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间充质干细胞外泌体在治疗衰老相关退行性疾病中的应用

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摘 要:随着全球老龄化趋势的加剧,老年人口健康需求的持续增长为医疗领域带来了重大挑战。间充质干细胞外泌体(mesenchymal stem cell exosomes,MSC-exosomes)含有具备炎症调节、促进组织修复及抗衰老等作用的生物活性分子,能通过多种机制改善衰老引起的组织功能衰退和病理变化,在抗衰老及衰老相关退行性疾病的治疗中发挥重要作用。尽管MSC-exosomes在临床应用中的效果还需要进一步验证,但其表现出的抗炎和组织修复特性与当前衰老相关的退行性疾病治疗中的再生医学和炎症消退方向相契合。本文概述了MSC-exosomes的生物活性分子组成,并根据当前MSC-exosomes应用基础技术的研究进展,重点讨论MSC-exosomes作为新兴治疗手段在衰老相关退行性疾病治疗中的应用。

关键词:间充质干细胞外泌体;退行性疾病;抗衰老;抗炎;组织修复
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Application of mesenchymal stem cell-derived exosomes in the treatment of aging-related degenerative diseases

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Abstract: The accelerating trend of global population aging poses unprecedented challenges to healthcare systems worldwide, driving an urgent need for innovative and safe therapeutic strategies to address age-related degenerative diseases. Although mesenchymal stem cells (MSCs) have shown broad application potential in clinical trials, their use is associated with significant risks, including tumorigenicity. This underscores the necessity to explore alternative, cell-free therapies that retain therapeutic efficacy while minimizing such risks. Mesenchymal stem cell-derived exosomes (MSC-exosomes) have emerged as a promising candidate in this regard, offering significant potential in mitigating tissue dysfunction, modulating inflammation, and promoting regeneration in aging-associated pathologies. This comprehensive review aims to elaborate on the bioactive composition of MSC-exosomes, outline recent advances in their preparation and application technologies, and critically evaluate their therapeutic efficacy in various aging-related degenerative conditions. MSC-exosomes are nanoscale extracellular vesicles (40-100 nm) enriched with a diverse cargo of lipids, proteins, and nucleic acids inherited from their parent cells. Their lipid bilayer membrane contains specialized components such as ganglioside GM1, which contributes to neuroprotection and exosome bioregulation. Proteomic analyses reveal that MSC-exosomes carry functional proteins, including growth factors, immune modulators, and tissue repair mediators, as well as the 20S proteasome complex capable of degrading misfolded proteins, a hallmark of many age-related diseases. Furthermore, MSC-exosomes are loaded with regulatory nucleic acids, particularly microRNAs (e.g., miR-146a, miR-let-7 family) and long non-coding RNAs (e.g., MALAT1, FENDRR), which collectively modulate inflammatory pathways, cellular senescence, oxidative stress, and regenerative responses. Importantly, the cargo profile of MSC-exosomes is highly dependent on their cellular origin, leading to significant compositional and functional

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heterogeneity. For instance, bone marrow-derived MSC-exosomes are rich in regeneration-related proteins, adipose tissue-derived exosomes are abundant in antioxidant proteins, and umbilical cord-derived exosomes highly express factors that promote wound healing. This source-dependent variation underpins the distinct functional properties and potential therapeutic specializations of different MSC-exosome populations. The review systematically details the technological foundations for MSC-exosome applications, covering isolation methods (e.g., ultracentrifugation, size-exclusion chromatography, microfluidic platforms), storage optimization (using cryoprotectants like trehalose and appropriate buffer systems), and delivery strategies (including systemic administration, localized injection, and biomaterial-based carriers such as hydrogels and microneedles). Advanced culture systems, notably three-dimensional (3D) scaffolds, enhance exosome yield and bioactivity compared to conventional 2D cultures. These advancements collectively establish a relatively complete technical pipeline for exosome production, from purification and preparation to storage and delivery, providing a solid foundation for the future clinical application of MSC-exosomes in treating aging-related degenerative diseases. Preclinical and emerging clinical evidence highlights the therapeutic potential of MSC-exosomes across multiple degenerative disease models. In neurodegenerative disorders, such as Alzheimer′s and Parkinson′s diseases, MSC-exosomes mitigate neuroinflammation, reduce amyloid-β and α-synuclein accumulation, and promote neuronal survival and synaptic repair. In bone degenerative conditions like osteoporosis and osteoarthritis, they enhance osteogenic differentiation, suppress bone resorption, and attenuate cartilage degradation through modulation of inflammatory and anabolic signaling pathways. For cardiovascular and cerebrovascular diseases, including atherosclerosis, ischemic stroke, and heart failure, MSC-exosomes improve vascular endothelial function, stimulate angiogenesis, reduce oxidative stress, and ameliorate fibrotic remodeling. In conclusion, MSC-exosomes hold immense clinical potential as a versatile and potent cell-free therapeutic tool, particularly in addressing the core inflammatory processes underlying aging and degenerative diseases. Evidence confirms the strong association between cellular signaling, chronic inflammation (″inflammaging″), and age-related pathology. The emerging therapeutic paradigm of ″inflammation resolution,″ an active and programmed process, suggests that multi-faceted agents may be more effective than single-target anti-inflammatory drugs. As carriers of ″youthful signals″, MSC-exosomes with their rich cargo of bioactive proteins, miRNAs, and lncRNAs can orchestrate a comprehensive, multi-level modulation of inflammatory responses, offering a novel possibility for treating aging-related conditions based on the principle of inflammation resolution. They are thus emerging as a promising next-generation tool in regenerative medicine. However, their path to clinical translation is impeded by several challenges, including a lack of systematic large-scale clinical trials, product heterogeneity due to variable MSC sources, the absence of unified quality control standards and dosing regimens, and technical immaturity in scalable manufacturing processes. Therefore, future progress hinges on robust clinical validation and targeted preclinical research that addresses these translational hurdles. With continued refinement in standardization, production, and delivery, MSC-exosomes possess substantial promise for transforming the therapeutic landscape for the aging population by decelerating degenerative processes and restoring tissue homeostasis.

