外泌体和热休克蛋白在炎症性肠病中的研究进展*

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摘要　炎症性肠病(IBD)包括克罗恩病和溃疡性结肠炎,其病因尚未完全明确,发病机制与宿主-微生物之间的动态平衡密切相关。外泌体是由多种细胞释放的囊泡状结构,可携带蛋白质、脂质、核酸等生物活性成分,参与细胞间通讯。热休克蛋白(HSP)是一类高度保守的蛋白质,在IBD的诊断、治疗、预后评估中具有重要作用。本文就外泌体、HSP与IBD三者之间的关联作一系统阐述,并探讨外泌体和HSP在IBD进展中的作用机制,以及外泌体作为新型药物载体在IBD治疗中的应用前景。

关键词　炎症性肠病;　外泌体;　热休克蛋白

Research Progress on Exosomes and Heat Shock Proteins in Inflammatory Bowel Disease　*WAN Yuhong[1], BAI Xinyu[2], MIAO Yinglei[2]. [1]Kunming Medical University, Kunming (650500); [2]Department of Gastroenterology, the First Affiliated Hospital of Kunming Medical University, Kunming (650032)*

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Abstract　Inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis, has an unclear etiology, and its pathogenesis is closely associated with the dynamic homeostasis between the host and microbiota. Exosomes are vesicular structures released by various cells, carrying bioactive components such as proteins, lipids, and nucleic acids, and are involved in intercellular communication. Heat shock proteins (HSPs) are a family of highly conserved proteins that play important roles in the diagnosis, treatment, and prognosis assessment of IBD. This article systematically reviewed the relationship among exosomes, HSPs, and IBD, and explored the mechanisms of exosomes and HSPs in the progression of IBD, as well as the prospects of exosomes as novel drug delivery vehicles in the treatment of IBD.

Key words　Inflammatory Bowel Disease;　Exosomes;　Heat Shock Proteins

炎症性肠病(inflammatory bowel disease, IBD)包括克罗恩病(Crohn's disease, CD)和溃疡性结肠炎(ulcerative colitis, UC)两种亚型,其病因尚未完全明确,发病机制与宿主-微生物相互作用密切相关。外泌体(exosome)是由多种细胞释放的囊泡状结构,可携带蛋白质、脂质、核酸等生物活性成分,参与细胞间通讯或相互作用。热休克蛋白(heat shock protein, HSP)是一类高度保守的蛋白质,在IBD诊断、治疗、预后评估中起有重要作用。本文就外泌体、HSP与IBD三者之间的关联作一系统阐述,并探讨外泌体和HSP在IBD进展中的作用机制以及外泌体作为新型药物载体在IBD治疗中的应用前景。

一、外泌体与IBD(图1)

20世纪80年代初,Trams等[1]通过电镜发现的一类直径为500~1 000 nm的囊泡结构,其内部还含有直径约40 nm的次级囊泡结构,并将其命名为"外泌体"。外泌体是一类起源于内体系统的双层脂质膜囊泡,直径约30~150 nm,可由多种细胞通过胞吐方式释放。其形成过程始于细胞膜内陷并内吞胞外物质形成内吞囊泡,继而转化为早期内体,再进一步成熟为晚期内体。在晚期内体中,膜结构进一步向内出芽形成管腔内囊泡(intraluminal vesicles, ILVs)并聚集为多泡体(multivesicular bodies, MVBs)。MVBs可与溶酶体融合降解,也可与质膜融合,将其中的ILVs释放至细胞外环境中,参与细胞间通讯,这些被释放的囊泡即为外泌体[2-4]。外泌体几乎存在于所有细胞中,能携带亲代细胞的蛋白质、脂质、核酸等多种生物成分参与细胞间信息传递,在疾病诊断和治疗中发挥重要作用。

外泌体来源丰富,其中动植物来源的外泌体样纳米颗粒因其良好的生物相容性、抗炎、免疫调节等特性,在IBD治疗中展现出广阔的应用前景。有研究[5]表明,口服姜黄来源的外泌体样纳米颗粒可有效缓解葡聚糖硫酸钠(dextran sulfate sodium, DSS)诱导的小鼠结肠炎,抑制肿瘤坏死因子(tumor necrosis factor, TNF)-α、白细胞介素(interleukin, IL)-6、IL-1β等促炎因子表达,并增强肠道屏障功能。利用活体成像显示

