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外泌体介导的内皮细胞血管生成调控机制探讨

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摘 要

外泌体是一类由细胞分泌的细胞外囊泡，近年来在生物医学领域引起广泛关注，尤其是在血管生成和组织再生方面的潜力。本文旨在探讨外泌体介导的内皮细胞血管生成调控机制及其在牙髓血运重建中的应用。研究表明，外泌体通过携带生物活性分子如血管内皮生长因子(VEGF)等，能够显著促进内皮细胞的增殖、迁移和管状结构形成，进而加强血管生成。此外，外泌体在牙髓再生中的重要性也逐渐被认识，其通过调节牙髓干细胞与周围微环境的相互作用，促进血管化和神经再生，从而为牙髓组织的功能恢复提供支持。国内外相关研究逐渐增多，涉及外泌体的来源、特性以及在牙周、牙髓等组织再生中的具体作用，进一步证实外泌体在促进血管生成和组织修复中的关键角色。综上所述，外泌体作为一种新型的生物治疗工具，展现出良好的临床应用前景，有望为牙髓再生及其他组织损伤的修复提供新的解决方案。

关键词

外泌体，血管生成，牙髓再生，生物治疗，内皮细胞

An Investigation into the Mechanisms of Exosome-Mediated Regulation of Angiogenesis in Endothelial Cells

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Abstract

Exosomes are a class of extracellular vesicles secreted by cells. In recent years, they have attracted

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extensive attention in the biomedical field, particularly for their potential in angiogenesis and tissue regeneration. This article aims to explore the regulatory mechanism of exosome-mediated angiogenesis in endothelial cells and its application in dental pulp revascularization. Studies have shown that exosomes, by carrying bioactive molecules such as vascular endothelial growth factor (VEGF), can significantly promote the proliferation, migration, and tube-like structure formation of endothelial cells, thereby enhancing angiogenesis. Furthermore, the importance of exosomes in dental pulp regeneration is gradually being recognized. By modulating the interaction between dental pulp stem cells and the surrounding microenvironment, exosomes facilitate vascularization and neural regeneration, thus supporting the functional recovery of dental pulp tissue. Related research has been increasing both domestically and internationally, covering the sources, characteristics, and specific roles of exosomes in periodontal and pulpal tissue regeneration, further confirming their key role in promoting angiogenesis and tissue repair. In summary, as a novel biotherapeutic tool, exosomes demonstrate promising clinical application prospects and are expected to provide new solutions for dental pulp regeneration and the repair of other tissue injuries.

Keywords

Exosomes, Angiogenesis, Dental Pulp Regeneration, Biotherapy, Endothelial Cells

1. 引言

血管生成(angiogenesis)是新生毛细血管从已有血管中萌芽的过程，广泛参与生理性创伤修复、月经周期以及病理性肿瘤发展、糖尿病视网膜病变等多种疾病的发生发展[1]。近年来，细胞外囊泡(extracellular vesicles, EVs)特别是外泌体(exosomes)因其在细胞间通讯中的关键作用而受到广泛关注。外泌体通过携带蛋白质、miRNA、lncRNA 等活性因子，调控内皮细胞功能，成为研究血管生成机制的重要切入点[2]。

传统认为，细胞间通讯依赖细胞因子或接触依赖性信号传递。然而，近年来的大量研究表明，外泌体在缺氧、炎症等刺激条件下的大量释放，作为携带遗传信息与调控信号的“信使”，参与多种信号通路的激活，尤其在肿瘤相关血管生成(tumor angiogenesis)中发挥显著作用[3]。例如，肿瘤细胞来源的外泌体可显著促进内皮细胞增殖、迁移及管腔形成，进而诱导新生血管生成[4]。