Key words: mesenchymal stem cell-derived exosomes; aging-related degenerative diseases; anti-aging; anti-inflammation; tissue repair

1 间充质干细胞外泌体简介

衰老是一个复杂的生物过程,其主要标志为细胞周期阻滞和产生衰老相关分泌表型(senescence related secretory phenotype,SASP)[1]。细胞衰老的其他特征主要是细胞活性氧含量升高、DNA损伤加剧等[2]。衰老细胞通过分泌SASP激活信号通路和炎症级联反应,从而改变体内微环境[3],进一步加速机体衰老乃至发展成衰老相关的疾病[4]。在老龄化加剧的当代社会中,延缓自然衰老对人类健康与社会发展具有重要意义。间充质干细胞(mesenchymal stem cell,MSC)具有抗炎和促进细胞更新等作用,可促进组织修复,具备抗衰老潜力[5]。MSC来源的外泌体(mesenchymal stem cell exosomes,MSC-exosomes)被认为是MSC发挥效应的主要旁分泌物,并且已被证明具有与MSC相似的生物学功能。同时,相比MSC存在着制备难、纯度低、传代效率低[6]、培养时间长、易恶化[7]等问题,MSC-exosomes具有低免疫原性和无伦理限制的优势。MSC-exosomes是一类直径40~100 nm的细胞外囊泡(extracellular vesicles,EVs),其密度为1.1~1.18 g/mL。这类细胞外囊泡具有脂质双分子层结构,表面表达外泌体特异性蛋白如CD9(cluster of differentiation 9)、CD81(cluster of differentiation 81)、肿瘤易感基因101蛋白(tumor susceptibility gene 101,TSG101)等,同时还具有如CD44(cluster of differentiation 44)和CD73等MSC特征性标志物,其内部包裹各类蛋白质、核酸等生物活性物质,构成传递亲本细胞的“年轻信号”的功能载体[8]。MSC-exosomes继承了亲本细胞的抗炎、减少

细胞凋亡以及组织修复等功能,具有靶向特定细胞或组织的特殊能力,有研究表明其可通过表面黏附蛋白的相互作用介导内容活性物质的水平转移,从而调节受体细胞的衰老信号。不同来源的MSC-exosomes的治疗能力已在各种疾病模型中进行了测试,证明其功能与MSC本身相似,甚至更为优越[9],预示着MSC-exosomes是极具潜力的天然抗衰药物。

2 间充质干细胞外泌体的组成成分

MSC-exosomes的活性成分由脂质、蛋白质和核酸组成,本节将探讨并总结MSC-exosomes的主要成分及其在抗衰老过程中的作用。

2.1 脂质

外泌体膜富含胆固醇、鞘脂等典型的脂筏成分。磷脂双层膜为内部核酸和蛋白质提供了有效的保护屏障;此外,鞘糖脂能够与功能性膜蛋白如生长因子受体、整合素和四跨蛋白相互作用以调节细胞生长、细胞黏附和细胞运动[10]。外泌体膜多富含神经节苷脂M1(ganglioside M1,GM1)等鞘糖脂[11]。GM1在MSC-exosomes中高度富集,与MSC-exosomes生成有关[12],同时具有神经修复和抗氧化的保护作用[13],这预示着GM1具有保护和修复衰老有关的神经退行性病变的功能。

2.2 蛋白质

MSC-exosomes含有丰富的蛋白质,膜表面有大量的外泌体标志蛋白以及MSC-exosomes特异性标志蛋白,参与调控外泌体发生、识别靶细胞等过程,膜内还包裹有大量参与组织再生、免疫调节等功能蛋白。不同来源的MSC-exosomes蛋白质组成具有显著差异,其差异富集的蛋白质组分赋予其特定的生物学功能。此外,MSC-exosomes含有能够降解错误折叠蛋白的20S蛋白酶体系统,为治疗与错误蛋白质积累相关的衰老相关疾病提供了分子基础。

2.2.1 功能蛋白

外泌体作为复杂的生物纳米载体,富含超过一千种已鉴定的蛋白质,包括定位于外泌体表面的四跨膜蛋白(tetraspanins,CD9、CD63、CD81、CD82)、调控外泌体产生的ALIX(ALG-2-interacting protein X),以及热休克蛋白70(heat shock protein 70,HSP70)等[14]。MSC-exosomes除了含有其特异性表达的标志蛋白,还含有调控外泌体发生的蛋白(TSG101;Alix;kidney and brain expressed protein,KIBRA)、细胞骨架蛋白(β-actin、γ-actin、moesin)[8],以及参与组织再生与免疫调控的白细胞介素-10(interleukin-10,IL-10)、肝细胞生长因子(hepatocyte growth factor,HGF)和白血病抑制因子(leukemia inhibitory factor,LIF)等[15,16]。此外,MSC-exosomes富含血管生成有关的蛋白质,例如血小板源性生长因子(platelet-derived growth factor,PDGF)、表皮生长因子(epidermal growth factor,EGF)和成纤维细胞生长因子(fibroblast growth factor,FGF)等[17]。研究表明,虽然不同来源的MSC-exosomes具有富集与细胞外基质-受体相互作用有关的蛋白等共同组成特点,但它们在整体蛋白质组成上仍然具有显著差异。骨髓来源的MSC-exosomes富含如神经源性基因座Notch同源蛋白2(neurogenic locus Notch homolog protein 2,Notch2)、去整合素金属蛋白酶10(a disintegrin and metalloproteinase domain-containing protein 10,ADAM10)等介导组织再生、调控发育的蛋白质。脂肪组织来源的MSC-exosomes富含过氧化物氧化酶家族(peroxiredoxins,PRDX1/2/4/6),可通过降低氧化应激、调节免疫以保护损伤组织。人脐带来源的MSC-exosomes高表达的纤溶酶原激活物抑制因子1(plasminogen activator inhibitor-1,PAI-1)能抑制尿激酶型/组织型纤溶酶原激活物-基质金属蛋白酶(urokinase-type/tissue-type plasminogen activator-matrix metalloproteinase,uPA/tPA-MMP)轴,促进伤口愈合[18]。

2.2.2 蛋白酶体

外泌体中存在蛋白酶体,其中20S蛋白酶体(20S proteasome)是细胞内重要的蛋白质降解系统[19]。蛋白酶体活性的下降与阿尔茨海默病、帕金森病等神经退行性疾病及心血管疾病等多种衰老相关疾病的发病紧密相关。蛋白酶体活性减弱会加剧衰老相关的炎症反应和动脉粥样硬化进展。此外,心肌缺血再灌注损伤[20]及阿尔茨海默病等退行性疾病[21]中的错误折叠蛋白积累也与蛋白酶体的缺少有关。在MSC-exosomes蛋白质组中存在20S蛋白酶体的所有7α链和7β链以及免疫蛋白酶体(immunoproteasome)的3个β亚基,能显著降低小鼠心脏组织中错误折叠蛋白及寡聚体的积累[22],这预示着MSC-exosomes可在衰老相关疾病中发挥补充有活性的蛋白酶体的作用。

