

植物来源的外泌体样纳米颗粒调节 炎症微环境的研究进展

王学宇¹ 杨思颖¹ 宋圣花^{1,2} 俞晨杰^{1,2*}

(¹南京中医药大学鼓楼临床医学院耳鼻咽喉头颈外科, 南京 210008;

²南京大学医学院附属鼓楼医院耳鼻咽喉头颈外科, 南京 210008)

摘要 植物来源的外泌体样纳米颗粒是从植物中提取的天然纳米囊泡, 其特点是产量丰富、免疫原性低和无毒副作用, 其因能够参与炎症调节和维持免疫稳态而成为研究热点。炎症微环境是指炎症反应发生的局部特异性微环境, 在驱动炎症性疾病的起始与进展中发挥核心调控作用, 是多种慢性疾病病因学中普遍存在的关键病理特征。炎症微环境的平衡失调会导致免疫细胞的异常活化、细胞间信号传递的失调和炎症介质的过度分泌, 从而促使炎症性疾病的发展。现有的治疗炎症性疾病的化学合成药物常因副作用明显而使其临床应用受到限制, 开发兼具高效抗炎作用和低毒副作用的天然药物成为当前炎症性疾病治疗的迫切需求。该文主要综述了植物来源的外泌体样纳米颗粒的形成、分离、纯化以及其在炎症微环境中调控关键信号通路和炎症介质的机制, 为拓展其在生物医药领域的实践应用提供了重要参考。

关键词 植物来源的外泌体样纳米颗粒; 炎症微环境; 天然药物

Recent Advances in the Regulation of the Inflammatory Microenvironment by Plant-Derived Exosome-Like Nanoparticles

WANG Xueyu¹, YANG Siying¹, SONG Shenghua^{1,2}, YU Chenjie^{1,2*}

(¹Department of Otorhinolaryngology & Head and Neck Surgery, Nanjing Drum Tower Hospital Clinical College of Nanjing University of Chinese Medicine, Nanjing 210008, China; ²Department of Otorhinolaryngology & Head and Neck Surgery, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing 210008, China)

Abstract Plant-derived exosome-like nanoparticles are natural nanovesicles isolated from plants with high yield, low immunogenicity, and low toxicity, which have attracted increasing attention for their roles in regulating inflammation and maintaining immune homeostasis. The inflammatory microenvironment is defined as the specific microenvironment in which inflammatory responses occur. It plays a pivotal regulatory role in driving the onset and progression of inflammatory diseases and is a hallmark pathological feature commonly found in the aetiology of various chronic diseases. Disruption of the inflammatory microenvironment homeostasis leads to aberrant activation of immune cells, dysregulated intercellular signaling, and overproduction of inflammatory mediators, thereby contributing to the development of inflammatory diseases. The clinical application of existing chemically synthesised drugs for treating inflammatory diseases is often limited by significant side effects, drugs derived from natural sources that combine potent anti-inflammatory activity with low toxicity are urgently needed for the treatment of

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*通信作者。Tel: 025-83106666, E-mail: entphd@163.com

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*Corresponding author. Tel: +86-25-83106666, E-mail: entphd@163.com

inflammatory diseases. The present article reviews the formation, isolation, and purification of plant-derived exosome-like nanoparticles, as well as the mechanisms by which they regulate key signalling pathways and inflammatory mediators in the inflammatory microenvironment. This review provides a significant reference for the expansion of their practical applications in the field of biomedicine.

Keywords plant-derived exosome-like nanoparticles; inflammatory microenvironment; natural medicines

1 植物来源的外泌体样纳米颗粒(plant-derived exosome-like nanoparticles, PELNs)的介绍

1.1 PELNs的基本特征

外泌体(exosomes, EXOs)是直径为40~160 nm的细胞外囊泡,它们包裹蛋白质、脂质和核酸,在细胞间通信中起着至关重要的作用^[1]。EXOs在疾病治疗中的应用成为研究热点。天然外泌体可以分为动物源性外泌体(animal-derived exosomes, ADEs)和植物源性外泌体(plant-derived exosomes, PDEs)^[2]。与ADEs相比,PELNs有许多优点,这些优点包括易于大规模生产^[3]、较低的毒性和免疫原性^[4-5]、高效的细胞摄取^[6]以及良好的生物相容性和稳定性^[7]。

