

## 间充质干细胞凋亡囊泡在皮肤损伤修复中的研究进展

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**摘要:**皮肤损伤修复是人体内一个复杂的生物学过程, 涉及炎症反应、细胞增殖和分化、细胞迁移、血管生成和细胞外基质重塑等多个方面的发展变化。近年来, 间充质干细胞(mesenchymal stem cells, MSCs)已被证明在皮肤损伤修复过程中具有显著的促进作用, 但是干细胞移植入体内后, 在复杂的宿主环境中很快会发生凋亡, 形成包含细胞成分的凋亡囊泡(apoptotic extracellular vesicles, apoEVs), 并能够保留干细胞促进组织修复再生的功能。本文对间充质干细胞凋亡囊泡(apoptotic extracellular vesicles derived from mesenchymal stem cells, MSC-apoEVs)的产生、生物学特性以及其在促进皮肤损伤修复的研究现状进行综述, 总结遇到的瓶颈问题, 并提出未来的研究方向。

**关键词:**间充质干细胞凋亡囊泡; 无细胞治疗; 皮肤损伤修复; 组织再生

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### Research advances in apoptotic extracellular vesicles derived from mesenchymal stem cells in skin wound repair

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**Abstract:** Cutaneous wound repair is a complex biological process which involves the development and changes of multiple aspects such as inflammatory response, cell proliferation and differentiation, cell migration, angiogenesis, and extracellular matrix remodeling. In recent years, mesenchymal stem cells (MSCs) have a significant promoting effect on skin wound repair. However, after being transplanted into the host, stem cells will undergo apoptosis in a short time due to the unfamiliar microenvironments, producing a large number of endogenous apoptotic extracellular vesicles (apoEVs). ApoEVs contain cellular components including microRNAs, mRNAs, DNAs, proteins, and lipids, and also inherit the function of MSCs in promoting tissue repair and regeneration. This article reviews the biogenesis and biological characteristics of apoptotic extracellular vesicles derived from mesenchymal stem cells (MSC-apoEVs), with emphasis on the current research status of apoEVs contribute to cutaneous wound repair, and summarizes the problems encountered and proposes future research directions.

**Keywords:** apoptotic extracellular vesicles; cutaneous wound repair; cell-free therapy; tissue regeneration

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间充质干细胞凋亡囊泡(mesenchymal stem cell-derived apoptotic extracellular vesicles, MSC-apoEVs)是近年来备受关注的一类具有重要治疗潜力的细胞外囊泡。研究表明, MSC-apoEVs在多种疾病治疗中展现出显著优势, 特别是在炎症性疾病和组织再生领域。与间充质干细胞本身相比,

MSC-apoEVs具有更低的免疫原性、更强的组织穿透能力以及更稳定的治疗效果。近年来, 许多研究证明MSC-apoEVs在皮肤损伤修复领域也有优异的性能, 为皮肤损伤修复提供了无细胞治疗新策略。本文对间充质干细胞凋亡囊泡的产生、生物学特性以及其在促进皮肤损伤修复的研究现状进行综述, 以期明确未来的研究方向。

### 1 皮肤损伤修复概述

皮肤是人体最大的器官, 是帮助人体抵御外

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界刺激的第一道防线。正常情况下,皮肤具有一定的自我修复能力,其修复的基本过程包括止血、炎症、增殖及重塑4个阶段。止血阶段在损伤后立即启动,通过血管收缩、血小板活化和凝血级联反应迅速形成纤维蛋白凝块,防止进一步失血,并释放生长因子为后续修复提供信号<sup>[1]</sup>。随后进入炎症阶段,中性粒细胞率先浸润伤口,清除病原体和坏死组织<sup>[2]</sup>,随后巨噬细胞成为主导,通过吞噬作用及分泌促炎因子(如IL-1、TNF- $\alpha$ )和促修复因子(如VEGF、FGF)协调组织清理与再生<sup>[3]</sup>。淋巴细胞作为最后到达的免疫细胞群体,通过细胞间通讯调节巨噬细胞表型转换,分泌的IL-4、IL-10和TGF- $\beta$ 则促进炎症消退和组织修复<sup>[4]</sup>。进入增殖阶段后,成纤维细胞大量增殖并分泌胶原和纤连蛋白,形成富含新生血管的肉芽组织,为伤口提供临时基质<sup>[5]</sup>。同时,角质形成细胞迁移覆盖创面,完成上皮化<sup>[6]</sup>。最后,重塑阶段则可持续数月甚至数年,通过胶原交联和基质金属蛋白酶(matrix metalloproteinase, MMPs)介导的降解与再生平衡,逐步提高组织强度并减少瘢痕体积。

