

硫化氢对脓毒症肠黏膜损伤的保护机制研究

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【摘要】 脓毒症是一种临床常见的急危重疾病,因其极高的发病率及致死性被广泛关注。肠道作为脓毒症损伤的靶器官,其细胞紧密连接等物理屏障及抗原呈递细胞相关免疫屏障的破坏促进了多器官损伤的发生。自噬作为生物进化中保守的细胞代谢过程,通过清除细胞内坏死的细胞器、异常蛋白质聚集体及微生物等调控组织器官的稳态和细胞更新。因此,自噬在维持肠道稳态中起关键作用。有研究表明,自噬功能障碍与脓毒症肠损伤密切相关,但其作用的特异性机制仍不清楚。硫化氢作为一种新型气体信号传递分子,有大量研究证明其可以通过腺苷酸活化蛋白激酶/哺乳动物雷帕霉素靶蛋白(AMPK/mTOR)、丝裂素活化蛋白激酶/硫氧还蛋白结合蛋白(MAPK/TXNIP)、转录因子 E2 相关因子 2(Nrf2)-活性氧(ROS)-AMPK 等通路上调或下调自噬对脓毒症组织器官发挥保护作用。尽管如此,脓毒症仍无特异性的治疗方案,这可能与我们目前的研究尚未发现器官损伤的特异性通路信号有关。为此,我们探讨了硫化氢通过 AMPK/沉默信息调节因子 1(SIRT1)途径调控自噬缓解脓毒症相关性肠损伤的可能性,以期对脓毒症的精准治疗及药物研究提供思路。

【关键词】 脓毒症; 自噬; 磷酸腺苷依赖性蛋白激酶; 沉默信息调节因子 1; 硫化氢; 肠损伤

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Study on protective mechanism of hydrogen sulfide in intestinal mucosal injury in sepsis

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【Abstract】 Sepsis is a common clinical emergency and critical illness, which has attracted wide attention due to its extremely high morbidity and lethality. The intestine is the target organ of sepsis injury. The destruction of physical barriers such as tight cell junctions and immune barriers related to antigen-presenting cells promotes the occurrence of multiple organ injuries. Autophagy, as a conservative cell metabolism process in biological evolution, regulates the homeostasis and cell renewal of organs and tissues by removing necrotic organelles, abnormal protein aggregates, and microorganisms, etc. in cells. Therefore, autophagy plays a key role in maintaining intestinal lumen homeostasis. Studies have shown that autophagy dysfunction is closely related to septic intestinal injury, but the specific mechanism of its action is still unclear. As a new type of gas signal transmission molecule, a large number of studies have proved that hydrogen sulfide can up-regulate or down-regulate autophagy through AMP-activated protein kinase/mammalian target of rapamycin (AMPK/mTOR), mitogen-activation protein kinase/thioredoxin interacting protein (MAPK/TXNIP), nuclear factor-erythroid 2-related factor 2-reactive oxygen species-AMPK (Nrf2-ROS-AMPK) and other pathways to play a role to protect tissues and organs in sepsis. Despite this situation, there is still no specific plan for treatment of sepsis, which may be related to the fact that our current research has not found specific pathway signals for organ damage. For this reason, we explored the regulation of autophagy by hydrogen sulfide through AMPK/silence information regulator 1 (SIRT1) pathway that may get the possibility of alleviating the sepsis-related intestinal injury, which will help provide ideas for the precise treatment and drug research of sepsis.

【Key words】 Sepsis; Autophagy; AMP-activated protein kinase; Silence information regulator 1; Hydrogen sulfide; Intestinal injury

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脓毒症是一种由感染引起全身炎症反应失调并导致一种或多种器官损伤的综合征^[1],是临床上常见的急危重症。一项研究数据显示,脓毒症患者的总体重症监护病房(intensive care unit, ICU)和医院病死率分别为 25.8% 和

35.3%,由于受医疗水平的限制,在欠发达国家和地区情况可能更差、病死率更高^[2]。由于脓毒症在世界各地的高流行和高病死率,2017 年世界卫生组织(World Health Organization, WHO)将脓毒症归为全球公共卫生重点疾病^[3],需引起人

们的广泛重视。目前脓毒症的治疗仍以抗菌药物、液体复苏等对症治疗为主,因其尚无特异性的治疗方法,其病死率居高不下的结果令人不满。针对这一现象人们开始关注脓毒症治疗相关靶标及信号通路机制的研究,其中肠功能损伤的自噬障碍调控机制研究成为热点,这将为后续脓毒症的精准治疗提供依据,从而降低脓毒症患者的病死率。

