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周细胞和内皮细胞在经皮冠状动脉介入治疗术后无复流现象中的作用机制进展

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[关键词]　周细胞；　内皮细胞；　无复流现象；　经皮冠状动脉介入治疗

[摘　要]　无复流现象常在经皮冠状动脉介入治疗术中或术后出现，是急性心肌缺血不良预后的风险因子。周细胞和内皮细胞互相调节、联系紧密，两种细胞在无复流现象的发生中有重要作用，其机制较为复杂，也是近年来的研究热点。本文就近年来周细胞和内皮细胞在经皮冠状动脉介入治疗术后无复流现象中的相关机制进展作一综述。

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The mechanisms by which pericytes and endothelial cells can participate in no reflow phenomenon after percutaneous coronary intervention

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[**KEY WORDS**]　pericytes;　endothelial cells;　no reflow phenomenon;　percutaneous coronary intervention

[**ABSTRACT**]　No reflow phenomenon that occurs after percutaneous coronary intervention is related to adverse cardiovascular events.　The mechanisms by which pericytes and endothelial cells can participate in no reflow phenomenon are vital but complicated.　This review will discuss the various aspects of the mechanisms.

冠状动脉粥样硬化性心脏病是世界范围内致死、致残的主要病因[1]。经皮冠状动脉介入治疗(percutaneous coronary intervention，PCI)是治疗冠心病的重要手段，然而在 PCI 术后即使排除了栓塞、管腔狭窄、动脉夹层、血管痉挛等减少冠状动脉血流的常见情况，仍会出现心脏得不到有效血流灌注的情况，也就是无复流现象[2]。尤其是急诊 PCI 术后，无复流现象发生率可高达 60%，成为急性心肌缺血不良预后的风险因子[3-4]。发生无复流现象的相关病理生理机制较为复杂，目前仍在不断地研究中。近年来，周细胞和内皮细胞在无复流现象发生机制中的相关研究越来越深入，现就周细胞和内皮细胞参与无复流现象相关发生机制作一综述。

1　周细胞与内皮细胞

血管内皮位于血管壁腔面，是一层由单层内皮细胞构成的完整结构，直接与血流接触，具有抗凝、

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抗炎、维持血管通畅等功能[5]。周细胞位于血管内膜的内皮层之下,包裹着内皮层,有维持内皮功能的作用[6]。过去人们认为周细胞仅存在于微血管和毛细血管中,而越来越多的研究表明,周细胞也存在于大动脉和大静脉中[7]。同时,周细胞也是一种多能干细胞,与间充质干细胞有共同的表型、相似的多向发育特征和分化潜能。周细胞的数量在不同的组织中不一样,决定了组织特异性的内皮屏障功能。在中枢神经系统和视网膜组织中,周细胞对内皮细胞的比例高达 1∶1,并参与形成血脑屏障和血视网膜屏障。在肺与皮肤组织中,这一比例为 1∶10[8]。在骨骼肌组织中,周细胞与内皮细胞的比例低至 1∶100。在心脏组织中,周细胞主要分布在冠状动脉、小动脉、小静脉的内膜以及毛细血管中,占心脏组织非肌细胞类细胞的 5%[9],与内皮细胞的比例通常为 1∶2 或 1∶3[10]。周细胞与内皮细胞联系紧密,共享一层基膜,并通过这层基膜建立细胞间联系,通过出胞和入胞的胞间转运方式交换 miRNA,组成一个相互作用的单位[11-12]。内皮细胞分泌的基质金属蛋白酶可以调节细胞外基质促进周细胞迁移[13],血小板源性生长因子 BB 和肝素结合表皮生长因子可以促使周细胞归巢并发挥稳定新生血管的作用[14-15]。周细胞分泌的血管内皮生长因子 A 与血管内皮生长因子受体 2 结合来促进内皮细胞增殖并刺激新生血管出芽和形成[16],而其分泌的转化生长因子 β 可以抑制内皮细胞的持续增殖[17]。周细胞在缺血缺氧时表达的长链非编码 RNA 可以调节周细胞的活力、增殖以及与内皮细胞的相互作用[18]。通过与内皮细胞的紧密联系,周细胞在促进新生血管形成、促进血管稳定和成熟以及维持血流灌注等方面发挥重要作用[19-21],并可以通过调节血管通透性来维持血管完整,通过调节血管紧张性影响血流动力学[22-23]。

2 内皮细胞和周细胞的收缩与无复流现象

心肌缺血时,尽快恢复缺血区的血流供应是治疗首要任务。而缺血心肌的血流灌注再次恢复,对心肌的结构和功能造成更严重的损伤,这种损伤被称为缺血再灌注损伤(ischemia reperfusion injury, IRI)[24]。这也是 PCI 术后无复流现象发生的重要原因之一。