皮肤修复过程依赖细胞、细胞外基质及生长因子的密切协作,任何环节异常均可导致慢性伤口或病理性瘢痕。在这4个阶段中,从初始炎症期到增殖期的转变是决定伤口愈合结果的关键调控点<sup>[7]</sup>。过度或持续的炎症反应(如糖尿病伤口)会通过大量活性氧和促炎因子加剧组织损伤,而炎症不足则易导致病原体清除障碍及组织再生信号启动失败,继发感染或愈合障碍<sup>[8]</sup>。研究表明,间充质干细胞来源的凋亡囊泡在皮肤损伤修复的各个阶段均发挥重要作用,可以通过直接激活凝血途径、调节炎症阶段的免疫反应、促进增殖阶段的组织与血管新生、改善重塑阶段的胶原排列与基质重塑等过程促进皮肤组织的修复。尤其在糖尿病足溃疡、深度烧伤等难愈性创面中, MSC-apoEVs 被证实能突破高糖微环境障碍,显著加速上皮化和肉芽组织形成,为细胞治疗提供高效替代方案<sup>[9-13]</sup>。

## 2 凋亡囊泡的形成和生物学特性

细胞凋亡即细胞的程序性死亡,是多种信号通路通过激活特定的蛋白酶来执行细胞分解的过程。与细胞坏死不同,它是一个有序、主动的过程,在生理学中起着关键作用,除了正常的细胞更新和稳态维持外,也是发育和免疫调节的核心

环节<sup>[14]</sup>。

当体内的细胞受到损伤或不再需要时,凋亡的发生可以清除这些细胞,防止它们对机体造成损伤。凋亡细胞经历一系列生物事件,包括起泡、细胞体积收缩、细胞核断裂、染色质浓缩和染色体DNA断裂<sup>[15]</sup>。在凋亡晚期,细胞膜破裂,形成凋亡细胞外囊泡(apoptotic extracellular vesicles, apoEVs),其中包含来源细胞成分,如microRNA、mRNA、DNA、蛋白质和脂质<sup>[16]</sup>。但是这些apoEVs不仅仅是细胞碎片或凋亡副产物,它通过表达“find-me”或“eat-me”信号,被邻近的吞噬细胞识别并清除,可以有效防止继发性坏死和避免炎症反应的发生<sup>[17]</sup>。

凋亡细胞分解成凋亡小体(apoptotic bodies, apoBDs)的过程涉及3个主要的形态学步骤。第一步是质膜起泡,即在凋亡细胞表面形成大的圆形凸起,该阶段的关键调节因子为caspase 3,它激活Rho相关激酶1(ROCK1),导致肌球蛋白轻链磷酸化,并触发肌动蛋白收缩,从而驱动质膜起泡<sup>[18]</sup>。第二步是细胞凋亡膜突起的形成,是指一些细胞在质膜起泡后,会继续产生长的、串珠状的凋亡膜突起,这些突起由连成一排的多个apoBDs组成<sup>[19]</sup>。与该过程相关的分子和生物过程包括Pannexin 1(PANX1)通道、Plexin B2受体(PlexB2)、细胞骨架网络和囊泡运输<sup>[20]</sup>。第三步是分解过程,即凋亡细胞的膜突起裂解为离散的apoBDs。相较于apoBDs,凋亡微囊泡(apoptotic microvesicles, apoMVs)和凋亡外泌体(exosome-like apoEVs, apoExos)的形成机制不同。凋亡过程会改变细胞膜的稳定性和流动性,在凋亡早期阶段,质膜的脂质双层结构受到凋亡信号(如细胞内钙离子浓度升高或酶活性改变)的扰动,导致质膜局部向外出芽,形成apoMVs并释放到细胞外<sup>[21]</sup>。而apoExos则是通过凋亡细胞内产生的多囊泡体(multivesicular bodies, MVBs)与质膜融合后释放产生的,但通过比较活细胞释放的传统外泌体和apoExos的蛋白质表达,发现apoExos除了表达传统外泌体表面标记物CD63、LAMP1、HSP70以外,同时高表达S1P、S1PR1、S1PR3等表面标记物。这说明apoExos的产生可能不依赖于转运途径所需的内体分选转运复合体(endosomal sorting complex required for transport, ESCRT),而是依赖于S1P-S1PR信号传导<sup>[22]</sup>。此外,caspase-3的激活对apoExos的释放也十分重要<sup>[23-24]</sup>。