1 肠道的生理作用及损伤机制

众所周知,肠道是人体最大的免疫及营养吸收器官,是人体代谢最活跃的系统之一,也是肠道菌群的储存库。肠道的稳态依赖于肠黏膜屏障的完整性,肠屏障主要包括杯状细胞、紧密连接和潘氏细胞构成的物理屏障以及树突状细胞(dendritic cell, DC)和肠上皮细胞(intestinal epithelial cell, IEC)微细胞(M细胞)等抗原呈递细胞构成的免疫屏障^[4-5]。其中,因 Paneth 细胞在肠道生理和病理中的重要作用,被称作是小肠隐窝的守护者。Paneth 细胞是分布于小肠隐窝底部的特征性肠上皮细胞,其成熟依赖于肝配蛋白 B 受体 3(recombinant ephrin type B receptor 3, EphB3)介导的强 Wnt 信号转导作用,主要分泌包括 α -防御素和隐蛋白在内的抗微生物肽(antimicrobial peptides, AMPs)。在生理状态下,肠道通过不同的机制及生物因子不断地平衡营养物质代谢和肠道菌群以及预防腔内菌群入侵和易位导致的过度炎症反应^[6]。

然而,在烧伤、营养不良、肿瘤等应激条件存在时,因氧自由基和炎症介质如白细胞介素(interleukin, IL)、肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、核转录因子- κ B(nuclear factor- κ B, NF- κ B)、Toll 样受体(Toll-like receptor, TLR)等损伤因子的产生,导致肠黏膜炎性损伤。据报道, NF- κ B 和激活蛋白-1(activator protein-1, AP-1)/丝裂素活化蛋白激酶(mitogen-activated protein kinase, MAPK)信号通路(AP-1/MAPK)与肠道炎性疾病相关^[7-8]。肠道致病菌成分脂多糖(lipopolysaccharide, LPS)可激活 TLR4 正向调节 NF- κ B 和 AP-1 通路,促进炎症因子如 IL-1 β 、TNF- α 、诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)及环氧合酶-2(cyclooxygenase-2, COX-2)的产生^[4],导致炎症反应失衡,细胞间紧密连接等物理屏障及免疫屏障破坏,肠黏膜通透性增加,菌群易位入血,进一步引起脓毒症多系统组织器官功能障碍。同时, He 等^[9]的研究发现,微小 RNA-146a(microRNA-146a, miR-146a)通过下调 TLR4/NF- κ B 的途径保护小鼠小肠免受缺血/再灌注性(ischemia/reperfusion, I/R)损伤。总之,关于肠道损伤机制的研究颇多,但关于脓毒症肠道炎性损伤的治疗尚无进展,这可能与我们的研究尚未发现肠损伤的特异性信号作用机制相关。

2 硫化氢(H₂S)的生物学功能

H₂S 作为一种新发现的气体信号传递分子,越来越多的研究显示其参与机体的许多生理及病理过程。H₂S 最初被认为是一种有臭鸡蛋气味的有害气体,但是,随着研究及认识的深入,发现在哺乳动物体内 H₂S 可以内源性产生,并在神经系统、心血管功能、炎症反应及胃肠道系统^[10]等调节中发挥重要作用。机体内的 H₂S 是以 L-半胱氨酸或同型半胱氨酸