2.3 核酸

MSC-exosomes携带多种核酸,主要包括微小

RNA(microRNA,miRNA)、长链非编码RNA(long non-coding RNA,lncRNA)等生物活性分子[23]。这些活性分子通过靶向调控基因表达、介导表观遗传修饰及协调信号网络可修复因衰老受损的组织。此外,lncRNA与miRNA具有调节关系,二者能协调发挥动态平衡关键衰老信号通路的功能。

2.3.1 miRNA

研究证实MSC-exosomes通过特异性miRNA递送可有效改善细胞衰老表型。Ferguson 等[24]通过高通量测序分析发现,MSC-exosomes中79.1%的miRNA是包括miR-let-7a、miR-let-7b等在内的23种关键分子,这些分子可调控与心血管发育、血管生成和纤维化密切相关的Wnt、PDGF及转化生长因子-β(transforming growth factor-β,TGF-β)信号通路等。miR-423-5p[25]、miR-146a[26]以及miR-126[27]均具有挽救衰老细胞的血管生成障碍的功能。值得注意的是,MSC-exosomes中某些miRNA具有多器官保护作用:miR-124-3p可通过调控肝细胞凋亡相关通路显著减轻脂肪肝供体的缺血再灌注损伤[28];miR-17-92基因簇不仅能通过调控 PTEN/PI3K/Akt/mTOR信号通路促进中枢神经系统损伤后的轴突再生[29,30],还可在心血管系统中逆转心肌纤维化[31],并调节动脉粥样硬化[32]。这些研究共同表明,MSC-exosomes通过其携带的特异性miRNA网络来多维度干预衰老相关病理过程。

2.3.2 LncRNA

LncRNA是长度超过200个核苷酸、不具备编码蛋白质能力的核酸,与miRNA相比,lncRNA具有组织特异性和发育阶段特异性[33]。MSC-exosomes含有大量的lncRNA,它们参与表观遗传、细胞重编程以及基因组稳定性的调控[34]。lncRNA FENDRR通过靶向miR-28抑制细胞凋亡、氧化应激以及炎症反应,随后减少氧化低密度脂蛋白的积累,最终抑制衰老相关的动脉粥样硬化斑块的形成[35]。MSC-exosomes中的lncRNA MALAT1能够改善线粒体代谢[36],提高成骨细胞活性以缓解骨质疏松症[37]、预防衰老诱导的心脏功能障碍[33],以及增加神经元的增殖能力与存活率[38]。因此,lncRNA MALAT1在抗衰老中发挥重要的作用。

综上所述,MSC-exosomes含有与组织修复再生相关的脂质、蛋白质、miRNA及lncRNA,能为MSC-exosomes改善衰老引起的组织病理变化及治疗衰老相关退行性疾病提供相应的分子基础(表1)。

3 间充质干细胞外泌体的应用技术基础

3.1 间充质干细胞外泌体的制备

细胞培养、传代和扩增是细胞治疗产品CMC(化学、生产和控制)的关键环节,目前间充质干细胞的培养模式主要有二维(2D)和三维(3D)两种方式。3D培养是使用三维支架材料模拟细胞外基质成分并与干细胞共同培养的模式,这能为细胞培养提供必要的结构和机械支持,并有效促进细胞的附着和生长以制备MSC-exosomes[51]。3D培养主要包括基于3D支架开发的中空纤维培养体系[52]、基于微载体的悬浮培养技术[53],以及3D打印多孔生物材料支架培养技术[54] 等。与2D培养系统相比,3D培养系统能够提高MSC-exosomes的产量以及生物活性[55] ,如促神经再生特性[56]、抗炎作用[57]等。

3.2 间充质干细胞外泌体的提取分离

由于MSC-exosomes在生物样本中含量极低且常与其他细胞成分共存[58],其高效分离需综合考量产量、纯度与功能完整性。在传统分离方法中,超速离心法(ultracentrifugation,UC)虽被视为“金标准”,但其操作复杂、耗时长且易因离心剪切力导致外泌体结构损伤[59]。为此,研究人员开发了密度梯度超速离心法(density gradient ultracentrifugation,DGU)与移动区带离心法(moving zone ultracentrifugation,MZU),通过优化离心介质密度梯度减少分离步骤,但仍受限于样本处理量低、设备要求严苛及外泌体活性损失等问题[58]。基于尺寸差异的分离技术中,超滤法(ultrafiltration,UF)凭借操作简便、成本低及低损伤性优势,成为商业试剂盒的主流选择,但其仍然具有通量低的缺点,且存在滤膜阻塞或外泌体破裂风险[60]。切向流过滤法(tangential flow filtration,TFF)通过平行流设计可以维持稳定过滤速率,但需精确控制跨膜压力等参数,设备成本高昂[61]。尺寸排阻色谱(size exclusion chromatography,SEC)可避免超速离心造成的机械损伤及蔗糖介质污染[62]。相比缺少特异性的聚合物共沉淀法(polymer co-precipitation)[63],免疫捕获亲技术利用特异性抗体结合外泌体标志物可实现高效的特异性分离[64],例如,免疫捕获亲和技术能根据MSC-exosomes特异性表达的黏附分子,如CD29、CD44等,区分MSC-exosomes和其他来源的外泌体[65]。尽管免疫磁珠法(immunomagnetic

表1　间充质干细胞外泌体的活性组成分子功能汇总

Table 1　Functional summary of bioactive components in mesenchymal stem cell-derived exosomes