IRI 常发生在心肌缺血持续 3 h 以上,这是因为持续的缺血缺氧造成三磷酸腺苷减少,抑制钠钾泵活性,降低钠钙交换效率,使内流钙离子增多,且限制了内质网对钙离子的吸收,造成了细胞内钙离子超载。钙离子超载一方面可导致肌纤维过度收缩,压迫血管进一步增加无复流现象的风险[25-26];另一方面,胞质钙离子升高可以激活黄嘌呤氧化酶(xanthine oxidase, XO), XO 促进活性氧簇(reactive oxygen species, ROS)产生,ROS 被缺血细胞的线粒体获取后会损伤线粒体功能[27]。受损的内皮细胞释放大量的内皮素 1,可以剂量依赖性地导致周细胞收缩[28]。周细胞可以表达收缩蛋白 α 平滑肌肌动蛋白,在控制血流方面,周细胞可以发挥像毛细血管前、后括约肌样的作用,通过收缩能力控制血流和血管口径[29]。当周细胞收缩时,微血管关闭、毛细血管收缩、毛细血管床减少,缺血缺氧区域的血流灌注难以重建[22,30-31]。受损内皮细胞释放的内皮素 1 还可促进白细胞黏附于内皮层并释放弹性蛋白酶,造成内皮进一步损伤,突出、肿胀并挤压微血管,使毛细血管管腔狭窄[32-33]。有研究将首次因急性 ST 段抬高型心肌梗死直接 PCI 的患者,根据造影影像评估心肌梗死溶栓试验(thrombolysis in myocardial infarction, TIMI)血流分级,按 TIMI 血流分级情况分组,发现 TIMI 0 级和 TIMI 1 级患者血清内皮素 1 浓度显著高于 TIMI 2 级和 TIMI 3 级的患者[34-35]。在缺血再灌注小鼠模型中,缺血引起周细胞收缩,p75 神经营养因子受体表达上调,导致心肌梗死面积增加和心肌纤维化[36-37]。应用周细胞舒张剂腺苷则可以使梗死区域的再灌注增加 30%[22]。有研究发现,应用脂联素治疗的大鼠血清内皮素 1 水平显著降低,冠状动脉无复流损伤也得到明显改善[38]。周细胞的收缩阻止血流向缺血区域灌注的现象在脑和视网膜中同样存在[39-41]。

3 周细胞和内皮细胞的减少与无复流现象

内皮细胞和周细胞都是重要的血管壁细胞,对于维持血管的通透性有着不可替代的作用。持续的缺血缺氧促进了细胞内 ROS 的产生,ROS 蓄积是诱导心脏微血管内皮细胞凋亡的关键因素[42-43]。内皮细胞分泌的一氧化氮(nitric oxide, NO)伴随内皮细胞的凋亡而减少,NO 具有血管舒张功能,并具有抗氧化的能力可阻止内皮的进一步损伤[44]。在急性 ST 段抬高型心肌梗死直接 PCI 的患者中,与 TIMI 2 级和 TIMI 3 级相比,TIMI 0 级和 TIMI 1 级的患者血清 NO 浓度显著降低[34]。

血小板源性生长因子受体 β(platelet derived growth factor receptor β, PDGFRβ)是周细胞的表面

分子标记物之一,也是影响周细胞生存的信号通路中重要一环,敲除 PDGFRβ 基因的小鼠胚胎会出现血管畸形和血管出血,敲除 PDGFRβ 基因的成年小鼠则会出现血管通透性增加、渗血以及血流灌注差[45-48]。PDGFR 和酪氨酸激酶抑制剂可以减少心脏血管周细胞的数量,引起心脏微血管功能障碍[49]。

在小鼠缺血再灌注模型中,敲除 sirtuin-3 基因和 Notch-3 基因的小鼠缺乏维持微血管完整稳定和成熟的蛋白,血管中的周细胞数量显著减少,血管完整性遭到破坏,血管内大量的中性粒细胞和血小板渗出、浸润,压迫微循环,心肌缺血后梗死面积更大,心脏功能下降更明显,死亡率更高[39,50]。

4 结 语

周细胞和内皮细胞是血管内膜的重要组成部分,两种细胞共享一层基膜,彼此互相作用,细胞间交流密切。两种细胞作为一个有机整体在无复流现象的发生中扮演重要角色,深入研究周细胞和内皮细胞在无复流现象中的作用机制,对改善 IRI 时周细胞和内皮细胞功能,进而预防 PCI 术后无复流现象的发生提供一种新的思路。

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