PELNs富含脂质、微小RNA(microRNA, miRNA)、蛋白质、小分子和其他生物活性成分^[2,8-10]。脂质是PELNs功能实现的核心要素,不仅是PELNs膜结构的基础,更能调控PELNs的靶向性和免疫调节功能^[11]。PELNs的脂质主要成分为磷脂酸、磷脂酰甘油、磷脂酰胆碱、磷脂酰肌醇、磷脂酰乙醇胺、单半乳糖甘油二酯和双半乳糖甘油二酯,这些脂质影响PELNs的膜稳定性、药物装载能力和生物相容性^[12-13]。PELNs含有多种功能蛋白,这些蛋白参与植物应激响应、膜稳定性维持及跨物种信号传递^[14-15]。PELNs还含有多种核酸成分,如miRNA、sRNA(small RNA)和DNA,不同的PELNs中核酸的种类和含量有所不同,PELNs中的核酸参与跨物种基因调控和免疫调节^[3]。此外,有研究发现,PELNs中还存在维生素C、多酚、黄酮类、类胡萝卜素等生物活性物质,这些生物活性物质也可能发挥相应的作用^[16]。

1.2 PELNs的发生过程

目前对PELNs的发生机制方面的研究还很缺乏。科学界普遍认为PELNs的形成有3种可能的途径:多泡体(multivesicular bodies, MVBs)途径、外囊阳性细胞器(exocyst-positive organelle, EXPO)途径和中央液泡(central vacuole)途径^[17]。MVBs介导的分泌被认为是PELNs的主要生物发生途径^[18-19]。具

体而言,细胞质膜内陷形成早期内体,早期内体逐步成熟为含有大量腔内囊泡的MVBs, MVBs最终与质膜融合,并将腔内囊泡释放至胞外,形成直径为60~150 nm的PELNs^[9,14,17,20]。PELNs的另一个来源是EXPO途径, EXPO途径是PELNs特有的生物发生途径, EXPO具有双膜性质,它可与质膜结合并产生单层膜囊泡^[21-22]。近年来,越来越多的学者发现,除了MVB和EXPO途径外,植物细胞中的液泡也可能参与PELNs的形成,液泡是植物细胞中的一种单膜细胞器,可直接与质膜融合,释放腔内物质(如抗菌蛋白、代谢物),形成液泡来源PELNs^[14,17,23]。

1.3 PELNs的分离和表征

精准获取高纯度、高活性的PELNs,是深入解析其生物学功能及挖掘其临床应用潜力的首要前提。目前,在PELNs的制备方法中,传统技术方法主要包含超速离心法、超滤法以及聚乙二醇沉淀法。随着分离科学与技术的持续发展,一系列新兴制备技术(诸如尺寸排阻色谱技术、场流分级技术以及免疫亲和富集技术等)也逐渐应用于该领域。这些方法为不同应用场景下的PELNs分离纯化提供了多样化的解决方案^[21,24-25]。这些方法利用EXOs的特性(例如粒径、密度和电荷)将这些囊泡与其他生物污染物分离。超速离心和蔗糖密度梯度离心仍然是大多数PELNs分离提纯的主要方法^[26-27]。这种分离方法是根据颗粒的尺寸和密度而定的,步骤首先是将植物研磨成汁并过滤,随后在4 °C条件下以1 000~5 000 ×g离心20~30 min,去除大的沉积物和死细胞;以10 000 ×g离心1 h,去除细胞碎片和细胞器;以100 000~150 000 ×g超速离心1~2 h,弃去上清,收集沉淀。为了进一步纯化PELNs,将获得的沉淀物重新悬浮,轻轻铺在不同的蔗糖密度梯度层(8%、30%、45%和60%蔗糖)上,然后在4 °C条件下再次以100 000~150 000 ×g超速离心1~2 h,弃去上清,在离心力驱动下,不同密度的成分沿密度梯度介质迁移至对应区域,形成界限清晰的分离条带。该方法用于提取大部

