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PCSK9抑制剂在颈动脉狭窄中的应用进展

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摘　要

颈动脉狭窄(Carotid Artery Stenosis, CAS)是急性缺血性脑卒中(Ischemic Stroke, IS)的原因之一，其主要原因是动脉粥样硬化(Atherosclerosis, AS)。低密度脂蛋白胆固醇(Low Density Lipoprotein Cholesterol, LDL-C)异常是导致AS的重要危险因素。近年的研究发现人前蛋白转化酶枯草溶菌素kexin 9型(proprotein convertase subtilisin/kexin type 9, PCSK9)在动脉粥样硬化斑块形成扮演者重要角色。PCSK9抑制剂已被证实可以改善心血管疾病的预后，目前广泛应用于心血管疾病，但是缺乏在CAS中应用的相关报道。本文对PCSK9抑制剂在CAS中的应用做一综述。

关键词

前蛋白转化酶枯草溶菌素Kexin 9型，颈动脉狭窄，PCSK9抑制剂，动脉粥样硬化

Application of PCSK9 Inhibitor in Carotid Stenosis

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Abstract

Carotid Artery Stenosis (CAS) is one of the causes of acute ischemic stroke (IS), and its main cause is atherosclerosis (AS). The abnormality of low density lipoprotein cholesterol (LDL-C) is an im-

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portant risk factor leading to AS. Recent studies have found that human prothrombin invertase kexin 9 (PCSK9) plays an important role in atherosclerotic plaque formation. PCSK9 inhibitors have been proved to improve the prognosis of cardiovascular diseases. They are widely used in cardiovascular diseases, but there is no relevant report on the application of PCSK9 inhibitors in CAS. This article reviews the application of PCSK9 inhibitors in CAS.

Keywords

Proprotein Convertase Subtilisin/Kexin Type 9, Carotid Stenosis, PCSK9 Inhibitor, Atherosclerosis

1. 引言

CAS 与动脉粥样硬化斑块发展有关。AS 本身是一种慢性的动脉疾病，血脂异常尤其是 LDL-C 在 AS 的过程中起着重要作用[1] [2] [3]。近年来的研究表明 PCSK9 在 AS 形成的每一步都起着重要作用[1]。PCSK9 抑制剂可以通过抑制 PCSK9 与低密度脂蛋白受体(Low-Density Lipoprotein Receptor, LDL-R)结合以及 PCSK9 合成等过程从而降低 LDL-C 水平，有助于减缓 AS 的进展，因此可作为 CAS 的一种新的治疗方案[4]。本文对 PCSK9 抑制剂在 CAS 中应用的进展进行综述。

2. PCSK9

PCSK9 于 2003 年由 Seidah 等[5]发现。PCSK9 基因定位于 1 号染色体的短臂(chr1p32.3)，长度为 22 kb，包含 12 个外显子和 11 个内含子[6]。PCSK9 是一种为分子量为 72 kDa 的含有 692 个氨基酸的酶原[7] [8]，由 N 端结构域、信号肽、催化结构域和 C 端结构域组成[7] [9] [10]。主要在肝脏、小肠、血管等器官表达。PCSK9 存在功能获得型(Gain Of Function, GOF)和功能缺失型(Loss Of Function, LOF)变异。PCSK9 GOF 变异降低循环中 LDL-R 的减少，与循环中 LDL-C 水平增加相关[11]。相反，PCSK9 LOF 变异可降低循环 LDL-C 水平[12]。

3. PCSK9 与颈动脉狭窄

CAS 的主要原因是动脉粥样硬化[13]。AS 过程开始于内皮细胞的功能改变，并伴随着动脉壁内层 LDL-C 的积累、氧化和糖基化，并持续于黏附分子的表达和趋化因子的释放[1]。单核细胞和 T 细胞在血管内膜空间被招募，单核细胞吞噬氧化的低密度脂蛋白(Oxidized low-density lipoprotein, ox-LDL)形成泡沫细胞[14]。在动脉粥样硬化的各种危险因素中，血脂异常，尤其是 LDL-C 异常，在 AS 的过程中起着重要作用[15]。除此之外，PCSK9 还能够通过促进炎症、促进斑块及血栓形成等方面加速动脉粥样硬化形成。

3.1. PCSK9 与脂质代谢

在没有 PCSK9 干扰的情况下，LDL-R 与肝细胞表面的低密度脂蛋白(Low-Density Lipoprotein, LDL)结合形成 LDL-R/LDL 复合体并将其转移到肝细胞的核内体中，由于 PH 值的变化导致二者分离，LDL 在溶酶体中降解，LDL-R 在循环到肝细胞表面继续循环。而 PCSK9 不仅可以与 LDL-R 的表皮生长因子同源域 A (EGF-A)结合使 LDL-R 无法结合 LDL-C 颗粒[16]，还可以增强 LDL-R 的内吞作用和阻断其循