分类		活性分子	功能	参考文献
脂质		GM1	调节间充质干细胞外泌体的生成	[12]
			神经修复和保护作用	[13]
蛋白质	功能蛋白	Notch2	介导胚胎发育和组织再生	[18]
		ADAM10	调节突触可塑性、神经发育	[18]
		PRDX1/2/4/6	发挥抗氧化作用以保护组织器官	[18]
		PAI-1	维持内皮稳态和调节纤维化,促进伤口愈合	[18]
	蛋白质酶体	20S蛋白酶体	降解细胞外液中的可溶性肽,减少致病的错折叠蛋白质、寡聚体聚集	[22]
核酸	miRNA	miR-let-7a、miR-let-7b、miR-let-7i、miR-23a-3p、miR-29a-3p	靶向参与心血管发育、血管生成、细胞生长和凋亡以及纤维化相关通路	[24]
		miR-146a	减少衰老相关分泌表型,促进伤口愈合和血管生成	[26]
		miR-126	促进组织再生和血管生成	[27]
		miR-124-3p	降低移植物缺血再灌注损伤	[28]
		miR-17-92	修复神经功能	[29]
			促进神经元生长和轴突再生	[30]
			逆转心脏纤维化	[31]
			调节动脉粥样硬化	[32]
		miR-29c-3p	减少淀粉样蛋白的积累,降低细胞炎症因子水平	[39]
		miR-181a-2-3p	减轻氧化应激水平和神经元凋亡	[40]
		miR-129-5p	下调炎症因子水平,有效缓解骨关节炎	[41]
			调控NF-κB信号通路,改善心力衰竭	[42]
		miR-9-5p	下调炎症因子水平和减少氧化应激水平,抑制OA	[43]
		miR-361-5p	抑制MMP水平和降低IL-1β诱导的炎症水平	[44]
		miR-100-5p	通过调节mTOR-自噬通路维持软骨稳态	[45]
		miR-150-5p	通过调节转化生长因子-β、VEGF以及MMP14改善血管组织损伤反应	[46]
		miR-423-5p	促血管生成	[25]
		miR-let7	促进斑块中巨噬细胞M2极化和抑制其浸润以改善动脉粥样硬化	[47]
		miR-21a-5p	促进巨噬细胞M2极化并减少浸润以延缓动脉粥样硬化发展	[48]
		miR-1246	靶向丝氨酸蛋白酶23抑制心肌损伤,有效改善慢性心力衰竭	[49]
	LncRNA	lncRNA FENDRR	抑制细胞凋亡、氧化应激和炎症反应,减少与衰老有关的动脉粥样硬化斑块的形成, 减少氧化低密度脂蛋白的积累	[35]
		lncRNA MALAT1	调节miR-92a-3p/ATG4a轴改善线粒体代谢	[36]
			调控microRNA-34c/SATB2轴并显著缓解骨质疏松	[37]
			预防衰老诱导的心脏功能障碍	[33]
			促进神经元的增殖与存活	[38]
		lncRNA H19	调控miR-675表达、激活促血管生成因子和细胞间黏附分子1以保护心血管	[47]

bead,IMB)分离具有高特异性[66],但其所需抗体成本高,不适用于规模化应用[67]。近年来,非接触式微流控技术快速发展:黏弹性微流控(viscoelastic microfluidics)通过流体黏弹效应分选颗粒[68],声学纳米滤波(acoustic nanofiltration)利用驻波场操控纳米颗粒[47],介电电泳微流控(dielectrophoresis microfluidics)则依赖非均匀电场介导分离[69]。这些技术可在避免样本污染的同时实现高通量、自动化分离,尤其适用于临床微量样本的实时分析(表2)。

3.3　间充质干细胞外泌体的储存

适宜的储存条件是决定外泌体实际应用可行性的关键因素,直接影响运输成本与产品保质期。目前,研究主要聚焦于储存温度与时间[70]、容器材质[71,72]及海藻糖(trehalose)等冷冻保护剂的优化[73]。-80 ℃是普遍认同的长期保存的温度条件。

表2 外泌体分离方式的比较

Table 2 Comparison of exosome isolation methods

收集方法		分离原理	优势	缺点	适用场景	参考文献
密度梯度法	超速离心法	密度差异	高纯度,国际金标准	操作复杂、耗时长,离心剪切力可能损伤外泌体结构,样本处理量低	科研研究、小样本验证	[59]
	梯度超速离心法	密度梯度差异	分离步骤少,产率较高	样本处理量低,设备要求严苛,外泌体活性可能损失	科研研究、高纯度外泌体提取	[58]
	移动梯度超离心法	动态密度梯度	分离步骤少,分离效率高	设备复杂,外泌体活性可能受损,样本处理量低	科研研究、需快速分离场景	[58]
尺寸筛选法	超滤法	尺寸和相对分子质量	操作简便、成本低、低损伤性,适合商业试剂盒	通量低,滤膜易阻塞,存在外泌体破裂风险	小规模样本预处理、试剂盒开发	[60]
	切向流过滤法	尺寸和相对分子质量	过滤速率稳定,适合大规模分离,减少膜阻塞	需精密控制跨膜压力,设备成本高昂	工业化生产、大样本处理	[61]
	尺寸排阻色谱	尺寸	避免机械损伤和蔗糖介质污染,操作温和	通量较低,可能受限于样本体积	功能研究、高活性外泌体分离	[62]
化学特性法	聚合物共沉淀法	聚合物与溶剂之间的亲疏水性差异	操作简单,适用于多种样本类型	特异性差,易引入污染性蛋白,纯度较低	初步筛查、快速粗提	[63]
	免疫捕获亲和技术	免疫亲和分离	高特异性,可区分MSC-exosomes与其他来源外泌体	抗体成本高,不适用于大规模应用,洗脱过程可能影响外泌体功能	科研研究、高精度少量提取	[64-67]
微流控技术	黏弹性微流控	黏弹性流体力学特性	高通量、自动化,非接触式分离,避免样本污染	设备成本高,操作需专业知识	临床微量样本、高通量分析	[68]
	声学纳米滤波	声辐射力	非接触式分离,避免污染	设备成本高,技术尚不成熟,通量受限	单细胞研究、微量样本精细分离	[47]
	介电电泳微流控	介电泳力	避免样本污染的同时实现高精度、自动化分离	设备复杂,需精密控制电场参数,成本高	临床微量样本、高精度分离	[69]

磷酸盐缓冲液(phosphate-buffered saline,PBS)是MSC-exosomes储存的常用介质,但单独使用难以满足长期保存需求。研究表明,在PBS体系中补充人血清白蛋白(human serum albumin,HSA)和海藻糖可显著提升MSC-exosomes的稳定性,使其耐受多次冻融循环并提高回收率[74]。此外,N-(2-羟乙基)哌嗪-N'-乙磺酸(4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid,HEPES)缓冲液因其pH稳定性优于PBS,可进一步提升外泌体回收率。添加牛血清白蛋白(bovine serum albumin,BSA)和聚山梨酯20(Tween 20)等辅料也被证实可有效延长外泌体保存期[72]。储存容器材质对外泌体稳定性具有显著影响。聚丙烯管(polypropylene tube)因其低蛋白吸附特性及耐低温性能,较玻璃管更适合外泌体储存[72]。此外,冻干保藏法是将添加海藻糖等冷冻保护剂的外泌体制备成冷冻干燥、便于运输的粉末[75],可在室温运输条件下有效保证外泌体的稳定性[76]。