与传统细胞外囊泡相似, apoEVs作为凋亡细胞的片段, 包含各种细胞成分, 包括膜蛋白或细胞内蛋白、细胞因子、RNA、DNA和细胞质基质, 因此可以作为载体, 运输生物活性分子, 介导细胞间通讯<sup>[25]</sup>。此外, 有研究表明apoEVs具有显著的免疫调节作用, 可介导自身免疫<sup>[26]</sup>、抗肿瘤免疫<sup>[27]</sup>、抗微生物免疫<sup>[28]</sup>、免疫细胞反应的调节<sup>[29]</sup>和炎症反应的调节<sup>[30]</sup>。例如, 凋亡中性粒细胞的apoEVs通过抑制辅助T细胞的活性促进炎症的消退<sup>[31]</sup>。值得注意的是, apoEVs介导的免疫调节作用也在apoEVs介导的组织再生促进中发挥关键作用<sup>[32]</sup>。

### 3 间充质干细胞凋亡囊泡对皮肤损伤修复的作用与机制

在过去的几十年里, 间充质干细胞(mesenchymal stem cells, MSCs)已成功应用于多种疾病的治疗, 其中, 在促进皮肤创面修复领域也取得了重大的成果<sup>[33-34]</sup>。近期一些研究发现, 大多数间充质干细胞在恶劣的宿主环境中(如炎症环境下)寿命短, 并发生快速凋亡, 但细胞凋亡后对于某些疾病的治疗作用仍然存在, 这种治疗机制被认为与MSCs产生的大量凋亡囊泡(MSC-apoEVs)有关<sup>[35]</sup>。

皮肤发生损伤后会立即进入止血阶段, 而MSC-apoEVs表面高表达组织因子(tissue factor, TF)和磷脂酰丝氨酸(phosphatidylserine, PS)。TF是凝血级联反应的关键启动因子, 而PS提供了促凝磷脂表面, 可直接激活凝血途径, 加速纤维蛋白形成, 从而快速止血<sup>[13]</sup>。这种促凝作用不依赖于血细胞或循环中的促凝因子, 是其独立止血能力的核心机制。此外, MSC-apoEVs在促进止血的同时, 还能通过携带的生物活性分子(如miRNA、蛋白质)启动后续再生程序, 调控后期修复阶段。例如, 在5-氟尿嘧啶诱导的皮肤损伤模型中, 脐带间充质干细胞(umbilical cord mesenchymal stem cells, UCMSCs)来源的apoEVs显著加速伤口愈合, 其作用贯穿止血、炎症、增殖和重塑全程<sup>[36]</sup>。其促凝活性与促血管生成、抗炎等再生功能协同, 形成“止血-再生”一体化修复模式<sup>[37]</sup>。

在皮肤损伤修复的炎症阶段, MSC-apoEVs通过调节免疫细胞功能和炎症因子的表达与释放, 影响局部免疫反应, 加快损伤修复的进程<sup>[38]</sup>。有研究者在兔皮肤伤口愈合模型中观察到, 移植进

入兔体内的骨髓间充质干细胞(bone marrow mesenchymal stem cells, BMMSCs)在短时间内大量凋亡。同时, 他们发现移植的BMMSCs通过释放apoBDs可以将巨噬细胞转化为抗炎表型, 导致抗炎细胞因子和生长因子分泌增加, 刺激成纤维细胞、上皮细胞、内皮细胞等增殖和分化, 以促进皮肤组织修复和再生<sup>[39]</sup>。类似的研究显示, 脂肪间充质干细胞(adipose-derived mesenchymal stem cells, ADSCs)来源的apoEVs可以降低M1型巨噬细胞、增加M2型巨噬细胞相关基因表达水平, 促进巨噬细胞由M1向M2表型的转变, 从而缓解慢性炎症状态(如糖尿病伤口), 改善组织微环境, 并提出apoEVs比apoBDs具有更加显著的功能<sup>[40]</sup>。进一步研究发现, ADSC-apoEVs通过由miR-20a-5p介导的JAK-STAT信号通路有效实现对巨噬细胞炎症表型的调控, 诱导巨噬细胞向M2极化, 从而促进皮肤伤口愈合<sup>[41]</sup>。