为底物,主要在胱硫醚- β -合酶(cystathionine- β -synthase, CBS)、胱硫醚- γ -裂合酶(cystathionine- γ -lyase, CSE)及 3-巯基丙酮酸硫转移酶(3-mercaptopyruvate sulfurtransferase, 3-MST)的作用下产生^[11]。目前,文献普遍认为:低浓度 H₂S(毒性脓毒以下)可促进线粒体的生物学功能,从而发挥抵抗细胞应激的保护作用,如充当血管扩张剂、细胞保护剂和抗炎剂;而较高浓度的 H₂S 则会抑制细胞色素 C 氧化酶,从而发挥细胞毒性和有害作用^[12-13]。目前关于 H₂S 保护作用的机制研究主要着眼于腺苷酸活化蛋白激酶/哺乳动物雷帕霉素靶蛋白(AMP-activated protein kinase/mammalian target of rapamycin, AMPK/mTOR)^[14]、磷脂酰肌醇-3-激酶(phosphatidylinositol 3-hydroxy kinase, PI3K)/丝氨酸/苏氨酸蛋白激酶(Akt)/mTOR(PI3K/Akt/mTOR)^[15-16]、丝裂素活化蛋白激酶/硫氧还蛋白结合蛋白(MAPK/thioredoxin interacting protein, MAPK/TXNIP)^[17]、核因子 E2 相关因子 2-活性氧-腺苷酸活化蛋白激酶(nuclear factor-erythroid 2-related factor 2-reactive oxygen species-AMPK, Nrf2-ROS-AMPK)^[18]等信号通路如何介导自噬从而发挥作用方面。如 H₂S 可以通过 AMPK/mTOR 途径激活自噬来抑制高糖所致的心肌损伤^[14]。此外,也有研究显示, H₂S 通过 TLR/Nod 样受体蛋白 3(Nod-like receptor protein 3, NLRP3)信号通路(TLR4/NLRP3)抑制炎症和氧化应激,从而在 LPS 诱导的急性肾损伤(acute kidney injury, AKI)中发挥保护作用^[19]。总之, H₂S 的作用复杂,目前关于其治疗的作用机制仍有争议,需要进一步研究。

3 自噬的生理病理机制

自噬作为生物体内清除坏死的细胞器、蛋白质聚集体等生物大分子有害物质的代谢过程^[20],在生物进化过程中主要发挥细胞保护作用。自噬是由自噬相关基因(Atg)调控的信号传递^[21],自噬的稳定有助于组织器官的稳态及细胞的自我更新,自噬不足或过度都将造成组织器官的损伤。自噬反应的机制复杂,受 AMPK-mTOR^[22]、NF- κ B^[23]、AMPK/沉默信息调节因子 1(silence information regulator 1, SIRT1)等信号通路的调控。迄今为止,已发现 42 个 Atg 基因与自噬相关^[24],其中有 16 种 Atg 基因被认为是自噬通路共同所需的“核心”基因,其他基因则是特定类型的选择性自噬(如线粒体自噬)所独有的^[25]。此外,在真核生物中还发现了其他自噬所需的相关基因 Atg101、VMP1、EPG5 和 EI24^[26]。这些基因的发现使我们对自噬反应机制有了进一步认识。相关研究显示,癌症、神经退行性疾病、炎症疾病和心脑血管疾病等多种疾病都与自噬反应途径的失调或失败及自噬相关基因突变密切相关^[27-29]。

4 AMPK/SIRT1 信号通路与自噬反应

AMPK(AMP 激活的蛋白激酶)是哺乳动物体内的一种由 α β γ 亚基组成的异源三聚体复合物,主要的核心作用是通过感受三磷酸腺苷(adenosine triphosphate, ATP)水平的变化来维持细胞能量的稳态^[30]。在能量紧张时, AMPK 直接磷酸化并参与多种途径以恢复能量平衡,所以被称为是能量代谢调节的关键分子^[31]。AMPK 因其各自亚基结

合域的多样性决定了其功能的多样性。据报道, AMPK 在自噬中也显示出重要作用并调控自噬反应的各个阶段, 例如, AMPK 将 mTOR 上游调节剂 TSC2 和 Ser722 及 Ser792 上的 mTORC1 亚基 Raptor 直接磷酸化, 引起 mTOR 活性的降低, 并减轻对 unc-51 类自噬激活激酶 1 (unc-51 like autophagy activating kinase 1, ULK1) 的抑制作用, 从而激活自噬反应^[32]。此外, AMPK 还可磷酸化自噬途径其他核心成分上的残基, 例如 Atg9 上的 Ser761^[33], VPS34 上的 Thr133 和 Ser135^[34], Beclin1 上的 Ser91 和 Ser94^[35], VPS34 相关蛋白 RACK1 上的 Thr50 和 PAQR3 (ATG14L-VPS34 支架蛋白)^[36]。