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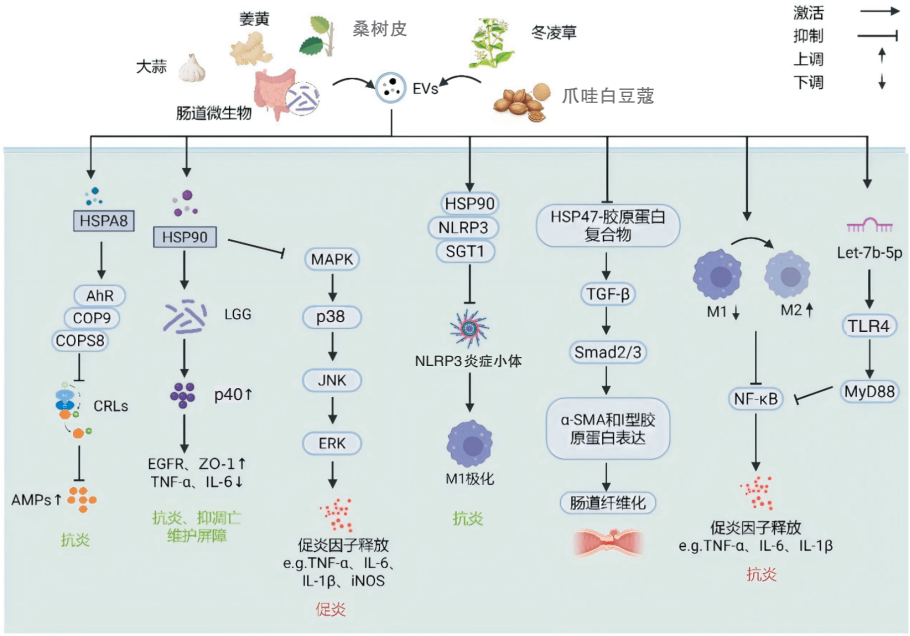

注：EVs为细胞外囊泡；HSP为热休克蛋白；AhR为芳香烃受体；COP9为组成型光形态建成蛋白9；COPS8为COP9信号小体亚基8；CRLs为Cullin-RING泛素连接酶；AMPs为抗菌肽；LGG为鼠李糖乳杆菌GG；EGFR为表皮生长因子受体；ZO-1为闭锁小带-1；TNF为肿瘤坏死因子；IL为白细胞介素；MAPK为丝裂原激活的蛋白激酶；JNK为c-Jun氨基末端激酶；ERK为细胞外信号调节激酶；iNOS为诱导型一氧化氮合酶；NLRP3为含pyrin结构域的NOD样受体家族蛋白3；SGT1为S期激酶相关蛋白1的G2等位基因抑制因子；TGF为转化生长因子；α-SMA为α-平滑肌肌动蛋白；NF-κB为核因子-κB；TLR4为Toll样受体4；MyD88为髓样分化因子88；IBD为炎症性肠病

图1　外泌体在IBD肠道微环境中的多重作用

外泌体可特异性富集于结肠区域。细胞实验进一步发现，姜黄来源的外泌体通过调控M1/M2型巨噬细胞极化和核因子-κB（nuclear factor-κB, NF-κB）信号通路发挥抗炎作用[6]。有研究[7]发现，大蒜来源的外泌体可通过miRNA抑制Toll样受体4（Toll-like receptor 4, TLR4）/髓样分化因子88（myeloid differentiation primary response protein 88, MyD88）/NF-κB信号通路，缓解DSS诱导的小鼠结肠炎。进一步的实验发现，其中一种高丰度miRNA peu-MIR2916-p3能特异性促进多形拟杆菌的生长，通过激活芳香烃受体（aryl hydrocarbon receptor, AhR）信号和调节$CD4^+$ T细胞分化，维持结肠上皮稳态并缓解结肠炎症[8]。此外，来自桑葚[9]、人参[10]、茶叶[11]、芹菜[12]、马齿苋[13]、牛奶[14-16]等来源的外泌体也被报道具有改善肠道微环境、抑制炎症等功能，在结肠炎治疗中表现出潜在的应用价值。