进入增殖阶段后, 一方面, MSC-apoEVs通过传递生物活性物质, 激活与细胞增殖或分化的相关通路, 加速皮肤形成相关细胞的增殖与迁移, 直接参与组织再生<sup>[42]</sup>。另一方面, MSC-apoEVs可以携带促血管生成因子(如VEGF, bFGF)激活内皮细胞, 刺激血管新生以增加微血管密度, 改善伤口局部血供, 间接支持细胞的增殖。同时还可以通过免疫调节作用减轻炎症对增殖期细胞的损伤, 为组织再生创造有利的微环境。例如, 胚胎干细胞(Embryonic stem cell, ESCs)来源的apoEVs可以通过SOX2/Hippo信号通路更好地调节小鼠皮肤MSCs的干性, 促进其增殖和成骨分化, 抑制成脂分化, 且促进皮肤愈合的效果优于UCMSC-apoEVs<sup>[43]</sup>。而另一项研究发现ADSC-apoEVs可以被成纤维细胞和内皮细胞吞噬, 显著增强其增殖和迁移能力。同时还可促进成纤维细胞的成脂分化, 抑制成纤维细胞的纤维向分化, 从而加速皮肤伤口愈合, 提高肉芽组织的质量, 减少疤痕面积<sup>[44]</sup>。

在重塑阶段, MSC-apoEVs主要通过增强胶原合成与沉积、调控MMP活性, 改变基质中不同胶原的比例及排列, 协调细胞外基质(extracellular matrix, ECM)重塑平衡, 促进高质量的皮肤损伤修复。研究显示, ADSC-apoEVs能通过调节成纤维细胞增殖和功能来促进组织修复。而成纤维细胞是ECM合成的关键细胞, ADSC-apoEVs可减少异常ECM沉积, 从而提高愈合质量和减少瘢

痕<sup>[40]</sup>。同时,氧化应激的MSCs产生的凋亡囊泡(Oxi-apoEVs)通过miR-210-3p诱导的Akt信号途径靶向内皮细胞以促进血管形成,同时Oxi-apoEVs也可改善Col I/Col III的沉积,减少瘢痕的形成<sup>[45]</sup>。

此外,与正常机体环境下的皮肤损伤相比,MSC-apoEVs在治疗糖尿病性难愈创面中显示出良好的治疗效果。糖尿病创面表现为慢性持续性炎症,炎症因子水平显著升高且难以消退,血管内皮功能受损和血管新生减少,导致局部缺血缺氧,创面愈合困难<sup>[46]</sup>。MSC-apoEVs可以同时调控炎症、血管生成、纤维化修复等关键环节,通过靶向炎症调控、增强血管生成、抵抗高糖毒性的多靶点协同作用来促进糖尿病创面的愈合<sup>[47]</sup>。

#### 4 凋亡囊泡的应用和安全性问题

凋亡囊泡基于其再生、免疫调节和信号传导能力,在多个领域展现出潜在应用价值,包括促进骨再生与组织修复<sup>[48]</sup>、治疗免疫性及炎症性疾病<sup>[49]</sup>、加快神经功能恢复等<sup>[50]</sup>。在促进皮肤损伤修复方面,MSC-apoEVs同样显示出显著的治疗潜力,这主要得益于其免疫调节和组织再生功能。但将其转化且应用于临床仍面临着一些问题,首先,MSC-apoEVs异质性的问题尤为突出<sup>[21,51]</sup>。例如,尺寸会影响apoEVs穿越生物屏障的能力,表面分子会影响其靶向和摄取能力,含量则会影响其在调节炎症和促进再生方面的作用等,这种形态及功能的异质性都需要进行更多的对照试验进行进一步的探索。其次,凋亡囊泡的大规模生产和应用面临挑战,包括细胞扩增需求、细胞核物质残留风险和提取难度。例如,获取足够量的凋亡囊泡需要进行细胞的大量扩增,但可能引入核物质污染,影响其安全性和功效<sup>[52]</sup>。此外,尽管已有研究证实了MSC-apoEVs对参与皮肤损伤修复的炎症和增殖阶段的关键细胞,如巨噬细胞、内皮细胞和成纤维细胞,在体外具有积极作用,能够加快皮肤损伤修复的过程,但其中起到关键作用的具体成分和信号途径尚不清楚,MSC-apoEVs调节各种细胞的分子机制需要进一步探索。

#### 5 结语和展望

综上所述,MSC-apoEVs作为细胞凋亡过程中释放的关键细胞外囊泡组分,在皮肤损伤修复领域展现出巨大的应用潜力。研究已证实,MSC-apoEVs能够在皮肤损伤修复的不同阶段发挥作用,

