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脂肪间充质干细胞及其衍生物改善皮肤衰老的研究进展

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摘　要

脂肪间充质干细胞(ADSC)及其衍生物在皮肤抗衰老领域展现出广阔的应用前景。皮肤衰老涉及氧化应激、自噬－凋亡失衡、慢性炎症及胶原代谢紊乱等多重机制。ADSC通过旁分泌效应，其条件培养基、细胞外囊泡及外泌体等衍生物能够在分子层面清除活性氧、修复线粒体功能；在细胞层面调控自噬与凋亡平衡、抑制炎症反应；在组织层面促进胶原合成、抑制胶原降解，从而维持皮肤稳态。尽管ADSC衍生物在标准化生产、递送效率及临床证据方面仍面临挑战，但随着工程化修饰与递送技术的进步，其有望成为改善皮肤衰老的关键治疗策略。

关键词

脂肪干细胞，皮肤衰老，细胞外囊泡，外泌体，氧化应激，胶原代谢

Research Progress on Anti-Skin Aging Effects of Adipose-Derived Mesenchymal Stem Cells and Their Derivatives

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Abstract

Adipose-derived stem cells (ADSC) and their derivatives demonstrate promising potential in the field of skin anti-aging. Skin aging involves multiple mechanisms including oxidative stress, dysregulation of autophagy-apoptosis balance, chronic inflammation, and collagen metabolic disorders. Through paracrine effects, ADSC-derived conditioned medium, extracellular vesicles, and exosomes exert therapeutic effects at multiple levels: eliminating reactive oxygen species and restoring mitochondrial function at the molecular level; regulating autophagy-apoptosis balance and inhibiting inflammatory responses at the cellular level; and promoting collagen synthesis while inhibiting collagen degradation at the tissue level, thereby maintaining skin homeostasis. Although challenges remain in standardized production, delivery efficiency, and clinical evidence for ADSC derivatives, advancements in engineering modification and delivery technologies position them as promising therapeutic strategies for ameliorating skin aging.

Keywords

Adipose-Derived Stem Cells, Skin Aging, Extracellular Vesicles, Exosomes, Oxidative Stress, Collagen Metabolism

1. 引言

作为人体最大的器官，皮肤承担了体温调节、抵御各种环境威胁的作用。皮肤老化是一个自然发生的过程，其中外界因素如紫外线、环境污染、作息、烟酒等都可能影响皮肤的衰老进程。皮肤衰老不仅伴随着皮肤外表的褶皱、弹性下降、色素沉积，还会影响正常功能，削弱其冷热觉及触觉感知能力、屏障功能等[1]，甚至可能形成老年雀斑样痣、光化性角化病等需要治疗的皮肤疾病，甚至发生恶变形成基底细胞癌、黑色素瘤和鳞状细胞癌[2]，从而对生命健康造成损害。因此，深入了解并寻找改善皮肤衰老的有效疗法具有科学意义与临床价值。

自 A. J. Friedenstein 首次报告间充质干细胞(MSC)以来，MSC 研究已经走过半个世纪的历程。作为能够分化为成纤维细胞及其他中胚层细胞谱系的克隆源性前体细胞，MSC 在再生医学中展现出巨大的应用潜力[3]。近年来，基于 MSC 的疗法已在多种疾病模型和临床试验中取得了良好成效[4]。在骨髓、脐带、胎盘、牙髓等多种来源的间充质干细胞中，脂肪组织提取的脂肪间充质干细胞(ADSC)以其来源易得、伦理安全性高、旁分泌丰富在研究中引起了广泛关注[5]。

