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小细胞外囊泡在代谢相关脂肪性肝病发病机制中的研究进展

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摘　要：代谢相关脂肪性肝病影响全球超过三分之一的人口，其中 5%~10% 的患者会进展为晚期肝病，包括非酒精性脂肪性肝炎或代谢相关脂肪性肝炎、肝硬化及肝细胞癌。目前临床上缺乏针对代谢相关脂肪性肝病的无创诊断标志物和有效治疗药物。因此，阐明其病因机制对开发有效疗法和诊断手段至关重要。小细胞外囊泡在代谢相关脂肪性肝病发生发展的生理病理过程中发挥多重作用，但目前领域内针对其参与代谢相关脂肪性肝病的具体病理机制仍缺乏共识。本文系统整合相关研究，从脂代谢调控、肝脏炎症及纤维化形成三个方面阐述小细胞外囊泡在代谢相关脂肪性肝病发病机制中的核心作用。

关键词：代谢相关脂肪性肝病；小细胞外囊泡；肝脏脂质代谢紊乱；肝脏炎症；肝脏纤维化
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Research progress on the role of sEV in the pathogenesis of MAFLD

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Abstract: Metabolic-associated fatty liver disease (MAFLD) affects over one-third of the global population, with 5%-10% of patients progressing to advanced liver diseases, including non-alcoholic steatohepatitis or metabolic-associated steatohepatitis, cirrhosis, and hepatocellular carcinoma. Currently, in clinical practice there lacks both non-invasive diagnostic biomarkers and effective pharmacotherapies specifically targeting MAFLD. Therefore, elucidating its etiopathogenesis is critical for developing targeted therapeutics and diagnostic modalities. Small extracellular vesicle (sEV) plays multifaceted roles in the pathophysiology of MAFLD onset and progression. However, consensus regarding their pathomechanisms in MAFLD remains elusive in the field. This review systematically consolidates current evidence to delineate the central role of sEV in MAFLD pathogenesis through three interconnected pathways: lipid homeostasis, hepatic inflammation, and fibrogenesis.

Key words: metabolic associated fatty liver disease; small extracellular vesicles; hepatic lipid metabolism disorder; hepatic inflammation; hepatic fibrosis

随着全球肥胖与糖尿病患病率的不断上升，代谢相关脂肪性肝病 (metabolic associated fatty liver disease, MAFLD)，即非酒精性脂肪性肝病 (non-alcoholic fatty liver disease, NAFLD) 已成为重大公共卫生问题。NAFLD 是一类疾病的总称，涵盖从非酒精性脂肪肝 (non-alcoholic fatty liver, NAFL) 到非酒精性脂肪性肝炎 (nonalcoholic steatohepatitis, NASH) 的疾病谱 [1]。NASH 作为 NAFLD 的严重形式，以脂肪堆积、炎症伴或不伴纤维化为特征，可进一步进展为肝纤维化 (liver fibrosis, LF)、肝硬化及肝细胞癌 (hepatocellular carcinoma, HCC) 等晚期

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肝病[2]。鉴于NAFLD与代谢紊乱密切相关，现已更名为代谢相关脂肪性肝病(MAFLD)，而NASH则更名为代谢相关脂肪性肝炎(metabolic dysfunction-associated steatohepatitis, MASH)[3]。尽管已知多种病理生理过程参与MAFLD的发生，但脂肪变性进展为MASH的机制尚未完全阐明，给临床诊疗带来巨大挑战。因此，阐明其潜在发病机制对其早期诊断与治疗至关重要。

MAFLD的全球患病率约30%，是最常见的慢性肝病[4]。此外，作为代谢综合征的肝脏表现，MAFLD还与肥胖、糖尿病、高血压、血脂异常、胰岛素抵抗等代谢综合征特征密切相关[5-7]。值得注意的是，MAFLD的发病机制复杂，由多种因素驱动，涉及脂质代谢紊乱、肝脏炎症加剧及肝纤维化形成[8]。其中，胰岛素抵抗和肥胖引起的肝细胞脂质积累是起始事件，有毒脂质蓄积诱导内质网应激，从而促进MAFLD的进展。脂质过载的肝细胞释放炎症因子、小细胞外囊泡(small extracellular vesicle, sEV)等介质，激活肝巨噬细胞等免疫细胞，促进肝脏炎症[9]。随着疾病进展，肝巨噬细胞浸润是触发MAFLD向MASH转变的关键驱动因素。肝巨噬细胞和脂毒性肝细胞局部分泌的细胞因子和趋化因子激活肝星状细胞，导致其过量产生细胞外基质蛋白，促进肝纤维化。然而，参与脂肪变性、炎症和纤维化过程的分子机制和信号通路尚未完全阐明。因此，深入研究其发病机制，对于建立无创诊断方法和制定有效治疗策略尤为重要。

越来越多的证据表明，sEV在MAFLD中发挥关键作用[10]。sEV研究是一个快速发展的领域，sEV有多种功能，例如参与免疫应答、细胞迁移、细胞间通讯，并通过其携带的脂质、蛋白质、核酸等运载物调控受体细胞的生物活性[11]。然而，sEV在MAFLD进展中的作用尚未完全阐明。因此，本综述旨在系统阐述sEV在MAFLD发病机制中的作用。

