体表溃疡研究与治疗
Research and Treatment of Surface Ulcers

内皮祖细胞在创面修复中的血管新生机制研究进展

Advances in Researching Angiogenesis Mechanism of Endothelial Progenitor Cells in Wound Repair

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【摘要】 血管新生是创面修复过程中不可或缺的一部分，包括内皮祖细胞参与新生血管及在原有血管基础上以出芽方式新生血管两种类型，其中内皮祖细胞参与的血管新生在创面修复过程中发挥着重要作用，同时也受到多种因子的干预及抑制，可直接影响创面的愈合。为此，笔者通过检索内皮祖细胞参与血管新生机制研究的相关文献，对其进行了总结分析，旨在为创面修复的临床治疗提供参考。

【关键词】 内皮祖细胞；创面；愈合；血管新生；综述
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【文章类型】 综述

【Abstract】 Angiogenesis is an integral part of wound repair, including the endothelial progenitor cells-involved neovascularization and neovascularization by germination of the original blood vessels. Of them, the former plays an important role in the process of wound repair, and is subject to the intervention and inhibition of multiple factors, affecting directly the wound healing. Therefore, this study summarized research advances of endothelial progenitor cells-involved angiogenesis mechanism by retrieving relevant literature, with the aim of providing reference for the clinical management of wound repair.

【Key words】 Endothelial progenitor cell; Wound; Healing; Angiogenesis; Summary

机体完整性是维持人体正常生理功能的保证。皮肤作为人体最大的器官，具有预防机体内部损伤、维持机体内环境稳定等作用，因此，一旦出现皮肤缺损，尽早恢复其完整性尤为重要。然而，研究显示，皮肤缺损创面修复过程中常因炎症反应、肉芽组织新生或组织重塑阶段出现机体调节紊乱而导致其迁延不愈，治疗较为棘手。为此，笔者鉴于血管新生是创面修复过程中不可或缺的一部分，遂于本研究中对血管新生的部分机制进行了综述分析，以期为创面的临床治疗提供参考。

1 创面血管新生概述

创面血管新生分为内皮祖细胞参与新生血管与在原有血管基础上以出芽方式新生血管两种类型，其中，内皮祖细胞参与新生血管是指内皮祖细胞聚

集后分裂、分化成有功能的血管[1-2]；在原有血管基础上以出芽方式新生血管是指以血管内皮生长因子（vascular endothelial growth factor，VEGF）、转化生长因子（transforming growth factor，TGF）、成纤维细胞生长因子（fibroblast growth factor，FGF）等促使新生血管形成。创面的血管新生可为创面肉芽组织的形成提供氧气及营养物质，为创面的再生修复打下坚实的基础。因此，在慢性难愈合创面修复过程中，血管新生受限可能是其迁延不愈的病理机制之一[3-4]，通过对血管新生机制的研究探索，寻求促进创面血管新生的方法应该能够为解决创面修复问题提供重要的参考依据。另外，在原有血管基础上以出芽方式新生血管的相关报道已有较多，本文暂不重述；内皮祖细胞参与新生血管的相关研究目前尚处于基础研究阶段，本文将重点予以挖掘分析。

2 内皮祖细胞参与的血管新生

1997 年，内皮祖细胞因具有血管新生功能而被研究学者发现，并从人的外周血中分离而出[5]。后经研究发现，根据是否来源于骨髓衍生，内皮祖细胞可分为骨髓源性内皮祖细胞和非骨髓源性内皮祖细胞两种，其中尤以来源于骨髓、间质细胞等的骨髓源性内皮祖细胞最为多见，而来源于外周血、脐带血及原位组织的非骨髓源性内皮祖细胞次之[6]；根据在体外培养过程中出现的时间和功能，内皮祖细胞可分为早期内皮祖细胞和晚期内皮祖细胞两种[5]；根据细胞的表面特征，内皮祖细胞早期可分为能够表达 CD133、CD34 及血管内皮细胞生长因子受体 2（vascular endothelial growth factor receptor 2，VEGFR2）的祖细胞三种，但在后期外周血中 CD133 的表达水平逐渐降低、CD34 的表达水平始终维持稳定、VEGFR2 的表达水平逐渐增加，而且同时出现血管内皮钙粘素及血管性血友病因子的表达，凸显了新生血管的活性及能力[7]。

