

· 综述 ·

自噬调节策略在炎症性肠病临床前研究中的进展

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摘要: 炎症性肠病 (inflammatory bowel disease, IBD) 是一种难治性肠道炎症性疾病, 包括溃疡性结肠炎和克罗恩病, 具有进行性且不可预测的病程特点。肠道炎症和免疫反应异常与 IBD 发病机制密切相关。自噬是细胞中重要的分解代谢过程, 已被证明与包括 IBD 在内的多种炎症性疾病存在联系。本文从自噬功能障碍与 IBD 的关系出发, 重点阐述了炎症小体抑制剂、肠道微生物群调节剂及其他信号调节剂等作用于肠上皮细胞和巨噬细胞的自噬调节剂在 IBD 中的研究进展。

关键词: 炎症性肠病; 自噬; 肠上皮细胞; 巨噬细胞; 肠道屏障

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Autophagy-regulated strategies in pre-clinical studies of inflammatory bowel disease

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Abstract: Inflammatory bowel disease (IBD) is a group of chronic idiopathic colorectal inflammatory diseases with a progressive and unpredictable course, including ulcerative colitis (UC) and Crohn's disease (CD). Abnormal intestinal inflammation and immune response contribute to the pathogenesis of IBD. Autophagy as an essential catabolic process in cells, has been demonstrated to have associations with a variety of inflammatory diseases including IBD. Here, we review the relationship between autophagy dysfunction and the process of IBD. The progress of several autophagy regulators for intestinal epithelial cells and macrophages is highlighted (inflammation inhibitors, intestinal flora regulators, and other signal regulators) in the current studies on IBD.

Key words: inflammatory bowel disease; autophagy; intestinal epithelial cell; macrophage; intestinal barrier

炎症性肠病 (inflammatory bowel disease, IBD) 是一种特发性慢性肠道炎症性疾病, 可分为两大类, 即溃疡性结肠炎 (ulcerative colitis, UC) 和克罗恩病 (Crohn's disease, CD), 已经成为世界性健康负担^[1]。IBD 累及黏

膜及黏膜肌层, 严重并发症较多, 发病机制尚不明确^[2]。肠道上皮细胞 (intestinal epithelial cells, IEC) 与黏液层共同组成的肠黏膜屏障被认为在防止侵袭性损伤和维持肠道微生物群稳态方面发挥着至关重要的作用^[3]。肠黏膜屏障稳态失衡是 IBD 发生、发展的关键环节^[4]。多种相互作用的因素会导致 IBD 相关的肠黏膜屏障稳态失衡, 包括饮食因素 (如长期西式饮食)^[5]、环境因素 (如空气污染增加 IEC 通透性)^[6]、肠道菌群组成变化 (如长期过量使用抗生素)^[7]、遗传因素 (如基因

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突变)^[8,9]等。目前, IBD 的药物疗法策略主要使用氨基水杨酸盐类、皮质类固醇、免疫抑制剂和治疗性抗体。然而, 现有治疗药物的临床疗效有限, 且容易发生严重的不良反应事件, 特别是在长期使用一线肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α) 抗体药物进行生物治疗期间, 约 50% 的 IBD 患者 2 年内产生耐药 (抗体抵抗), 约 30% 出现过敏反应^[10,11]。因此, 迫切需要创新 IBD 的治疗策略, 以克服现有疗法的局限性。

研究表明, 自噬失调与炎症性疾病相关^[12-14], 可引起肠黏膜屏障的破坏。自噬是细胞依赖溶酶体对细胞质中错误折叠或过度积累的蛋白及受损的细胞器进行溶酶体途径降解的一种过程, 它不断清除不必要或功能失调的细胞成分, 维持细胞稳态^[15,16]。根据底物进入溶酶体方式和途径的不同, 细胞自噬可分为大自噬 (macroautophagy)、分子伴侣介导的自噬 (chaperone-mediated autophagy, CMA)、微自噬 (microautophagy) 和异自噬 (xenophagy)。自噬在疾病中的作用得到了广泛的探索, 包括心血管疾病 (如心肌梗塞^[17,18]) 和动脉粥样硬化^[19]、神经退行性疾病 (如多发性硬化症^[20])、代谢疾病 (如糖尿病^[21,22]和肥胖症^[23]), 以及炎症和免疫相关疾病 (如 IBD^[12,13]和关节炎^[24])。自噬在维持肠黏膜屏障稳态及影响 IBD 发生、发展中所扮演的角色引起越来越多研究者的兴趣^[25]。本文着重介绍导致巨噬细胞和 IEC 中与自噬失调显著相关的基因突变, 强调自噬功能障碍与 IBD 的相关性, 并重点归纳几种新型自噬调节剂在 IBD 中的研究进展, 旨在阐述自噬调节策略应用于 IBD 治疗的前景。

1 自噬与 IBD

自噬对于细胞适应环境和维持细胞稳态至关重要, 尤其是在压力条件下, 如营养缺乏、缺氧、氧化应激、细胞内钙水平变化、感染、炎症细胞因子释放等^[15,16], 是不同类型细胞维持肠道免疫稳态的关键功能。基于自噬对感染和局部炎症反应的多方面影响, 研究人员正致力于探究自噬通路在非感染性炎症疾病中的作用, 特别是其对胃肠道生理性炎症反应的影响。目前的观点认为, 细胞自噬功能障碍增加了对感染性疾病和非感染炎症性疾病的易感性^[13,14]。