然而，活细胞移植仍面临伦理安全、致瘤性、免疫排斥等挑战。随着研究的不断深入，MSC 的作用机制逐渐明确，其治疗效应被认为主要依赖于旁分泌活性物质。基于这一认识，研究者们提取出干细胞治疗的无细胞替代物，即 ADSC 分泌组进行研究干预，其中尤以细胞外囊泡、外泌体等受到诸多关注[6]。许多研究表明，ADSC-EV、ADSC-Exo 能够在治疗中体现 ADSC 移植的优势，如促进组织再生、抗炎修复，在心脑血管疾病、肺炎、肝损伤及肝纤维化、皮肤创面、关节炎等问题中均能发挥作用[7]。此外，随着干细胞研究的深入发展，其他干细胞衍生物随之出现，包括大片段核酸、线粒体、细胞膜片复合型衍生物等[8]，这些衍生物的传递效用还处在研究早期，但在局部治疗中显现的生物学效应已初步印证了

其组织修复潜力。

MSC 具有促进组织修复和再生的强大能力，体内干细胞植入能够一定程度上延缓衰老，因此，干细胞移植在抗衰老治疗领域具有应用潜力[9]。在皮肤年轻化问题上，干细胞同样占据重要地位，以其促进胶原再生、抑制皮肤炎症的能力为改善皮肤衰老问题带来了新的解决思路。本综述系统梳理了 ADSC 在改善皮肤衰老领域的相关研究，重点关注干细胞分泌组、细胞器移植等无细胞衍生物的应用，旨在整合 ADSC 促进皮肤年轻化的证据，为干细胞相关治疗在皮肤抗衰领域中提供未来展望。

2. 皮肤衰老的特征与机制

人体皮肤主要由表皮层、真皮层及皮下组织三个层次组成[10]。表皮主要由角质形成细胞构成，它们产生的角蛋白构成角质层，形成机体的外层物理屏障。真皮层则主要包含成纤维细胞，其分泌的胶原纤维束紧密排列，与弹性纤维、透明质酸共同形成复杂的三维细胞外基质(ECM) [11]。胶原蛋白约占皮肤干重的 90%，是维持皮肤结构和功能的主要蛋白，因此成纤维细胞在 ECM 的合成和维持中发挥关键作用[12]。和其他器官类似，皮肤衰老涉及内源性老化和外源性老化两大维度。内源性老化由年龄增长和激素变化驱动；而作为身体的保护屏障，皮肤持续暴露于环境影响因素之下，其中尤以紫外线辐射带来的光老化最为显著。

首先，人体皮肤外观随着衰老发生显著改变，皱纹、色素沉积、干燥粗糙等都是常见的皮肤老化表现，这将从心理与情感上影响人们的生活质量。其次，从结构上讲，这些变化切实发生于表皮层和真皮层的萎缩，从功能上显著阻碍了表皮层抵御环境损伤和防止水分流失，也使得皮肤不再稳定、血运不佳，带来伤口愈合缓慢及皮肤肿瘤易感性增加等诸多问题[13]。

与年轻皮肤相比，衰老皮肤表皮基底的网状嵴扁平化，表皮－真皮接触面积缩小[13]；同时角质形成细胞的更新和分化能力下降，细胞间连接与粘附分子的表达减少[14]。分子层面的研究显示，老年或长期紫外线暴露的人体皮肤中，多种促进胶原降解的基质金属蛋白酶(MMPs)表达上调[15]，而胶原蛋白 17A1 (COL17A1)表达显著下调[16]。在真皮层，衰老带来了一系列胶原纤维排列紊乱、胶原合成减少以及慢性低度炎症状态[17]，最终形成了异常的 ECM 稳态。具体而言，MMPs 及促炎因子 Il-1β、IL-6 和 IL-8 表达增加[18]，同样地，I 型与 III 型胶原(COL-1、COL-3)的表达减少，而在调控 ECM 合成中占重要地位的 TGF-β/SMAD 信号通路表现出下调趋势，从而负向调节胶原蛋白稳态[13]。

从衰老相关分子的表达到衰老细胞的累积，再到皮肤结构退行性改变与功能衰退、疾病发生，皮肤衰老是一个多因素影响的复杂过程。清除衰老细胞和逆转衰老表型已成为皮肤衰老及相关疾病的重要策略[14]，而在多种临床或临床前的改善手段中，ADSC 及其衍生物正展现出广阔的治疗前景。