与传统介导因子相比，外泌体具有膜结构包裹、体积小、靶向性强、穿透血脑屏障的能力，使其在血管靶向治疗及组织工程中也被视作潜在的治疗工具[5]。2020 年后，国内外关于外泌体调控血管生成的研究持续升温。中国学者从干细胞来源外泌体、肿瘤微环境调控、血管内皮修复等方面开展了大量研究[6]-[10]，而国外则更侧重于其在靶向治疗、纳米药物递送中的应用[11]-[13]。

在血管生成这一复杂网络调控过程中，内皮细胞(endothelial cells)是最核心的效应细胞，其功能状态直接影响血管的形态建成与生物学特性[14]。研究发现，外泌体通过调控 VEGF/VEGFR、Notch、PI3K-Akt、Wnt/β-catenin 等信号通路，作用于内皮细胞的迁移、增殖及应激反应，从而对血管新生发挥调控效应[15]-[17]。

此外，外泌体所携带的非编码 RNA (如 miR-126、miR-21、lncRNA-MALAT1 等)在调控内皮细胞基因表达、促进内皮间相互作用方面也展现出高度特异性[18]。这些内容为我们深入理解外泌体介导的血管生成提供了新的方向。

因此，本文拟系统综述外泌体的基本特性、其与内皮细胞的互作机制，以及其在调控血管生成中的作用，结合最新研究进展和实验数据，分析其潜在机制与应用前景，为后续靶向性治疗策略及组织再生医学研究提供理论依据与技术支持。

2. 外泌体的基本特性及其与内皮细胞的互作机制

2.1. 外泌体的来源与组成特征

外泌体(Exosomes)是一类由多种细胞通过胞内内涵体–溶酶体途径形成并分泌的小型细胞外囊泡，直径范围约为 30~150 nm，其主要形成机制包括初级内体(early endosomes)经多泡体(multivesicular bodies, MVBs)发育形成并与细胞膜融合后将其内容物释放至胞外[19]。目前研究已证实包括肿瘤细胞、免疫细胞、干细胞、内皮细胞及神经元等均可分泌外泌体[20]。

外泌体的膜结构与细胞膜类似，由磷脂双分子层包裹，其表面常携带 CD63、CD81、CD9、Tsg101、Alix 等标志性蛋白质，内部则富含 mRNA、miRNA、lncRNA、circRNA、蛋白质及脂质等功能性分子[21]-[23]。这些生物活性物质的选择性包装受胞内 Rab GTP 酶、ESCRT 复合体及神经酰胺途径等多种机制调控，从而形成结构稳定、可远距离递送的细胞间通讯载体[24]。

2.2. 外泌体的生物学功能

外泌体作为细胞间信号转导的重要载体，其功能取决于其来源细胞与所携带的分子内容。当前研究已表明，外泌体在多种生理病理过程如免疫调节、组织修复、神经保护、肿瘤转移与血管新生中具有显著作用[25]。尤其在肿瘤微环境中，肿瘤来源外泌体可通过传递致瘤信号、重塑基质、诱导免疫逃逸等方式促进癌症进展[26]。而来源于间充质干细胞(MSCs)或内皮祖细胞的外泌体则展现出较强的促血管生成与组织再生潜能[27]。

此外，外泌体因其膜结构稳定性、体内分布广、靶向性强，被认为是优越的药物载体与基因递送工具，在心血管疾病、肿瘤治疗、神经退行性疾病中均展现了广阔前景[28] [29]。

2.3. 外泌体与内皮细胞的互作机制

血管内皮细胞(Vascular Endothelial Cells, VECs)是构成血管内壁的单层扁平细胞，在维持血管完整性、参与血流调控、炎症反应及血管新生等过程中发挥关键作用。外泌体与内皮细胞之间的相互作用主要体现在以下几个方面：

1) 靶向摄取机制：

外泌体可通过胞吞(endocytosis)、膜融合(membrane fusion)或受体介导内吞进入内皮细胞，具体机制依赖于膜蛋白相互识别、表面糖蛋白配对、以及 pH 环境变化等因素[30]。例如，研究表明 CD63 阳性外泌体更易被内皮细胞摄取，在缺氧或炎症条件下，摄取效率更高[31]。