自噬功能与 IBD 之间存在紧密联系。自噬相关基因突变可在感染和不健康饮食等因素下触发肠道细胞自噬障碍, 导致肠道黏膜屏障破坏和随后的 IBD 样表现, 如炎症小体的异常激活、肠道菌群紊乱、抗原递呈细胞 (antigen-presenting cell, APC) 的异常、巨噬细胞分泌细胞因子受损等^[12-14]。

1.1 重要自噬基因变异增加 IBD 的易感性

在肠道细胞自噬过程中, 自噬相关蛋白家族

(autophagy-related proteins, ATGs)、自噬相关 16 样蛋白 1 (autophagy-related protein 16 like 1, ATG16L1)、免疫相关 GTPase M (immunity-related GTPase M, IRGM)、含核苷酸结合寡聚化结构域蛋白 2 (nucleotide-binding oligomerization domain-containing protein 2, NOD2) 等蛋白至关重要^[8,9], 其基因功能失调与 IBD 相关。人类 *ATG16L1*、*IRGM* 等与 IBD 的易感性相关, *ATG16L1*、*ATG5*、*ATG4B* 或 *ATG7* 异常可导致潘式细胞和杯状细胞的形态学发生改变, 并出现分泌功能障碍及抗菌功能受损等情况, 从而增加了 IBD 的风险^[25]。

CD 患者存在 *ATG16L1*、*NOD2* 和 *IRGM* 多态性, 其所导致的巨噬细胞自噬缺陷被证明是 CD 的病因之一^[26,27]。这些突变 CD 患者的单核细胞衍生巨噬细胞无法限制黏附侵袭性大肠杆菌的复制, 使得炎症反应异常^[28]。如在 IBD 的小鼠模型中, 髓系 *Atg16L1* 缺陷的小鼠促炎细胞因子增加, 抗炎细胞因子减少, 在很大程度上加剧了结肠炎的严重程度^[29]。在巨噬细胞中检测到 *ATG16L1*^{T300A} 变异被证明是 CD 的危险因素^[29,30], 根据单核苷酸多态性 (single-nucleotide polymorphism, SNP) 的研究, *ATG16L1*^{T300A} (rs2241880) 与通过 caspase-3 激活 CD 的发生率密切相关^[31]。小鼠 *Nod2* 通过抑制革兰阳性菌的侵袭和损伤介导对葡聚糖硫酸钠 (dextran sulphate sodium, DSS) 诱导的结肠炎小鼠模型的缓解作用, 而敲除 *Nod2* 则消除了这种作用^[31]。*Irgm* 功能丧失突变则影响巨噬细胞对小鼠 IBD 模型中 CD 相关黏附侵袭性大肠杆菌的清除^[32]。

另外, Shen 等^[33]发现自噬和 *ErbB2* 相互作用蛋白 (*ErbB2* interacting protein, ERBIN) 之间存在联系, UC 患者、DSS 诱导结肠炎小鼠、*IL-10*^{-/-} 小鼠的结肠中该蛋白表达降低, 而小鼠 *Erbin* 缺陷导致 DSS 诱导结肠炎易感性增加, 诱导自噬过度激活导致 IEC 自噬性死亡。腹腔注射自噬抑制剂氯喹可减轻 DSS 处理 *Erbin*^{-/-} 小鼠的过度炎症反应^[33]。

1.2 自噬功能障碍触发肠屏障破坏

有研究显示自噬在肠道屏障功能中发挥保护作用。肠上皮将腔内内容物与黏膜免疫系统分离开来, 是保护肠道菌群稳态和最小化肠道炎症反应的重要防线。IBD 中的肠上皮通透性增加, 与紧密连接蛋白的异常表达有关^[34]。Nighot 等^[35]首次报道自噬通过诱导紧密连接蛋白 claudin 2 溶酶体降解, 从而降低上皮通透性, 调控肠道屏障功能。线粒体和内质网功能的缺陷可诱导肠道通透性增加, 促进大肠杆菌的内化和跨上皮的胞吞作用, 这些作用可通过异自噬介导的细胞内细菌的消除来抵消^[36]。除肠通透性外, 自噬也可调节细胞因子诱导 IEC 程序性死亡而破坏肠黏膜屏障, 同样与 IBD

发病机制密切相关^[37]。*Atg16L1^{AIEC}*小鼠表现为肠道条件致病菌肝螺杆菌 (*Helicobacter hepaticus*) 引发的慢性结肠炎, 而自噬可以保护 IEC 免受 TNF 诱导的凋亡, 从而维持肠道屏障的完整性^[38]。*Atg16L1^{AIEC}*小鼠感染诺如病毒后, 经 DSS 处理, 与对照组小鼠相比, 病理评分加重, 非凋亡上皮细胞死亡增加。

尽管这些研究在细胞死亡的确切机制上存在分歧, 但它们都表明有自噬功能障碍可能导致肠道 (上皮与免疫) 细胞过度死亡, 从而加速 IBD 的发展。

1.3 自噬与 IBD 的抗 TNF- α 治疗

TNF- α 抗体作为 IBD 的主要生物治疗手段, 可以诱导 M2 型巨噬细胞参与限制炎症^[39]。与野生型 (wild type, WT) 肠道类器官相比, 携带 CD 相关 *ATG16L1^{T300A}* 突变对 TNF- α 抗体治疗的反应降低^[37]。与 IFN- γ 诱导的巨噬细胞相比, TNF- α 抗体诱导的巨噬细胞的自噬水平增加; 而携带 *ATG16L1^{T300A}* 突变受试者的巨噬细胞与 WT 受试者相比, TNF- α 抗体诱导的巨噬细胞自噬受损^[39]。这些结果表明, 功能性自噬有利于在 IBD 中进一步实施抗 TNF- α 治疗。