3. ADSC 在皮肤衰老治疗中的应用

ADSC 是一种起源于脂肪组织的 MSC，具有与 MSC 相同的特征，能够向成骨、成软骨和成脂三种细胞谱系分化，同时表达 CD73、CD90 和 CD105 等表面标志物，不表达 CD11b、CD14、CD19、CD45 和 HLA-DR [19]。ADSC 的脂肪组织来源、分离方法都可能影响其细胞质量与治疗功能，目前多从易于取得的皮下白色脂肪组织中分离获得[20]。

自 1990 年代中期以来，自体脂肪移植便已成为整形外科的常规技术，脂肪填充也被认为是合成聚合物填充剂的替代方案[21]。作为脂肪移植后存活的关键细胞组分[22]，ADSC 在整形美容外科的应用中已被证明是安全的，且在减少和预防光老化的真皮细胞方面发挥关键的生物和治疗作用[23] [24]，体外数据表明，富血小板血浆(PRP)培养基中培养的 ADSC 对真皮成纤维细胞和角质形成细胞的增殖和迁移具有刺激作用[25]，提示其具备支持再上皮化潜力的能力，并通过旁分泌活性因子维持组织稳态。动物实验进

一步证明，ADSC 可上调部分促血管生长因子的表达，在大体层面改善皮肤灌注、增加皮肤厚度[26]。总的来说，ADSC 一方面通过分泌生长因子、细胞因子、趋化因子和血管生成因子发挥强大的旁分泌作用[27]，另一方面通过细胞分化补充衰老细胞池，从多维度促进衰老皮肤的再生修复，在皮肤年轻化治疗中展现出高度潜力[28]。然而，ADSC 在皮肤疾病的临床应用中仍存在许多问题：活细胞递送存在免疫排异与潜在致瘤风险；移植后的 ADSC 存活时间非常短暂；且获取自体 ADSC 需通过抽脂等侵入性操作，其风险收益比尚需进一步评估[29]。

4. ADSC 衍生物在皮肤衰老治疗中的应用

4.1. 条件培养基

基于 ADSC 强大的旁分泌作用，作为 ADSC 疗法的无细胞治疗替代，ADSC 来源的条件培养基(ADSC-CM)迈出了探索的第一步。许多研究表明，ADSC-CM 富含多种活性成分，如碱性成纤维细胞生长因子(bFGF)、肝细胞生长因子(HGF)及血管内皮生长因子(VEGF)等[30]。

一项随机对照试验显示，采用微针导入 ADSC-CM 蛋白提取物可改善皮肤黑色素水平、亮度、皮肤光泽、粗糙度、弹性和皱纹[31]。体外研究表明，ADSC-CM 能够上调真皮成纤维细胞和角质形成细胞中 I 型前胶原蛋白合成，促进 TGF-β 生成，同时抑制紫外线诱导的 AP-1 和 NF-κB 激活[32]。其还能够替代 ADSC 在成纤维细胞中产生的作用，即通过 Wnt/β-catenin 信号通路增大皮层厚度并刺激成纤维细胞增殖[33]，减少紫外线诱导的基质金属蛋白酶-1(MMP-1)表达和细胞凋亡，上调 COL-1 水平[34]。此外，一些研究尝试预处理 ADSC 并取得富含特定活性因子的 CM，如 H_2O_2 预处理 ADSC 以诱导其对氧化应激的反应能力[35]，或通过预缺氧处理 ADSC 激活缺氧诱导因子-1α (HIF-1α)分泌更多细胞因子[36]，以进一步提升治疗效果。ADSC-CM 不仅避免了干细胞治疗的安全性问题，还降低了治疗成本；同时，CM 的无细胞替代治疗大大增加了基于干细胞抗衰策略的灵活性与可控性。

