颈动脉斑块稳定性的研究进展

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摘 要: 颈动脉动脉粥样硬化的疾病进展与脑卒中疾病的发展密切相关。提高斑块稳定性对于降低脑卒中发病率和病死率尤为重要。本综述系统回顾了颈动脉粥样硬化斑块形成的背景,斑块稳定性的概念,颈动脉狭窄与斑块稳定性的关系以及斑块稳定性的发病机制,最后阐述评估斑块稳定性的影像学检查方法。

关键词: 颈动脉斑块; 斑块稳定性; 颈动脉狭窄; 发病机制

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Research progress of carotid atherosclerotic stability

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Abstract: The disease progression of carotid atherosclerosis is closely related to the development of stroke. Improvement of plaque stability is particularly important for reducing the incidence and mortality of stroke. This review systematically reviewed the background of carotid atherosclerotic plaque, the concept of plaque stability, the relationship between carotid artery stenosis and plaque stability, and the pathogenesis of plaque stability. Finally it explained the imaging methods in evaluation of plaque stability.

Key words: carotid plaque; plaque stability; carotid stenosis; pathogenesis

动脉粥样硬化是血管病中常见的一种疾病,该疾病以脂质代谢障碍为主,动脉狭窄和斑块破裂与冠状动脉心肌梗死综合征、脑卒中的发生密切相关。全球缺血性心脏病和缺血性脑卒中死亡人数占全球死亡人数的1/4, 1990年该比例仅为1/5[1]。2016年,中国动脉粥样硬化性心血管病死人数占心血管病总病死人数的61%, 占中国当年全因死亡人数的25%[2]。对于症状性颈动脉狭窄患者来说,目前最佳的治疗方法仍是颈动脉内膜切除术或颈动脉支架置入术,而对于无症状颈动脉狭窄患者,需要评估临床症状和斑块影像学检查来确定治疗方案[3]。近年来,学者发现,巨噬细胞表型极化和胞葬功能在斑块稳定性中的作用明确。本文针对巨噬细胞表型极化和胞葬功能在斑块稳定性中的作用研究进行总结阐述。此外,由于影像学检查和生物标志物常用于颈动脉斑块的术前评估,本文阐述了影像学检查方法,并对生物标志物与斑块稳定性的关系进行了综述。

1 斑块稳定性的概念

斑块稳定性的概念源于1844年,丹麦的著名雕塑家贝特尔·托瓦尔森死于心源性猝死,尸体解剖发现,其冠状动脉粥样硬化斑块破裂,由此产生了斑块破裂和斑块稳定性的概念[4]。随着尸体解剖和病理研究的深入, 1995年美国心脏病学会发布《动脉粥样硬化斑块组织病理学分型标准》,将斑块类型分为Ⅰ~Ⅵ 6类,且该标准也应

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用于颈动脉斑块的病理学分析研究中[5]。2000 年又对其部分内容进行修订,逐渐优化至今,见图 1。

但是颈动脉与冠状动脉的斑块稳定性评价标准不同,其中差别最为明显的是纤维帽厚度和斑块侵蚀。1997 年, BURKE A P 等[6]对冠状动脉梗死综合征致死的患者进行尸检,结果发现,冠状动脉斑块破裂引起猝死的患者冠状动脉斑块的纤维帽 <65 μm, 因此不稳定斑块的病理学定义应基于厚度小于 65 μm 的纤维帽。之后将这个定义更新到 2000 年的美国心脏病学会的罗马数字斑块分型标准中,将这样的斑块称之为薄纤维帽斑块 (TCFA)[7]。但是由于颈动脉斑块体积和解剖位置与冠状动脉斑块不同,研究[8-9]认为,颈动脉斑块趋于破裂的最小纤维帽厚度标准应是 200 μm, 大于冠状动脉斑块的 65 μm 标准。