有效促进损伤处愈合,并在难愈性创面如糖尿病皮肤损伤模型中,显示出比单纯MSC移植更具优势的治疗前景。目前,MSC-apoEVs的研究仍面临一些挑战,如大规模标准化制备及操作程序的优化尚需完善,其长期的临床安全性与疗效也需要通过更深入的研究和临床试验来全面验证。然而,鉴于其在炎症调控、促血管生成、促进细胞增殖迁移和基质重塑等方面的多功能效应,MSC-apoEVs无疑为开发新型、高效的无细胞皮肤修复治疗策略提供了重要的理论基础和实验依据。未来研究应着重于优化apoEVs的提取、纯化及储存工艺,深入解析其在特定微环境(如糖尿病伤口)中的具体作用靶点和分子机制,并积极推动其向临床应用转化,最终造福于皮肤损伤患者。

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#### 参考文献

- 1 Reish RG, Eriksson E. Scars: a review of emerging and currently available therapies [J]. *Plast Reconstr Surg*, 2008, 122 (4): 1068-1078.
- 2 Xu Y, Cohen E, Johnson CN, et al. Repeated stress to the skin amplifies neutrophil infiltration in a keratin 17- and PKC $\alpha$ -dependent manner [J]. *PLoS Biol*, 2024, 22 (8): e3002779.
- 3 Sousa AB, Águas AP, Barbosa MA, et al. Immunomodulatory biomaterial-based wound dressings advance the healing of chronic wounds via regulating macrophage behavior [J]. *Regen Biomater*, 2022, 9: rbac065.
- 4 Julier Z, Park AJ, Briquez PS, et al. Promoting tissue regeneration by modulating the immune system [J]. *Acta Biomater*, 2017, 53: 13-28.
- 5 Gharbia FZ, Abouhashem AS, Moqidem YA, et al. Adult skin fibroblast state change in murine wound healing [J]. *Sci Rep*, 2023, 13 (1): 886.
- 6 Dhandhi S, Goel B, Chauhan S, et al. The interplay of skin architecture and cellular dynamics in wound healing: Insights and innovations in care strategies [J]. *Tissue Cell*, 2024, 91: 102578.
- 7 Kim H, Wang SY, Kwak G, et al. Exosome-guided phenotypic switch of M1 to M2 macrophages for cutaneous wound healing [J]. *Adv Sci (Weinh)*, 2019, 6 (20): 1900513.
- 8 Liu Y, Wang L, Kikui T, et al. Mesenchymal stem cell-based tissue regeneration is governed by recipient T lymphocytes via IFN- $\gamma$  and TNF- $\alpha$  [J]. *Nat Med*, 2011, 17 (12): 1594-1601.
- 9 Zhang WY, Ling Y, Sun Y, et al. Extracellular vesicles derived from mesenchymal stem cells promote wound healing and skin regeneration by modulating multiple cellular changes: a brief review [J]. *Genes*, 2023, 14 (8): 1516.
- 10 Zhu YF, Chen XH, Liao YJ. Mesenchymal stem cells-derived apoptotic extracellular vesicles (ApoEVs): mechanism and application in tissue regeneration [J]. *Stem Cells*, 2023, 41