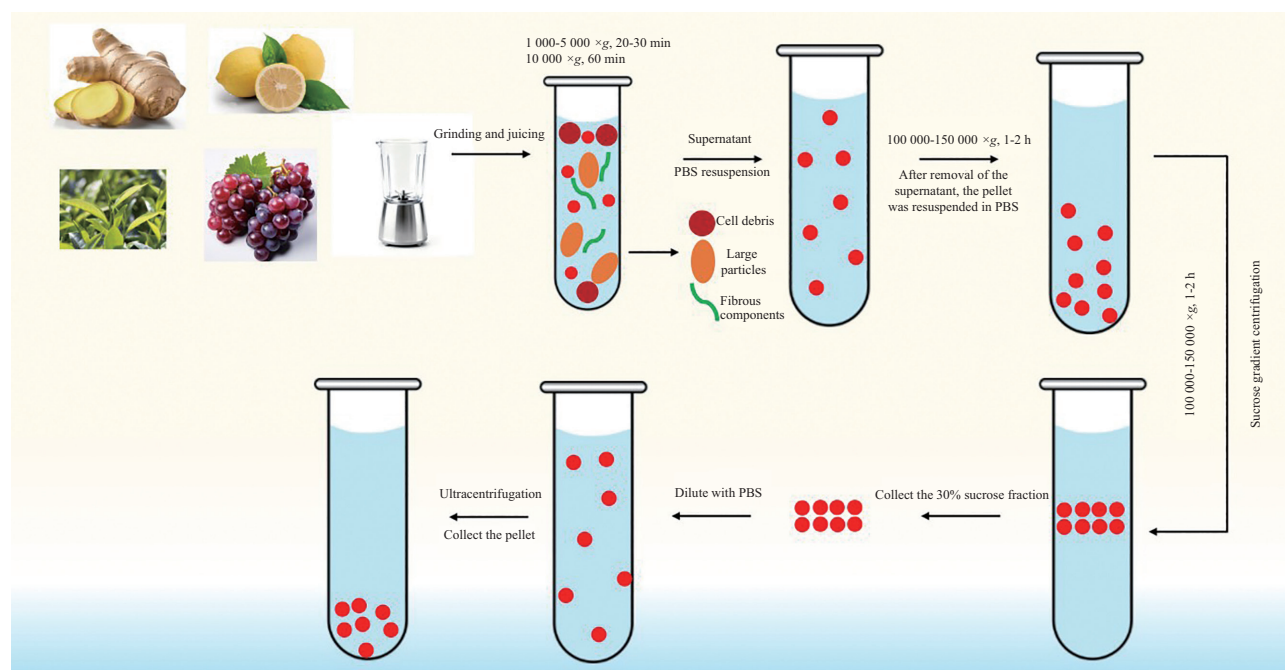


图1 植物来源的外泌体样纳米颗粒提取示意图

Fig.1 Schematic diagram of extracting plant-derived exosome-like nanoparticles

分PELNs^[28-34](图1)。

PELNs的物理特性主要根据三个方面进行评估:形态、粒径分布和Zeta电位。透射电子显微镜是直观观察EXOs形态结构的关键手段,透射电子显微镜能高分辨率显示外泌体双层膜结构^[35]。动态光散射和纳米颗粒跟踪分析均可用于测量粒径和Zeta电位。动态光散射检测灵敏度高,但是它的分辨率较低^[36]。通过动态光确定PELNs的直径为50~500 nm, PELNs多显示-25至-15 mV之间的负电荷^[37]。与动态光散射相比,纳米颗粒跟踪分析具有更高的分辨率,并且不易受到大颗粒高散射强度的影响。纳米颗粒跟踪分析记录单个粒子的布朗运动轨迹,确定它们的平均速度和扩散系数,并能够对颗粒的流体动力学直径和颗粒数浓度进行定量分析,但这些定量计算需要足够长的迹线,并要求样品浓度处于最佳范围内^[38]。

2 炎症微环境(inflammatory microenvironments, IMEs)

IMEs是指组织或细胞周围的生理或病理条件,其中各种成分如免疫细胞、炎症介质、血管、基质细胞和细胞外基质等共同相互作用,形成一个复杂的环境^[39]。IMEs的持续存在会促进各种炎症性疾病(如炎症性肠病、免疫性疾病、癌症等)的发生和发