4.2. 细胞外囊泡与外泌体

细胞外囊泡(EV)是由细胞分泌的脂质双层膜分隔的颗粒，通常大小不一，内含脂质、蛋白质、DNA、mRNA 和 miRNA 等多种生物活性分子。外泌体作为 EV 的一个亚群[37]，通常直径在 30~200 纳米[38]。EV 发挥作用的方式在于被微环境中的细胞摄取，以此传递蛋白质、核酸及其他活性物质，介导细胞间通讯，调控受体细胞的生物反应。与全细胞递送相比，EV 与 Exo 具有低免疫原性、伦理安全性、易于质控及保存等优点，同时又在功能上保留了 ADSC 对多种疾病有效的治疗潜能。

在体内与体外实验中，ADSC-EV 及 Exo 已被证实能够改善皮肤细胞衰老表型，其作用涉及调控氧化应激、细胞增殖及胶原代谢。另外，有研究者尝试对 EV 进行其他天然化合物的装载，利用其跨膜递送特性改进天然化合物稳定性差、皮肤吸收困难的缺陷，展现出良好的抗氧化、抗皱和抗黑色素作用[39]，这提示 EV 在高效传递内源性及外源性物质上都具备潜力。

得益于制备工艺的可控性，ADSC-EV 及 Exo 已进入多项临床研究，其安全性与有效性得到初步验证。一项前瞻性研究显示，运用微针导入 ADSC-Exo 可显著改善面部皮肤皱纹、弹性、水分和色素沉着[40]。另有一项研究分别运用射频微针与外用涂抹 Exo 进行面部抗衰治疗，结果显示其效果与富血小板血浆(PRP)无显著差异[41]。

4.3. 其他衍生物：线粒体与工程化微囊泡

MSC 移植后细胞间的线粒体转移现象于 2005 年的研究中首次报道[42]。随后研究发现，这一过程并非偶然，而是 MSC 修复受损细胞的重要机制之一。MSC 可通过隧道纳米管、微囊泡或细胞融合等方式，

将功能完整的线粒体转移至靶细胞，以恢复其氧化磷酸化功能和能量代谢平衡[43]。

近年来，ADSC 来源的线粒体移植(ADSC-mt)在多种疾病模型中展现出治疗潜力。Zhai 等建立了双侧海绵体神经损伤大鼠模型，发现 ADSC-mt 移植可显著改善勃起功能，其作用与降低活性氧水平、抑制细胞凋亡、恢复海绵体平滑肌细胞 ATP 生成密切相关[44]。在皮肤相关研究中，Dong 等构建了含有功能性线粒体的去核干细胞微囊泡(Mito-MVs)，证实其能够被高糖诱导的衰老成纤维细胞和内皮细胞摄取，恢复线粒体膜电位，延缓细胞衰老表型；在糖尿病小鼠全层皮肤缺损模型中，Mito-MVs 局部应用显著促进了创面再上皮化和血管新生[45]。这些研究提示，ADSC-mt 不仅能够通过能量补给直接挽救受损细胞，还可调控炎症反应和氧化应激，具有改善皮肤衰老微环境的潜力。

在递送方式上，除直接提取并移植外，研究者尝试将线粒体包裹于去核细胞形成的微囊泡中以保护线粒体完整性和促进靶细胞摄取[45]。此外，利用工程化外泌体递送线粒体 DNA，也在初步实验中显示出对线粒体功能的修复效应[46]。尽管如此，线粒体衍生物的研究仍处于早期阶段，但随着研究的深入，线粒体与工程化微囊泡有望作为现有无细胞疗法的进一步补充，在皮肤抗衰老治疗中发挥独特价值。

5. ADSC 及其衍生物改善皮肤衰老的作用机制

5.1. 通过抑制氧化应激延缓衰老

氧化应激是驱动皮肤衰老的核心机制之一，可导致细胞损伤、胶原合成减少及细胞通讯紊乱[47]。活性氧(ROS)主要来源于细胞氧化代谢和紫外线辐射，过量的 ROS 会直接损害细胞，激活 MAPK 和 NF-κB 信号通路，增加促炎细胞因子如 IL-1β、TNF-α、IL-6 和 COX-2 的表达[48]，同时激活 MMPs 和组织金属蛋白酶抑制剂(TIMPs)表达使二者出现比例失衡，减少胶原蛋白产生、破坏 ECM 稳态[49] [50]，最终加速皮肤衰老进程[51]。