- (9): 837-849.
- 11 Ding YH, Song MS, Huang R, et al. Adipose-mesenchymal stem cell-derived extracellular vesicles enhance angiogenesis and skin wound healing via bFGF-mediated VEGF expression [J]. *Cell Tissue Bank*, 2024, 26 (1): 2.
  - 12 Yan KX, Han L, Xu SW, et al. The effect of age on the regenerative potential of adipose stem-cell-derived apoptotic extracellular vesicles in rat skin wound healing [J]. *Int J Med Sci*, 2024, 21 (8): 1529-1540.
  - 13 Jiang YX, Hao M, Jiang FL, et al. Lyophilized apoptotic vesicle-encapsulated adhesive hydrogel sponge as a rapid hemostat for traumatic hemorrhage in coagulopathy [J]. *J Nanobiotechnology*, 2023, 21 (1): 407.
  - 14 Bock FJ, Riley JS. When cell death goes wrong: inflammatory outcomes of failed apoptosis and mitotic cell death [J]. *Cell Death Differ*, 2023, 30 (2): 293-303.
  - 15 Atkin-Smith GK, Poon IKH. Disassembly of the dying: mechanisms and functions [J]. *Trends Cell Biol*, 2017, 27 (2): 151-162.
  - 16 Atkin-Smith GK, Tixeira R, Paone S, et al. A novel mechanism of generating extracellular vesicles during apoptosis via a beads-on-a-string membrane structure [J]. *Nat Commun*, 2015, 6: 7439.
  - 17 Xiao LJ, Zhang LQ, Guo CL, et al. "Find Me" and "Eat Me" signals: tools to drive phagocytic processes for modulating antitumor immunity [J]. *Cancer Commun*, 2024, 44 (7): 791-832.
  - 18 Sebbagh M, Renvoizé C, Hamelin J, et al. Caspase-3-mediated cleavage of ROCK I induces MLC phosphorylation and apoptotic membrane blebbing [J]. *Nat Cell Biol*, 2001, 3 (4): 346-352.
  - 19 Caruso S, Atkin-Smith GK, Baxter AA, et al. Defining the role of cytoskeletal components in the formation of apoptodia and apoptotic bodies during apoptosis [J]. *Apoptosis*, 2019, 24 (11/12): 862-877.
  - 20 Santavanond JP, Rutter SF, Atkin-Smith GK, et al. Apoptotic bodies: mechanism of formation, isolation and functional relevance [J]. *Subcell Biochem*, 2021, 97: 61-88.
  - 21 Zou XH, Lei Q, Luo XH, et al. Advances in biological functions and applications of apoptotic vesicles [J]. *Cell Commun Signal*, 2023, 21 (1): 260.
  - 22 Park SJ, Kim JM, Kim J, et al. Molecular mechanisms of biogenesis of apoptotic exosome-like vesicles and their roles as damage-associated molecular patterns [J]. *Proc Natl Acad Sci USA*, 2018, 115 (50): E11721-E11730.
  - 23 Brodeur A, Migneault F, Lanoie M, et al. Apoptotic exosome-like vesicles transfer specific and functional mRNAs to endothelial cells by phosphatidylserine-dependent macropinocytosis [J]. *Cell Death Dis*, 2023, 14 (7): 449.
  - 24 Zhu CC, Fan FS, Li CY, et al. Caspase-3 promotes oncogene-induced malignant transformation via EndoG-dependent Src-STAT3 phosphorylation [J]. *Cell Death Dis*, 2024, 15 (7): 486.
  - 25 Liu DW, Kou XX, Chen C, et al. Circulating apoptotic bodies maintain mesenchymal stem cell homeostasis and ameliorate osteopenia via transferring multiple cellular factors [J]. *Cell Res*, 2018, 28 (9): 918-933.
  - 26 Khalilzad MA, Mohammadi J, Amirsadat S, et al. Therapeutic potential of apoptotic vesicles in modulating inflammation, immune responses, and tissue regeneration [J]. *J Nanobiotechnology*, 2025, 23 (1): 260.
  - 27 He XT, Ma YY, Wen YS, et al. Tumor-derived apoptotic extracellular vesicle-mediated intercellular communication promotes metastasis and stemness of lung adenocarcinoma [J]. *Bioact Mater*, 2024, 36: 238-255.
  - 28 Li Y, Qu GL, Dou G, et al. Engineered extracellular vesicles driven by erythrocytes ameliorate bacterial sepsis by iron recycling, toxin clearing and inflammation regulation [J]. *Adv Sci (Weinh)*, 2024, 11 (13): e2306884.
  - 29 Ye QY, Xu HK, Liu SY, et al. Apoptotic extracellular vesicles alleviate Pg-LPS induced inflammatory responses of macrophages via AMPK/SIRT1/NF- $\kappa$ B pathway and inhibit osteoclast formation [J]. *J Periodontol*, 2022, 93 (11): 1738-1751.
  - 30 Wu H, Fan H, Shou ZX, et al. Extracellular vesicles containing miR-146a attenuate experimental colitis by targeting TRAF6 and IRAK1 [J]. *Int Immunopharmacol*, 2019, 68: 204-212.
  - 31 Shen GF, Krienke S, Schiller P, et al. Microvesicles released by apoptotic human neutrophils suppress proliferation and IL-2/IL-2 receptor expression of resting T helper cells [J]. *Eur J Immunol*, 2017, 47 (5): 900-910.
  - 32 Xie M, Xiong W, She Z, et al. Immunoregulatory effects of stem cell-derived extracellular vesicles on immune cells [J]. *Front Immunol*, 2020, 11: 13.
  - 33 Guillamat-Prats R. The role of MSC in wound healing, scarring and regeneration [J]. *Cells*, 2021, 10 (7): 1729.
  - 34 Jo H, Brito S, Kwak BM, et al. Applications of mesenchymal stem cells in skin regeneration and rejuvenation [J]. *Int J Mol Sci*, 2021, 22 (5): 2410.
  - 35 Pang SHM, D' Rozario J, Mendonca S, et al. Mesenchymal stromal cell apoptosis is required for their therapeutic function [J]. *Nat Commun*, 2021, 12 (1): 6495.
  - 36 Lai HB, Lin L, Pan YR, et al. Umbilical cord mesenchymal stem cell-derived apoptotic extracellular vesicles improve 5-FU-induced delayed wound healing by mitochondrial transfer [J]. *Pharmaceutics*, 2025, 17 (4): 453.
  - 37 Yu L, Dou G, Kuang HJ, et al. Apoptotic extracellular vesicles induced endothelial cell-mediated autologous stem cell recruitment dominates allogeneic stem cell therapeutic mechanism for bone repair [J]. *ACS Nano*, 2024, 18 (12): 8718-8732.
  - 38 Wang YM, Jing L, Lei X, et al. Umbilical cord mesenchymal stem cell-derived apoptotic extracellular vesicles ameliorate cutaneous wound healing in type 2 diabetic mice via macrophage pyroptosis inhibition [J]. *Stem Cell Res Ther*, 2023, 14 (1): 257.
  - 39 Liu J, Qiu XY, Lv YJ, et al. Apoptotic bodies derived from mesenchymal stem cells promote cutaneous wound healing via regulating the functions of macrophages [J]. *Stem Cell Res Ther*, 2020, 11 (1): 507.
  - 40 Yang J, Zhang XH, Wang GY, et al. ApoSEVs-mediated modulation of versatile target cells promotes diabetic wound healing: unveiling a promising strategy [J]. *Int J Nanomedicine*, 2023, 18: 6955-6977.
  - 41 Mao JY, Qian ST, Zhao QY, et al. Balancing macrophage polarization via stem cell-derived apoptotic bodies for diabetic wound healing [J]. *Med*, 2024, 5 (2): 148-168. e8.
  - 42 Kang DN, Wang XX, Chen WT, et al. Epidermal stem cell-derived exosomes improve wound healing by promoting the proliferation and migration of human skin fibroblasts [J]. *Burns Trauma*, 2024, 12: tkae047.
  - 43 Qu Y, He YF, Meng BW, et al. Apoptotic vesicles inherit SOX2 from pluripotent stem cells to accelerate wound healing by energizing mesenchymal stem cells [J]. *Acta Biomater*, 2022,

