·综　述·

# 外泌体在自身免疫性疾病中的研究进展

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**摘要**：外泌体是细胞分泌的直径 40~160 nm 的双层脂质囊泡，可通过调节炎症及免疫反应参与自身免疫性疾病进展。外泌体不仅可作为疾病诊断和预后评估的生物标记物，而且可作为天然的纳米载体用于传递功能性 RNA、蛋白质和合成药物，在疾病治疗方面显示出临床应用的潜力。本文综述外泌体在自身免疫性疾病中的研究进展。

**关键词**：外泌体；自身免疫性疾病；细胞来源；间充质干细胞；类风湿关节炎；干燥综合征；炎症性肠病

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## Research progress of exosomes in autoimmune diseases

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**Abstract**: Exosomes are double-layer lipid vesicles with diameter in 40-160 nm secreted by cells, which can participate in the progression of autoimmune diseases by regulating inflammation and immune responses. Exosomes can be not only served as biomarkers for disease diagnosis and prognosis assessment, but also as natural nanocarriers for delivering functional RNA, protein and synthetic drugs, showing potential for clinical application in disease treatment. This paper reviews the research progress of exosomes in autoimmune diseases.

**Keywords**: Exosome; Autoimmune diseases; Cell source; Mesenchymal stem cells; Rheumatoid arthritis; Sjogren's syndrome; Inflammatory bowel disease

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外泌体(exosomes)是直径 40~160 nm 的细胞外囊泡[1]。细胞膜内陷形成了早期分选内小体(ESE)，ESE 成熟为晚期分选内小体(LSE)，最终形成富含腔内小泡的多囊体(MVBs)[2-3]。MVBs 可以与溶酶体或自噬小体融合而被降解，或可与细胞膜融合将所含的腔内小泡释放，即为外泌体[4-5]。释放至细胞外环境的外泌体可以被邻近细胞内化或经血液循环运送至机体远处，与靶细胞结合改变其生物学活性，参与组织修复与再生、妊娠、衰老、病毒致病性、癌症进展、自身免疫性疾病(autoimmune diseases, AIDs)等多种生理及病理过程[2, 6-8]。AIDs 是机体针对自身抗原发生免疫反应导致自身组织、器官损害的疾病，血液中常存在高滴度自身抗体和(或)能与自身组织成分反应的致敏淋巴细胞。外泌体通过囊泡运输在细胞间传递蛋白质、脂质、核酸，调节炎症、免疫反应参与 AIDs 发生发展[9-10]。本文概述外泌体在 AIDs 中的研究进展以及目前外泌体研究的局限性。

### 1　外泌体在 AIDs 中的研究进展

1.1　类风湿关节炎(rheumatoid arthritis, RA)　RA 是一种以侵袭性、对称性多关节炎为主要表现的慢性 AIDs。外泌体具有高度异质性，不同细胞来源的外泌体发挥的作用不同[11]。成纤维样滑膜细胞(fibroblast-like synoviocytes, FLS)来源的外泌体(FLS-exos)调控趋化因子和细胞因子的释放，在滑膜炎症和血管翳生成过程中发挥作用，导致 RA 关节炎症与破坏[12]。而巨噬细胞、髓样树突状细胞来源的外泌体则具有保