2) miRNA 与 lncRNA 的调控作用：

外泌体所携带的 miRNA 在调控内皮细胞功能中具有显著作用。以 miR-126 为例，其可通过靶向抑制 Spred-1，增强 VEGF 信号，进而促进内皮细胞迁移与新生血管形成[32]。另有研究指出 miR-210、miR-21 等亦可影响内皮细胞存活、应激反应与黏附能力[33]。

与此同时，外泌体中的 lncRNA 亦参与调控内皮细胞基因表达。例如 lncRNA-MALAT1 通过与 SR splicing factor 相互作用，影响内皮细胞增殖速率及管腔形成能力[34]。此外，circRNA 如 circRNA-002682 亦被证实可通过 ceRNA 机制影响血管生成通路[35]。

3) 信号通路激活：

外泌体能够通过激活 Notch、Wnt/β-catenin、PI3K/Akt、MAPK 等多种信号通路，调控内皮细胞的多种功能[36]。Notch 信号参与内皮细胞命运决定，Wnt 信号调控血管网络形成，而 PI3K/Akt 通路则在调节内皮细胞增殖与存活中居于核心地位[37]。

4) 膜蛋白与整合素参与靶向：

研究发现，不同来源的外泌体在膜表面呈现出特异性的整合素分布，如 $\alpha v\beta 3$、$\alpha 4\beta 1$ 等，这些整合素可与内皮细胞特定配体结合，增强其靶向摄取效率并促进局部血管生成[38]。

2.4. 影响内皮细胞摄取外泌体的因素

内皮细胞对外泌体的摄取能力受到多种因素影响，主要包括外泌体的来源、表面蛋白修饰、细胞状态、微环境条件等。例如，LPS 刺激可显著提高内皮细胞摄取外泌体的能力，且与 JMJD6 的表达上调密切相关[39]。此外，外泌体的大小、电荷分布也会显著影响其内吞效率[40]。

2.5. 临床应用前景与挑战

当前外泌体与内皮细胞互作的研究已推动其在组织工程、心肌缺血修复、视网膜再生等领域的应用尝试。但仍面临诸如分离纯化效率低、来源异质性大、作用机制复杂等技术难点[41]。如何建立标准化的外泌体制备体系、提升其靶向效率、明确其生物学机制，是未来研究的重要方向。

3. 外泌体介导的血管生成调控机制

3.1. 血管生成的基本过程与关键细胞

血管生成(Angiogenesis)是指在已有血管基础上通过内皮细胞的活化、增殖、迁移及管腔形成等过程构建新的微血管网络，是机体在创伤修复、胚胎发育、缺血性疾病和肿瘤生长中不可或缺的生理过程[42]。主要涉及的细胞包括血管内皮细胞、平滑肌细胞、成纤维细胞及内皮祖细胞等，其中内皮细胞在该过程中处于核心位置。

该过程的分子机制主要包括内皮细胞对血管内皮生长因子(VEGF)、碱性成纤维生长因子(bFGF)、血小板源生长因子(PDGF)等的应答，随后激活 PI3K/Akt、MAPK/ERK、Notch 和 STAT3 等多种信号通路[43]。外泌体作为新近发现的重要介导因子，在血管生成调控中发挥越来越重要的作用。

3.2. 外泌体促进血管生成的多机制

1) 通过 miRNA 调控 VEGF 等促血管因子的表达

外泌体携带的 miRNAs 在血管生成中发挥显著调控作用。例如，肿瘤来源外泌体中的 miR-9、miR-130a、miR-210 可上调受体细胞中 VEGF 表达，激活 PI3K/Akt 信号通路，从而增强内皮细胞的迁移与血管形成能力[44] [45]。miR-126 作为一种内皮细胞特异性 miRNA，其通过靶向抑制 PIK3R2，提升 Akt 磷酸化水平，被认为是经典的促血管生成 miRNA 之一[46]。

