑块的产生及破裂[1],而忽略其愈合过程。许多斑块破裂或侵蚀能够自身修复,而不引起急性冠状动脉综合征(acute coronary syndrome,ACS),我们把这一过程称为斑块愈合。最近,随着冠状动脉腔内影像技术的发展,尤其是分辨率极高的光学相干断层扫描(optical coherence tomography,OCT)[2],斑块愈合被认为可能在AS发展中起关键作用[3]。本文将根据近年来斑块愈合的最新进展,对斑块愈合的病理表现、影响因素、影像学表现以及临床治疗作一综述。

1 概 念

AS斑块愈合是斑块破裂或侵蚀后发生的动态过程,可防止血栓形成,促进斑块修复,并恢复血管的完整性[4]。当出现斑块破裂或侵蚀时,机体通过血栓溶解、肉芽组织形成和血管再次内皮化等生理过程,抑制血栓形成,避免ACS发生[5]。

提到斑块愈合,需要与斑块稳定区别开来。斑块稳定是通过降脂、抗炎等手段,促进富含脂肪的斑块向纤维化和钙化斑块的转化,从而预防易损斑块发生破裂、脱落等。通过药物治疗稳定斑块,可降低ACS发生率,减少支架植入。

2 病理表现

斑块愈合主要包含以下三个阶段。

2.1 血栓溶解

斑块破裂或侵蚀后,在致血栓性物质(如坏死核心或纤维蛋白)的刺激下,血小板在破裂部位发生活化及聚集,同时激活血液中的凝血因子,凝血因子级联反应也激活内源性纤溶系统[6]。在有效的内源性纤溶系统中,致血栓性物质触发一连串的酶释放过程,促进纤维蛋白分解,从而溶解血栓[7,8]。

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2.2 肉芽组织形成

平滑肌细胞(smooth muscle cell,SMC)的增殖及迁移是AS斑块愈合的关键机制。生长因子的释放,刺激了斑块处SMC的增殖反应以及SMC从局部血管壁向内膜的迁移[9],P-选择素及基质细胞衍生因子1α表达的增加促进骨髓衍生SMC祖细胞从血液循环的归巢[10]。增生的SMC依次合成蛋白聚糖和Ⅲ型胶原,生成临时的细胞外基质,形成肉芽组织。

2.3 血管再次内皮化

当斑块完全愈合后,Ⅰ型胶原逐渐取代Ⅲ型胶原,新生的内皮细胞覆盖于斑块表面,再次内皮化发生。

斑块愈合过程可以阻止斑块破裂的快速发展,但会导致富含脂质的斑块缓慢发展为纤维性病变,导致管腔的进一步狭窄。虽然愈合过程本身用胶原封闭了破裂或侵蚀的部位,但血管脆弱性、局部炎症以及更大的斑块负荷可能超过斑块愈合的保护能力,使反复斑块愈合的患者在未来发生ACS[3]。对此,把握斑块愈合的"度"显得尤为重要。如何既防止愈合失败导致ACS的产生,又避免同一部位反复愈合引起的过度纤维化,导致斑块负荷过重,是下一步亟待解决的问题。

3 影响因素

3.1 炎症与巨噬细胞极化

炎症已被证实与AS斑块形成密切相关,但炎症与斑块愈合的关系并不明朗。由活化的1型辅助T(type 1 helper T,Th1)细胞分泌的干扰素γ,可以抑制SMC产生间质胶原,从而抑制SMC修复纤维帽和保持其完整性的能力。Th1细胞和巨噬细胞之间的相互作用,促进间质胶原酶的产生,如基质金属蛋白酶1、8和13等,它们促进间质胶原的分解,削弱纤维帽[11,12]。

巨噬细胞在AS疾病中不是终末分化,活化的Th2细胞触发巨噬细胞向M2巨噬细胞的极化,M2巨噬细胞被认为有利于伤口愈合,产生促纤维化因子,如纤连蛋白、胰岛素样生长因子1和转化生长因子-β,促进SMC的成熟和扩散,使胶原产生增多。M2巨噬细胞还促进炎症细胞的凋亡,可能有利于斑块愈合过程中炎症的缓解。在愈合过程后期,M2巨噬细胞还可能通过刺激成骨细胞分化和血管SMC成熟来促进斑块钙化,为斑块愈合提供机械支撑[12,13]。