3.4 间充质干细胞外泌体的递送

MSC-exosomes在抗衰老应用中的递送策略大致分为系统递送与局部递送。系统递送可利用归巢效应(homing effect)[77]靶向病灶,技术难度低,但存在MSC-exosomes损失大,靶部位浓度不足的缺点。局部递送有在病灶部位直接注射和微针给药两种方式。海绵骨针[78]、可溶性微针贴片[79]、滚轮微针[80]等微针系统均能延长MSC-exosomes在皮肤中的渗透效果、分布均匀度以及保留效果。研究证实聚乙烯醇(polyvinyl alcohol,PVA)微针有利于提高MSC-exosomes治疗角膜炎症的效果[81]。外泌体与水凝胶等生物材料的复合应用是一种延长外泌体保留时间的有效策略。氧化透明质酸-聚赖氨酸(oxidized hyaluronic acid-polylysine,OHA-PLL)水凝胶、聚乙二醇F-127(PEG F-127)水凝胶封装MSC-exosomes可提高其修复心肌[82]和促进皮肤伤口愈合[83]的效果。纤维状聚酯材料支架(fibrous polyester scaffolds)与MSC-exosomes混合更有利于其发挥调控免疫反应的作用[84]。此外,3D打印生物材料支架(3D-printed biomaterial scaffolds)作外泌体递送载体提高了其促血管生成和成骨作用的效果[85]。

综上所述,目前已有一套较为完备的外泌体生

产技术流程，从纯化制备环节到递送及储存的应用环节均有许多可行且适用于不同应用场景的技术，为未来MSC-exosomes应用于衰老相关退行性疾病的治疗奠定了技术基础(图1)。

4 间充质干细胞外泌体在治疗衰老有关的退行性疾病中的应用

MSC-exosomes载有大量能够改善衰老相关症状的活性物质，如前文所述的能够降解衰老细胞中错误蛋白的20S蛋白酶体，大量抗炎的miRNA，具有调节免疫反应、促进组织再生的功能蛋白，以及能够改善神经损伤的GM1等成分。MSC-exosomes已经被证实可以干预正常的衰老如皮肤光老化等进程，具有成为天然美容抗衰产品的潜力，如人脐带来源的MSC-exosomes 显著促进真皮成纤维细胞增殖，并限制 UVB 诱导的活性氧(reactive oxygen species，ROS)形成[86]。此外，其对紫外线诱导的 DNA 损伤和细胞凋亡能产生类似的抗氧化和抗炎作用，能通过调节细胞衰老相关蛋白1(sirtuin 1，SIRT1)依赖性抗氧化途径来促进自噬发挥细胞保护功能，从而有效改善皮肤光老化[87]。此外，MSC-exosomes具有在未来临床上治疗衰老相关疾病的潜力。在多类衰老相关的退行性疾病模型中，MSC-exosomes具有减少组织细胞凋亡、调节炎症、降低导致病理变化的错误折叠蛋白积累等作用。本节将从改善神经退行性疾病、骨退行性疾病以及心脑血管疾病三大类典型衰老退行性疾病的角度，分别阐述MSC-exosomes治疗衰老相关退行性疾病的作用。

4.1 神经退行性疾病

神经退行性疾病如阿尔茨海默病和帕金森病的患病风险随年龄增长显著增加[88]。随着衰老的进程，大脑细胞内会发生DNA损伤[89]、蛋白质异常[90]以及慢性炎症[91]等一系列病理变化，这些病理变化会引发突触可塑性受损、蛋白质淀粉样斑块、神经纤维缠结以及脑体积减少等一系列神经变性的结构改

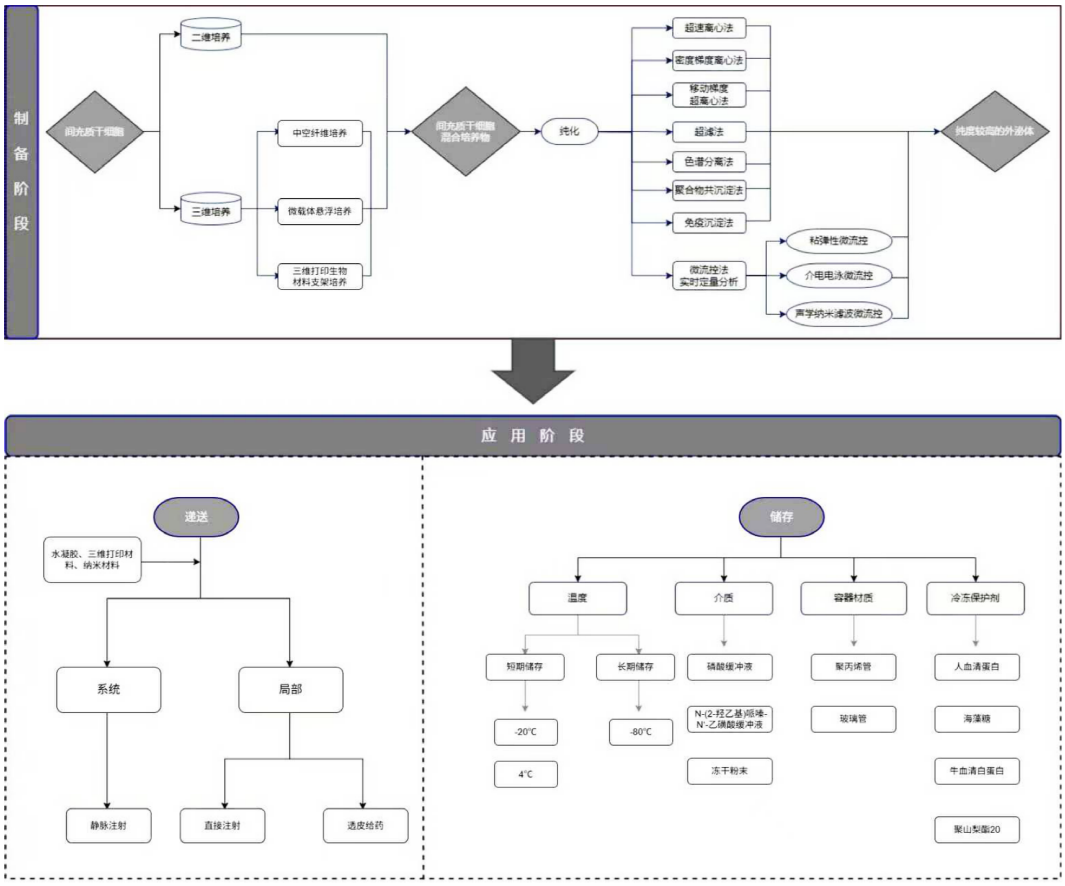

图 1 间充质干细胞外泌体的培养、纯化、储存及递送应用技术流程示意图

Figure 1 The basic process overview for the techniques of culturing, purification, storage, and delivery applications of mesenchymal stem cell-derived exosomes

变,进一步损伤大脑认知功能,最终增加罹患神经退行性疾病的风险。神经退行性疾病相关的基因在大脑不同区域随着大脑老化进程呈现显著的区域特异性表达变化[92]。目前,临床仍然缺乏有效治疗神经退行性疾病的药物与手段[93],而MSC-exosomes可自由穿过血脑屏障[94],具有治疗神经退行性疾病的潜力。