除动植物来源的外泌体外，人体自身细胞衍生的外泌体也受到广泛研究。其中，间充质干细胞（mesenchymal stem cells, MSC）因其显著免的疫调节能力和组织再生潜力，一直是该领域的研究热点，其衍生的外泌体在多种疾病乃至癌症治疗方面显示出巨大潜力。Wei等[17]的研究发现，人脐带间充质干细胞来源的外泌体（human umbilical cord mesenchymal stem cell-derived exosomes, hucMSC-Exo）可通过miR-129-5p靶向长链酰基辅酶A合成酶4（acyl-CoA synthetase long-chain family member 4, ACSL4），抑制肠上皮细胞（intestinal epithelial cells, IECs）铁死亡，从而减轻肠道炎症。Liang等[18]的研究表明，hucMSC-Exo还可通过激活Wnt/β-连环蛋白（β-catenin）通路，促进肠道干细胞增殖和上皮修复。此外，hucMSC-Exo还可通过调节Th17/调节性T细胞（regulatory T cell, Treg细胞）和肿瘤坏死因子-α刺激基因6（tumor necrosis factor-α stimulated gene 6, TSG-6）介导肠道屏障修复[19]。Yu等[20]发现，人脂肪间充质干细胞来源的外泌体（human adipose mesenchymal stem cell-derived exosomes, hADSC-Exo）同样可促进IECs增殖和再生，从而缓解DSS诱导的小鼠结肠炎。类似地，hADSC-Exo通过降低炎症细胞因子和调节Th17/Treg细胞，减轻DSS诱导的结肠炎[21]。嗅上皮[22]、毛囊[23]、骨髓[24-25]等不同组织来源的MSC外泌体在结肠炎中亦显示出治疗潜力。

免疫细胞来源的外泌体同样参与IBD的免疫调控。树突细胞来源的外泌体可靶向递送雷公藤甲素，通过改变树突细胞表面因子和细胞因子的分泌，降低$CD4^+$ T细胞比例并提高体内Treg细胞水平，从而有效治疗小鼠结肠炎[26]。在肠道免疫稳态中，巨噬细胞作为第一道防线，通常可极化为M1和M2型两种表型，两者均与IBD的发生、发展密切相关。Lu等[27]的研究结果证实，M1型巨噬细胞来源的外泌体主要通过miR-21a-5p抑制肠黏膜屏障关键蛋白E-钙黏蛋白（E-cadherin）表达，进而激活2型固有淋巴细胞和Th2免疫反应，加剧DSS诱导的小鼠结肠炎。有研究[28]发现，M2型巨噬细胞来源的外泌体携带miR-590-3p，可将其转运至IECs，通过抑制大型肿瘤抑制激酶1（large tumor suppressor kinase 1, LATS1）表达激活Yes相关蛋白（Yes-associated protein, YAP）/β-catenin/转录因子4（transcription factor 4, TCF4）复合

物，从而促进IECs增殖，显著降低IL-1β、TNF-α、IL-6等促炎因子水平，保护隐窝结构完整性，缓解结肠炎症状。但该研究也指出，miR-590-3p过表达可能促进结肠炎相关癌变。此外，肥大细胞[29]、Treg细胞[30]等其他免疫细胞来源的外泌体也参与IBD进展。

临床研究[31]表明，IBD患者与健康人体液中外泌体的组分和含量差异显著。有研究指出，CD患者血清外泌体RNA总量显著高于健康对照者，并可促进促炎因子表达，增加肠道通透性，破坏屏障完整性，加剧DSS诱导的小鼠结肠炎。而外泌体携带的Let-7b-5p则可通过TLR4/NF-κB和p38丝裂原激活的蛋白激酶（mitogen-activated protein kinase, MAPK）信号通路发挥抗炎和屏障保护作用[32]。这些发现为CD发病机制和潜在治疗策略的研究提供了新思路。

近年发现某些细菌可通过其外泌体携带自身相关抗原或致病因子影响IBD进程。Guo等[33]报道，幽门螺杆菌（*Helicobacter pylori*, Hp）外泌体中的细胞毒素相关基因蛋白A（cytotoxin-associated gene A, CagA）可能通过激活转录因子CDX2上调密封蛋白（claudin）-2，从而破坏紧密连接，加剧肠上皮屏障功能障碍。然而，Chen等[34]的研究显示，来自Hp阳性胃炎患者的血清外泌体能够促进IECs中含pyrin结构域的NOD样受体家族蛋白（NOD-like receptor family pyrin domain containing protein, NLRP）12的表达，抑制Notch信号通路，进而下调趋化因子单核细胞趋化蛋白-1（monocyte chemoattractant protein-1, MCP-1）和巨噬细胞炎症蛋白-1α（macrophage inflammatory protein-1α, MIP-1α），最终改善DSS诱导的小鼠结肠炎。目前Hp感染与IBD之间的相关性尚存在争议。此外，产肠毒素脆弱拟杆菌可通过甲基转移酶样14（methyltransferase-like 14, METTL14）依赖的N^6-甲基腺苷（N^6-methyladenosine, m^6A）甲基化下调外泌体miR-149-3p，进而通过PHF5A/KAT2A/SOD2信号通路促进Th17分化和结肠炎相关癌变[35]。