ADSC 衍生物在清除 ROS 及保护线粒体功能方面表现出直接效应。ADSC-Exo 能够穿越细胞双层以靶向作用于特定的细胞区域，维持细胞活性、促进组织修复，从而减轻氧化应激[52]，实现预防和治疗皮肤衰老。另外，ADSC-Exo 可显著降低衰老成纤维细胞中的 ROS 水平[53]，以此维持皮肤关键细胞的功能与活性；ADSC-EV 可减轻光老化小鼠皮肤中巨噬细胞浸润和 ROS 产生，上调光老化成纤维细胞中抗氧化酶的表达，抑制成纤维细胞产生细胞周期停滞[54]。机制层面上，ADSC-Exo 通过激活 PINK1/Parkin 通路促进受损线粒体自噬，遏制氧化损伤进展[55]；也可通过 TIMP1/Notch1 通路抑制 Notch1 和下游靶点 Hes1、p16、p21、p53 表达，减轻 DNA 损伤和 ROS 水平[56]。

5.2. 通过调控自噬与凋亡平衡维持细胞稳态

自噬通过清除受损蛋白、脂质及细胞器维持细胞稳态，是细胞应对损伤应激的重要机制[57]。MAPK/NF-κB 信号通路与自噬密切相关，可能作为氧化应激诱导皮肤衰老与自噬的潜在连接点[51]。在皮肤衰老过程中，自噬功能在不同情境下表现出复杂的双重效应：一方面，基础水平的自噬通过清除受损蛋白质和细胞器发挥保护效应；另一方面，应激诱导的自噬失调则可导致细胞功能障碍[58]。自噬与凋亡之间亦存在交互调控，自噬功能受损常伴随凋亡信号的激活。而过度凋亡会导致皮肤成纤维细胞和角质形成细胞数量减少[59]，组织结构退行性变。

研究显示，ADSC-Exo 能通过多种途径恢复衰老细胞中受损的自噬功能。在成纤维细胞衰老模型中，ADSC-Exos 显著上调自噬相关蛋白 LC3II/I 比值，降低 p62 水平，提示细胞自噬功能得到恢复。该效应部分依赖于 PINK1/Parkin 通路介导的线粒体自噬[55]。也有体外实验表明，ADSC-EV 通过激活自噬减少肌腱成纤维细胞纤维化，能够促进组织高质量愈合[60]。此外，经成纤维细胞生长因子 1 (FGF1)预处理

ADSC 来源的工程化外泌体可抑制氧化应激，减轻内皮细胞中的凋亡[61]，显著提高皮瓣移植的存活率。

5.3. 通过免疫与炎症调节改善衰老微环境

衰老过程伴随 DNA 损伤和 ECM 碎片累积，可激活炎症小体，促进 IL-1β、IL-1α、IL-6 和 TNF-α 等炎症因子分泌[62]；另外，衰老细胞的堆积并呈现出促炎的衰老相关分泌表型(SASP)，能够刺激大量促炎和抗炎介质的表达[63] [64]，进一步放大局部炎症反应。紫外线暴露还能引发皮肤免疫失调，且持续的炎症和免疫抑制状态可能参与皮肤光老化进程[65]。持续的炎症与紫外线直接作用都会引起 Treg 细胞的扩增[66] [67]，引发免疫抑制，虽可避免组织发生过度强烈的炎症反应，但长期的免疫失衡同样会扰乱皮肤稳态[65]，诱导免疫衰老。

ADSC 及其衍生物可通过多种途径调控炎症与免疫微环境。光老化裸鼠皮肤经 ADSC 干预后，巨噬细胞浸润减少，且呈现出从促炎 M1 表型向抗炎 M2 表型转变的趋势，提示 ADSC 具有较强的免疫调节作用[68]。此外，ADSC-Exo 携带的 miRNA 可靶向 NF-κB 通路，抑制 SASP 相关促炎因子 IL-6、MMP-1 的释放，从而调节免疫微环境，改善衰老相关的慢性炎症[69]。