2 自噬调节策略在 IBD 中的研究

IBD 易感患者 *ATG16L1*、*IRGM*、*ATG5*、*ATG4B* 和 *NOD2* 等基因表达失调, 它们在自噬过程所承担的重要功能随之发生严重改变。自噬功能障碍导致肠道细胞和免疫细胞均受到影响, 抵御病原体感染的第一道防线 (如 IEC) 以及先天性 (如巨噬细胞) 和适应性 (如 T 细胞) 免疫反应严重失衡^[40,41]。自噬调节策略是帮助

机体纠正失衡的过程, 可以避免传统抗炎药物反复使用而造成的治疗上限或疗效欠佳, 同时避免生物制剂的免疫原性。现有动物与临床的证据均表明, 关键自噬相关基因的缺失增加了 IBD 的易感性, 自噬缺陷介导的肠黏膜屏障功能障碍在 IBD 的发病过程中起着关键作用, 而自噬与细胞的大多数炎症途径之间存在强烈的信号串扰^[42]。鉴于自噬高度参与 IBD 的发病机制和进展, 调节自噬活性可能成为 IBD 的治疗新策略。目前在研的自噬调节剂包括免疫微环境调节剂 [NLR 家族含有 pyrin 结构域 3 (NLR family pyrin domain containing 3, NLRP3) 炎症小体抑制剂、AMPK-mTOR-p70S6K 信号相关调节剂] 和肠道微生物群调节剂 (表 1)^[43-55]。

2.1 免疫微环境调节剂

2.1.1 NLRP3 炎症小体抑制剂

炎症小体 (inflammasome) 被认为是负责激活炎症反应的多蛋白寡聚体, 它属于先天免疫家族, 主要存在于 IEC 和大部分炎症和免疫细胞, 如巨噬细胞和树突状细胞^[56]。炎症小体和自噬之间的信号串扰已在许多疾病中得到充分研究^[56,57]。到目前为止, 已经描述了自噬相关炎症小体的几个成员, 包括 NLRP1、NLRP3、NLR 家族含有半胱天冬酶募集结构域蛋白 4 (NLR family caspase recruitment domain-containing protein 4, NLRC4) 和黑色素瘤 2 缺乏双链 DNA 传感器 (double-stranded DNA sensors absent in melanoma 2, AIM2)。

非 NLRP3 炎症小体 (如 NLRP1、NLRC4、AIM2)

Table 1 Regulators taking advantage of autophagy in inflammatory bowel disease (IBD) research. NLRP3: NLR family pyrin domain containing 3; AMPK: Adenosine 5'-monophosphate (AMP)-activated protein kinase; HSP90: Heat shock protein 90; GPR35: G protein-coupled receptor 35; VDR: Vitamin D receptor; TREM-1: Triggering receptor expressed on myeloid cells 1; CB2R: Cannabinoid receptor 2; mTOR: Mammalian target of rapamycin; $\alpha 7$ nAChR: Alpha 7 nicotinic acetylcholine receptor; STAT: Signal transducing activator of transcription

Category	Regulator	Key pharmacological effect	Reference
NLRP3 inhibitors	GL-V9	Activate AMPK Induce macrophage autophagy	[43]
	Ginsenoside Rd	Induction of mitochondrial autophagy	[44]
	Palmitine	Induction of mitochondrial autophagy	[45]
	Evodiamine	Inhibit the apoptosis-associated speck-like protein oligomerization and caspase-1 in macrophages	[46]
	Metformin/MCC950	Regulate HSP90/NLRP3 interaction	[47]
Intestinal flora regulators	Kynurenic acid	Regulate kynurenic acid/GPR35 axis	[48]
	Vitamin D	Regulate VDR signal	[49]
	Galangin	Regulate inflammatory response and myeloperoxidase activity	[50]
AMPK-mTOR-p70S6K signal regulators	LR12	Inhibit TREM-1	[51,52]
	HU308	Activate CB2R	[53]
	Nicotine	Mediate AMPK-mTOR-p70S6K signal	
		Activate $\alpha 7$ nAChR	[54]
PNU282987	Inhibit pro-inflammatory cytokines via microRNA-124/STAT		
	Mediate AMPK-mTOR-p70S6K signal	[55]	
	Activate $\alpha 7$ nAChR		
	Mediate AMPK-mTOR-p70S6K signal		

与自噬之间的信号串扰在炎症性疾病中少见报道^[58]。NLRP3与其他炎症小体不同,可被更广泛的刺激物激活,因此是目前研究最多、表征最完整的炎症小体;其介导的自噬调节机制及其与炎症性疾病的关系已被逐步阐明^[59],尤其是发现自噬相关蛋白 IRGM 在细胞内的自噬调节是通过抑制 NLRP3 而实现的^[60]。NLRP3 被鉴定为自噬抑制剂雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR) 的一种结合伴侣^[61]。在炎症条件下, NLRP3 炎症小体结合并促进 mTOR 磷酸化,抑制自噬,破坏自噬介导的促炎介质的消除,从而加剧炎症^[61]。NLRP3 与自噬之间的串扰在针对细菌、真菌和病毒感染的先天免疫中发挥着重要作用^[62],已被广泛报道与 IBD 的发病机制和进展有关^[61,63,64]。在 DSS 诱导的结肠炎小鼠模型或 *IL-10*^{-/-} 小鼠模型中,缺氧可通过下调 NLRP3-mTOR 结合,从而激活自噬介导的 NF- κ B 信号介质降解,降低促炎基因的表达,从而抑制肠道炎症^[61]。在应对细胞内病原体时, caspase-4 (CASP4) 被激活,导致炎症小体激活,从而正向调节巨噬细胞自噬小体的生物生成和向溶酶体的转运,这增加了异自噬介导的病原体的消除^[64]。上述证据认为, NLRP3 炎症小体的过度激活对 IBD 的发生和发展有很大影响。