二、HSP与IBD

HSP是一类从细菌到哺乳动物中普遍存在且高度保守的蛋白质家族。在高温、化学刺激、紫外线辐射、自身免疫、慢性炎症等应激条件下高度表达，可激活热休克反应（heat shock response, HSR）途径，促使热休克转录因子（heat shock transcription factor, HSF）与DNA结合，进而启动下游分子伴侣的转录。根据分子质量大小，HSP主要分为HSP110、HSP90、HSP70、HSP60、HSP40、小分子HSP等多个亚类。HSP具有分子伴侣功能，能促进新生蛋白质的正确折叠，或对错误折叠的蛋白进行重折叠。在IECs中，HSP大量存在，并可在肠道菌群作用、食物发酵产物等生理刺激或环境应激状态下上调表达[36]。除参与蛋白质稳态维持外，HSP还在IBD等多种疾病中异常表达。越来越多的证据表明，HSP90表达参与IBD的发生、发展。从中药冬凌草中提取的活性成分Ponicidin可与HSP90结合，抑制MAPK信号通路下游分子p38/c-Jun氨基末端激酶（c-Jun N-terminal kinase, JNK）/细胞外信号调节激酶（extracellular signal-regulated kinase, ERK）的磷酸化水平，降低TNF-α、IL-6、IL-1β、诱导型一氧化氮合酶（inducible nitric oxide synthase, iNOS）等炎症因子的表达，同时上调紧密连接蛋白闭锁小带-1（zonula occludens-1, ZO-1）表达，从而减轻DSS诱导的小鼠结肠炎[37]。另一项研究[38]显示，从爪哇白豆蔻提取的主要活性成分1,8-桉叶素可通过调节HSP90-NLRP3-S期激酶相关蛋白1的G2等位基因抑制因子（suppressor of G-two allele of S-phase kinase-associated protein 1, SGT1）复合物，抑制NLRP3炎症小体活化和M1型巨噬细胞极化，从而减轻肠道炎症。HSP90抑制剂17-烯丙胺-17-去甲氧基格尔德霉素可通过调节MAPK信号通路、调节凋亡相关蛋白表达，显著改善DSS诱导的结肠炎，其疗效可被复方苦参汤进一步增强[39]。

肠道纤维化所致狭窄是IBD患者常见且严重的慢性并发症。超过半数CD患者会因肠道纤维化出现肠狭窄或穿孔，UC患者也可发生一定程度纤维化，但目前临床上仍缺乏有效防治该病变的药物。肠纤维化的主要特征包括胶原蛋白、纤连蛋白等细胞外基质（extracellular matrix, ECM）成分过度沉积，以及活化的肌成纤维细胞、α-平滑肌肌动蛋白（α-smooth muscle actin, α-SMA）阳性间充质细胞和基质金属蛋白酶共同介导的ECM重塑。有研究[40]表明，HSP47参与纤维化进程。作为胶原特异性分子伴侣，HSP47协助胶原的加工和分泌，并与ECM中胶原异常沉积密切相关。在CD患者肠道组织中可检测到HSP47高表达，其血清HSP47水平和抗HSP47抗体滴度均显著高于UC患者，尤其是伴肠道狭窄的CD患者，血清抗HSP47抗体水平明显高于无狭窄者。从白鲜根皮提取的栾酮（fraxinellone）可与胶原竞争性结合HSP47的Tyr383和Asp385位点，干扰HSP47-胶原复合物形成，并通过调节转化生长因子（transforming growth factor, TGF）-β/Smad2/3信号通路，降低α-SMA和Ⅰ型胶原表达，从而减轻小鼠肠道纤维化[41]。HSP72在肠道纤维化进程中发挥关键的抑制作用。研究[42]证实，HSP72表达下调会显著促进肌成纤维细胞活化，并增强其迁移和ECM合成能力；同时，下调的HSP72还可诱导IECs发生上皮-间质转化，表现为E-cadherin表达减少、纤连蛋白和α-SMA表达上调。这些变化共同推动了CD患者肠道纤维化的病理进展。