SIRT1 是 SIRT 家族的成员之一, 是高度保守的 NAD⁺ 依赖性组蛋白脱乙酰基酶, 它通过去除各种蛋白质中的乙酰基, 在许多生理和病理过程中起调节作用^[37]。SIRT1 控制许多转录因子和辅因子的活性, 这会影响到下游基因的表达, 并最终减轻氧化应激和相关组织的损伤。已有证据表明, SIRT1 直接通过脱乙酰作用调控 AMPK、NF- κ B、Forkhead 转录因子 (forkhead box transcription factor O, FOXO) 家族等因子起关键作用^[38]。值得注意的是 AMPK 也可通过调节 NAD⁺ 及其调节剂烟酰胺磷酸核糖基转移酶 (nicotinamide phosphate ribosyltransferase, Nampt) 的水平来控制 SIRT1 的活性^[39]。最近有报道称 H₂S 通过上调 SIRT1 信号通路来减弱香烟烟雾诱导的气道重塑, 从而缓解慢性阻塞性肺疾病 (chronic obstructive pulmonary disease, COPD)^[40]。总之, SIRT1 与炎症、细胞凋亡、基因组稳定性、代谢调节、衰老、细胞分化及致癌等疾病相关。同时, SIRT1 在自噬调控过程中也扮演重要角色, 比如, 鱼油可通过 AMPK/SIRT1 信号转导途径诱导自噬来减轻肠 I/R 诱导的肝、肺损伤^[41-42]。除此外, 郭焱等^[43]发现, 给予 II 型糖尿病肾损伤大鼠运脾和络方治疗后, 肾组织中 SIRT1、AMPK 及自噬相关蛋白微管相关蛋白 1 轻链 3-II (microtubule-associated protein 1 light chain 3-II, LC3-II) 显著升高, 肾组织损伤减轻, 说明 SIRT1/AMPK 信号通路参与自噬的调节。因此, H₂S 是否也可通过调控 AMPK/SIRT1 信号转导途径诱导自噬来缓解脓毒症的肠黏膜损伤还有待研究。

5 总结与展望

总之, 越来越多的研究已经证明, 低浓度的 H₂S 有助于缓解脓毒症相关的心、肺、肝等器官功能障碍。肠道作为脓毒症的效应器官, 在脓毒症发生时, 肠黏膜屏障受损, 肠黏膜通透性增加, 菌群及内毒素易位入血, 进一步加重肝、肺等靶器官损伤, 因此, 肠道也被认为是脓毒症的始动器官。肠黏膜损伤的机制复杂多样, 也就导致了脓毒症治疗的困难, 目前肠道损伤的治疗仍以对症治疗为主, 但疗效欠佳。自噬作为一种细胞保护机制, 在维持肠黏膜屏障及稳态中起关键作用。据报道, 自噬相关基因 ATG16L1、GPR65 与炎症肠病 (inflammatory bowel disease, IBD) 相关^[44], ATG16L1 控制自噬体的延伸, GPR65 则调节溶酶体功能; 二者的损伤或缺失将导致自噬反应的异常。考虑到自噬在肠道动态平衡中的

关键作用以及自噬功能障碍对 IBD 的影响, 寻找 H₂S 激活自噬的途径对于脓毒症的靶向治疗具有重要的临床意义。

利益冲突 所有作者均声明不存在利益冲突

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《中国中西医结合急救杂志》关于基金项目标注的写作要求

论文所涉及的课题若取得国家或省市级以上基金资助或属于攻关项目时,应附基金证书复印件。如:基金项目:国家自然科学基金(59637050);国家高技术研究发展计划(863计划)项目(102–10–02–03)等。基金项目:采用双语著录,分别置于中、英文摘要关键词下方。示例如下:

基金项目:国家重点基础研究发展计划(973计划)项目(2013CB532002);国家自然科学基金(30271269)

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《中国中西医结合急救杂志》关于中、英文摘要的写作要求

除消息类文章外,所有类型论文在正文前应有内容、格式相同的中、英文摘要。论著、临床经验类文章采用结构式摘要,包括目的(Objective)、方法(Methods)、结果(Results,应给出主要数据和统计值)及结论(Conclusions)四部分,各部分冠以相应的标题。指南、共识、述评、专家论坛、发明与专利、临床病例、综述类文章可采用指示性摘要。摘要采用第三人称撰写,不用“本文”等主语。英文摘要前需列出英文题名,全部作者姓名(汉语拼音,姓和名均首字母大写,双字名中间不加连字符),全部作者工作单位名称、所在城市名、邮政编码和国名。通信作者在单位名称后应另起一行,以“Corresponding author”字样开头,注明其电子邮箱。示例如下:

Safety criteria for early goal-oriented rehabilitation exercise in patients undergoing mechanical ventilation in intensive care unit: a systematic review

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