抑制 NLRP3 炎症小体的激活是炎症性疾病的潜在疗法^[62]。一些自噬调节剂通过抑制 NLRP3 炎症小体的激活来缓解 IBD^[43-48]。小分子 AMP 依赖蛋白激酶 [adenosine 5'-monophosphate (AMP)-activated protein kinase, AMPK] 的激动剂 GL-V9 通过诱导自噬显著降解巨噬细胞中的 NLRP3 炎症小体复合物,从而预防结肠炎^[43]。Liu 等^[44]的研究表明,四环三萜衍生物人参皂苷 (ginsenoside) Rd 通过诱导 p62 驱动的线粒体自噬介导 NLRP3 炎症小体失活,这显著减轻了 DSS 诱导的 UC 模型中结肠炎的严重程度。天然衍生物 palmitate 通过促进线粒体自噬介导的 NLRP3 炎症小体抑制来改善 DSS 诱导的结肠炎^[45]。另一项天然产物的研究也发现,吴茱萸碱 (evodiamine) 可以抑制 NLRP3 炎症小体组装激活细胞自噬,减轻实验性 DSS 诱导的结肠炎损伤,并通过抑制巨噬细胞中凋亡相关斑点样蛋白寡聚化和 caspase-1 活性来抑制 NLRP3 炎症小体^[46]。MCC950 是一种小分子 NLRP3 炎症小体抑制剂,可减少促炎细胞因子如 IL-1 β 和 IL-18 的产生^[65]。Sabre 和 Abd El-Kader^[47]证明二甲双胍与 MCC950 联合治疗对 UC 产生了缓解作用,该策略通过调节热休克蛋白 90 (heat shock protein 90, HSP90) 与 NLRP3 相互作用,抑制自噬介导的 NLRP3,减轻 DSS 诱导的结肠炎。犬尿氨酸 (kynurenic acid) 是一种结肠炎相关的内源性调节剂,研究发现,通过犬尿氨酸/G 蛋白偶联受体 35 (G

protein-coupled receptor 35, GPR35) 轴可诱导巨噬细胞中 NLRP3 的自噬依赖性降解^[48]。

2.1.2 与 AMPK-mTOR-p70S6K 信号相关的调节剂 在免疫微环境中, AMPK 和 mTOR 是参与细胞自噬调节的重要分子^[14],其中 AMPK-mTOR-p70S6K 通路也介导除炎症小体外的各类靶点的促自噬作用^[53-55]。大麻素受体 2 (cannabinoid receptor 2, CB2R) 是 G 蛋白偶联受体 (G-protein-coupled receptors, GPCR) 家族的成员,作为免疫和炎症调节剂越来越多地被研究^[34]。与主要在中枢神经系统中表达的 CB1R 不同, CB2R 主要位于免疫系统中,包括外周组织中的巨噬细胞和其他炎症和免疫细胞^[34]。给予 CB2R 激动剂 HU308 可诱导肠道巨噬细胞自噬激活以减轻 DSS 诱导小鼠结肠炎的严重程度,其对 IBD 的保护作用是由自噬相关通路 AMPK-mTOR-p70S6K 信号介导^[53]。 α 7 烟碱乙酰胆碱受体 (alpha 7 nicotinic acetylcholine receptor, α 7nAChR) 是“半胱氨酸-环” (Cys-loop) 阳离子配体门控通道超家族的成员,已被证明可通过触发“胆碱能抗炎通路”发挥作用^[55]。尼古丁 (nicotine) 是一种 α 7nAChR 非选择性激动剂,可通过 IBD 中的 microRNA-124/信号转导转录激活因子 (signal transducing activator of transcription, STAT) 系统抑制巨噬细胞产生促炎细胞因子^[54]。PNU282987 是另一种选择性 α 7nAChR 激动剂,通过在肠道巨噬细胞中诱导 AMPK-mTOR-p70S6K 信号介导自噬,以抵抗 DSS 诱导的结肠炎^[55]。

2.1.3 其他免疫微环境相关靶点 选择性自噬受体 optineurin 也被认为是维持病原体清除和调节巨噬细胞细胞因子产生的关键因素^[66,67]。Optineurin 可介导巨噬细胞自噬,从而抑制肠道巨噬细胞介导的炎症反应,有助于减轻 IBD 的黏膜损伤,是 IBD 治疗的潜在靶点^[67]。

2.2 肠道微生物群调节剂

肠道微生物群稳态紊乱与 IBD 的发生发展密切相关,而恢复该稳态则是潜在的 IBD 治疗策略^[68]。自噬已被揭示在肠道调节中发挥重要作用,有助于调节 IBD 中的肠道微生物群。因此,可利用自噬介导的肠道微生物群调节来缓解 IBD^[69]。

维生素 D 促进肠道自噬而减轻 IBD,维生素 D/维生素 D 受体 (vitamin D receptor, VDR) 信号被证明有利于维持和恢复肠道微生物群的稳态^[49]。Xuan 等^[50]发现天然黄酮类化合物高良姜素 (galangin) 可通过促进 IEC 自噬介导的肠道微生物群良性调节,以治疗 DSS 诱导的结肠炎。髓样细胞 1 上表达的触发受体 (triggering receptor expressed on myeloid cells 1, TREM-1) 在大多数先天免疫细胞上表达,而在实质细胞上表达较少;