展。在炎症性疾病(如炎症性肠病等)中,IMEs通过诱导缺氧应激以及调控免疫细胞代谢与功能,促进黏膜屏障破坏、免疫失衡及炎症持续进展,同时参与组织修复与炎症消退的动态调控^[40]。在肿瘤领域,持续的IMEs不仅可促进肿瘤发生,还可加速肿瘤进展并促进新血管的形成、癌症相关成纤维细胞的激活和细胞外基质的重塑,这在肿瘤的发生、发展和转移中起着重要作用^[41]。

IMEs的动态平衡与功能实现,依赖于一组关键促炎介质的精准调控,其中以白细胞介素-1 β (interleukin-1 β , IL-1 β)、白细胞介素-6(interleukin-6, IL-6)、白细胞介素-8(interleukin-8, IL-8)、肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)及 γ 干扰素(interferon- γ , IFN- γ)等细胞因子为代表的信号分子构成了IMEs的核心调控网络,这些介质在炎症过程中起核心作用,在炎症发生初期由巨噬细胞、单核细胞等免疫细胞释放,并受关键信号通路如NF- κ B、JAK/STAT、PI3K/Akt、MAPK、TGF- β 、Wnt和NLRP3信号通路等的调节,它们能够激活周围组织细胞,促使免疫细胞向炎症部位趋化,增强炎症反应,引起发热、急性期蛋白合成等全身反应,在抵御病原体入侵方面发挥重要作用^[42]。然而,过度的促炎因子释放会打破机体免疫平衡,导致慢性炎症发生,而慢性炎症与癌症、自身免疫性疾病和代谢性疾病相关^[43]。

3 PELNs对IMEs的影响

在炎症性疾病研究领域, PELNs因有潜力成为新型治疗药物, 而具有不可忽视的重要性。现有研究证明, PELNs可以通过调节特定信号通路和介质因子, 在预防或治疗各种炎症性疾病中显示出疗效^[44]。目前, 治疗炎症性疾病的药物包括皮质类固醇、非甾体抗炎药和生物制剂等, 尽管有效, 但可能伴随各种不良反应^[45-46]。PELNs因其化学多样性和产量丰富特性, 在抗炎药物研发领域展现出巨大潜力。此外, PELNs展现出良好的安全性, 与化学合成药物相比优势显著, 具有广阔的临床应用前景^[47]。因此, 研究PELNs在IMEs中的作用不仅能增进我们对疾病机制的理解, 还有望助力开发更安全有效的治疗方法(图2)。

3.1 PELNs调控NF- κ B信号通路

NF- κ B是急性和慢性炎症性疾病中的关键调节因子。在生理状态下, NF- κ B信号通路被激活后, 会促进下游基因转录, 进而促进IL-6、IL-1 β 等促炎因子的翻译和合成。这些细胞因子的过量释放会加重炎症反应^[48]。研究发现PELNs可以通过NF- κ B途径发挥作用, 包括抑制NF- κ B活化, 减少I κ B激酶(I κ B kinase, IKK)介导的NF- κ B及c-Jun N-末端激酶(c-Jun N-terminal kinase, JNK)磷酸化, 阻断促炎因子的转录和翻译, 从而抑制多种炎症因子的分泌和表达。

生姜来源的外泌体样纳米颗粒在结肠炎治疗研究中展现出独特的抗炎潜力。生姜来源的外泌体样纳米颗粒主要通过抑制NF- κ B信号通路的激活, 从根源上阻断IL-6、IL-1 β 等促炎因子的转录和翻译以减

少这些促炎因子的产生, 为结肠炎的治疗提供了新思路 and 潜在方案^[7]。此外, 生姜来源的外泌体样纳米颗粒也能通过调节NF- κ B信号治疗肺炎, 其携带的aly-miR396a-5p在其中发挥抗炎作用^[49]。人参来源的外泌体样纳米颗粒能够通过降低NF- κ B的mRNA表达水平进而减轻脂多糖(lipopolysaccharide, LPS)诱导的RAW264.7巨噬细胞炎症^[50]。在LPS刺激的巨噬细胞中, 柠檬来源的外泌体样纳米颗粒不仅可抑制NF- κ B核转位和磷酸化, 下调IL-6、TNF- α 、IL-1 β 表达, 还可显著降低细胞外信号调节激酶1/2(extracellular signal-regulated kinase 1/2, ERK1/2)磷酸化水平; 在T细胞中其可降低IFN- γ /TNF- α 水平并上调IL-10/IL-9表达。这表明PELNs能协同靶向NF- κ B与MAPK通路, 实现多节点抗炎调控^[51]。