三、HSP与外泌体

作为细胞内的分子伴侣，HSP最初在细胞内部被发现。随着研究的深入，发现HSP也可存在于细胞外环境中，如细胞膜表面、外泌体等细胞外囊泡（extracellular vesicles, EVs）中，或在癌症和其他病理状态下以游离形式存在。HSP可通过被动释放（如细胞坏死）或主动分泌（如外泌体携带）等机制进入胞外环境。在肿瘤细胞中，由于长期处于低氧、治疗或免疫应激等条件下，HSP表达上调，参与蛋白质折叠调控并发挥抗凋亡作用[43]。外泌体所携带的HSP在多种癌症中的表达水平发生变化，作为生物学标志物在预防、监测和预后评估中发挥作用[44]。桑树皮来源的外泌体样纳米颗粒

(mulberry bark-derived exosome-like nanoparticles, MBELN)可靶向递送其携带的HSPA8至IECs,通过激活AhR/组成型光形态建成蛋白9(constitutively photomorphogenic 9, COP9)/COP9信号小体亚基8(COP9 signalosome subunit 8, COPS8)轴抑制Cullin-RING泛素连接酶活性,进而减轻结肠炎;其中COPS8对维持Paneth细胞功能和菌群平衡具有关键作用[45]。IBD患者因长期处于持续反复的肠道黏膜炎症状态,其病理生理机制主要包括活性氧/氮等基因毒性物质的异常蓄积、免疫细胞功能紊乱导致的异常活化,以及肠道微生物稳态的失调。这些机制相互关联,显著增加了结直肠癌(colorectal cancer, CRC)的发生风险[46]。在CRC进展过程中,Soloveva等[47]发现患者血浆来源的EVs中HSPA8蛋白表达显著降低。与此同时,富含HSP70的肿瘤源性EVs可通过蛋白激酶B(protein kinase B, AKT)-信号转导与转录激活因子(signal transduction and activator of transcription, STAT)信号通路上调巨噬细胞表面清道夫受体MARCO的表达,增强巨噬细胞吞噬功能并促进肿瘤微环境重塑,从而加速疾病进展。此外,CRC患者外泌体中HSP70水平也显著高于健康对照者[46-49]。此外,肠道微生物群与宿主间的共生稳态对IBD进展具有重要调控作用。鼠李糖乳杆菌GG分泌的蛋白p40可通过维持屏障功能、抑制细胞凋亡、促进黏蛋白生成和刺激增殖诱导配体表达以增强IgA应答,从而缓解小鼠结肠炎。IECs来源的EVs所携带的HSP90能显著上调p40表达,该作用强于其他肠上皮来源囊泡,且不依赖于淋巴细胞[50]。在肿瘤微环境中,HSP90还可特异性介导突变型p53蛋白向小细胞外囊泡(small extracellular vesicles, sEVs)的装载,进而驱动成纤维细胞向癌症相关表型转化,促进CRC进展;而抑制HSP90活性则可选择性阻断这一信号轴[51]。

外泌体因其可携带多种生物活性因子参与细胞间通讯,也被广泛研究作为靶向药物递送载体。有研究[52]表明,源自葡萄柚和番茄汁液的植物来源细胞外囊泡(plant-derived extracellular vesicle, PEVs)在大小和形态上与哺乳动物外泌体相似,对胃酸环境具有天然抗性,可被胃肠道细胞摄取,表现出抗炎、促进肠道干细胞增殖等功能。其中,葡萄柚外泌体样囊泡在装载HSP70以及递送药物至神经胶质瘤细胞方面的效率高于番茄外泌体样囊泡。尽管PEVs抗氧化活性较低,其在细胞氧化应激中的作用仍需进一步探索。此外,乳源性外泌体同样具有良好的递送潜能。Kumar等[53]将装载氨苄青霉素的乳源性外泌体(milk exosomes encapsulating aminobenzylpenicillin, mENs-AMP)治疗牛乳腺炎。该系统装载率88.61%,可持续释药,且与乳腺上皮细胞的生物相容性良好。相比游离AMP,mENs-AMP抗菌活性提高11倍,最低抑菌浓度降低4倍,并能有效降低体细胞计数和细菌载量,疗效显著优于未装载AMP。

四、总结

IBD因其病因尚未明确、病程迁延难愈且易反复发作,给医疗系统和患者带来了显著的经济负担,且其发病率正逐年上升。常规治疗药物因潜在全身并发症和患者个体间疗效差异,在临床应用中受到一定限制。HSP作为调控蛋白质正确折叠的分子伴侣,在IBD的发生、发展和治疗中发挥关键作用。外泌体凭借其优良的生物相容性、靶向性和载药能力,已成为IBD治疗研究的热点。进一步阐明HSP与外泌体在IBD中的相互作用机制,将为开发新型免疫治疗策略和药物递送系统提供重要的理论基础和临床转化前景。

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