UC和CD患者的活检组织中,高表达TREM-1的中性粒细胞和巨噬细胞的比例在炎症活检组织中显著高于非炎症活检组织^[70]。Kökten等^[52]表明抑制TREM-1有助于恢复中性粒细胞和巨噬细胞受损的自噬活性,从而积极调节结肠炎小鼠的肠道微生物群。肽LR12在研究中被证明可抑制TREM-1,并在临床症状、内窥镜和组织学水平上缓解DSS诱导小鼠的结肠炎^[51]。在DSS诱导小鼠中注射LR12后,大自噬(ATG1、ATG13、ATG5和ATG16L1)及CMA(HSPA8和HSP90AA1)相关蛋白表达显著增加,这种效果也通过使用*Trem-1*基因敲除小鼠实验得到证实^[52]。

2.3 自噬调节剂的临床转化

虽然自噬调节剂的研究仍处于细胞及动物水平的阶段,未有成熟的临床试验报道,但根据现有的动物与临床证据,自噬调节策略可被认为是一种潜在的IBD治疗方法(图1)。首先,已证实关键自噬相关基因的缺失增加了IBD的易感性^[38,42];其次,自噬功能障碍可介导IBD相关的肠黏膜屏障破坏^[35-37];另外,自噬与细胞

的几乎大多数炎症途径之间存在强烈串扰^[42]。自噬调节策略可以帮助机体纠正失衡的过程,可避免现有生物制剂反复使用而造成的治疗上限或疗效欠佳;且现有的候选物均为小分子调节剂或小肽,成药性上规避了免疫原性,适用于对生物大分子制剂不耐受或对抗体治疗抵抗的患者。就当前而言,自噬调节策略的临床转化面临的主要挑战包括:①缺少临床试验的支撑;②该治疗策略的意外后果或不良反应未知;③利用自噬调节剂在TNF- α 抗体抵抗型IBD中的扩展研究;④准确监测IBD患者黏膜愈合的可用生物标记物有待确定^[71]。

3 结语

IBD的发病机制尚未完全阐明,目前的研究揭示了自噬在IBD发病机制和进展中的作用,这在很大程度上开拓了治疗新策略的发展空间。大量研究发现了自噬功能障碍与IBD之间的紧密联系。目前有3类广泛研究的自噬调节剂可作为IBD治疗的候选药物,包括炎症小体抑制剂、肠道微生物群调节剂及AMPK-

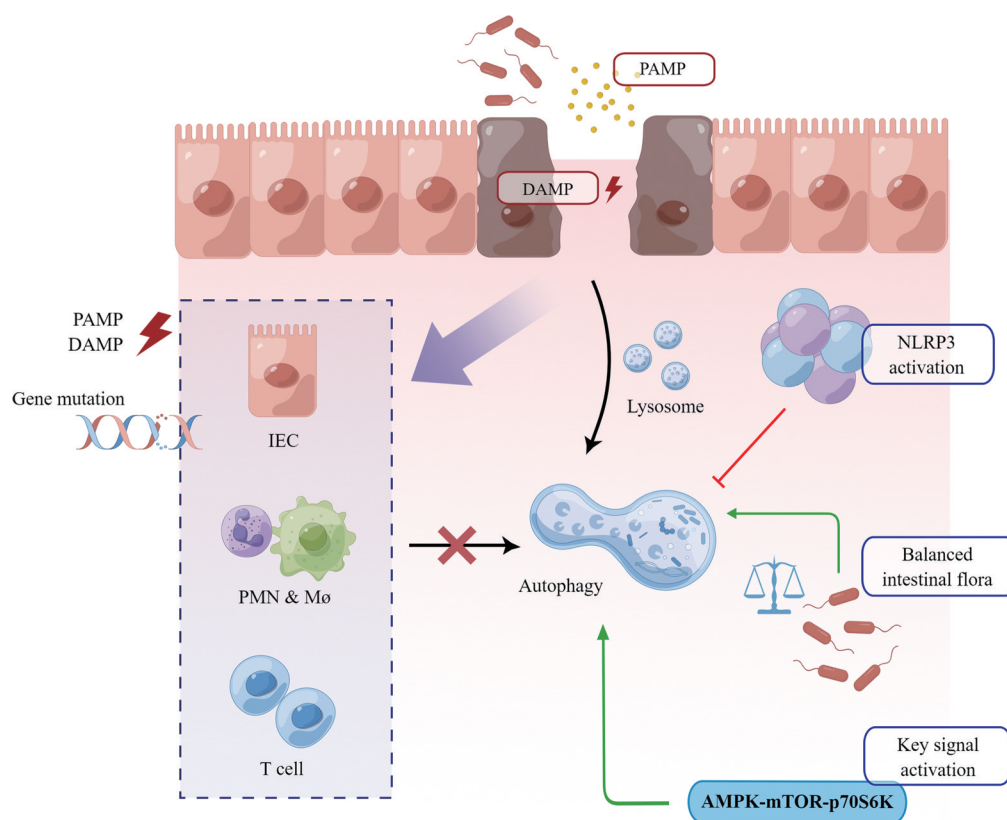


Figure 1 Autophagy regulation in the gastrointestinal tract of IBD. Gene mutations of autophagy (e.g., *ATG16L1*^{T300A}) can be triggered when injury or infection (DAMPs and PAMPs) occurs. Such autophagy dysregulation is found in general IECs, PMNs, M ϕ , and less in T cells, resulting in an inflammatory response of IBD. NLRP3 activation inhibits the autophagy function of these cells, whereas balanced intestinal flora and AMPK-mTOR-p70S6K signal contribute to the recovery of autophagy processes. DAMP: Damage-associated molecular pattern; IEC: Intestinal epithelial cell; PAMP: Pathogen-associated molecular pattern; PMN: Polymorphonuclear neutrophil; M ϕ : Macrophage. This figure was generated by an open-type platform FigDraw (<http://www.figdraw.com/>)