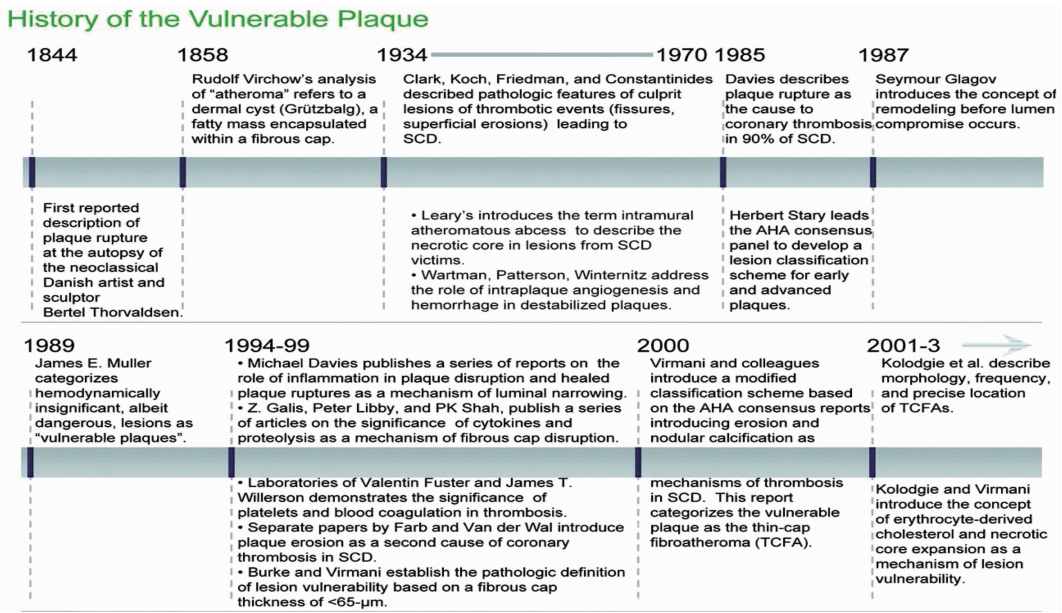


图 1　斑块稳定性概念的产生

2　颈动脉狭窄与斑块稳定性

颈动脉粥样硬化引起的动脉狭窄或者闭塞可引起同侧脑缺血或缺血性脑卒中。从解剖学看,颈动脉动脉粥样硬化主要累及颅外段颈动脉分叉处以及颈内动脉起始处,可导致远心端相应供血区的血运障碍[10]。

3　动脉粥样硬化与斑块稳定性的发病机制

动脉粥样硬化的发生有多种学说,但是目前主流学说是"内皮损伤-炎症反应"学说[11]。在各种危险因素的刺激下,富含胆固醇的低密度脂蛋白(LDL)会渗入内皮或黏附到蛋白聚糖等细胞外基质成分上,因此会在血管内膜下积累并且被活性氧所氧化变成氧化低密度脂蛋白(oxLDL), 巨噬细胞不断摄取 oxLDL 并逐渐转为泡沫细胞,但巨噬细胞过度吞噬 oxLDL 会导致内质网应激过载,引起巨噬细胞的凋亡[12]。巨噬细胞凋亡会被吞噬细胞吞噬,其中大致经历了 3 个过程:"寻找我""吃我""吞噬我",凋亡的巨噬细胞会发出信号,吞噬细胞会循着信号找到凋亡的巨噬细胞并将其吞噬降解[13]。动脉粥样硬化的早期,巨噬细胞的凋亡能够被吞噬细胞及时清除,有效阻止脂质核心扩大; 动脉粥样硬化进展期,越来越多的巨噬细胞凋亡,再加上吞噬过程中的信号通路受阻,这样的吞噬作用越来越不足以清除凋亡的巨噬细胞,因此脂质核心逐渐扩大[14]。因此,巨噬细胞在动脉粥样硬化发病全程均有重要作用,并且巨噬细胞极化表型与胞葬功能密切相关。