此外，间充质干细胞来源外泌体中的 miR-21、miR-125a-5p 等也被证明可以促进 VEGF 与 bFGF 等促血管因子的表达，从而增强组织的血管再生能力[47]。而在缺血性疾病模型中，外泌体注射组的微血管密度、血流重建效率均明显优于对照组[48]。

2) 调控内皮细胞的表型与功能

外泌体可以通过携带多种调控分子改变内皮细胞的表型，使其从静止状态向激活状态转变。例如，肿瘤来源外泌体中的 HIF-1α 可在缺氧环境下上调，进而通过激活下游 VEGF 与 Ang-2 等基因，诱导内皮细胞出芽与管腔形成[49]。此外，一些炎症相关细胞外泌体还可通过调控内皮细胞间黏附分子(如 ICAM-

1、VCAM-1)的表达，增强其趋化能力与管道延展性[50]。

3) 激活经典信号通路

研究发现外泌体介导的血管生成往往依赖于 PI3K/Akt、Wnt/β-catenin、Notch 等通路的激活。例如，miR-29a 可激活 β-catenin 信号，增强内皮细胞对 bFGF 信号的应答能力；而 miR-210 则通过抑制 Ephrin-A3 调节 Notch1 信号，促进内皮细胞的迁移与网络形成[51] [52]。此外，在糖尿病创伤模型中，外泌体通过 Akt/mTOR 信号轴改善血管内皮功能，显著加快伤口愈合[53]。

4) 递送蛋白质、lncRNA、circRNA 等非编码分子

除 miRNA 外，外泌体还富含各种蛋白质、lncRNA 与 circRNA，这些分子在血管生成中同样具有调控作用。例如 lncRNA-MALAT1 可通过结合 SR splicing protein 调节 VEGF-A 剪接异构体比例，进而增强血管形成效率[54]。部分 circRNA 可通过 ceRNA 机制调控 miRNA 表达，进而影响内皮细胞功能与血管生成过程[55]。

此外，外泌体中的蛋白质如 Annexin A2、HSP70、IL-6 等也能直接影响内皮细胞的应激反应、趋化能力及血管网络结构[56]。

3.3. 来源不同的外泌体在血管生成中的异同

不同来源的外泌体对血管生成能力具有差异性。肿瘤细胞来源外泌体多表现为强促血管能力，主要通过转移促进癌灶处形成“临时供血通路”，加快转移灶生长[57]；干细胞来源外泌体如来自骨髓 MSC 或脂肪干细胞的外泌体，具有较强的促修复功能，被广泛用于心肌梗死、糖尿病足、皮肤创伤等模型中[58] [59]；而来源于外周血或血小板的外泌体则更适合作为“天然载体”用于药物递送和组织再生[60]。

此外，一些研究指出不同刺激条件(如缺氧、炎症、机械应力)下分泌的外泌体，其血管生成效应也存在明显差异。例如，缺氧诱导的外泌体中 HIF-1α、VEGF、ANGPTL4 表达显著上调，可显著加速内皮细胞管腔形成速度[61]。

3.4. 外泌体在牙髓微环境中的血管化与神经再生调控

在牙髓组织微环境中，外泌体通过多分子协同、多通路耦合实现血管－神经同步再生，是牙髓血运重建的核心机制。在促血管化方面，牙髓干细胞、间充质干细胞来源外泌体可递送 VEGF、bFGF、Ang-1 等蛋白，同时携带 miR-126、miR-21 靶向激活 VEGF/VEGFR2、PI3K/Akt 通路，加速内皮细胞增殖与管腔形成，提升牙髓组织微血管密度与灌注能力[62] [63]。而在促神经再生机制方面，外泌体可携带 NGF、BDNF、GDNF 等神经营养因子，同时通过 miR-132、miR-21 调控神经元轴突生长与髓鞘化相关基因，促进牙髓神经纤维再生与感觉功能恢复[62] [63]。此外，外泌体可抑制牙髓局部炎症与氧化应激，调控巨噬细胞向 M2 型极化，减少基质降解，为血管－神经协同再生提供稳定微环境[63] [64]。