1 小细胞外囊泡：形成与结构

sEV是直径约30~160 nm的细胞外囊泡[12]，几乎所有哺乳动物细胞均可分泌，包括人脐静脉内皮细胞(human umbilical vein endothelial cell, HUVEC)、间充质干细胞(mesenchymal stem cell, MSC)、T细胞(T cell)、B细胞(B cell)、巨噬细胞(macrophage)、树突状细胞(dendritic cell, DC)及自然杀伤细胞(natural killer cell, NK cell)等[13-17]。其形成主要通过内体途径，涉及质膜的双重内陷及细胞内多泡体(multivesicular body, MVB)的形成[18]。初次内陷时，质膜与细胞表面蛋白及胞外可溶性蛋白共同形成杯状结构，产生早期分选内体。此外，高尔基体及内质网也参与早期分选内体的形成与内容物补充，最终成熟为晚期分选内体并生成MVB[19, 20]。第二次质膜内陷时，MVB通过内体膜向内出芽形成，内含腔内囊泡(即未来的sEV)。当MVB与细胞膜融合后，腔内囊泡释放至胞外环境，根据直径可分为30~150 nm的sEV、100~1000 nm的微囊泡(microvesicle, MV)及1~5 μm的凋亡小体(apoptotic body, AB)[21]。此外，溶酶体可与MVB融合，介导其降解。

sEV为生物源性球形脂质双层囊泡，其内包含蛋白质、脂质、核酸、细胞因子、转录因子受体等生物活性分子[22]。值得注意的是，即使由同一细胞分泌，sEV在尺寸及运载物组成上仍具有异质性[23]。sEV不仅携带分泌细胞的特定蛋白，如对肝再生至关重要的原代肝细胞来源sEV中的鞘氨醇激酶2(sphingosine kinase 2, SPHK2)[24]，还包含跨膜蛋白家族成员(如对肝再生至关重要的CD63、CD9、CD81及CD82等sEV标志物[25])，这些蛋白在细胞靶向与黏附中发挥关键作用[23, 26]。除蛋白质外，sEV还含有核酸成分。Validi等[27]于2007年首次报道其携带信使核糖核酸(messenger RNA, mRNA)与微小核糖核酸(microRNA, miRNA)；后续研究进一步发现其包含线粒体脱氧核糖核酸(mitochondrial DNA, mtDNA)、双链脱氧核糖核酸(double-stranded DNA, dsDNA)、单链脱氧核糖核酸(single-stranded DNA, ssDNA)、小核核糖核酸(small nuclear RNA, snRNA)、小胞质核糖核酸(small cytoplasmic RNA, scRNA)及多种非编码核糖核酸(non-coding RNA, ncRNA)[28]。此外，sEV的生物活性不仅源于蛋白质与核酸，其脂质组分(如鞘磷脂、胆固醇、鞘糖脂及磷脂酰丝氨酸)同样重要，既参与囊泡形成与分泌，也介导功能调控[29, 30]。因此，sEV独特的结构与复杂组成决定了其多样的生物学功能。

2 sEV在MAFLD发病机制中的作用

MAFLD的典型病理特征包括脂质代谢紊乱、肝脏炎症及纤维化。肝脏中几乎所有类型的细胞都能分泌sEV，这些sEV在成分和功能上都表现出高度的异质性[31, 32]。部分sEV释放到细胞外液后，通过短距离传播介导肝脏细胞间的串扰，而另一些则通过较长距离传播介导器官间的串扰[33, 34]。在病理

条件下，sEV 的释放量及其携带介质的组成可受多种因素的影响。例如，高脂、高果糖和高胆固醇饮食诱导小鼠发生 MASH，激活肝细胞中的肌醇需求酶 1α (inositol-requiring enzyme 1 alpha, IRE1A)，激活的 IRE1A 通过 X- 框结合蛋白 1 (X-box binding protein 1, XBP1) 促进丝氨酸棕榈酰转移酶基因转录，导致神经酰胺的生物合成和 sEV 的释放 [35]。另一项研究显示，过量脂质通过激活死亡受体 5 (death receptor 5, DR5) 信号通路诱导肝细胞 sEV 的释放，并同时激活巨噬细胞的炎症表型 [36]。本节重点探讨 sEV 对肝脏脂质代谢紊乱、炎症反应及纤维生成的调控作用。