环来促进 LDL-R 降解，通过这两种途径导致 LDL-C 循环水平增高，导致 LDL-C 在体内堆积。除了 LDL-C 之外，PCSK9 还可以通过参与甘油三酯(Triglyceride, TG)和脂蛋白 a (Lipoprotein-a, Lp(a))来加速 AS 的发展[17] [18]。

3.2. PCSK9 与炎症

2019 年的一项研究使用多局部正电子发射断层扫描/磁共振成像(Positron emission tomography/magnetic resonance imaging, PET/MRI)揭示了 AS 早期处于炎症状态[19]。欧洲动脉粥样硬化血管内超声(ATHEROREMO-IVUS)研究中的炎症和血管壁重塑合作项目研究表明，血清 PCSK9 水平与炎症斑块和坏死核心组织的绝对体积有关[20]。PCSK9 可以通过调节 Ly-6Chi [21]单核细胞导致炎症细胞因子如肿瘤坏死因子-α (TNF-α)、白细胞介素-1β (IL-1β)、白细胞介素-6 (IL-6)等的过量分泌，并减少抗炎细胞因子如白细胞介素-10 (IL-10)和精氨酸酶等的分泌[22] [23] [24]；通过诱导核因子 Kappa B (NF-KB)易位从而增加促炎细胞因子 mRNA 水平和 toll 样受体 4 (TLR4)的表达[23]；还可以激活血管细胞黏附分子 1 (Vascular cell adhesion molecule-1, VCAM-1)的表达以增加单核细胞、淋巴细胞、嗜酸性粒细胞等在血管壁的黏附[25]。这些相关研究都表明了 PCSK9 促进炎症反应从而加速 AS 的进展。

3.3. PCSK9 与斑块形成

斑块形成包括脂蛋白滞留、炎症细胞募集、血管平滑肌细胞(vascular smooth muscle cell, VSMC)增殖、基质合成、钙化、泡沫细胞的形成、凋亡和坏死等一系列复杂的过程。这些过程之间存在复杂的相互作用，并且由于在斑块的发展过程中的作用各不相同，导致不可预测的进展率、不同的斑块形态和不同的临床结果[26]。PCSK9 增加巨噬细胞的清道夫受体(Scavenger receptor, SR)对 LDL 的摄取形成更多的泡沫细胞[27]；通过诱导黏附分子、趋化剂和炎症细胞因子的表达促进血管壁的炎症[28]，促使血管平滑肌细胞凋亡从而降低血管的稳定性[29]，加速动脉粥样硬化斑块的形成。一些动物实验和人体研究证实了 PCSK9 促进小鼠和人类斑块的形成[30] [31]。

3.4. PCSK9 与血栓形成

血栓形成依赖于血小板的粘附、活化和聚集[32]。血小板在止血启动和血栓形成中起着重要作用，并被认为可能是连接血栓和炎症的多功能效应细胞[33]。一方面在动物实验模型中证明 PCSK9 水平与血小板激活标志物糖蛋白IIb/IIIa (GP IIb/IIIa)和 p-选择素(P-selectin)呈正相关[34] [35] [36]；另一方面 PCSK9 已被证明可以显著增强血小板聚集和整合素 αIIbβ3 的表达[34]，并直接诱导血小板释放颗粒中的 ATP 和 p-选择素，并且在 SR 的作用下合成血栓素 A2 [35]。其次由于 PCSK9 可以导致 LDL-C 水平升高，而 LDL-C 又可以刺激血小板聚集[37]。因此 PCSK9 通过多种途径导致血小板聚集和活化，促进血栓生成。

4. PCSK9 抑制剂

目前多种 PCSK9 抑制剂已经被开发出来，其机制大致可分为 3 类：1) LDL-R 结合抑制：通过阻止 PCSK9 与 LDL-R 结合，允许更多的受体循环到细胞表面以进一步去除 LDL-C；2) PCSK9 合成抑制：在翻译水平上阻止 PCSK9 的形成，使 PCSK9 基因沉默；3) 自催化过程抑制：包括中断 PCSK9 的自催化过程，从而禁止成熟和细胞分泌[38] [39]。依洛尤单抗和阿利西尤单抗都属于单克隆抗体，通过结合 PCSK9 的相对平坦区域阻断 PCSK9 与 LDL-R 的相互作用，降低 LDL-C 水平，从而抑制 PCSK9 [4]。

依洛尤单抗(AMG-145)于 2015 年上市，用于经过饮食调脂和药物治疗无法达到 LDL-C 目标水平的患者[40]。OSLER-1 和 OSLER-2 实验以及 FOURIER 实验证实了依洛尤单抗能够有效降低 LDL-C、胆固醇、TG、apoB、Lp(a)水平，除注射部位不良反应高于安慰剂组之外，两组间在不良事件(包括新发糖尿