- 149: 258-272.
- 44 Dong J, Wu B, Tian WD. Preparation of apoptotic extracellular vesicles from adipose tissue and their efficacy in promoting high-quality skin wound healing [J]. *Int J Nanomedicine*, 2023, 18: 2923-2938.
- 45 Zhao QY, Lu BL, Qian ST, et al. Biogenerated oxygen-related environmental stressed apoptotic vesicle targets endothelial cells [J]. *Adv Sci (Weinh)*, 2024, 11 (20): e2306555.
- 46 Zhang Y, Bai XZ, Shen K, et al. Exosomes derived from adipose mesenchymal stem cells promote diabetic chronic wound healing through SIRT3/SOD2 [J]. *Cells*, 2022, 11 (16): 2568.
- 47 Bray ER, Kirsner RS, Badiavas EV. Mesenchymal stem cell-derived extracellular vesicles as an advanced therapy for chronic wounds [J]. *Cold Spring Harb Perspect Biol*, 2022, 14 (10): a041227.
- 48 Li MJ, Tang Q, Liao CC, et al. Extracellular vesicles from apoptotic BMSCs ameliorate osteoporosis via transporting regenerative signals [J]. *Theranostics*, 2024, 14 (9): 3583-3602.
- 49 Wang RC, Hao M, Kou XX, et al. Apoptotic vesicles ameliorate lupus and arthritis via phosphatidylserine-mediated modulation of T cell receptor signaling [J]. *Bioact Mater*, 2023, 25: 472-484.
- 50 Song QF, Cui Q, Wang YS, et al. Mesenchymal stem cells, extracellular vesicles, and transcranial magnetic stimulation for ferroptosis after spinal cord injury [J]. *Neural Regen Res*, 2023, 18 (9): 1861-1868.
- 51 Dou G, Tian R, Liu XM, et al. Chimeric apoptotic bodies functionalized with natural membrane and modular delivery system for inflammation modulation [J]. *Sci Adv*, 2020, 6 (30): eaba2987.
- 52 Shao YZ, Jiang YH, Yang KK, et al. Apoptotic vesicles derived from human red blood cells promote bone regeneration via carbonic anhydrase 1 [J]. *Cell Prolif*, 2024, 57 (2): e13547.