3.2 PELNs调控MAPK信号通路

MAPK信号通路主要包含三条核心调节途径, 即ERK1/2途径、JNK途径和p38丝裂原活化蛋白激酶(p38MAPK)途径^[52]。当细胞受到外界刺激时, MAPK信号通路被迅速激活, 进而调节细胞生长、分化、应激及炎症反应^[53]。PELNs可通过激活或抑制该通路, 发挥增强免疫和减轻炎症的作用。

黑枸杞来源的外泌体样纳米颗粒可通过抑制MAPK信号通路减轻痴呆相关症状。用与痴呆严重程度相关的 β -淀粉样蛋白处理PC12细胞, 可激活MAPK通路, 使p38、ERK、JNK的磷酸化水平升高; 而黑枸杞来源的外泌体样纳米颗粒能显著降低它们的磷酸化水平, 抑制MAPK通路过度激活, 从而减少

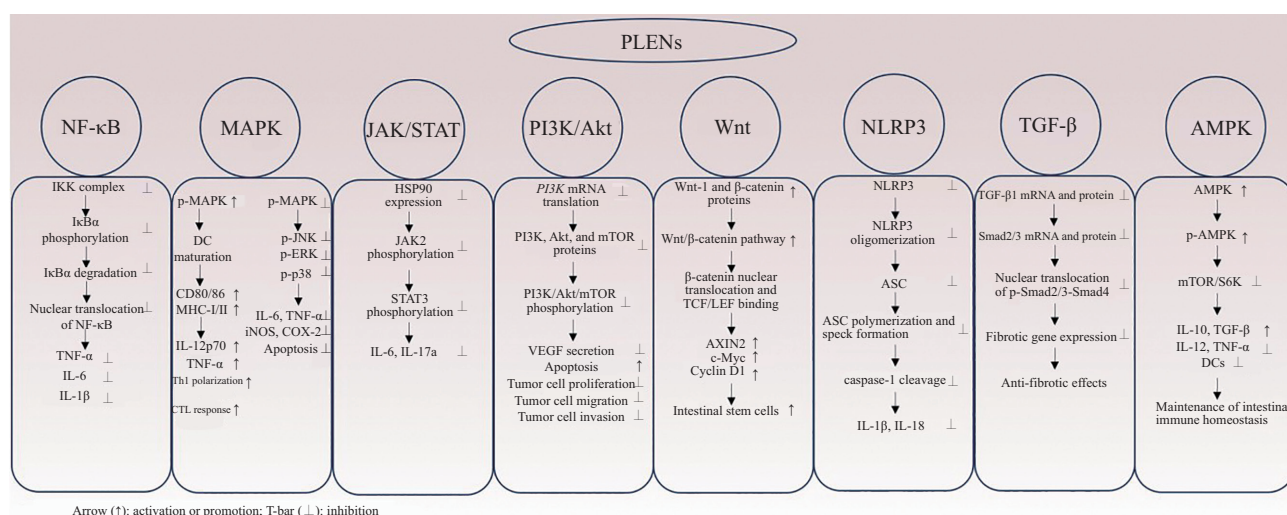


图2 植物来源的外泌体样纳米颗粒调节信号通路机制图

Fig.2 Schematic diagram of plant-derived exosome-like nanoparticles regulating signaling pathways

细胞凋亡、减轻炎症,黑枸杞来源的外泌体样纳米颗粒中的 *ata-miR156c-3p* 是其发挥上述作用的关键效应分子,此外,黑枸杞来源的外泌体样纳米颗粒还可通过激活 PI3K/Akt 信号通路,提高 PI3K 和 Akt 的磷酸化水平,发挥神经保护作用^[54]。这提示 PELNs 对炎症信号通路的调节并不是单一的,而是多通路协同的。