5.4. 通过缓解胶原代谢失衡维持 ECM 稳态

ECM 的完整性决定了皮肤的厚度与弹性，而组成 ECM 的胶原代谢受 TGF-β/SMAD 与 MAPK/AP-1 通路的精密调控。经紫外线照射产生的皮肤衰老通常使得 ECM 稳态从胶原生成与沉积转变为胶原破裂与降解，导致胶原流失与真皮变薄[70]。

ADSC 通过促进胶原合成与抑制胶原降解的双向调节机制，维持真皮厚度与 ECM 稳态。一方面，ADSC 可直接分泌 TGF-β1 等生长因子，激活成纤维细胞 TGF-β/SMAD 信号通路[32]；或通过 Wnt/β-catenin 通路促进成纤维细胞增殖，增加胶原合成[33]。另一方面，ADSC-Exo 可通过 miR-1246 靶向调控 TGF-β/SMAD 通路、抑制 MAPK/AP-1 通路活性，下调 MMP-1 表达，上调 I 型前胶原蛋白分泌[71]。动物实验显示，ADSC-Exo 局部注射能够增加光老化小鼠皮肤胶原沉积和真皮厚度[54]；临床研究中，ADSC 局部皮下注射也能够观察到真皮浅层弹性纤维增加，胶原和网状纤维网络排布更为有序[24]。这些机制共同支持 ADSC 相关治疗在改善皮肤厚度与弹性、减少皮肤皱纹及松弛方面的应用潜力。

6. ADSC 衍生物的临床转化现状

6.1. 与现有主流抗皮肤衰老疗法的比较

现有抗皮肤衰老疗法主要分为外用药物、能量设备和注射填充[72]。外用维 A 酸类药物是目前治疗光老化的金标准药物[73]，通过激活维 A 酸受体调节基因转录，促进胶原合成、抑制 MMP 表达[74]。但其主要局限包括：皮肤刺激和光敏性，长期使用耐受性下降[75]。射频、超声、激光等仪器类疗法通过可控的热损伤启动皮肤修复机制，诱导胶原重塑，其疗效稳定但存在恢复期、术后色素沉着风险，且对皮肤水合作用和色素改善的综合效果有限[76]。透明质酸(HA)、聚左旋乳酸、多核苷酸等注射材料则通过容积补充刺激胶原再生，其效果立竿见影但维持时间短暂，并且对操作者的技术与审美有较高的要求[72]。

与现有疗法相比，ADSC 衍生物的核心特征在于：从单一的成分补充转向多靶点的内源性修复。外源性 HA 填充在体内代谢迅速，而工程化 ADSC-EV 递送的 HYAL2 siRNA 可刺激内源性 HA 代谢平衡，维持时间更长[77]。与光电仪器相比，ADSC 分化细胞不仅促进胶原再生，还通过调节色素相关基因表达改善肤色不均[78]。如同前文所提，ADSC 衍生物对皮肤年轻化的作用是体现在多方面、多维度的，包括抑制氧化应激、维持 ECM 与细胞稳态、调控炎症与免疫。然而，其疗效主要体现在基础研究中，在人体上能否同样发挥良好作用有赖于临床试验的进一步推进。

6.2. ADSC 衍生物临床试验进展

截至 2025 年，ADSC 衍生物抗皮肤衰老的临床研究仍处于早期探索阶段，以单臂、小样本、短期随访研究为主(见表 1)。研究类型主要包括 ADSC 条件培养基(ADSC-CM)和外泌体(ADSC-Exo)两大类，给药方式以微针或激光辅助透皮递送为主[79]。

Table 1. Clinical study of ADSC derivatives on anti-skin aging
表 1. ADSC 衍生物抗皮肤衰老临床研究