3.2 内膜新生血管生成

一项关于斑块愈合的OCT研究显示[14]:与长期稳定性心绞痛(long-standing stable angina pectoris,ls-SAP)患者相比,复发性急性冠脉综合征(recurrent acute coronary syndromes,rACS)患者斑块的核心长轴长度更长,且内膜微血管主要在管腔内膜中沿纵向行走,而非向心方向[15],长轴的长度过长导致新生血管往往难以覆盖斑块表面。新生血管是愈合的斑块中修复细胞的"供给线",为愈合组织提供氧气和营养物质。长坏死核心的斑块中,通往受损区域的"供给线"无法可靠建立,愈合组织的原料来源不足,影响斑块愈合进程[16]。

4 腔内影像表现

近年来,随着腔内成像技术的蓬勃发展,涌现了大量关于AS斑块的形态学特征研究。

愈合的斑块在OCT上通常为具有1层或多层的斑块,具有不同的光密度,并且与血管壁有明确的界限,即层状斑块[2]。在29%最常见类型的ACS病变中,三分之一具有多层模式,在患有高脂血症、糖尿病和心肌梗塞史的ACS患者中更常见[17]。多层斑块提示该病变部位曾发生过多次的斑块破裂及愈合过程,与单层斑块相比,多层斑块呈现更严重的管腔狭窄、更长的病变长度、更复杂的病变类型、和更大的斑块负荷[18]。层状斑块很少在rACS患者中被发现,而在ls-SAP患者中,大约有三分之一的患者可以观察到层状斑块[14],提示个体对于斑块破裂的反应可能是决定破裂斑块走向的关键。层状斑块表型的频率和层状组织的最大面积由非罪犯的薄纤维帽粥样硬化斑块(thin-capped fibroatheroma,TCFA)、非罪犯血管斑块破裂、罪犯血管斑块破裂依次增加[19]。分层斑块比非分层斑块显示更多的脂质浸润、更多TCFA和更多巨噬细胞浸润[20],提示分层斑块不稳定性更高且局部炎症更明显。

当斑块愈合反应失败,斑块中的坏死核心进入血管腔,堵塞血管,则会发生ACS,OCT可见血管内皮的不连续性,斑块中存在空洞,可见血栓物质,且缺乏再内皮化的迹象[21]。

5 治 疗

5.1 降脂饮食

通过胸主动脉球囊损伤和高脂饮食诱导AS兔的实验显示:降脂饮食降低了基质金属蛋白酶的蛋白水解活性,增加了斑块纤维帽内的间质胶原,这有利于斑块愈合过程中纤维骨架的形成[22],还可降低组织因子的表达量[23]。

5.2 降脂治疗

虽然此前大量研究聚焦在 AS 斑块体积的减少,但斑块成分可能在 ACS 及斑块愈合中起着关键作用,特别是富含脂质的斑块会增加斑块破裂风险[24]。在接受高强度他汀治疗的 ST 段抬高型心肌梗死患者的非罪犯病变中,最小纤维帽厚度显著增加,可见薄纤维帽粥样硬化斑块(thin-capped fibroatheroma ,TCFA)向其他斑块表型转化[25]。

5.3 抗炎药物

许多研究已经证明抗炎药物(如白细胞介素-1β 拮抗剂,秋水仙碱)在 AS 治疗中的积极效果[26]。最近的一项研究表明,低剂量秋水仙碱有利于改变 AS 斑块的形态学特征,形成更稳定的斑块表型[27],减少斑块愈合时局部的炎症因子的作用,促进斑块愈合。

5.4 新的治疗方向

一些新的治疗靶点正在研究中。CD31 激动剂[28,29]、表观遗传疗法(如微小核糖核酸[30,31]、非编码核糖核酸[32])、髓系细胞触发受体 1[33]等被证明在斑块愈合中具有治疗潜力,相关研究正在进行中。

6 结论和展望

尽管有关 AS 斑块的产生及其不稳定的机制已经获得一些令人振奋的进展,但我们相信随着斑块愈合研究进一步深入,将开启 AS 防治的崭新局面。随着腔内影像的发展,斑块愈合的研究已跨出一大步,然而,如何促进 AS 斑块的良好愈合以及预防斑块反复愈合导致的慢性管腔狭窄,仍然是未解之谜,斑块愈合的探索任重而道远。

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