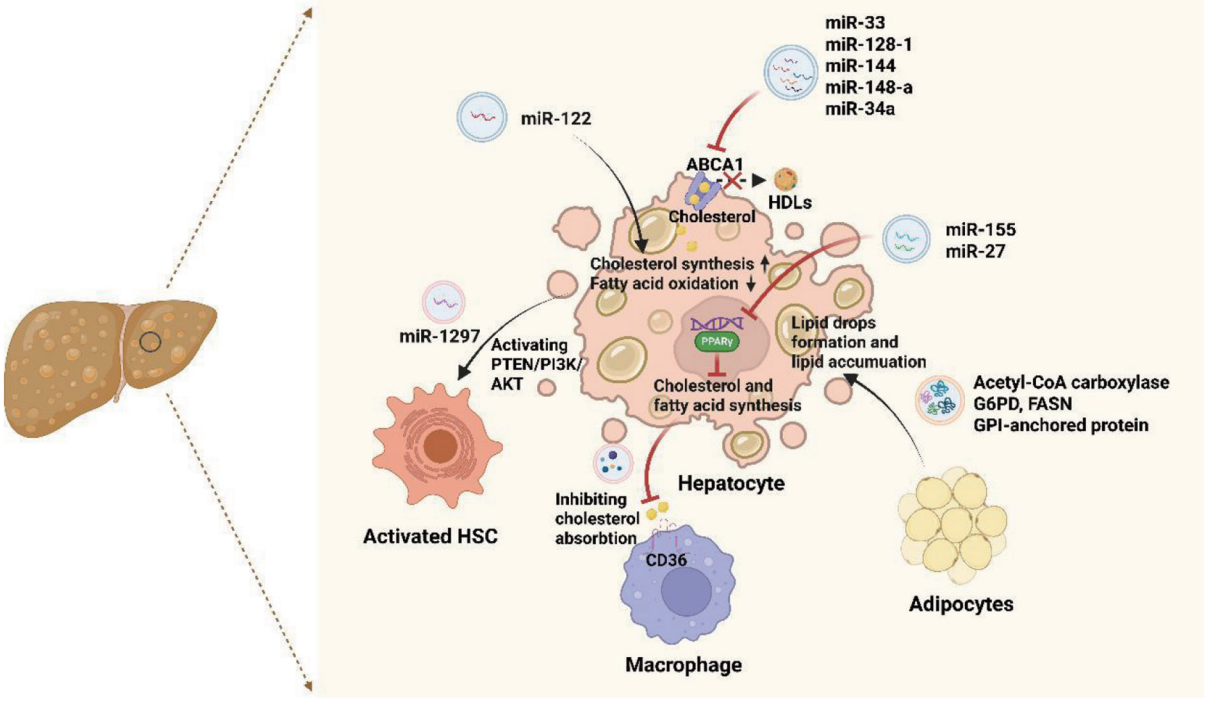
2.1　sEV在肝脏脂质代谢紊乱中的作用

肝脏脂质代谢紊乱与 MAFLD 的严重程度密切相关，涉及氧化应激、自噬、细胞凋亡及炎症反应等多种病理过程 [37]。值得注意的是，sEV 可作为“信使”，通过与受体细胞结合并释放生物活性成分，传递遗传或代谢信息。多项研究证实，sEV 参与脂质合成、转运及降解等代谢环节。作为核心代谢器官，肝脏是脂蛋白代谢的主要调控者，其脂肪酸与胆固醇的生物合成对维持生理功能至关重要。肝脂肪酸合成紊乱可导致肝细胞损伤及炎症等病变 [38]。肝细胞占肝脏总细胞的 80% 左右，因此是 MASH 发生和发展的主要细胞类型。肝细胞中有害脂质，如脂肪酸、胆固醇、二酰基甘油、磷脂、鞘脂的积累可能是 MASH 病理生理学的第一步 [39]。

2.1.1　sEV来源的miRNA在肝脏脂质代谢紊乱中的作用

sEV 携带的遗传物质 (如 RNA，包括 mRNA、miRNA、snRNA、ncRNA、scRNA，以及 DNA，如 dsDNA、ssDNA 和 mtDNA) 在 MAFLD 中的功能已被广泛研究 [28]。其中，sEV miRNA 因在脂质代谢中的关键作用而比 sEV DNA 更受关注。本节重点讨论 sEV miRNA 对肝脂代谢的调控 (图 1)。

miRNA 在脂代谢调控中发挥核心作用。肝脏游离胆固醇蓄积是驱动 MASH 进展的关键因素之一 [40]。MAFLD 患者普遍存在肝胆固醇水平升高，而高胆固醇饮食可显著促进小鼠及非人灵长类动物的 MASH 进展 [41]。因此，本综述着重关注了胆固醇代谢机制。例如，miR-122 作为肝脏中丰度最高的 miRNA，参与胆固醇和脂质代谢调控 [42]。miR-122 直接靶向抑制多个参与脂肪酸氧化和胆固醇合



sEV miRNA (如miR-122、miR-33、miR-128-1、miR-144、miR-148a、miR-34a, miR-155和miR-27)在调控肝脏脂质代谢中发挥重要作用。此外，肝细胞来源sEV miRNA (如miR-1297)可作用于肝星状细胞与巨噬细胞，从而推动MAFLD进展。脂肪细胞来源的sEV携带多种生物活性分子，进一步加剧肝细胞内脂质蓄积。

图1　sEV miRNA对肝脏脂质代谢的调控(图片由BioRender绘制)

成的关键基因，如羟甲基戊二酰辅酶 A 还原酶 (3-hydroxy-3-methylglutaryl-coenzyme A reductase, HMGCR) 等，促进脂肪酸合成并抑制脂肪酸氧化，同时促进胆固醇合成，共同加剧肝细胞内脂质蓄积 [43, 44]。ATP 结合盒转运蛋白 A1 (ATP binding cassette transporter A1, ABCA1) 是细胞清除过量胆固醇的核心转运蛋白，当胞内胆固醇水平过高时，细胞膜上的 ABCA1 蛋白数量显著增加，并通过介导胆固醇与磷脂向载脂蛋白 A 转运，从而组装成新生的高密度脂蛋白 (high-density lipoprotein, HDL)，进而避免肝细胞内脂质蓄积。除 miR-122 外，miR-33、miR-128-1、miR-144、miR34a 和 miR-148a 等也可通过抑制 ABCA1 表达来削弱胆固醇向载脂蛋白 A 的转运，从而抑制 HDL 的生成，进一步加重肝细胞脂质蓄积 [45-51]。

核转录因子过氧化物酶体增殖物激活受体 γ (peroxisome proliferator-activated receptor gamma, PPAR-γ) 调控肝脏脂质摄取、储存及代谢。sEV 中的循环 miRNA (如 miR-155 和 miR-27) 通过结合靶基因 3' 非翻译区 (3' untranslated region, 3'UTR) 抑制 PPAR-γ 表达，进而抑制脂肪酸和胆固醇合成 [28, 52]。此外，脂毒性肝细胞分泌的胞外囊泡 miR-1297 可通过激活 PTEN/PI3K/AKT 信号通路促进肝星状细胞活化和增殖，加速 MAFLD 进展 [53]。综上所述，sEV 来源的 miRNA 在 MAFLD 肝脏脂质代谢紊乱中发挥重要调控作用。