研究来源	衍生物	样本量	年龄范围	干预方式	治疗频率	随访时间	疗效	不良事件
Yusharyahya 等[80]	ADSC-CM	30	35~59 岁	微针或点阵激光辅助	4 周 1 次，共 2 次	6 周	细纹改善，色素、弹性等无显著差异	红斑、疼痛、烧灼感，可能与递送方式相关
Wang X 等[31]	ADSC-CM 蛋白提取物	30	40~63 岁	微针	2 周 1 次，共 6 次	12 周	黑色素指数、皮肤亮度、光泽、皮肤粗糙度、弹性和皱纹方面改善	未见
Estupiñan B 等[41]	ADSC-Exo	15	44~68 岁	涂抹	4 周 1 次，共 3 次	6 个月	皱纹、肤色、红斑、肤质改善	未见
Park GH 等[40]	ADSC-Exo	28	43~66 岁	微针	3 周 1 次，共 3 次	12 周	皱纹、弹性、水合、色素改善，胶原、弹性纤维增加	一过性红斑、水肿、瘀点，1 周内消退
Svolacchia F 等[81]	ADSC-Exo、ADSC-纳米囊泡	72	34~68 岁	注射	1 次	1 月	皱纹、柔软度、皮肤含水改善	未见

6.3. 监管挑战与产业化瓶颈

上述临床试验表明，ADSC 衍生物虽具有安全性和有效性，但存在局限性：其分离纯化方式、给药剂量尚未统一[82]；为提高衍生物递送效率，现有研究多联合微针，有创的递送方式可能引发红斑、疼痛等局部反应[80]。超速离心法作为目前分离 EV 最常用的手段，也还是存在回收率低、EV 聚集等缺点[83]。因此，尽管 ADSC 衍生物在临床前和早期临床研究中展现出良好前景，从实验室走向临床应用仍面临多重障碍。

除此之外，ADSC 衍生物的产品属性认定不清晰也使其在监管上存在困难。ADSC 外泌体应归类为生物制品、细胞治疗产品还是化妆品原料，各国监管机构尚未形成共识。在美国，外泌体可能被食品药品监督管理局(FDA)监管为生物药品[84]，欧盟则可能将其归入先进治疗药物产品(ATMP)范畴[85]。我国国家药监局药品审评中心(CDE)目前将 Exo、EV 列入先进治疗药品(ATMP)中[86]，ADSC 衍生物的皮肤抗衰应用将接受更严格的监管。

在脂肪组织的采集上，如为异体来源，其伦理合规性、商业化后的利益分配等问题，也需充分考量[87]。使用 ADSC 衍生物虽可减小干细胞移植的致瘤性与免疫原性风险，实现规模化生产，但异体来源的生物制品的病原传播风险仍需在临床转化中持续监测[88]。

7. 总结与展望

ADSC 及其衍生物能够通过多靶点干预皮肤衰老，已展现出独特的抗衰潜力。它能够在分子层面清除 ROS 并修复线粒体功能，抑制过度的氧化应激；在细胞层面抑制衰老相关炎症，调节免疫[89]；在组

织层面通过 TGF-β/SMAD 通路促合成、MAPK/AP-1 通路抑降解维持皮肤的胶原代谢平衡[90] [91]。这种多个层次发挥作用的治疗模式，使其区别于传统疗法仅作用于单一通路的局限。

然而，ADSC-Exo 在临床应用仍存在挑战。大规模的标准化生产体系还未建立，临床应用证据也尚不充分。基于上述分析，ADSC 衍生物抗衰的临床转化需要多维度协同推进：1) 外泌体的标准化生产与储存工艺，如低温真空条件下脱水干燥，从而延长其储存时间并维持活性[92]；2) 工程化修饰 ADSC 后获取衍生物，如予基因修饰、低氧预处理、3D 培养等处理[35] [36]；3) 改进递送方法，从局部注射、静脉注射到联用微针、水凝胶等递送系统，以实现缓释功能、提高皮肤吸收效能[93] [94]。可以预见，外泌体改善皮肤衰老的领域正从基础迈向临床转化，该领域将向着更加安全、更加精准、更加产业化的方向发展。随着基础研究向临床转化加速，ADSC 及其衍生物有望成为皮肤抗衰领域的关键性疗法。

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