3.3 PELNs 调控 JAK/STAT 信号通路

JAK/STAT 信号通路的激活始于配体与细胞表面受体的结合,该结合进而诱导受体二聚化,并激活与受体结合的 JAK。激活的 JAK 磷酸化受体酪氨酸残基,为 STAT 提供结合位点;STAT 被 JAK 磷酸化后从受体上解离,随后形成二聚体并进入细胞核,结合靶基因启动子,从而调控转录^[55]。不同 STAT 成员发挥不同炎症调控功能:STAT1 通过抑制细胞生长、促进凋亡及调节免疫稳态参与炎症调控;STAT3 调控 Th17 细胞分化、细胞生长与凋亡,并与肿瘤相关炎症密切相关;STAT4、STAT5、STAT6 等参与特定细胞分化及免疫调节,它们共同维持机体炎症稳态^[56]。JAK/STAT 通路是炎症调控的关键信号通路,PELNs 可通过抑制热休克蛋白 90 表达从而阻断该通路的激活,发挥抗炎及疾病缓解作用。

热休克蛋白 90 是 JAK/STAT 信号通路和 NF- κ B 信号通路的共同上游触发靶点。紫苏叶来源的外泌体样纳米颗粒可通过其携带的特异性 *pab-miR396a-5p* 抑制热休克蛋白 90 表达,减少 JAK2 磷酸化及 STAT3 核转位(降低 p-STAT3 水平),阻断 JAK/STAT 通路激活;此外,其还可以通过降低 NF- κ B 通路中 p65 的磷酸化水平及上游调控基因的表达水平,阻断 NF- κ B 信号通路的激活,进而抑制 IL-6 等促炎因子的分泌,抑制角质形成细胞增殖并促进其凋亡,最终缓解银屑病^[57]。

3.4 PELNs 调控 PI3K/Akt 信号通路

PI3K/Akt 通路是人类炎症与癌症中最常被激活的通路之一,作为细胞内调控生长、增殖、代谢及存活的关键通路,其在整个生命过程中维持体内平衡^[58]。该通路被激活后,PI3K 将磷脂酰肌醇 4,5-二磷酸磷酸化生成磷脂酰肌醇 3,4,5-三磷酸(phosphatidylinositol 3,4,5-trisphosphate, PIP3);PIP3 作为第二信使将 Akt 招募至细胞膜,使其在磷酸肌醇依赖性蛋白激酶 1 和雷帕霉素靶蛋白复合物 2 作用下磷酸化^[59]。PI3K/Akt 信号通路异常激活是癌症、免疫疾

病、代谢紊乱及组织过度生长的关键驱动因素^[60-61],PELNs 可通过递送 miRNA 靶向抑制该通路,发挥抗肿瘤作用。

在三阴性乳腺癌中,PI3K/Akt 信号通路呈现异常激活状态^[62]。鸦胆子来源的外泌体样纳米颗粒可通过向 4T1 三阴性乳腺癌细胞递送功能性 miRNA,抑制 PI3K/Akt/mTOR 通路活性,下调 p-PI3K、p-Akt、p-mTOR 蛋白水平,为 PELNs 调控 PI3K/Akt 信号通路提供了依据^[63]。

3.5 PELNs 调控 Wnt 信号通路

Wnt 信号通路在细胞间通信、细胞迁移、细胞极性调控和细胞命运决定等中发挥着关键作用,并且对胚胎发育、器官形成及成体组织稳态维持至关重要^[64-65]。Wnt 信号通路分为经典 Wnt 信号通路和非经典 Wnt 信号通路;其中经典 Wnt 通路即 Wnt/ β -catenin 通路,通过调控 β -catenin 的稳定性与核转录活性,在细胞增殖、胚胎发育、组织修复与再生等生理过程中起核心作用,其异常激活与癌症、炎症性疾病及神经系统疾病等多种疾病的病理进程密切相关^[66]。PELNs 能够调节 Wnt 信号通路,通过促进干细胞增殖介导组织稳态重塑,为炎症性疾病及再生医学提供了新的治疗策略。

葡萄来源的外泌体样纳米颗粒能穿透小鼠肠道黏液屏障被肠道干细胞摄取,进入细胞后,葡萄来源的外泌体样纳米颗粒激活 Wnt/ β -catenin 信号通路,促使 β -catenin 在细胞质中积累并转位入核,进而与 TCF/LEF 转录因子结合,上调 *AXIN2*、*c-Myc* 等靶基因表达,从而促进肠道干细胞增殖,有效缓解结肠炎症状^[67]。