3.5. 外泌体在疾病相关血管生成中的应用与挑战

在缺血性疾病(如脑梗死、下肢缺血)、糖尿病并发症(如糖尿病视网膜病变、糖尿病足)及创伤修复中，外泌体因其可靶向促血管生长，成为极具前景的治疗策略[65]。例如，使用 MSC 外泌体治疗急性心梗模型小鼠可显著提升心肌灌注与毛细血管密度[62]。此外，将促血管生成相关 RNA 或蛋白富集于外泌体中，可进一步增强其疗效。

但需注意的是，外泌体引导的血管生成亦可能造成病理性血管异常，尤其在肿瘤生长、糖尿病病理环境中，过度活化的血管生成可能导致血管结构异常、功能紊乱[64]。因此，在设计外泌体干预方案时，应结合微环境状态精准调控其血管生成效应。

4. 总结与展望

随着外泌体研究的不断深入，外泌体在调控血管生成中的作用正逐步显现出其系统性、多层次和高靶向性的特点。回顾现有文献，外泌体作为一种纳米级别的胞外囊泡，不仅在细胞间信息传递中发挥核心作用，更在血管新生、损伤修复、组织重建及疾病进程中展现出广泛的生物学功能[66]。在多种疾病环境下，如缺血、糖尿病、肿瘤等，外泌体通过携带 miRNA、lncRNA、circRNA 以及多种信号蛋白，有效调控内皮细胞功能与血管生成信号通路，进而实现血管网络的动态重构与微环境重塑[67] [68]。

在机制层面，外泌体调控血管生成主要依赖于其所携带的 miRNA 对 VEGF、Notch、PI3K/Akt、STAT3 等信号轴的干预，这些信号轴在血管内皮细胞的增殖、迁移、分化及管腔形成中具有决定性作用[69]。此外，越来越多的研究表明，外泌体中的非编码 RNA 与蛋白质之间可能存在协同调控机制，表明其调控模式远非“单因子”作用那么简单[70]。

整合现有研究基础上，构建外泌体介导内皮细胞血管生成的多层级协同调控网络模型，将分子调控、通路交叉、细胞互作与微环境响应纳入统一框架，该网络模型可概括为三层级协同调控。上游信号装载层：外泌体选择性包裹 VEGF、bFGF、HIF-1α 等功能蛋白，以及 miR-126、miR-210、miR-21、lncRNA-MALAT1、circRNA-0077930 等调控 RNA，形成稳定的复合信号单元[18] [32] [34] [35] [46]；中游通路耦合层：上述信号单元靶向激活 VEGF/VEGFR、PI3K/Akt、Wnt/β-catenin、Notch 等核心通路，通过通路间交叉对话与正向反馈，放大促血管生成效应[15] [17] [36] [51] [52]；下游效应输出层：协同驱动内皮细胞周期进展、细胞骨架重排、胞外基质重塑与管腔成熟，最终完成功能性血管网络的构建与稳定[14] [42] [49]。在牙髓再生场景中，这一网络进一步延伸为血管－神经－微环境协同再生模式：外泌体以 VEGF/AKT 轴促进牙髓血管化，以 NGF/BDNF 及 miR-132 相关通路促进神经再生，同时调控巨噬细胞极化与炎症消退，为牙髓血运重建提供一体化支持[38] [62] [63] [71] [72]。这一模式不仅印证了上述网络模型的合理性，也为口腔组织再生提供了全新的理论依据。