病和神经认知事件)方面无显著差异，而且并未观察到严重不良事件[41]。阿利西尤单抗在 ODYSSEY LONG TERM 试验以及 ODYSSEY OUTCOMES 试验中能够显著的长期降低 LDL-C 水平，且不良事件与依洛尤单抗相似[42] [43]。尽管两种药物疗效及不良事件相似，但有研究表明依洛尤单抗较阿利西尤单抗能更有效地降低 LDL-C [44]。

Inclisiran (Leqvio®)是一种基于 siRNA(小干扰 RNA)的治疗药物，由诺华公司开发，是一种合成的长效 siRNA，靶向于 PCSK9 mRNA 以阻止其表达，于 2020 年 12 月在欧盟上市，相关研究证实了其安全性和有效性[45] [46]，但该药在我国尚未被批准上市。其它的 PCSK9 抑制剂如小分子药物(small molecules)以及 PCSK9 疫苗等药物目前仍处于研发中，如果研发成功，未来可能会提供更多的治疗方案。

5. PCSK9 抑制剂在 CAS 中的应用

CAS 根据 6 个月内有无短暂性脑缺血发作和缺血性卒中发生可分为症状性(Symptomatic carotid artery stenosis)和无症状性(Asymptomatic carotid artery stenosis)。目前其主要治疗包括颈动脉内膜剥脱术(carotid endarterectomy, CEA)、颈动脉支架成形术(carotid artery stenting, CAS)以及最佳药物治疗(best medical therapy, BMT) [47]。经颈动脉支架成形术(transcarotid artery revAScularization, TCAR)由于其良好的成功率以及低卒中发生率和低颈动脉损伤率也逐渐进入了人们的视野[48]。指南推荐在 CAS 的药物治疗中使用他汀类药物以降低胆固醇和 LDL-C [13]。但是，由于他汀类药物个体差异，以及部分接受他汀类药物治疗的患者出现肌痛、抽筋甚至横纹肌溶解症等不良反应，因此在这些患者中如何选择降脂药物，以及如何强化降脂治疗是目前关注的焦点。

大量的研究证实了 PCSK9 抑制剂在在降脂、抗炎及抗血小板聚集等方面的功能。Alessandro 等人在家族性高胆固醇血症(FH)患者接受 PCSK9 抑制剂治疗 12 周后观察到炎症和血小板激活代谢物同时减少[49]。Marcin 等人观察到在在不稳定动脉粥样硬化斑块患者中，接受阿利西尤单抗治疗 3 个月后，炎症因子如 IL-6、IL-8、TNF-α 等影响动脉粥样硬化斑块稳定性的因素明显降低[50]。Nathaniel 等人观察到高胆固醇血症患者接受依洛尤单抗治疗后 Lp(a)水平显著下降[51]，还证实了 PCSK9 抑制剂具有稳定斑块等作用。Atsushi 等人在一份病例汇报中描述了 3 例拒绝接受手术的 CAS 患者，在接受阿利西尤单抗治疗 6 个月后，观察到纤维冒形成以及富含脂质坏死核的消退，首次证明了 PCSK9 抑制剂可以稳定颈动脉斑块[52]。Norman 等人在颈动脉 MRI 上观察到接受阿利西尤单抗治疗后斑块组成和新生血管的退化[53]。Matteo 等人观察到接受依洛尤单抗治疗 12 周后，颈动脉硬度和颈动脉膨胀性均有改善[54]。Nicholas 在 FOURIER 试验中观察到 PCSK9 抑制显著降低了静脉血栓栓塞(Venous thromboembolism, VTE)的风险[55]。此外，根据 FOURIER 试验中的数据显示，依洛尤单抗在亚洲人群中显著降低了 LDL-C，在降低心血管事件风险和在其它地区具有相同的安全性和有效性[56]。

虽然 PCSK9 抑制剂尚未进入国内的颈动脉狭窄指南，但是《缺血性脑卒中强化血脂管理上海专家建议》[57]以及《中国缺血性卒中和短暂性脑缺血发作二级预防指南(2022)》[58]都推荐在接受他汀治疗后 LDL-C 未达标的患者可使用 PCSK9 抑制剂，为临床治疗提供了依据。

6. 未来与展望

PCSK9 自 2003 年被发现至 2015 年 PCSK9 抑制剂获得 FDA 批准上市，越来越多的研究挖掘出 PCSK9 的多种作用机制及功能，也开发出来越来越多的 PCSK9 抑制剂，对于他汀药物部耐受的患者提供了更多的选择，使降脂治疗进入了一个新的时代。但是仍有相当数量的高危患者 LDL-C 仍未达标。目前对于 PCSK9 基因的仍处于不断研究的状态，未来可能开发出的 PCSK9 抑制剂的口服制剂或疫苗等药物，能够为高 LDL-C 患者的治疗方案提供了更有价值的补充。

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