mTOR-p70S6K 信号调节剂, 极大地扩展了自噬调节策略应用于 IBD 治疗的新视野。尽管近年来对肠道细胞自噬调节机制的研究越来越多, 仍少有自噬调节剂被成功应用于临床实践。鉴于 IBD 中自噬调节作用的复杂性, 最终能否实现在临床中应用自噬治疗策略, 还需要未来更进一步的研究。

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References

- [1] Kaplan GG. The global burden of IBD: from 2015 to 2025 [J]. *Nat Rev Gastroenterol Hepatol*, 2015, 12: 720-727.
- [2] Kaplan GG, Windsor JW. The four epidemiological stages in the global evolution of inflammatory bowel disease [J]. *Nat Rev Gastroenterol Hepatol*, 2021, 18: 56-66.
- [3] Mehandru S, Colombel JF. The intestinal barrier, an arbitrator turned provocateur in IBD [J]. *Nat Rev Gastroenterol Hepatol*, 2021, 18: 83-84.
- [4] Chang JT. Pathophysiology of inflammatory bowel diseases [J]. *N Engl J Med*, 2020, 383: 2652-2664.
- [5] Bischoff SC, Escher J, Hébuterne X, et al. Espen practical guideline: clinical nutrition in inflammatory bowel disease [J]. *Clin Nutr*, 2020, 39: 632-653.
- [6] Chen WY, Wang M, Zhang J, et al. Acrolein disrupts tight junction proteins and causes endoplasmic reticulum stress-mediated epithelial cell death leading to intestinal barrier dysfunction and permeability [J]. *Am J Pathol*, 2017, 187: 2686-2697.
- [7] Sartor RB, Wu GD. Roles for intestinal bacteria, viruses, and fungi in pathogenesis of inflammatory bowel diseases and therapeutic approaches [J]. *Gastroenterology*, 2017, 152: 327-339.e4.
- [8] Saxena A, Lopes F, Poon KKH, et al. Absence of the NOD2 protein renders epithelia more susceptible to barrier dysfunction due to mitochondrial dysfunction [J]. *Am J Physiol Gastrointest Liver Physiol*, 2017, 313: G26-G38.
- [9] Schwerd T, Pandey S, Yang HT, et al. Impaired antibacterial autophagy links granulomatous intestinal inflammation in niemann-pick disease type C1 and XIAP deficiency with NOD2 variants in Crohn's disease [J]. *Gut*, 2017, 66: 1060-1073.
- [10] Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial [J]. *Lancet*, 2017, 390: 2779-2789.
- [11] Li J, Liu Z, Hu P, et al. Indicators of suboptimal response to anti-tumor necrosis factor therapy in patients from China with inflammatory bowel disease: results from the explore study [J]. *BMC Gastroenterol*, 2022, 22: 44.
- [12] Tapias NS, Vergnolle N, Denadai-Souza A, et al. The interplay between genetic risk factors and proteolytic dysregulation in the pathophysiology of inflammatory bowel disease [J]. *J Crohns Colitis*, 2020, 14: 1149-1161.
- [13] Dalmaso G, Nguyen HTT, Fais T, et al. Crohn's disease-associated adherent-invasive *Escherichia coli* manipulate host autophagy by impairing sumoylation [J]. *Cells*, 2019, 8: 35.
- [14] Matsuzawa-Ishimoto Y, Hwang S, Cadwell K. Autophagy and inflammation [J]. *Annu Rev Immunol*, 2018, 36: 73-101.
- [15] Galluzzi L, Baehrecke EH, Ballabio A, et al. Molecular definitions of autophagy and related processes [J]. *EMBO J*, 2017, 36: 1811-1836.
- [16] Reggiori F, Ungermann C. Autophagosome maturation and fusion [J]. *J Mol Biol*, 2017, 429: 486-496.
- [17] Liu H, Liu SY, Qiu XY, et al. Donor MSCs release apoptotic bodies to improve myocardial infarction *via* autophagy regulation in recipient cells [J]. *Autophagy*, 2020, 16: 2140-2155.
- [18] Shi CC, Pan LY, Peng ZY, et al. miR-126 regulated myocardial autophagy on myocardial infarction [J]. *Eur Rev Med Pharmacol Sci*, 2020, 24: 6971-6979.
- [19] Cao Q, Du HJ, Fu X, et al. Artemisinin attenuated atherosclerosis in high-fat diet-fed Apoe^{-/-} mice by promoting macrophage autophagy through the AMPK/mTOR/ULK1 pathway [J]. *J Cardiovasc Pharmacol*, 2020, 75: 321-332.
- [20] Andhavarapu S, Mubariz F, Arvas M, et al. Interplay between ER stress and autophagy: a possible mechanism in multiple sclerosis pathology [J]. *Exp Mol Pathol*, 2019, 108: 183-194.
- [21] Marasco MR, Linnemann AK. Beta-cell autophagy in diabetes pathogenesis [J]. *Endocrinology*, 2018, 159: 2127-2141.
- [22] Ding F, Shan CY, Li HW, et al. Simvastatin alleviated diabetes mellitus-induced erectile dysfunction in rats by enhancing AMPK pathway-induced autophagy [J]. *Andrology*, 2020, 8: 780-792.
- [23] Bartelt A, Widenmaier SB. Proteostasis in thermogenesis and obesity [J]. *Biol Chem*, 2020, 401: 1019-1030.
- [24] Vomero M, Barbati C, Colasanti T, et al. Autophagy and rheumatoid arthritis: current knowledges and future perspectives [J]. *Front Immunol*, 2018, 9: 1577.
- [25] Kabat AM, Pott J, Maloy KJ. The mucosal immune system and its regulation by autophagy [J]. *Front Immunol*, 2016, 7: 240.
- [26] Caprilli R, Lapaquette P, Darfeuille-Michaud A. Eating the enemy in Crohn's disease. An old theory revisited [J]. *J Crohns Colitis*, 2010, 4: 377-383.
- [27] Homer CR, Richmond AL, Rebert NA, et al. Atg16L1 and NOD2 interact in an autophagy-dependent antibacterial pathway implicated in Crohn's disease pathogenesis [J]. *Gastroenterology*, 2010, 139: 1630-1641,1641.e1-2.
- [28] Lapaquette P, Nguyen HTT, Faure M. Regulation of immunity and inflammation by autophagy: all is well, all is fine, all goes as well as possible [J]. *Med Sci (Paris)*, 2017, 33: 305-311.
- [29] Zhang H, Zheng L, McGovern DPB, et al. Myeloid Atg16L1