2.1.2 sEV来源的生物活性分子在肝脏脂质代谢紊乱中的作用

除 miRNA 外，sEV 携带的脂质、酶及蛋白质等生物活性分子也参与脂质代谢的调控 [28]。例如，缺氧脂肪细胞分泌的 sEV 富含乙酰辅酶 A 羧化酶 (acetyl-CoA carboxylase, ACC)、葡萄糖 -6- 磷酸脱氢酶 (glucose-6-phosphate dehydrogenase, G6PD) 及脂肪酸合酶 (fatty acid synthase, FASN) 等新生脂质合成相关酶，这些酶通过 sEV 直接递送至肝细胞胞浆，协同促进脂质合成：ACC 催化乙酰辅酶 A 生成丙二酰辅酶 A，G6PD 提供 NADPH，FASN 则利用前体合成脂肪酸。这种 sEV 介导的活性酶直接递送机制，独立于基因转录调控，显著增强肝细胞内脂肪生成通路活性，是驱动脂质蓄积的重要途径 [54]。脂肪细胞 sEV 中的糖基磷脂酰肌醇 (glycosylphosphatidylinositol, GPI) 锚定蛋白可增强酯化反应，减少三酰甘油 (triglyceride, TG) 分解，促进脂滴形成 [55]。类似地，胰腺癌来源的 sEV 携带肾上腺髓质素 (adrenomedullin, AM)，可激活脂肪细胞脂解 [56, 57]。

抵抗素 (resistin, RETN) 是脂肪细胞 sEV 中的一种激素。褪黑素 (melatonin, MT) 可通过抑制脂肪细胞 sEV 向肝细胞传递 RETN，减轻内质网应激诱导的肝脂肪变性 [58]。此外，sEV 还可通过降低巨噬细胞表面 CD36 的表达抑制胆固醇摄取 [28]。这些生物活性分子还通过调控炎症反应、免疫过程及细胞凋亡等途径影响脂代谢平衡 [11, 18, 59]。例如，肝细胞来源的 sEV 携带肿瘤坏死因子相关凋亡诱导配体 (TNF-related apoptosis-inducing ligand, TRAIL)(凋亡信号通路的关键驱动因子)，其与巨噬细胞表面 DR5 结合后，可激活趋化作用并导致肝细胞损伤 [36, 60]。综上，sEV 中的生物活性分子 (如酶、蛋白质及脂质) 在肝脏脂质代谢紊乱中发挥重要调控功能。

2.2 sEV对肝脏炎症的影响

在 MAFLD 进展中，MASH 诱导的肝损伤涉及多种细胞。其中，sEV 等细胞外囊泡的相互作用可能通过介导细胞间通讯参与这一过程 [61]，从而促进 MASH 发展。除调控肝脏脂质代谢外，sEV 在肝脏炎症中也发挥重要作用。脂类的积累导致肝细胞脂毒性，脂毒性肝细胞激活局部炎症细胞，从血液中招募淋巴细胞和单核细胞来源的巨噬细胞，并通过分泌炎症和纤维化介质激活肝星状细胞 [62, 63]，促进 MASH 进展。本节重点讨论不同来源的 sEV 及其携带的“分子货物”对肝脏炎症的调控作用。

2.2.1 不同来源sEV对肝脏炎症的调控作用

脂质蓄积导致肝细胞 sEV 的生成与释放，这是 MAFLD 肝损伤及进展的关键机制 [64]。例如，脂肪变性肝细胞释放的 sEV 激活单核 - 巨噬细胞 (如 NF-κB 信号通路激活) 引发炎症反应 [60, 65]。此外，非实质细胞，如肝星状细胞 (hepatic stellate cell, HSC)、肝窦内皮细胞 (liver sinusoidal endothelial cell, LSEC)、胆管细胞 (biliary epithelial cell, BEC) 及库普弗细胞 (Kupffer cell, KC)，在肝损伤过程中通过分泌 sEV 调控肝脏重塑并参与炎症反应 [66-68]。其中，BEC 约占肝实质细胞的 3%~5%，在胆汁淤积性肝损伤中具有重要病理生理功能 [69]。原发性硬化性胆管炎 (primary sclerosing cholangitis, PSC) 小鼠胆管细胞来源的 sEV 在胆汁淤积过程中富集长链 ncRNA H19，体内外实验证实，这些 sEV 可将 H19 转移至肝细胞，并抑制小异二聚体伴侣蛋白 (small heterodimer partner, SHP) 的表达，进而引发炎症及严重肝损伤 [70]。综上所述，肝内不同细胞来源的 sEV 均与肝脏炎症密切相关，其携带的“分子货物”