研究显示，内皮祖细胞诱导血管新生的过程包括动员、游走、聚集及血管新生。创面形成后，其缺氧环境可增加缺氧诱导因子（hypoxia inducible factor，HIF）的表达水平[8]，而 HIF 又可诱导 VEGF、FGF 等多种细胞生长因子的高表达[9-10]，进而激活内皮祖细胞动员的关键因子金属蛋白激酶[2,9,11]，动员内皮祖细胞向局部创面游走、聚集，最终转化为内皮细胞并形成新生血管。另外，在内皮祖细胞的动员过程中，表达水平明显升高的基质细胞衍生因子-1α（stromal cell derived factor-1α，SDF-1α）可促进内皮祖细胞自骨髓向外周血动员[12-13]。Asai J 等的研究发现，糖尿病小鼠创面应用内皮祖细胞治疗后，创面组织内的 VEGF 及碱性成纤维细胞生长因子（basic fibroblast growth factor，bFGF）的表达水平明显升高，创面肉芽组织中血管的新生速度明显加快[14]；二甲双胍可通过激活一磷酸腺苷活化蛋白激酶/内皮型一氧化氮合酶（adenosine monophosphate-activated proteinkinase/endothelial nitric oxide synthase，AMPK/eNOS）信号通路改善内皮祖细胞的血管新生功能[15]；内皮祖细胞体外培养的外分泌液可增加 VEGFA、VEGFR2、eNOS 等血管生成相关因子的表达水平，促进血管新生，加快糖尿病大鼠创面的再生修复[16]；体外培养的骨髓源性内皮祖细胞可在培养基中形成血管管道，并且在与胃内皮细胞共同培养时，内皮祖细胞镶嵌在胃内皮细胞中，形成的血管管道明显增宽[17]；将慢病毒的内皮抑制素与内皮祖细胞融合后治疗眼部疾病，内皮抑制素的表达水平明显升高，而 VEGF 的表达水平明显降低，血管新生减少[18]；天然药物提取物补骨脂查尔酮可通过调节视黄酸相关孤儿核受体 α-红细胞生成素-磷酸腺苷蛋白激酶的表达促进内皮祖细胞的分化和血管新生[19]；MEBO 可通过下调 PTEN 基因的表达水平，降低其抑制磷脂酰肌醇 3-激酶/蛋白激酶 B（PI3K/AKT）信号通路的作用，诱导 PI3K 因子活化 PIP3，进而激活并磷酸化 AKT 因子，诱导细胞 HIF-1 与 VEGF 的高表达，促进创面细胞的增殖、分化及迁移，调控血管的新生[20-24]。影响内皮祖细胞功能的相关因素见表 1。

3 小结

血管新生是创面修复过程中的永恒议题，加强创面血管新生程度可明显提高创面的愈合率，降低慢性难愈合创面的发生率。与通过药物激活 VEGF 等细胞因子的作用而促进原有血管以出芽方式新生血管相比，内皮祖细胞是通过被动员后游走、聚集于局部创面而形成新生血管的，若在后期研究过程中能够将两种方式结合起来，即通过药物调节 VEGF 等细胞因子的释放，激发创面组织以出芽方式新生血管的同时，改善内皮祖细胞的数量及功能，促进内皮祖细胞向缺血创面的聚集，理论上可明显加快血管的新生，提高创面的愈合率，有待进一步深入研究探讨。

表 1 影响内皮祖细胞功能的相关因素

Table 1 Relevant factors affecting the functions of endothelial progenitor cells

影响因素 Relevant factors	表现 Manifestation
年龄 Age	随着年龄的增长，血液循环中内皮祖细胞的数量逐渐减少[25] The quantity of endothelial progenitor cells will decrease gradually in blood circulation with age[25]
疾病 Diseases	冠状动脉粥样硬化性心脏病、慢性肾功能衰竭、糖尿病等可降低内皮祖细胞的数量[26-29] Coronary atherosclerotic heart disease, chronic renal failure, diabetes and etc. can decrease the quantity of endothelial progenitor cells[26-29]
运动 Movements	耐力训练可增加血液循环中内皮祖细胞的数量[30] Endurance training can increase the quantity of endothelial progenitor cells in blood circulation[30]
药物 Drugs	二甲双胍可改善糖尿病患者内皮祖细胞的血管新生能力，阿托伐他汀可增加血液循环中内皮祖细胞的数量[15,31-32] Metformin can improve the angiogenesis ability of endothelial progenitor cells in diabetic patients. Atorvastatin can increase the quantity of endothelial progenitor cells in blood circulation[15,31-32]
红细胞生成素 Erythropoietin	可增加血液循环中内皮祖细胞的数量[33] Can increase the quantity of endothelial progenitor cells in blood circulation[33]
丝氨酸蛋白酶抑制剂 Serine protease inhibitor	可通过 PI3K/AKT/eNOS 信号通路改善持续高血糖状态引起的内皮祖细胞功能障碍[29] Can improve the functional disorders of endothelial progenitor cells caused by sustained hyperglycemic state through the PI3K/AKT/eNOS signaling pathway[29]
人源性激肽释放酶结合蛋白 Kallistatin	人源性激肽释放酶结合蛋白表达水平过高可降低内皮祖细胞的动员水平[34] Overexpression of Kallistatin can decrease the mobilization level of endothelial progenitor cells[34]

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