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护作用。巨噬细胞来源的外泌体抑制自身反应性淋巴细胞增殖、增加抗炎因子的释放,发挥抗炎、抗凋亡、抗纤维化作用,减少软骨的降解和关节破坏,抑制滑膜增生和促进软骨再生[13];髓样树突状细胞来源的外泌体则通过主要组织相容性复合体Ⅱ类分子(MHC Ⅱ类分子)和部分 Fas 配体/Fas 依赖机制调节体内抗原提呈细胞和 T 淋巴细胞的活性,有效缓解关节炎症[14]。炎症因子失衡在 RA 的发病和进展中也发挥着重要作用。外泌体 miR-6089 调节 LPS/TLR4(脂多糖/Toll 样受体 4)介导的炎症反应,减少白细胞介素(IL)-6、IL-29、肿瘤坏死因子(TNF)-α 等炎性细胞因子的生成,缓解 RA 症状;外泌体 miR-548a-3p 靶向作用 TLR4 下调炎症反应,有效缓解 RA 关节炎症[15]。破骨细胞和成骨细胞之间的平衡失调导致的异常骨形成或骨丢失也是 RA 重要的发病机制。FLS-exos miR-486-5p 降低人类 ErbB2 转录因子 1 (Tob1)的表达,激活骨形态发生蛋白(BMP)/Smad 信号通路促进成骨细胞的增殖、分化、矿化过程[16];而外泌体 miR-221-3p 则可下调 Dickkopf 相关蛋白 2(Dkk2)的表达来抑制成骨细胞的分化[17]。此外,外泌体还通过其他机制参与 RA 发生发展。外泌体高表达核富集转录本 1(NEAT1),抑制 miR-144-3p 表达,上调 Rho 相关卷曲蛋白激酶 2(ROCK2)的表达,激活 Wnt/β-catenin 通路,促进 $CD4^+$T 细胞的增殖及向 Th17 细胞分化,抑制其凋亡[18];FLSs-exo 携带 miR-106b 从 FLS 转移至软骨细胞,下调丙酮酸脱氢酶激酶 4(PDK4)基因表达,调节核因子 κB 受体活化因子/核因子 κB 受体活化因子配体/骨保护素(RANKL/RANK/OPG)系统,抑制软骨细胞的增殖及迁移,促进其凋亡[19]。外泌体作为 RA 新的生物标记物亦得到了关注。RA 患者血清外泌体 miR-6089、miR-548a-3p 表达水平明显低于健康对照组,且与疾病活动性指标(C 反应蛋白、红细胞沉降率、类风湿因子)呈负相关[15, 20];早期 RA 患者外泌体 miR-451a、miR-25-3p 表达增加,两者联合肿瘤坏死因子样凋亡弱诱导物可用于 RA 的早期临床诊断,敏感性、特异性均良好[21]。外泌体的特性使其成为潜在的生物载体得到了广泛关注,具有以下优点:(1) 特异性高,可将内容物运送到特定的靶细胞;(2) 安全性高,外泌体具有低免疫原性,不会引起不必要的免疫应答且降解后低细胞毒性;(3) 稳定性好,外泌体可在体液中稳定存在;(4) 可穿透多种生物屏障;(5) 分子量小,生物相容性好[22-23]。携带 miR-486-5p 的 FLSs-exo 可抑制关节炎小鼠的软骨侵蚀[16];滑膜间充质干细胞(MSC)来源的外泌体携带 circEDIL3 转移至 FLS,激活信号转导和转录激活因子(STAT)蛋白抑制因子 3,从而抑制 STAT3 的活性并降低下游的血管内皮生长因子的表达,改善 RA 小鼠关节炎的严重程度[24];包封地塞米松磷酸钠的外泌体可下调 RA 小鼠促炎细胞因子水平,上调抗炎细胞因子水平,减轻 RA 关节炎症,保护骨骼和软骨[25]。外泌体可能成为 RA 的新的诊断标记物及疾病活动度指标,其靶向干预也可能成为 RA 潜在的治疗方法。

1.2　系统性红斑狼疮(systemic lupus erythematosus,SLE)　SLE 是一种多系统受累的 AIDs,其特征是机体产生大量致病性自身抗体和炎性细胞因子,导致多器官损伤并伴有各种临床表现。衰老的骨髓 MSC(BM-MSC)在 SLE 发病机制中起着重要作用,外泌体 miR-146a 可被 BM-MSC 内化,靶向调控 TRAF6/NF-κB 通路参与 BM-MSC 衰老[26]。T 细胞来源的外泌体过表达杀菌/通透性增加蛋白,负性调节 Treg 细胞分化,参与 SLE 关节炎、肝炎和肾炎发病[27]。外泌体 microRNAs 作用于浆细胞样树突状细胞中诱导Ⅰ型干扰素的产生,调节炎症反应和适应性免疫,参与 SLE 发病[28]。SLE 患者血清外泌体水平较健康组升高,且高水平的外泌体与疾病活动度有关[29];活动期 SLE 患者外泌体 miR-21 水平显著高于非活动期,与 SLEDAI 评分相关[30];活动期 SLE 患者的血清外泌体 miR-451a 水平相对于非活动期和健康对照组显著降低,且 miR-451a 水平与 SLEDAI 评分呈负相关[31]。活动性狼疮性肾炎(lupus nephritis,LN)患者外泌体 miR-146a 表达增加,与蛋白尿、SLIDAI 评分有相关性[32];SLE 患者外泌体 tRF-His-GTG1 表达上调,联合双链 DNA(dsDNA)作为 SLE 诊断生物标志物的敏感性及特异性均高[33];活动期 LN 患者尿外泌体 miR-21 和 let-7a 水平显著降低,且与 LN 的临床分期密切相关,尿液中 miR-21 可以作为肾脏纤维化和损伤的生物标志物[34-35];治疗应答者组 LN 患者的尿外泌体 miR-31-5p、miR-107 和 miR-135b-5p 水平升高,可作为预测 LN 结局的早期标志物;血清外泌体 miR-451a 表达下调与 SLE 疾病活动和肾损害相关,可作为 SLE 肾损害的生物标记物,经糖皮质激素、羟氯喹等药物治疗可显著提高其表达水平[31]。MSC 来源的外泌体 tsRNA-21109 可抑制巨噬细胞 M1 极化缓解 SLE 症状,可作为 SLE 治疗的新靶点[36]。