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- 12 Kunath BJ, De Rudder C, Laczny CC, et al. The oral - gut microbiome axis in health and disease [J]. *Nat Rev Microbiol*, 2024, 22 (12): 791-805.
- 13 Zhou Z, Sun B, Yu DS, et al. Gut microbiota: an important player in type 2 diabetes mellitus [J]. *Front Cell Infect Microbiol*, 2022, 12: 834485.
- 14 吴金春, 刘彦民, 苏晓灵. 肠道菌群/肠道微生态与心血管疾病发生的关系研究进展 [J]. *解放军医学杂志*, 2023, 48 (7): 851-855.
- 15 Verduci E, Mameli C, Amatruda M, et al. Early nutrition and risk of type 1 diabetes: the role of gut microbiota [J]. *Front Nutr*, 2020, 7: 612377.
- 16 Liu X, Cheng YW, Shao L, et al. Gut microbiota dysbiosis in Chinese children with type 1 diabetes mellitus: An observational study [J]. *World J Gastroenterol*, 2021, 27 (19): 2394-2414.
- 17 Huang Y, Li SC, Hu J, et al. Gut microbiota profiling in Han Chinese with type 1 diabetes [J]. *Diabetes Res Clin Pract*, 2018, 141: 256-263.
- 18 Stojanov S, Berlec A, Štrukelj B. The influence of probiotics on the firmicutes/bacteroidetes ratio in the treatment of obesity and inflammatory bowel disease [J]. *Microorganisms*, 2020, 8 (11): 1715.
- 19 Chen PB, Black AS, Sobel AL, et al. Directed remodeling of the mouse gut microbiome inhibits the development of atherosclerosis [J]. *Nat Biotechnol*, 2020, 38 (11): 1288-1297.
- 20 Bielka W, Przekaz A, Pawlik A. The role of the gut microbiota in the pathogenesis of diabetes [J]. *Int J Mol Sci*, 2022, 23 (1): 480.
- 21 喻静, 彭红英. 肠道菌群介导的免疫反应与高血压和慢性肾脏病的关系研究进展 [J]. *解放军医学杂志*, 2021, 46 (9): 865-870.
- 22 Endesfelder D, Engel M, Davis-Richardson AG, et al. Towards a functional hypothesis relating anti-islet cell autoimmunity to the dietary impact on microbial communities and butyrate production [J]. *Microbiome*, 2016, 4 (1): 17.
- 23 Bahar-Tokman H, Demirci M, Keskin F, et al. Firmicutes/bacteroidetes ratio in the gut microbiota and IL-1 $\beta$ , IL-6, IL-8, TLR2 TLR4 TLR5 gene expressions in type 2 diabetes [J]. *Clin Lab*, 2022, 68 (9/2022): 1-5.
- 24 Rizzatti G, Lopetuso LR, Gibiino G, et al. Proteobacteria: a common factor in human diseases [J/OL]. <https://doi.org/10.1155/2017/9351507>.
- 25 Yao MF, Lu YM, Zhang T, et al. Improved functionality of *Ligilactobacillus salivarius* Li01 in alleviating colonic inflammation by layer-by-layer microencapsulation [J]. *NPJ Biofilms Microbiomes*, 2021, 7 (1): 58.
- 26 Dos Santos Cruz BC, da Conceição LL, de Oliveira Mendes TA, et al. Use of the synbiotic VSL#3 and yacon-based concentrate attenuates intestinal damage and reduces the abundance of *Candidatus Saccharimonas* in a colitis-associated carcinogenesis model [J]. *Food Res Int*, 2020, 137: 109721.
- 27 Xu J, Huang GN, Guo TL. Bisphenol S modulates type 1 diabetes development in non-obese diabetic (NOD) mice with diet- and sex-related effects [J]. *Toxics*, 2019, 7 (2): 35.
- 28 刘军, 丁登峰, 高伟, 等. 应用16S rRNA基因测序比较分析不同品系1型糖尿病小鼠肠道菌群的异同 [J]. *实验动物科学*, 2023, 40 (5): 24-32.

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