4.1.1 阿尔茨海默病

阿尔茨海默病(Alzheimer's disease,AD)是老年人中最常见的神经退行性疾病,以进行性记忆力减退、认知功能障碍及行为改变为主要临床表现[95]。其核心病理特征包括:β-淀粉样蛋白(amyloid-β,Aβ)异常沉积形成的斑块、过度磷酸化微管相关蛋白 Tau 聚集导致的神经纤维缠结(neurofibrillary tangles,NFTs),以及小胶质细胞介导的慢性神经炎症反应[96]。近年来,小胶质细胞在AD病理进程中异常活化导致炎症的作用备受关注。目前,AD的临床治疗主要依赖乙酰胆碱酯酶抑制剂(acetylcholinesterase inhibitors,AChEIs)和N-甲基-D-天冬氨酸受体(N-methyl-D-aspartate receptor,NMDAR)拮抗剂等药物,辅以认知训练等非药物干预手段[97]。然而,这些方法只有微弱的改善作用[98]。MSC-exosomes因其抗炎、促进Aβ清除及神经修复等多重作用,成为AD治疗研究的热点[99]。侧脑室注射骨髓间充质干细胞外泌体能够抑制AD小鼠模型的小胶质细胞活化和炎症[100],其机制可能与MSC-exosomes递送的miR-29c-3p有关:miR-29c-3p通过抑制β-位点淀粉样前体蛋白裂解酶1(β-site amyloid precursor protein cleaving enzyme 1,BACE1)表达,减少Aβ生成;同时激活Wnt/β-catenin信号通路,上调Aβ降解酶(如neprilysin,NEP)表达,从而减少Aβ斑块沉积并降低炎症因子水平[39]。此外,Cone等[101]发现,鼻内给药途径递送MSC-exosomes可显著减少AD小鼠海马区Aβ斑块,抑制神经炎症,并改善认知功能。

4.1.2 帕金森病

帕金森病(Parkinson's disease,PD)是仅次于AD的第二大神经退行性疾病,好发于55~65岁人群,严重威胁老年人群健康[102]。其核心病理特征为黑质多巴胺能神经元进行性丢失,与细胞内α-突触核蛋白(α-synuclein,α-Syn)异常聚集形成路易小体(Lewy bodies)密切相关。此外,年龄相关的线粒体功能失调和溶酶体降解能力下降,与α-Syn病理性累积形成恶性循环,共同加速神经元退行性变[103]。MSC-exosomes携带的miR-181a-2-3p可靶向抑制早期生长反应蛋白1(early growth response protein 1,EGR1),进而下调NADPH氧化酶4(NADPH oxidase 4,NOX4)表达,显著减轻PD模型中的氧化应激损伤与神经元凋亡[40]。MSC-exosomes通过上调细胞间黏附分子1(intercellular adhesion molecule 1,ICAM1),激活SMAD家族成员3(mothers against decapentaplegic homolog 3,SMAD3)和p38丝裂原活化蛋白激酶(p38 mitogen-activated protein kinase,p38MAPK)信号通路,促进脑血管新生,改善PD小鼠神经功能[104]。人脐带来源MSC-exosomes通过上调特异性AT序列结合蛋白1(special AT-rich sequence-binding protein 1,SATB1),激活Wnt/β-catenin信号通路并调节自噬水平,有效减少PD模型中的神经元损伤[105]。研究人员将MSC-exosomes与载有抗淀粉样化合物的纳米脂质体(nanoliposomes,NLPs)结合,可协同抑制α-Syn纤维化进程,降低其神经毒性,显著增强PD治疗效果[106]。

4.2 骨退行性疾病

老年人易患衰老导致的骨退行性疾病。随着衰老进展,骨细胞、血管内皮及造血干细胞功能下降,影响骨代谢、营养供给及免疫反应[107]。衰老会破坏骨稳态,降低骨转换率,造成骨髓脂肪堆积[108],同时导致的骨炎症、骨量减少及结构弱化[109]会增加骨退行性疾病发生的风险[107]。MSC-exosomes被证明对骨细胞存活、增殖、迁移、成骨和血管生成等有积极作用,在动物骨缺损和骨坏死、骨质疏松等疾病模型中可改善形态学、生物力学和组织学的指标[110]。

4.2.1 骨关节炎

骨关节炎(osteoarthritis,OA)是一种以关节软骨退行性变、滑膜炎症及骨赘形成为特征的年龄相关性关节疾病。随着全球老龄化加剧,OA已成为导致中老年人群伤残调整寿命年(disability-adjusted life years,DALYs)升高的重大公共卫生问题[111]。其核心病理机制涉及软骨细胞外基质合成与分解代谢失衡,表现为胶原纤维网络破坏、蛋白聚糖丢失及软骨下骨硬化[112]。由于软骨组织自我修复能力极弱,现有治疗手段难以逆转损伤进程[113],而MSC-exosomes通过多靶点调控炎症、细胞凋亡与再生,为OA治疗提供新方向[114]。人滑膜间充质干细胞外泌体(synovial MSC-exosomes)携带的miR-129-5p通过抑制高迁移率族蛋白B1(high mobility group

box 1,HMGB1)释放,下调诱导型一氧化氮合酶(inducible nitric oxide synthase,iNOS)、环氧合酶2(cyclooxygenase-2,COX2)、基质金属蛋白酶13(matrix metalloproteinase 13,MMP13)及核因子κB(nuclear factor kappa-B,NF-κB)表达,有效缓解白细胞介素-1β(interleukin-1β,IL-1β)诱导的OA炎症反应[41]。人骨间充质干细胞外泌体中的miR-361-5p通过靶向DEAD盒解旋酶20(DEAD-box helicase 20,DDX20),抑制MMP生成,并阻断IL-1β介导的炎症级联反应[44]。骨髓间充质干细胞外泌体(bone marrow MSC-exosomes)通过miR-9-5p调控多配体聚糖1(syndecan-1,SDC1)来发挥抗炎与软骨保护作用[43]。此外,诱导多能干细胞(induced pluripotent stem cells,iPSCs)分化产生的MSC-exosomes可显著促进软骨细胞迁移与增殖,加速OA关节修复[115]。MSC-exosomes通过双重机制改善颞下颌关节OA:抑制IL-1β/iNOS介导的炎症反应,同时激活蛋白激酶B(protein kinase B,AKT)和细胞外信号调节激酶(extracellular signal-regulated kinase,ERK)信号通路,减少细胞外基质降解[116]。膝盖下脂肪垫间充质干细胞外泌体(infrapatellar fat pad MSC-exosomes)通过递送miR-100-5p靶向 mTOR通路,调控自噬水平以维持软骨稳态[45]。