- facilitates host-bacteria interactions in maintaining intestinal homeostasis [J]. *J Immunol*, 2017, 198: 2133-2146.
- [30] Samie M, Lim J, Verschueren E, et al. Selective autophagy of the adaptor TRIF regulates innate inflammatory signaling article [J]. *Nat Immunol*, 2018, 19: 246-254.
- [31] Luo X, Wang X, Huang S, et al. Paconiflorin ameliorates experimental colitis by inhibiting Gram-positive bacteria-dependent MDP-NOD2 pathway [J]. *Int Immunopharmacol*, 2021, 90: 107224.
- [32] Parkes M. Evidence from genetics for a role of autophagy and innate immunity in IBD pathogenesis [J]. *Digest Dis*, 2012, 30: 330-333.
- [33] Shen T, Li S, Cai LD, et al. Erbin exerts a protective effect against inflammatory bowel disease by suppressing autophagic cell death [J]. *Oncotarget*, 2018, 9: 12035-12049.
- [34] Zheng Y, Yu Y, Chen XF, et al. Intestinal macrophage autophagy and its pharmacological application in inflammatory bowel disease [J]. *Front Pharmacol*, 2021, 12: 803686.
- [35] Nighot PK, Hu CAA, Ma TY. Autophagy enhances intestinal epithelial tight junction barrier function by targeting claudin-2 protein degradation [J]. *J Biol Chem*, 2015, 290: 7234-7246.
- [36] Lopes F, Keita AV, Saxena A, et al. ER-stress mobilization of death-associated protein kinase-1-dependent xenophagy counteracts mitochondria stress-induced epithelial barrier dysfunction [J]. *J Biol Chem*, 2018, 293: 3073-3087.
- [37] Matsuzawa-Ishimoto Y, Shono Y, Gomez LE, et al. Autophagy protein Atg16L1 prevents necroptosis in the intestinal epithelium [J]. *J Exp Med*, 2017, 214: 3687-3705.
- [38] Pott J, Kabat AM, Maloy KJ. Intestinal epithelial cell autophagy is required to protect against TNF-induced apoptosis during chronic colitis in mice [J]. *Cell Host Microbe*, 2018, 23: 191-202. e4.
- [39] Levin AD, Koelink PJ, Bloemendaal FM, et al. Autophagy contributes to the induction of anti-TNF induced macrophages [J]. *J Crohns Colitis*, 2016, 10: 323-329.
- [40] Levine B, Kroemer G. Biological functions of autophagy genes: a disease perspective [J]. *Cell*, 2019, 176: 11-42.
- [41] Ke P, Shao BZ, Xu ZQ, et al. Intestinal autophagy and its pharmacological control in inflammatory bowel disease [J]. *Front Immunol*, 2017, 7: 695.
- [42] Mizushima N, Levine B. Autophagy in human diseases [J]. *N Engl J Med*, 2020, 383: 1564-1576.
- [43] Zhao Y, Guo Q, Zhao K, et al. Small molecule GL-V9 protects against colitis-associated colorectal cancer by limiting NLRP3 inflammasome through autophagy [J]. *Oncoimmunology*, 2018, 7: e1375640.
- [44] Liu C, Wang J, Yang Y, et al. Ginsenoside Rd ameliorates colitis by inducing p62-driven mitophagy-mediated NLRP3 inflammasome inactivation in mice [J]. *Biochem Pharmacol*, 2018, 155: 366-379.
- [45] Mai CT, Wu MM, Wang CL, et al. Palmatine attenuated dextran sulfate sodium (DSS)-induced colitis *via* promoting mitophagy-mediated NLRP3 inflammasome inactivation [J]. *Mol Immunol*, 2019, 105: 76-85.
- [46] Ding W, Ding Z, Wang Y, et al. Evodiamine attenuates experimental colitis injury *via* activating autophagy and inhibiting NLRP3 inflammasome assembly [J]. *Front Pharmacol*, 2020, 11: 573870.
- [47] Saber S, Abd El-Kader EM. Novel complementary coloprotective effects of metformin and MCC950 by modulating HSP90/NLRP3 interaction and inducing autophagy in rats [J]. *Inflammopharmacology*, 2021, 29: 237-251.
- [48] Zheng X, Hu M, Zang X, et al. Kynurenic acid/GPR35 axis restricts NLRP3 inflammasome activation and exacerbates colitis in mice with social stress [J]. *Brain Behav Immun*, 2019, 79: 244-255.
- [49] Bakke D, Sun J. Ancient nuclear receptor VDR with new functions: microbiome and inflammation [J]. *Inflamm Bowel Dis*, 2018, 24: 1149-1154.
- [50] Xuan HZ, Ou AQ, Hao SY, et al. Galangin protects against symptoms of dextran sodium sulfate-induced acute colitis by activating autophagy and modulating the gut microbiota [J]. *Nutrients*, 2020, 12: 347.
- [51] Parent M, Boudier A, Maincent P, et al. LR12-peptide quantitation in whole blood by RP-HPLC and intrinsic fluorescence detection: validation and pharmacokinetic study [J]. *Biomed Chromatogr*, 2017. DOI: 10.1002/bmc.3877.
- [52] Kökten T, Gibot S, Lepage P, et al. Trem-1 inhibition restores impaired autophagy activity and reduces colitis in mice [J]. *J Crohns Colitis*, 2018, 12: 230-244.
- [53] Ke P, Shao BZ, Xu ZQ, et al. Activation of cannabinoid receptor 2 ameliorates DSS-induced colitis through inhibiting NLRP3 inflammasome in macrophages [J]. *PLoS One*, 2016, 11: e0155076.
- [54] Qin Z, Wan JJ, Sun Y, et al. Nicotine protects against DSS colitis through regulating microRNA-124 and STAT3 [J]. *J Mol Med*, 2017, 95: 221-233.
- [55] Shao BZ, Wang SL, Fang J, et al. Alpha7 nicotinic acetylcholine receptor alleviates inflammatory bowel disease through induction of AMPK-mTOR-p70S6K-mediated autophagy [J]. *Inflammation*, 2019, 42: 1666-1679.
- [56] Shao BZ, Wang SL, Pan P, et al. Targeting NLRP3 inflammasome in inflammatory bowel disease: putting out the fire of inflammation [J]. *Inflammation*, 2019, 42: 1147-1159.
- [57] Deretic V, Levine B. Autophagy balances inflammation in innate immunity [J]. *Autophagy*, 2018, 14: 243-251.
- [58] Yuk JM, Silwal P, Jo EK. Inflammasome and mitophagy connection in health and disease [J]. *Int J Mol Sci*, 2020, 21: 4714.
- [59] Zewinger S, Reiser J, Jankowski V, et al. Apolipoprotein C3 induces inflammation and organ damage by alternative inflam-