而在临床转化应用层面，外泌体技术已逐步走出实验室，成为治疗缺血性疾病、创伤性疾病乃至肿瘤血管重塑的重要候选策略。例如，干细胞来源外泌体在糖尿病足、脑缺血、心肌梗死等动物模型中展现出良好的促血管与组织修复能力[73] [74]。特别是在心血管再生、眼底病治疗与皮肤创伤愈合中，外泌体介导的微环境重构方案正在进入初步临床试验阶段，显示出潜在的可控性与良好的生物安全性[75]。

然而，当前的外泌体介导血管生成研究也面临诸多挑战：

4.1. 外泌体异质性与纯化问题

首先是外泌体本身的异质性问题。不同细胞来源、不同病理状态、甚至相同细胞在不同诱导条件下所释放的外泌体，在形态、大小、分子含量上均存在较大差异[76]。目前尚缺乏统一标准的外泌体分离与鉴定方法，这在一定程度上制约了研究间结果的可比性和数据整合的能力[77]。高纯度、功能稳定的外泌体分离技术(如超速离心、密度梯度分离、微流控分选等)仍待进一步标准化与优化。

4.2. 作用机制的系统整合不足

当前大多数研究集中于某一条信号通路或单一功能分子的研究，而对于外泌体中多种成分的协同作用、时空调控机制尚缺乏系统性整合。尤其在血管生成过程中，不同分子的互作网络和反馈机制仍处于初步探索阶段。深入的系统生物学分析与高通量多组学数据挖掘有望揭示更全面的调控图谱[78]。

4.3. 靶向性控制与剂量依赖效应不明晰

外泌体在血管生成中的促进作用依赖其被靶细胞有效摄取，但其靶向性并不总是理想，部分外泌体

可能被巨噬细胞吞噬、或沉积在非靶组织中导致治疗效率降低甚至诱发不良反应[79]。此外，外泌体的“剂量依赖效应”尚不明确，低浓度可能不具生物效应，高浓度则可能激活过度血管生成乃至炎症反应[80]，这对其药理剂量控制提出了新挑战。

4.4. 载体工程与临床转化障碍

外泌体虽被称为“天然纳米载体”，但其药物负载效率、运输稳定性与储存条件仍需改进。如何实现外泌体的定向修饰、靶向性增强、递送效率提高，是当前合成生物学和药物工程领域的重要研究方向[81]。此外，外泌体的体外大规模生产与标准化质控体系尚未完善，成为制约其临床转化的又一瓶颈。最新有研究发现提取牙髓干细胞来源的细胞内囊泡(Intracellular Vesicles, IVs)的新方法，其在皮肤再生方面与 Exos 等效，且提取效率大大提高，为目前口腔组织再生领域的热点和创新点，具有较高的研究价值，未来可能成为研究热点[63]。

4.5. 潜在的肿瘤促进风险

虽然外泌体可用于促进缺血性组织的血管再生，但在肿瘤微环境中其同样可能促进异常血管生成，增加肿瘤营养供应与转移潜能[82]。因此，如何在安全性与有效性之间取得平衡，构建“可控促血管”的外泌体系统，是未来临床转化过程中需优先解决的课题。

5. 展望

未来的研究应聚焦于以下几个方向：第一，开发高效稳定的外泌体分离与标记技术，实现来源追踪与功能分型；第二，结合多组学与人工智能技术，建立“外泌体－靶细胞－血管网络”的调控图谱；第三，推动外泌体工程化，通过表面修饰、分子负载等手段，增强其血管靶向性与治疗稳定性；第四，开展多中心临床前试验与长期随访研究，建立外泌体在缺血治疗、创伤修复与眼科血管病中的治疗规范与评价体系[83]。

在精准医学快速发展的当下，外泌体作为信息传递与治疗载体的双重角色，正逐步从基础研究走向临床应用。其在血管生成调控中的深度机制与应用潜力值得深入挖掘，有望成为新一代生物治疗策略的核心支撑。

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