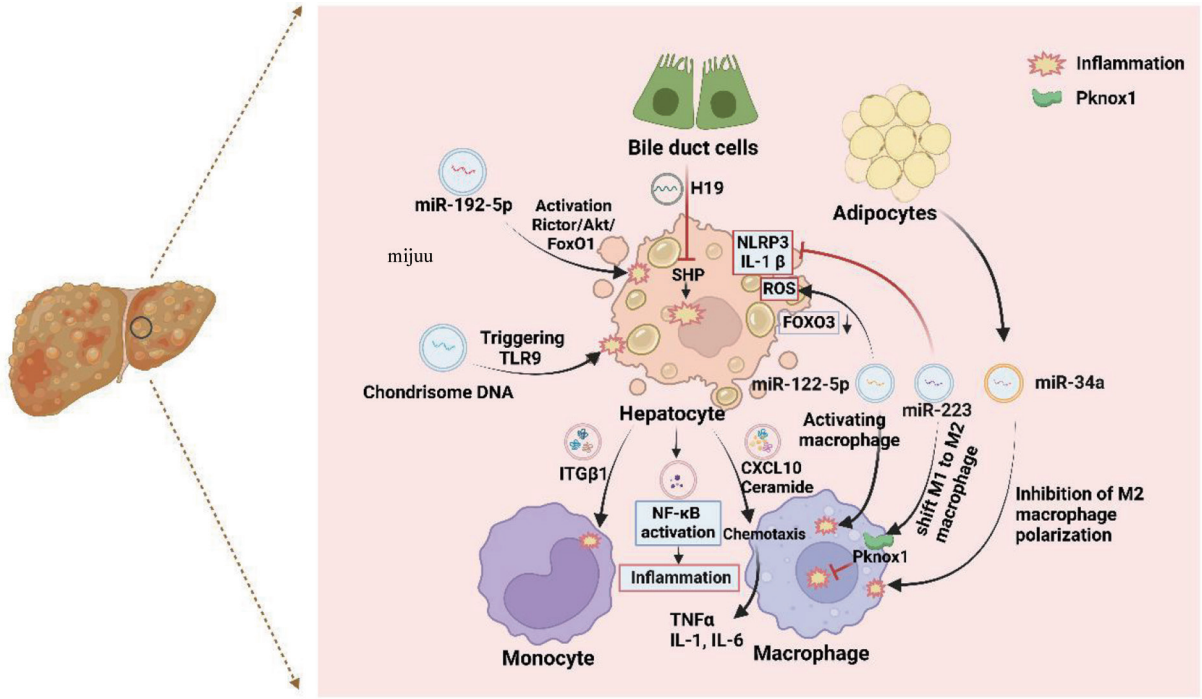
在炎症中的作用如图 2 所示。

2.2.2　sEV携带的核酸分子在肝脏炎症中的作用

miR-122 是肝脏中最常见的 miRNA 之一，有两个成熟亚型 miR-122-3p 和 miR-122-5p[71, 72]。其中，miR-122-5p 可促进人类急性单核细胞白血病细胞系 (THP-1) 细胞向促炎表型 (M1) 型巨噬细胞极化，而敲低人肝癌细胞系 Huh7 细胞中的 miR-122-5p 可抑制巨噬细胞活化及其介导的炎症反应 [73, 74]。miR-122-5p 参与脂质及胆固醇代谢的调控，并在肝细胞增殖与分化中发挥重要作用 [75, 76]。抑制肝脏 miR-122-5p 可上调叉头框蛋白 O3 (forkhead box protein O3, FOXO3) 表达，减轻炎症及氧化应激 [77]。FOXO3 参与脂代谢、炎症及纤维化调控 [78, 79]，是 MAFLD 发展过程中促进炎症与纤维化的潜在因子 [80]。因此，抑制 miR-122-5p 对 MAFLD 具有防护作用 [77]，提示其参与肝脏炎症的发病机制。

miR-192-5p 属于 miR-192 家族，广泛分布于血液、尿液等体液 [81, 82]。脂毒性损伤后，肝细胞来源的 sEV 富含 miR-192-5p，介导 M1 型巨噬细胞活化，促进肝脏炎症。MAFLD 中 miR-192-5p 的高表达与肝脏炎症密切相关，其可通过降低哺乳动物雷帕霉素 (rapamycin, RAPA) 靶基因雷帕霉素不敏感型 mTOR 伴侣蛋白 (rapamycin-insensitive companion of mTOR, Rictor) 调控的 AKT 及叉头框蛋白 O1 (FOXO1) 磷酸化水平，促进 FOXO1 活化并转位入核。活化的 FOXO1 作为转录因子，直接上调促炎因子基因 (如 IL-1β、TNF-α) 的表达，同时下调抗炎因子 (如 IL-10) 的表达，驱动巨噬细胞向 M1 型极化，释放大量炎症因子 [83]。因此，miR-192-5p 可通过调控 Rictor/AKT/FOXO1 信号转导通路参与肝脏炎症的发生。

miR-223 在免疫系统发育与稳态中发挥重要作用 [84]。miR-223 负向调控多种炎症因子，如白细胞介素 -6 (interleukin-6, IL-6)、NLR 家族吡啶结构域蛋白 3 炎症小体 (NLR pyrin domain containing 3, NLRP3) 等 [85, 86]。除参与免疫细胞分化外，miR-223 还可通过调节巨噬细胞极化、炎症小体激活及 NF-κB 信号通路影响其活化模式 [87, 88]。值得注意的是，巨噬细胞极化与炎症激活是 MAFLD 发生发展的核心环节 [89, 90]。miR-223 通过靶向巨噬细胞极化的重要调控因子 Peroxiredoxin-like protein NOX1 (Pknox1)，将巨噬细胞从经典活化的促炎表型 (M1) 向替代性抗炎表型 (M2) 转换 [88]，从而通过控制巨噬细胞表型转化缓解 MAFLD 进展。此外，miR-223 还作为胆



来自胆管细胞、脂肪细胞、巨噬细胞、单核细胞等的sEV miRNA、线粒体DNA、蛋白质及脂质，通过多种信号通路参与肝脏炎症反应。

图2　sEV在肝脏炎症中的作用(图片由BioRender绘制)

固醇外排和炎症相关 RNA 的调节因子，参与动脉粥样硬化的预防[91]。给予 miR-223 可抑制肝脏 NLRP3 炎症小体活化及 IL-1β 释放，减轻 MASH 小鼠的肝脏炎症[92, 93]。这些发现均提示 miR-223 在缓解肝脏炎症中的重要作用。

miR-34a 通过促进脂质吸收、脂肪生成、炎症及细胞凋亡，并抑制脂肪酸氧化，在 MAFLD 发生发展中起重要作用。炎症、活性氧 (reactive oxygen species, ROS) 生成及细胞凋亡是 MAFLD 向 MASH 转化的共同原因[94]。miR-34a 可特异性诱导肝脏发生饮食性脂肪性肝炎。脂肪细胞 sEV miRNA-34a 通过阻断 M2 型巨噬细胞极化，诱导炎症反应[64]，提示 miR-34a 在触发肝炎中的关键作用。