- masome activation [J]. *Nat Immunol*, 2020, 21: 30-41.
- [60] Mehto S, Jena KK, Nath P, et al. The Crohn's disease risk factor irgm limits NLRP3 inflammasome activation by impeding its assembly and by mediating its selective autophagy [J]. *Mol Cell*, 2019, 73: 429-445.e7.
- [61] Cosin-Roger J, Simmen S, Melhem H, et al. Hypoxia ameliorates intestinal inflammation through NLRP3/mTOR downregulation and autophagy activation [J]. *Nat Commun*, 2017, 8: 98.
- [62] Biasizzo M, Kopitar-Jerala N. Interplay between NLRP3 inflammasome and autophagy [J]. *Front Immunol*, 2020, 11: 591803.
- [63] Hanaei S, Sadr M, Rezaei A, et al. Association of NLRP3 single nucleotide polymorphisms with ulcerative colitis: a case-control study [J]. *Clin Res Hepatol Gastroenterol*, 2018, 42: 269-275.
- [64] Krause K, Caution K, Badr A, et al. Casp4/caspase-11 promotes autophagosome formation in response to bacterial infection [J]. *Autophagy*, 2018, 14: 1928-1942.
- [65] Bakhshi S, Shamsi S. MCC950 in the treatment of NLRP3-mediated inflammatory diseases: latest evidence and therapeutic outcomes [J]. *Int Immunopharmacol*, 2022, 106: 108595.
- [66] Xu Y, Shen J, Ran Z. Emerging views of mitophagy in immunity and autoimmune diseases [J]. *Autophagy*, 2020, 16: 3-17.
- [67] Tschurtschenthaler M, Adolph TE. The selective autophagy receptor optineurin in Crohn's disease [J]. *Front Immunol*, 2018, 9: 766.
- [68] Lavelle A, Sokol H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease [J]. *Nat Rev Gastroenterol Hepatol*, 2020, 17: 223-237.
- [69] Sui XB, Liang X, Chen LX, et al. Bacterial xenophagy and its possible role in cancer: a potential antimicrobial strategy for cancer prevention and treatment [J]. *Autophagy*, 2017, 13: 237-247.
- [70] Brynjolfsson SF, Magnusson MK, Kong PL, et al. An antibody against triggering receptor expressed on myeloid cells 1 (TREM-1) dampens proinflammatory cytokine secretion by lamina propria cells from patients with IBD [J]. *Inflamm Bowel Dis*, 2016, 22: 1803-1811.
- [71] Ho GT, Cartwright JA, Thompson EJ, et al. Resolution of inflammation and gut repair in IBD: translational steps towards complete mucosal healing [J]. *Inflamm Bowel Dis*, 2020, 26: 1131-1143.