1.3　干燥综合征(Sjögren's syndrome,SS)　SS 是一种以外分泌腺淋巴细胞浸润为特征的 AIDs,常累及泪腺、唾液腺等外分泌腺体。外泌体 miR-142-3p 影响肌浆网 $Ca^{2+}$ ATP 酶 2b(SERCA2B)和雷诺丁受体 2(RyR2)调节 $Ca^{2+}$ 和 cAMP 通路从而影响腺体的外分泌功能,参与 SS 的发病[37]。SS 早期临床症状不典型,诊断困难,确诊平均需要 4~5 年[38]。因此,相当多的研究人员深入研究了 SS 外泌体中 RNA 的表达,企图寻找早期诊断 SS 的新型生物标记物。circ-IQGAP2 和 circ-ZC3H6 在 pSS 中表达上调,且与临床特征、血清 IgG 水平和小涎腺病灶积分有相关性[39]。外泌体 miR-142-3p 在 SS 患者唾液腺上皮细胞及炎性浸润细胞中表达上调,而在健康人群低表达或不表达,可作为 SS 早期诊断的新型生物标记物[37]。嗅觉外 MSC 来源的外泌体通过上调精氨酸酶表达、增加活性氧和一氧化氮水平,显著增强了髓源性抑制细胞的抑制功能,从而改善干燥小鼠的症状[40]。唇腺来源 MSC 外泌体治疗可以抑制 Th17 细胞分化,促进 Treg 细胞增殖,减少 IL-17、IFN-γ、IL-6 炎症因子的分泌,减轻干燥小鼠的唾液腺炎症浸润,恢复唾液腺分泌功能[41]。

1.4　炎症性肠病(inflammatory bowel disease, IBD)　IBD 是遗传易感宿主对病原体的免疫应答引起的肠道慢性炎症性疾病,其特征包括黏膜异常免疫应答和肠道屏障功能失调[42]。肠炎小鼠 M1 型巨噬细胞来源的外泌体 miR-21a-5p 表达增

加,降低肠上皮细胞钙黏蛋白表达导致肠黏膜上皮破坏,从而参与 IBD 发病[43]。IBD 患者血浆外泌体中 miR-149-3p 水平显著下调,且 IBD 活动期 miR-149-3p 水平低于缓解期,可用于 IBD 诊断及疾病活动度判断[44]。外泌体作为药物载体在 IBD 领域中也有相应进展。MSC 来源外泌体通过增加 Treg 细胞和 M2 巨噬细胞的比例缓解结肠炎的严重程度[45];调节性 T 细胞来源外泌 miR-195a-3p 增加结肠组织中紧密连接蛋白-1(ZO-1)的表达,降低了 TNF-α、IL-1β、IL-6 等炎性因子表达,有效的减轻小鼠结肠黏膜损伤、炎症细胞浸润、肠上皮细胞凋亡[46];脂肪来源的 MSC 外泌体通过 Treg 细胞诱导和降低 IFN-γ、TNF-α、IL-12、IL-17 等炎症细胞因子的水平,有效缓解结肠炎小鼠的结肠缩短、体重减轻、出血和结肠损伤[47];M2b 型巨噬细胞来源外泌体可转运 CC 趋化因子(CC chemokine, CCL)1 至小鼠结肠,与 CCR8 相互作用,促进 IL-4 的表达,下调 IL-1β、IL-6、IL-17A 的表达,增加 Treg 细胞的百分比,从而缓解小鼠结肠炎严重程度[48]。

## 2　展　望

近年来,外泌体作为液体活检得到了突飞猛进的发展,具有稳定、易获得、鉴定简易、准确度高、非侵入性等优点[49]。目前在 AIDs 领域的外泌体研究仍有不足。第一,虽然外泌体作为新型诊断生物标记物得到了广泛关注,某些生物学分子甚至可以反映疾病活动度及判断预后,但目前尚未应用于临床,与传统生物学标记物相比尚缺乏大规模临床研究证实[50]。第二,尽管外泌体在潜在的治疗应用中显示出了良好的效果,但局限于实验阶段,尚无大规模的临床应用。第三,当前对外泌体作用及作用机制的研究多采用动物模型或离体细胞实验,无相关的体内实验。未来应该更加深入探索外泌体在 AIDs 中的调控机制,为其临床转化提供理论依据。

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