除 miRNA 外，mtDNA 也与肝脏炎症相关。MASH 患者肝细胞分泌的 sEV 携带更多 mtDNA，可能通过激活 Toll 样受体 9 (Toll-like receptor 9, TLR9) 引发炎症反应[95, 96]。TLR9 作为模式识别受体 (pattern recognition receptors, PRRs)，可识别未甲基化的胞嘧啶 - 磷酸 - 鸟嘌呤 (CpG) 基序并激活先天性免疫应答，因此携带 mtDNA 的 sEV 也是 MASH 中无菌性炎症反应激活的重要原因[64]。对照小鼠肝脏出现显著脂质蓄积，伴随炎性细胞浸润、肝细胞死亡及纤维化，而 TLR9 基因敲除 ($TLR9^{-/-}$) 小鼠的脂肪变性、炎症及纤维化程度均显著减轻[97]。TLR9 参与肝脏纤维化，并在慢性肝病期间促进肝细胞癌的发生和发展[98]。这表明 sEV 中的 mtDNA 可能通过触发 TLR9 激活启动肝脏炎症。

2.3 sEV携带的蛋白质在肝炎中的作用

除核酸分子外，sEV 携带的蛋白质也参与 MAFLD 相关肝炎的发病机制。例如，在脂毒性应激下肝细胞释放的 sEV 富含细胞黏附分子整合素 β1 (integrin β1, ITG β1)[99]。ITG β1 介导单核细胞与肝窦内皮间相互作用，阻断 ITG β1 可减轻 MASH 小鼠的肝脏炎症、损伤及纤维化[99]，提示其在 MASH 中的关键作用。脂毒性肝细胞分泌的 sEV 中还富含 C-X-C 基序趋化因子 10 (CXC chemokine ligand 10, CXCL10) 蛋白，其可诱导 KC 趋化迁移，活化的 KC 进一步释放 TNF-α 等促炎因子，协同 IL-1 与 IL-6 促进 MAFLD 向 MASH 转化[100, 101]。此外，脂毒性肝细胞来源的 sEV 富含的 LIMA1 (LIM domain and actin binding 1) 通过负向调节线粒体自噬，在促进 MAFLD 相关肝纤维化中发挥关键作用[102]。

2.3.1 sEV携带的脂质在肝炎中的作用

肝脏巨噬细胞 (包括定居型巨噬细胞 KC 及单核来源巨噬细胞) 在肝脏损伤的炎症反应中起核心作用[103, 104]。脂毒性肝细胞释放的 sEV 携带 TRAIL，可诱导小鼠骨髓源性巨噬细胞呈现促炎表型[36, 60]。此外，脂毒性肝细胞还释放富含神经酰胺 (ceramide) 的 sEV，其可通过趋化作用募集巨噬细胞至肝脏[105, 106]，进而引发肝脏炎症。

2.4 sEV在MAFLD纤维化形成中的作用

肝纤维化是由多种致病因素引起的肝脏结缔组织异常增生，表现为肝内纤维生成与降解失衡导致胶原过度沉积，常伴随炎症反应，并可进展为肝硬化[107, 108]。肝细胞通过过度产生 α- 平滑肌肌动蛋白 (alpha-smooth muscle actin, α-SMA)、细胞外基质 (extracellular matrix, ECM) 等纤维相关蛋白激活 HSC，进而驱动纤维化。sEV 在 MAFLD 纤维化形成中亦发挥重要作用。例如，miR-128-3p、miR-214、miR-19b、miR-107、miR-4715-3p 及 miR-690 等来源的 sEV 均参与纤维化形成 (图 3)[60, 76, 103, 109-115]。