3.1　巨噬细胞凋亡和胞葬功能

巨噬细胞凋亡和平滑肌细胞凋亡是动脉粥样硬化发展过程中的一把双刃剑。斑块产生的早期阶段,巨噬细胞凋亡的作用是保护斑块稳定性。然而,在随后的阶段,当凋亡细胞变成碎片,胞葬功能不足时,会导致继发性坏死性凋亡,引起继发的炎症反应,坏死脂质核心扩大[15]。胞葬功能清除凋亡细胞共有 4 个步骤: 巨噬细胞凋亡、"寻找我""吃我"和吞噬过程。见图 2。

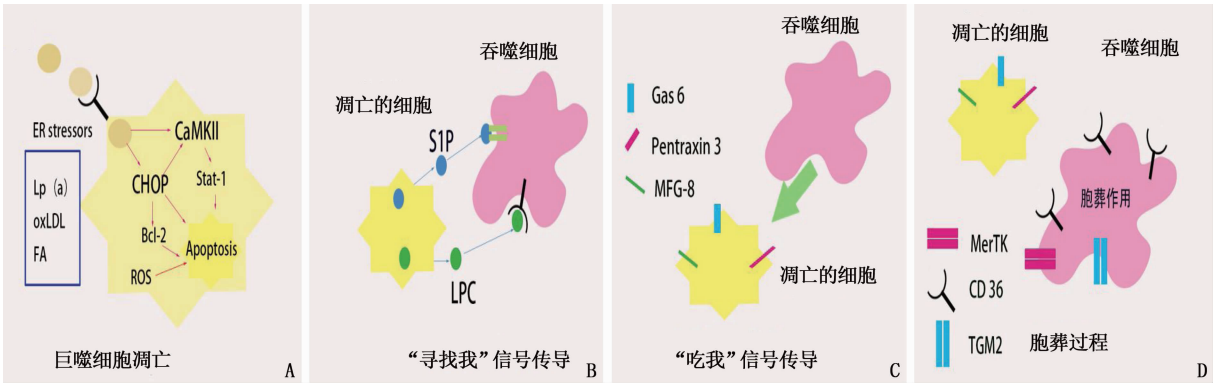
3.1.1　巨噬细胞凋亡: 巨噬细胞大量吞噬 oxLDL 后,内质网应激过载,分别通过 C/EBP 同源蛋白

(CHOP)/B 淋巴细胞瘤-2(Bcl-2),钙/钙调蛋白(CaM)依赖的蛋白激酶Ⅱ(CaMKⅡ)/信号转导与转录激活子 1(STAT-1)以及还原型烟酰胺腺嘌呤二核苷酸(NADPH)氧化酶/活性氧等信号通路启动凋亡程序[16-18]。

3.1.2 “寻找我”:巨噬细胞凋亡后即可释放“找我”信号 1-磷酸鞘氨醇(S1P)或者溶血磷脂酰胆碱(LPC),吞噬细胞即可通过与“找我”信号分子的结合寻找凋亡细胞[19-20]。

3.1.3 “吃我”:吞噬细胞根据“找我”信号分子的指引找到凋亡细胞,此时的凋亡细胞可发出“吃我”信号分子,包括生长抑制特异性蛋白 6(Gas6)、正五聚蛋白 3(Pentraxin 3)、乳脂肪球表皮生长因子 8(MFG-E8)等信号分子,吞噬细胞可根据这些信号分子与凋亡细胞结合[21-23]。

3.1.4 吞噬过程:与凋亡细胞结合后,吞噬细胞需要通过特殊受体将凋亡细胞传送到吞噬细胞内部进行消化,Mer 受体酪氨酸激酶(MerTK)、谷氨酰胺酶 2(TGM2)、B 类清道夫受体(CD36)是介导凋亡细胞进入吞噬细胞内部的重要受体,通过其引导,才能将凋亡细胞成功运送到吞噬细胞体内并完成消化[24-26]。由于胞葬功能不足以清除越来越多的凋亡细胞,最终可能导致斑块破裂[13]。除了以上吞噬过程,胞葬功能本身也能激发多种抗炎和促分解的信号通路,具有增强抗炎细胞因子释放同时减少促炎细胞因子分泌的作用。