4.2.2 骨质疏松症

骨质疏松症(osteoporosis,OS)是以骨量丢失、骨微结构破坏及骨脆性增加为特征的骨退行性疾病,显著增加髋部骨折风险及致残致死率[117]。OS病理表现为多能干细胞增殖与分化的抑制,骨形成与骨基质生成减少[118],巨噬细胞复极化障碍诱发的慢性炎症微环境[119]。间充质干细胞移植(mesenchymal stem cell transplantation,MSCT)已被证实通过提供MSC-exosomes以改善骨质疏松,同时MSC-exosomes通过传递Fas细胞表面死亡受体(Fas cell surface death receptor,FAS)调控miRNA/DNA甲基化级联,在表观遗传水平上改善了骨基质减少[120]。骨髓间充质干细胞外泌体携带的lncRNA-MALAT1通过microRNA-34c/SATB2信号轴,显著增强成骨细胞分化活性,促进骨基质矿化[38]。Cui等[121]开发的骨靶向工程化外泌体(bone-targeting exosome,BT-Exo-siShn3)整合了MSC-exosomes与靶向Shn3基因的小干扰RNA(small interfering RNA,siRNA),通过骨靶向肽(bone-targeting peptide)精准递送,能够同时发挥增强成骨分化、抑制破骨细胞及促进血管化的多种作用。联合MSC-exosomes与生物仿生材料支架也是一种有效的治疗策略。 将诱导多能干细胞衍生的MSC-exosomes与β-磷酸三钙(β- tricalcium phosphate,β-TCP)支架联用,可显著增强MSC-exosomes在颅骨缺损部位促进骨再生与血管生成的效果[122]。此外,使用微滴支架封装MSC-exosomes与靶向NFATc1(nuclear factor of activated T-cells cytoplasmic 1)基因的siRNA,这一方面能够通过抑制破骨细胞分化的关键转录因子NFATc1,另一方面促进BMSCs的成骨分化,从而实现对骨质疏松性骨折进程的双向调控[123]。

4.3 心脑血管疾病

MSC-exosomes通过递送血管生成相关细胞因子、功能蛋白及非编码RNA等协同调控血管新生与修复,在心血管退行性疾病治疗中展现出显著的血管重塑能力[23]。MSC-exosomes中的miR-150-5p通过靶向调控TGF-β、VEGF及MMP14,改善血管内皮损伤反应并促进血管成熟[46]。此外,MSC-exosomes的miR-423-5p可以转移至人脐静脉内皮细胞(human umbilical vein endothelial cells,HUVECs)发挥促血管生成功能[25]。骨髓来源的MSC-exosomes中的lncRNA H19 通过调控miR-675上调促血管生成因子及细胞间黏附分子1(intercellular adhesion molecule 1,ICAM1),发挥心血管保护效应[47]。MSC-exosomes在治疗心脑血管退行性疾病如动脉粥样硬化、缺血性卒中预防及预后、心力衰竭等方面已有广泛研究。

4.3.1 动脉粥样硬化

动脉粥样硬化(atherosclerosis,AS)是以动脉内膜脂质沉积、炎症细胞浸润及斑块形成为特征的慢性血管病变,其衰老相关的血管内皮功能障碍主要与氧化应激及炎症密切相关[124]。MSC-exosomes可调节AS中的炎症和保护内皮细胞,通过多靶点干预AS核心病理进程。MSC-exosomes 含有的miR-let-7家族通过HMGA2/ NF-κB通路促进斑块内巨噬细胞向抗炎M2型极化,同时经胰岛素样生长因子2 mRNA结合蛋白1(insulin-like growth factor 2 mRNA-binding protein 1,IGF2BP1)/PTEN通路抑制巨噬细胞浸润,显著改善载脂蛋白E(apolipoprotein E,ApoE)缺陷小鼠的动脉粥样硬化[125]。miR-21a-5p通过靶向KLF6/ERK1/2信号轴,抑制促炎M1型巨噬细胞活化,减轻斑块炎症负荷[48]。脂肪间充质干细胞外泌体通过下调动脉粥样硬化相关miR-342-5p,抑制血

管内皮细胞凋亡与氧化损伤[126]。

4.3.2 缺血性中风

缺血性中风(ischemic stroke,IS)是一种与衰老相关的退行性疾病,随着人口老龄化的加剧,IS的绝对数量将显著增加[127]。衰老引发的神经元数量减少、老年胶质细胞积累、炎症因子增多、信号转导异常等会形成促损伤性微环境,进一步导致脑血管发生如动脉硬化和内皮功能受损等退行性变化,减少脑组织对局部缺血的抵抗和恢复能力,使脑组织更易受到缺血性损伤,这些都可能促进缺血性中风的发生[128]。MSC-exosomes可降低脑血管相关炎症反应,改善脑血管受损,可作为预防老年人缺血性中风及改善其后遗症的有效治疗手段。MSC-exosomes被证实可迁移到缺血性脑中,使IL-1β 的表达降低,血管生成和神经发生显著改善[129]。骨髓来源的MSC-exosomes携带的lncRNA ZFAS1通过抑制miRNA-15a-5p缓解IS中的氧化应激和炎症[130]。MSC-exosomes还能够改善缺血性中风后遗症,例如,骨髓来源的MSC-exosomes通过拮抗小窝蛋白-1(caveolin-1,Cav-1)依赖性的闭锁小带蛋白-1(zonula occludens-1,ZO-1)和闭合蛋白-5(Claudin-5)内吞作用,显著修复IS导致的血脑屏障(blood-brain barrier,BBB)损伤[131]。

4.3.3 心力衰竭

心力衰竭(heart failure,HF)是一种与衰老相关的复杂临床综合征,主要由心脏结构或功能异常导致[132]。随着年龄增长,心脏会发生氧化应激、线粒体功能受损等变化,最终导致心肌细胞纤维化或凋亡,成为老年人产生 HF的重要病因[133]。间充质干细胞在治疗HF中已有广泛应用[134],并已被证实主要通过旁分泌外泌体改善HF [135]。MSC-exosomes递送的miR-129-5p通过靶向TNF受体相关因子3(TNF receptor-associated factor 3,TRAF3),抑制NF-κB信号活化,减少HF中的氧化应激、细胞凋亡、炎症和纤维化[42]。此外,MSC-exosomes中的miR-1246通过抑制丝氨酸蛋白酶23(serine protease 23,PRSS23)表达,显著缓解慢性HF模型的心肌损伤[49]。骨髓MSC-exosomes富集的长链非编码RNA GAS5通过激活UL3(ubiquitin-like protein 3)依赖性Hippo通路,促进Yes相关蛋白(Yes-associated protein,YAP)及其PDZ结合基序转录共激活因子(transcriptional coactivator with PDZ-binding motif,TAZ)核转位,有效抑制铁死亡,减轻心肌氧化损伤[50]。