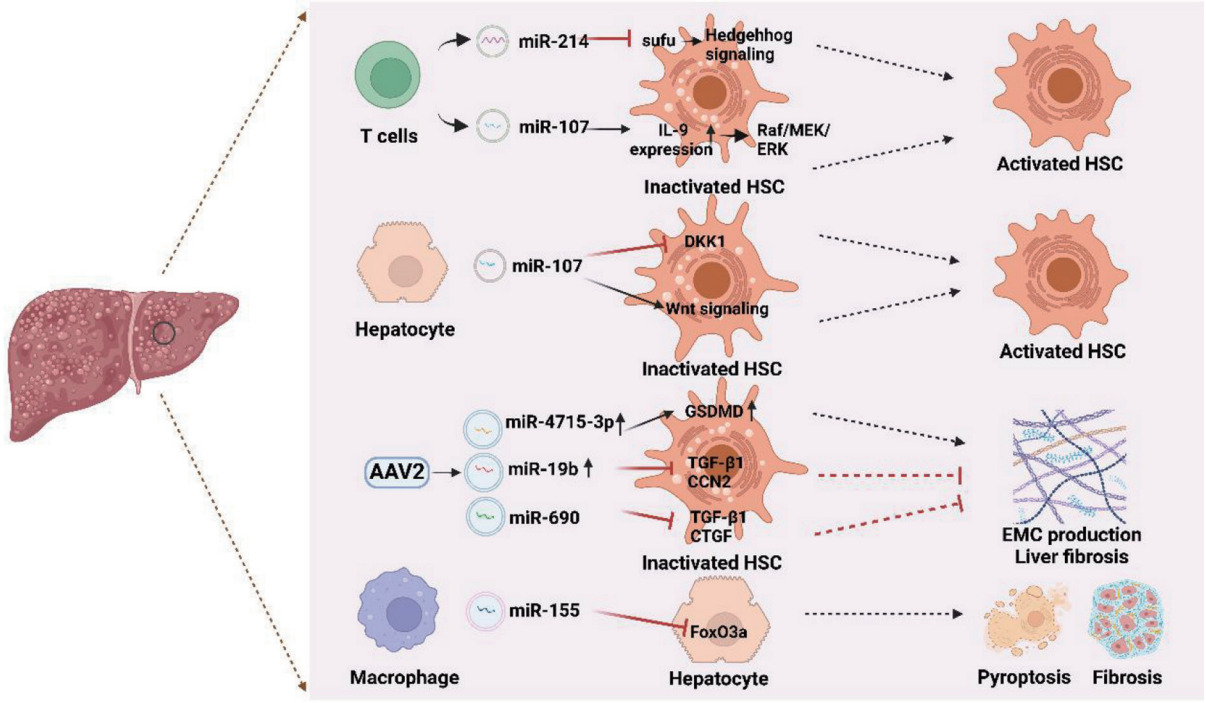
2.4.1 sEV来源的miRNA在肝纤维化中的作用

2.4.1.1 HSC激活与miR-128-3p在肝纤维化中的作用

上皮细胞损伤等胞外事件可产生多种炎症介质，诱导 HSC 活化[116]。其中，miR-128-3p 可被 HSC 高效摄取，通过抑制 PPAR-γ 的表达促进 HSC 活化[109]。正常 HSC 以储存维生素 A (vitamin A) 的静息状态存在，而活化后则转化为表达 α-SMA 的肌成纤维细胞 (myofibroblasts)，促进创面闭合并分泌胶原基质。值得注意的是，胶原等 ECM 蛋白的过度沉积是肝纤维化的标志性特征[116, 117]。因此，miR-128-3p 可能通过激活 HSC 驱动纤维化进程。

2.4.1.2 sEV来源的miR-214在肝纤维化中的功能与机制

除 miR-128-3p 外，T 细胞中 miR-214 的诱导表达可显著影响血管周围纤维化[118]。微阵列分析显示，在活化 HSC 或经旁分泌信号 (如 TGF-β) 刺激的细胞 (如损伤的胆管细胞、肝细胞) 来源的 sEV 中，miR-214 表达上调，其转录受转录因子扭转相关蛋白 1 (twist-related protein 1, Twist1) 通过结合 E-box 元件调控[119]。然而，Chen 等[120] 发现，miR-214 表达降低可导致结缔组织生长因子 (connective tissue growth factor, CTGF) 表达升高，进而促进 HSC 活化及纤维化分子分泌。尽管 miR-214 的调控机制存在争议，但其通过不同通路促进肝纤维化的作用已被明确。



T细胞及肝细胞来源的sEV miRNA (如miR-214、miR-107)通过不同信号通路参与肝星状细胞的活化，从而促进肝纤维化发生。此外，miR-4715-3p、miR-19b、miR-690及miR-155亦参与细胞外基质生成与肝纤维化进程。

图3　sEV在MAFLD纤维化形成中的作用(图片由BioRender绘制)

2.4.1.3　sEV来源的miR-19b在肝纤维化中的功能与机制

HSC 活化是肝纤维化形成的关键环节。HSC 活化过程中 miR-19b 水平显著降低。miR-19b 通过直接靶向抑制肝细胞中转化生长因子β1 (transforming growth factor beta 1, TGF-β1) 和 CCN2 的表达，而 TGF-β1 与 CCN2 可促进 ECM 生成与沉积 [121]。miR-19b 水平降低导致 TGF-β1 和 CCN2 表达升高，加剧纤维化。腺相关病毒 2 型 (adeno-associated virus 2, AAV2) 介导的 miR-19b 过表达可减轻肝损伤及纤维化 [111, 117]。此外，鞘氨醇激酶 (sphingosine kinase, SPHK) 通过降低 miR-19b-3p (miR-19b 衍生物) 的表达，上调 C-C 基序趋化因子受体 2 (CCR2)，促进单核细胞向肝脏浸润，进而启动纤维化进程 [114, 122, 123]。因此，sEV miR-19b 在纤维化形成中具有重要作用。

2.4.1.4　sEV来源的miR-107在肝纤维化中的功能与机制

棕榈酸 (palmitic acid, PA) 处理的肝细胞分泌的 sEV 可将 miR-107 转移至 LX-2 细胞 (人肝星状细胞系)，通过抑制 Dickkopf 相关蛋白 1 (Dickkopf-related protein 1, DKK1) 激活 Wnt 信号通路，诱导 LX-2 细胞活化。此外，miR-107 还可进入 $CD4^+$ T 细胞抑制 FOXP1 表达，促进 Th9 (辅助性 T 细胞的一个亚群) 分化并增加 IL-9 分泌。IL-9 通过激活 Raf/MEK/ERK 通路进一步促进 LX-2 细胞活化及促纤维化因子释放 [124]。上述机制共同表明 sEV miR-107 参与 MAFLD 的纤维化过程。

2.4.1.5　sEV来源的miR-4715-3p指示MAFLD纤维化进展

肝巨噬细胞与 HSC 的相互作用可促进纤维化。多项 RNA 测序分析显示，MAFLD 纤维化进展伴随巨噬细胞浸润增加与巨噬细胞相关的 Gasdermin D (GSDMD) 基因表达上调。同时，巨噬细胞相关 miR-4715-3p 的表达与 GSDMD 显著相关，提示 miR-4715-3p/GSDMD 轴通过调控巨噬细胞免疫反应参与纤维化进程 [125]。