A:巨噬细胞凋亡过程(大量内质网应激物刺激巨噬细胞,激活凋亡信号通路,使巨噬细胞凋亡);

B:“寻找我”信号传导(凋亡细胞释放 S1P 和 LPC 等凋亡信号,促使吞噬细胞趋向凋亡细胞);

C:“吃我”信号传导(吞噬细胞找到凋亡细胞后,凋亡细胞释放“吃我”信号);

D:胞葬过程(吞噬细胞通过 MerTK、CD36、TGM2 等受体介导凋亡细胞至吞噬细胞内部进行胞葬消化)。

图 2 胞葬过程示意图

3.2 巨噬细胞表型极化与斑块稳定性

除巨噬细胞胞葬功能可调控斑块稳定性之外,巨噬细胞的表型极化还可通过介导胞葬功能参与斑块稳定性的调控。巨噬细胞根据激活方式的不同可分为经典激活的 M1 型巨噬细胞和替代激活的的 M2 型巨噬细胞,M1 型和 M2 型巨噬细胞在表面受体表达。细胞因子和趋化因子对胞葬功能的影响截然不同。M1 型促炎的巨噬细胞活化是由 γ-干扰素(IFN-γ)、脂多糖(LPS)等促炎因子激活产生的,主要表现是巨噬细胞的抗原提呈能力提升,补体介导的吞噬能力增强,加剧炎症的因子大量释放,同时 CXC 趋化因子配体 10(CXCL10)、CXC 趋化因子配体 9(CXCL9)等也同时释放[27]。研究[28]表明,M1 巨噬细胞是分布于人斑块肩部的巨噬细胞的主要类型,其位置易发生斑块破裂,M1 型巨噬细胞可通过减弱胞葬功能来影响斑块稳定性。

M2 型巨噬细胞是由白细胞介素 1β(IL-1β)、白细胞介素 4(IL-4)和白细胞介素 13(L-13)激活,形成 M2 型巨噬细胞,分泌白细胞介素 10(IL-10),白细胞介素-1 受体拮抗剂(IL-1Ra)等细胞因子,发挥免疫调节和抑制免疫反应的发生[29]。研究[30]表明,M2 巨噬细胞能够增强胞葬功能,增加斑块稳定性。M2 巨噬细胞聚集在斑块周围区域,通过致力于增加胞葬功能和避免斑块中心坏死核心的生长,从而有效清除凋亡细胞,延缓脂质坏死核心增大,从而增强了斑块稳定性。

4 影像学评估与斑块稳定性

颈动脉硬化狭窄和斑块不稳定性的危害性大,目前颈动脉硬化狭窄的治疗手段以手术治疗为主,但是根据国际血管外科指南推荐,部分颈动脉狭窄患者的治疗方案仍需要良好的术前影像学评估。因此,斑块稳定性的影像学评估对于颈动

脉狭窄治疗方案的选择相当重要。

目前临床上颈动脉斑块的影像学评估包括 B 型超声检查、超声造影(CEUS)、高分辨核磁共振成像、CT 血管造影(CTA)和分子影像等影像学方法。B 型超声检查是较早应用于颈动脉斑块的技术,主要用于评估颈动脉斑块的回声强度,但 B 型超声检查是定性检查,主观性强,不同操作者得出的结论可能不同。因此,B 型超声的应用范围相对有限[31]。CEUS 是在常规超声基础上,通过外周静脉注射造影剂增强血流散射强度。斑块磁共振成像 (MRI)适合于评价纤维帽厚度、脂质核心大小和斑块内出血。学者[32-33]发现,颈动脉狭窄患者的斑块 MRI 可显示出斑块内出血、钙化灶、斑块溃疡、富含脂质的核心、纤维帽变薄或者斑块破裂的影像学特征,而且这些特征与脑卒中或者一过性脑缺血症状具有相关性[34]。CT 血管造影亦可以评价斑块特征,特别是多层螺旋 CT 血管造影,早期显影和延迟显影的 CT 值增加预示着斑块纤维帽的厚度增加,脂质核心减小,新生血管密度和斑块内出血减少[35]。