3.6 PELNs 调控 NLRP3 信号通路

NLRP3 炎性小体是调控宿主免疫防御与炎症稳态的关键胞内多蛋白复合体,由模式识别受体 NLRP3、ASC(apoptosis-associated speck-like protein containing a CARD)及效应分子 procaspase-1 组成^[68]。在炎症刺激下,NLRP3 被激活后触发 ASC 多聚化,形成炎性小体复合物;该复合物募集并激活 procaspase-1,使其转化为成熟 caspase-1;后者切割 pro-IL-1 β 和 pro-IL-18,使它们分别转变成 IL-1 β 和 IL-18 并从细胞中释放出来,从而引发炎症^[69]。因此,靶向该通路已成为炎症性疾病治疗前沿策略。PELNs 可通过自身的脂质成分和 RNA 成分靶向调控 NLRP3 炎性小体活性,为开发天然抗炎药物及治疗炎症性疾病

提供了新思路。

生姜来源的外泌体样纳米颗粒以自身脂质组分为作用媒介, 靶向ASC接头蛋白, 阻断NLRP3炎性小体复合物组装, 进而抑制促炎因子释放。该研究揭示了ASC是生姜来源的外泌体样纳米颗粒的直接分子靶点, 为生姜来源的外泌体样纳米颗粒应用于炎症性疾病治疗提供了理论支撑^[70]; 韭菜来源的外泌体样纳米颗粒的活性脂质成分1,2-二亚油酰-sn-甘油-3-磷酸胆碱可抑制NLRP3激活^[71]。PELNs既可通过其自身的脂质调控NLRP3, 还可通过其内部的RNA对NLRP3进行调控, 苦瓜来源的外泌体样纳米颗粒携带的RNA能靶向NLRP3 mRNA, 降低NLRP3蛋白水平, 也能上调JUN表达, 诱导肿瘤细胞凋亡^[72]。鱼腥草来源的外泌体样纳米颗粒携带的黄酮类等生物活性分子可抑制NLRP3活化从而治疗溃疡性结肠炎^[73]。香菇来源的外泌体样纳米颗粒通过抑制NLRP3炎性小体组装, 减少促炎因子释放, 为肝损伤治疗提供了新思路^[74]。

3.7 PELNs调控TGF- β 信号通路

TGF- β 家族构成了重要的细胞信号调控网络, 含33种哺乳动物蛋白, 在胚胎发育、成体组织稳态等关键生理过程中起核心调控作用, 成员包括TGF- β 1/2/3及骨形态发生蛋白、生长分化因子等, 其信号异常与多种疾病的病理进程密切相关^[75-78]。近年研究表明, PELNs在炎症调控中展现出独特作用, 其核心机制之一是对TGF- β 信号通路的精准调节。这类天然外泌体可以通过多种机制调节TGF- β 信号通路的活性, 从而调节炎症反应: 它们可能靶向调控Smad蛋白家族等下游关键分子和相关转录因子以及抑制上游配体, 从而影响炎症相关基因的表达。

茶叶来源的外泌体样纳米颗粒通过其携带的功能性miRNA(如miR-44)靶向调控TGF- β 1/Smads通路发挥抗肝纤维化作用: 茶叶来源的外泌体样纳米颗粒被肝星状细胞(hepatic stellate cells, HSCs)摄取后, 剂量依赖性抑制TGF- β 1诱导的HSCs活化, 下调TGF- β 1及其下游Smad2/3的mRNA与蛋白表达, 阻断Smad复合物核转位及纤维化相关基因转录激活, 进而抑制HSCs增殖和迁移以及细胞外基质沉积^[79]。这种对TGF- β 的调节为PELNs在炎症性疾病治疗中的应用提供了新思路。