2.4.1.6　sEV来源的miR-155促进肝细胞焦亡与肝纤维化

miR-155 主要在巨噬细胞等炎症细胞中表达，与炎症反应密切相关 [126, 127]。在高脂饮食 (high-fat diet, HFD) 诱导的 MAFLD 小鼠模型中，巨噬细胞来源的 sEV miR-155 转移至肝细胞，通过抑制 FOXO3a 引发肝细胞焦亡及纤维化。敲低 miR-155

或阻断 sEV 分泌可显著减轻 HFD 小鼠的肝细胞焦亡和纤维化[128]，表明巨噬细胞来源的 miR-155 在 MAFLD 肝纤维化中起关键作用。

2.4.1.7 sEV来源的miR-690直接缓解肝纤维化

与上述 miRNA 不同，miR-690 (主要来源于 KC) 可通过多种机制直接抑制肝纤维化。miR-690 作为胰岛素增敏剂，其水平降低会加剧肝细胞胰岛素抵抗并削弱 KC 的吞噬功能，进而激活 HSC 导致纤维化[103, 129]。此外，miR-690 通过靶向抑制 TGF-β1 和结缔组织生长因子 (connective tissue growth factor, CTGF) 的表达，减少 ECM 蛋白 (如胶原) 的生成，从而进一步缓解纤维化。

2.4.1.8 sEV作为促凝剂参与MAFLD纤维化

除携带 miRNA 外，sEV 本身也通过凝血途径促进纤维化。sEV 作为促凝血微粒，与活化血小板结合后可诱发静脉血栓[130, 131]，静脉腔闭塞导致血管通透性改变及扩张，进而促进纤维化等病理过程[132, 133]。此外，血小板、内皮细胞等来源的微粒可通过促进炎症、激活 HSC 及诱导肝细胞纤维化表型转变加剧肝纤维化。

3 总结与展望

3.1 既往研究存在的问题

sEV 在 MAFLD 发病机制中的调控作用已被广泛关注，但其分子机制与调控网络尚不完全清晰。例如，内脏和皮下脂肪来源的 sEV 是否通过特异性 miRNA 或脂质等代谢相关分子驱动肝脏脂质代谢失衡，其传递规律尚未完全解析；肠道菌群紊乱衍生的 sEV 虽被推测通过 TLR4/NF-κB 通路激活肝脏炎症，但其是否直接递送菌群代谢产物 (如短链脂肪酸) 或毒素仍需多组学联合验证。在 MAFLD 纤维化进程中，巨噬细胞 sEV 促进炎症微环境形成的原因也不清楚，而肝星状细胞激活相关 sEV 可能诱导胶原沉积，但 sEV 促纤维化与抗纤维化亚群的互作机制仍不明确。此外，sEV 分离技术、动物模型代谢微环境异质性，均为机制解析与临床转化带来显著挑战。

3.2 该综述区别于他人他篇的特点

与国内外同类综述相比，本文以 sEV 携带的生物活性内容物 (miRNA、脂质、蛋白质) 为核心，不仅介绍了来源的细胞类型，并且细致全面地从肝脏脂质代谢紊乱、炎症，以及纤维化的角度介绍了 MAFLD 的发病机制。

3.3 该综述的局限性

由于 MAFLD 发病机制的复杂性，各种细胞来源的 sEV 在其过程中具有不同作用，各细胞之间如何相互联系在本文中未进行深入讨论。因为检索不全和篇幅有限，sEV 对于 MAFLD 治疗的作用 (如间充质干细胞来源的 sEV 对于 MAFLD 的治疗效果) 未作讨论。

3.4 综述的重要意义

MAFLD 已成为全球公共卫生的重要挑战，其诊断与治疗面临严峻考验。与游离因子 (如 TNF-α、IL-6) 的短半衰期、激素的局部作用等局限性相比，sEV 凭借其长循环稳定性、跨器官靶向递送能力及跨细胞表观重编程作用，在介导器官间通讯、驱动多器官病理网络形成及 MAFLD 进展中发挥独特且关键的作用[109, 134, 135]。此外，sEV 广泛存在于血清、尿液和唾液等多种体液，其作为液体活检标志物可规避肝活检的创伤性风险，显著提升诊断安全性[136]。因此，携带核酸、脂质和蛋白质的 sEV 在肝脏疾病无创诊断领域展现出日益重要的应用潜力[137]。例如，在 MAFLD 患者中，sEV 携带的核酸标志物 (如 miR-122、miR-192) 和蛋白质标志物 (如 GLUT1) 表达显著升高[83, 115, 138, 139]，同时脂类成分 (如 SFAs) 在患者及疾病模型小鼠中也与疾病严重程度呈正相关[140]。

本文系统梳理与整合了 sEV 在 MAFLD 发病机制中的作用，为 sEV 在 MAFLD 临床诊疗中的应用提供了理论依据。尽管饮食诱导 MAFLD 模型证实 sEV 的细胞来源与分泌量呈时间依赖性变化[141]，其含量与功能的疾病阶段特异性差异仍缺乏共识。未来仍需解决以下问题：(1) 明确 MAFLD 各阶段细胞来源 sEV 的动态变化规律；(2) 在患者队列中解析 sEV 的阶段依赖性功能特征。此外，sEV 也参与酒精性肝病、病毒性肝炎等肝脏疾病[142, 143]，但 MAFLD 相关 sEV 与其他肝病的差异尚不清晰。深入阐明 MAFLD 进展中 sEV 的组成与功能演变，将推动肝病精准诊疗策略的发展。

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