除了上述常见影像学技术,分子影像和基于新技术的成像方法也可用于斑块稳定性评估。氟代脱氧葡萄糖(^{18}FDG)显像不仅可以反映斑块内炎症严重程度,而且颈动脉^{18}FDG 显像增加预示着颈动脉硬化狭窄患者的脑卒中复发率更高[35];偏振敏感光学相干断层扫描(PSOCT)和激光散斑成像(LSI)等激光相干成像技术,可以通过测量纤维帽胶原含量来评估纤维帽厚度[36]。

因此,无论是术前、术中还是术后,斑块稳定性与脑卒中事件息息相关。因此,术前进行斑块稳定性影像学评估能够提早发现不稳定斑块,从而做出相应预防措施,减少脑卒中事件的发生。

5　生物标志物与斑块稳定性

除应用影像学检查直接评估斑块形态外,还可以通过血液或斑块内的分子标志物来评估斑块稳定性。这些分子标志物能够在一定程度上预测斑块稳定性,并评估疾病是否进展和治疗干预试剂的有效性。这些分子标志物大概分为 11 类,均能对应美国心脏学会的罗马数字病理学分型[37]。本文选择近年来在冠状动脉和颈动脉研究中具有代表性的 5 类分子标志物进行讨论,包括超敏 C 反应蛋白(hs-CRP)、单核细胞趋化蛋白-1(MCP-1)、基质金属蛋白酶-9(MMP-9)、妊娠相关血浆蛋白 A(PAPP-A)和微小核糖核酸(MicroRNA)。

hs-CRP:研究[38]认为,颈动脉或冠状动脉斑块中,患者血液高表达的 hs-CRP 均提示斑块不稳定;但另有研究[39]认为,高血压人群的颈动脉斑块稳定性与 CRP 表达水平无相关性。2 个研究结论不同,可能是由所选研究人群的高血压患者比例不同导致的。

MCP-1:MCP-1 是调节单核-巨噬细胞迁移和穿梭最终重要的细胞因子。临床研究[40]发现,血液中较高 MCP-1 水平与随访 10 个月的心肌梗死事件发生率或者病死率有关,并且是独立风险因子。但颈动脉斑块研究[41]却发现, MCP-1 与斑块稳定性无明显相关性。

MMP-9:在众多基质金属蛋白酶中, MMP-9 与心血管事件发生率最为相关,原因可能是 MMP-9 能够促进脂质核心扩大和分解纤维帽的细胞外基质,导致斑块不稳定,从而导致心血管事件发生率增高[42-43]。

妊娠相关蛋白 A(PAPP-A):在大型临床研究[44]中, PAPP-A 对缺血性心脏病、心肌梗死及病死率有独立预测作用。同时在颈动脉斑块研究[45]中, PAPP-A 的 rs7020782 单核苷酸多态性可能是颈动脉不稳定斑块的独立危险因子。

MicroRNA:冠状动脉研究[46]中,部分 MicroRNAs 与冠状动脉的斑块稳定性相关,而颈动脉研究发现, MicroRNA-23a-5p 可通过影响脂质代谢来促进斑块进展[47]。

因此,生物标志物与斑块稳定性进展息息相关,但是这些生物标志物目前的研究仍有争议,是否能够直接应用于颈动脉术前诊断仍需要更多的临床试验加以验证。

6　小　结

研究证实,巨噬细胞表型极化和胞葬功能在斑块稳定性发展过程中具有重要作用,进一步加深了对巨噬细胞表型极化和胞葬功能清除凋亡细胞的细胞功能和分子机制的理解。同时,本文回顾了影像学评估以及生物标志物与斑块稳定性的关系,为术前治疗方案提供了更多的选择。未来应进一步对巨噬细胞功能与斑块稳定性进行研究,并与影像学或生物标志物结合,为颈动脉狭窄患者的治疗方案选择提供参考依据。

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