以上大量研究证实了MSC-exosomes在治疗退行性疾病中的应用潜力:其可通过各类活性成分调节炎症反应以促进神经、骨及心脑血管退行性疾病中的组织修复,同时能保护神经细胞和骨细胞而改善神经及骨退行性疾病;此外,MSC-exosomes还能够降解与神经退行性疾病病理相关的异常蛋白质(图2)。

5 未来展望

衰老及多种退行性疾病已被证实与细胞信号通路失调以及炎症衰老密切相关[116,136]。目前,越来越多的退行性疾病治疗开始注重“炎症消退”理念,炎症消退被认为是一个主动的、程序化过程。在炎症治疗中,综合型的消退素可能比单一的抗炎药物更有效[1]。间充质干细胞外泌体作为一种细胞的“年轻信号”,其内含的抗炎相关蛋白质、大量的miRNA,以及lncRNA能在多个层面上调节衰老及疾病状态下的炎症反应,为基于炎症消退理念治疗衰老相关疾病提供了新可能。MSC-exosomes正在成为无细胞疗法治疗衰老相关退行性疾病的新兴工具。然而,MSC-exosomes的临床应用也面临诸多挑战:缺乏足够数量的系统临床试验,产品存在异质性,缺乏统一的质量规范和剂量标准,以及满足大规模生产的各环节的技术均不成熟等。因此,需要更多临床研究以及能够解决临床转化问题的临床前研究才能将MSC-exosomes真正推向临床应用。

大量研究表明MSC-exosomes含有多种有效抗衰成分,在衰老有关的退行性疾病的治疗中有着广阔的应用前景。然而,目前的相关研究多集中于精密的基础研究,缺少系统整体的临床试验,阻碍了MSC-exosomes临床转化。最近的临床研究有了一项新突破,2023年,上海交通大学医学院附属瑞金医院王刚教授团队完成了采用MSC-exosomes喷鼻治疗AD的国际首个临床试验(Clinical Trial NCT04388982),结果表明,人脂肪来源的MSC-exosomes经鼻内给药治疗AD是安全的,并指出能够大规模进行临床应用的安全高剂量为4×10^8颗粒[137]。在该临床研究的成果基础上,相信未来会有更多可靠的临床试验完成,MSC-exosomes在抗衰老相关疾病中的临床转化将

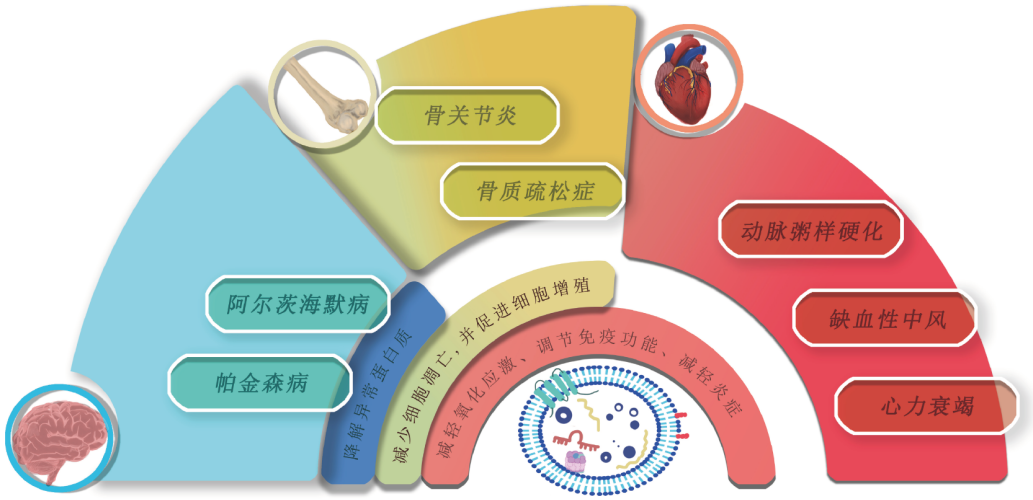

图2　间充质干细胞外泌体通过多种机制协同改善多系统退行性疾病

Figure 2　Mesenchymal stem cell-derived exosomes ameliorate neurodegenerative, osteodegenerative diseases, and cardiovascular degenerative diseases via multi-mechanism synergy

会得到进一步推动。

由于MSC及MSC-exosomes的异质性，MSC-exosomes 的表型和功能可能因 MSC 的来源而异，如前文所述，不同来源的MSC-exosomes富集的蛋白质组分具有显著差异；此外，人骨髓和脂肪组织中MSC-exosomes的RNA组成成分也有差异，这可能与MSC的分化状态有关[138]。MSC 的来源被认为会影响 MSC-exosomes的治疗效果[65]，研究表明，MSC-exosomes的来源会导致其在免疫表型、分化能力和免疫细胞调控等方面上存在差异，从而影响其在不同临床应用中的适用性[139]。目前，不同类型的MSC-exosomes适用于具体某一类衰老退行性疾病尚无明确研究，因此MSC-exosomes在正式应用于临床前还需开展更多验证MSC-exosomes的系统作用机制的研究，明确不同来源的MSC-exosomes适用疾病类型的问题。尽管目前有大量的研究基础，但研究中的给药剂量因给药途径和疾病而异，也缺乏统一的MSC-exosomes的质量规范和剂量单位，如有的研究根据MSC-exosomes的质量（微克为单位）制定剂量，有的则以MSC-exosomes的颗粒数目（个/mL为单位）为依据[140]，这导致整合各类基础研究之间的参照剂量存在困难，进一步导致难以明确临床应用剂量的问题。因此，在设计临床应用的MSC-exosomes前需制定统一的质量规范和剂量单位，或者探索两种单位之间可以明确转化的关系。此外，在规模化生产过程中，MSC-exosomes的分离纯化、储存以及递送等关键技术仍面临诸多挑战，这些问题也限制了其临床转化和应用。在应用前生产中，可以考虑结合两种或多种提纯技术，如利用超滤技术先对MSC-exosomes进行预处理，再结合免疫捕获亲和对其进一步纯化与富集，在生产的关键阶段运用微流控系统对外泌体进行定时定量的质量分析以把控外泌体质量。为了在递送MSC-exosomes时最大限度地发挥其的治疗功能，将MSC-exosomes与多种生物支架材料进行复合应用可提高滞留效果与释放效率。然而，有研究表明生物支架材料的降解产物可能引发机体免疫反应等系统性副作用[141]。因此，设计MSC-exosomes抗衰产品的递送载体时需进一步探究和评估其安全性。

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