3.8 PELNs调控其他炎症途径

PELNs 还可通过其他机制(包括调控 AMPK

信号通路与维持肠道菌群稳态)调控炎症性疾病。AMPK是一种重要的蛋白激酶, 其介导的信号通路在调节免疫稳态中起重要作用^[80-82]。西兰花来源的外泌体样纳米颗粒以脂质双层包裹萝卜硫素等活性成分, 将其靶向递送至肠道树突状细胞(dendritic cells, DCs), 激活AMPK通路, 抑制下游mTOR/S6K表达, 抑制DCs活化并诱导免疫耐受, 同时促进IL-10、TGF- β 等抗炎因子分泌, 抑制IL-12、TNF- α 等促炎因子分泌, 从而在维持肠道免疫稳态及预防小鼠结肠炎中发挥关键作用^[4]。肠道屏障的破坏会导致肠道微生物群的紊乱, 改变肠道的完整性和通透性, 并可能导致IMEs的失调^[83]。人参、马齿苋和桑树皮来源的外泌体样纳米颗粒均可通过不同信号途径调节肠道菌群微环境的平衡, 从而减缓葡聚糖硫酸钠诱导的结肠炎的进展^[28,50,84]。

综上所述, PELNs对炎症信号通路的调控并非相互独立, PELNs是通过多通路协同及多重反馈环路实现对炎症的抑制的。概括而言, 柠檬来源的外泌体样纳米颗粒能协同靶向NF- κ B与MAPK通路, 实现多节点抗炎调控; 热休克蛋白90是JAK/STAT信号通路和NF- κ B信号通路的共同上游触发靶点, 紫苏叶来源的外泌体样纳米颗粒可抑制热休克蛋白90表达, 同时阻断JAK/STAT通路和NF- κ B信号通路的过度激活, 进而发挥抗炎作用; 黑枸杞来源的外泌体样纳米颗粒既可抑制MAPK信号通路, 又能通过激活PI3K/Akt信号通路, 提高PI3K和Akt磷酸化水平, 通过多条通路协同抗炎; 苦瓜来源的外泌体样纳米颗粒既能抑制NLRP3 mRNA的表达, 从而降低NLRP3蛋白水平, 又能上调JUN表达。这种多通路、多靶点的调控模式, 是PELNs相较于单一靶向药物的重要优势。

4 总结及展望

本文全面讨论了PELNs如何通过IMEs调节炎症性疾病, 为将PELNs开发为抗炎药物提供了理论基础。需要特别强调的是PELNs与人工合成纳米载体存在本质差异: 人工合成纳米载体(如脂质体、聚合物纳米颗粒等)本质上是载体递送系统, 本身不具备治疗活性, 而PELNs则是天然的信息囊泡, 具有载体和药物的双重属性, 其自身携带的miRNA、脂质、蛋白质及多酚类等活性成分本身就具有跨物种治疗功能。在调控IMEs方面, PELNs能够通过激活抗炎

信号通路、调节免疫细胞功能以及促进组织修复等多种分子机制进行炎症的调控。

尽管 PELNs 展现出广阔的临床应用前景,但其从实验室研究走向临床转化仍面临多方面的技术挑战。在制备技术方面,超速离心法虽为目前的金标准方法,但存在制备产量低、操作耗时、难以规模化等固有局限。针对这些问题,未来可探索将超速离心法与尺寸排阻色谱、微流控分级等技术联用的策略,并优化聚乙二醇沉淀法,在保证产品纯度的同时显著提高产量。在储存稳定性方面,PELNs 天然脂质双层膜结构在常温或酸碱环境下易破损。冷冻干燥技术结合优化的冻干保护剂(如海藻糖、甘露醇、蔗糖等)可显著提高制品的长期稳定性,所得冻干制品的稳定性优于液体剂型,且便于运输和临床使用,或许能够延长 PELNs 的储存时间及提高其药效稳定性。未来还需要建立符合药品生产质量管理规范(Good Manufacturing Practice, GMP)要求的规模化生产工艺路线,并进行长期的安全性检测。为解决这一难题,未来的研究首先应在源头实施原材料标准化,采用标准化种植以减少环境因素带来的批次波动;其次,采用标准统一的工艺参数提取纯化外泌体;再次,运用纳米颗粒跟踪分析测定粒径分布与浓度、透射电子显微镜确认形态完整性等表征手段对外泌体进行质量把控,才有望在临床转化层面进一步研究。相信在不久的将来,PELNs 将为 IMEs 的精准调控开辟新的路径,为广大患者带来福音,成为生物医学领域的研究热点和重要发展方向。

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