

p38丝裂原活化蛋白激酶信号通路在脓毒症器官功能障碍中的作用

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摘要 p38丝裂原活化蛋白激酶(p38 mitogen-activated protein kinase, p38 MAPK)信号通路是多种细胞信号转导、疾病的发生发展中的重要信号通路,在脓毒症的病情进展中发挥重要作用,是导致器官功能障碍发生的关键通路之一。该文就p38 MAPK在炎症介质的释放、氧化应激损伤、细胞凋亡、钙离子超载等方面的作用进行综述,阐述了p38 MAPK在脓毒症器官功能障碍方面的作用及其近年来的研究进展。

关键词 p38 MAPK; 脓毒症; 多器官功能障碍

The Role of p38 Mitogen-Activated Protein Kinase Signaling Pathway in the Sepsis with Multiple Organ Dysfunction Syndrome

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Abstract p38 mitogen-activated protein kinase (p38 MAPK) signaling pathway is an important signal pathway in the conduction process of cell signaling and the occurrence and development of disease. Especially, p38 MAPK plays an crucial role in the disease progression of sepsis and it is one of the key links leading to organ dysfunction. In this paper, the role of p38 MAPK in the release of inflammatory mediators, oxidative stress injury, apoptosis and calcium overload were reviewed, meanwhile, the role of p38 MAPK in organ dysfunction of sepsis and the recent research progress were also discussed.

Keywords p38 MAPK; sepsis; multiple organ dysfunction syndrome (MODS)

脓毒症是机体对入侵的病原微生物产生的免疫防御反应^[1],伴随着激素水平、炎症介质、细胞代谢等多方面的改变,机体的各器官系统之间产生了一系列复杂的作用,甚至导致致命性的器官功能障碍。外界刺激因子通过激活细胞内外信号转导途径,调节细胞内基因转录、蛋白表达、细胞凋亡等生理过程,导致细胞生物学功能的改变。丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)在信号转导通路中有着广泛而重要地调控作用,包括细胞外信号调节激酶(extracellular signal-regulated

kinase, ERKs)、c-Jun N-端蛋白激酶(c-Jun N-terminal kinase, JNKs)等多个亚族,其中p38 MAPK是重要的成员之一,能够调节细胞凋亡、炎症因子的产生,诱导细胞增殖、分化,被认为是细胞信号的交汇点。本文就p38 MAPK信号通路在脓毒症器官功能障碍方面的作用及其近年来的研究进展作一综述。

1 脓毒症器官功能障碍

多器官功能障碍综合征(multiple organ dysfunction syndrome, MODS)是脓毒症常见的并发症之一,其

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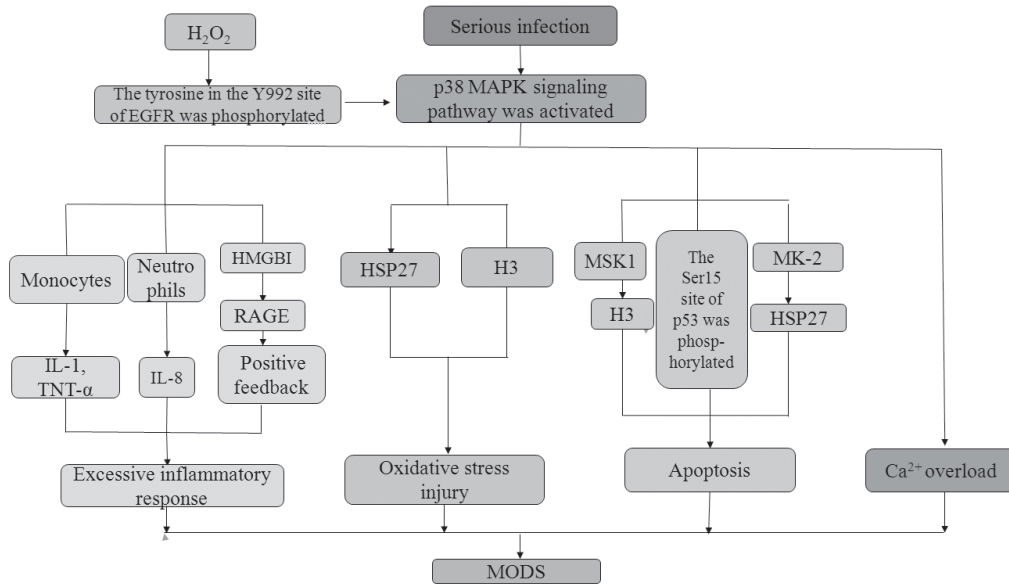


图1 p38 MAPK信号通路在脓毒症MODS中的作用机制示意图

Fig.1 The schematic representation of p38 MAPK signaling pathway in the sepsis induced MODS

死亡率高、发病机制复杂,已逐渐成为重症医学科医生们面临的棘手问题。在临床工作中常常将一些重要的症状、体征和生理参数赋值,从而量化评价MODS的严重程度。目前较公认的诊断标准有1994年欧洲重症医学会提出的针对呼吸、凝血、肝脏、循环、神经、肾脏六个器官系统功能进行评价的序贯器官功能衰竭评分(SOFA评分)和1995年Marshall^[2]提出的MODS评分。这两种评分能够很好地反应MODS病情的发展及预后。MODS的发病机制主要包括三个互相重叠的病理过程:(1)炎症细胞的过度激活导致炎症因子的大量释放;(2)组织细胞缺血再灌注损伤产生大量自由基,发生氧化应激损伤;(3)肠道黏膜柱状上皮细胞损伤导致肠黏膜屏障功能障碍,肠道细菌移位使感染更加难以控制。p38 MAPK信号通路的激活与脓毒症多脏器功能衰竭有着密切的关系(图1)。

2 p38 MAPK信号通路

2.1 p38 MAPK的分子结构与亚型分布

MAPK家族是一种存在于哺乳动物的大多数细胞内的丝氨酸/苏氨酸蛋白激酶,催化可逆的蛋白质磷酸化而激活级联酶反应,具有高度保守的分子结构。1993年, Brewster等^[3]在研究高渗透压液体对酵母菌内环境的改变时,发现了MAPK信号通路。随后, Han等^[4]使用细菌脂多糖(lipopolysaccharide, LPS)诱导CD14转染的小鼠前B细胞系产生p38 MAPK酪氨

酸磷酸化,并进一步证实p38 MAPK的激活是介导LPS诱导的细胞活化的关键环节。目前学者们发现的p38 MAPK具有p38 α (MAPK14)、p38 β (MAPK11)、p38 γ (MAPK12)和p38 δ (MAPK13)四种亚型^[5]。p38 α 是众多家族成员中最先被发现的,也是分子特征及生物学影响研究最透彻的一类,广泛分布在所有组织细胞中。p38 β 主要分布在脑、胸腺、脾中^[6]。p38 γ 仅在骨骼肌中大量表达^[7]。p38 δ 主要存在于胰腺、肠、肾上腺和肾脏等组织中^[8]。

2.2 p38 MAPK的激活

p38 MAPK家族的四个亚型均是被MAPK激酶(MAPK kinases, MKK)经过苏氨酸(threonine, T)和酪氨酸(tyrosine, Y)位点的双重磷酸化激活的,两位点之间由一氨基酸隔开,形成TGY模体活化区,进一步激活下游细胞因子,调节炎症反应、细胞凋亡及氧化应激等生理过程。MKK主要为MKK3、MKK6和MKK4^[5,9],可被细胞内多种细胞因子激活,如凋亡信号调节激酶-1(apoptosis signal regulating kinase-1, ASK-1)、转化生长因子- β 激活激酶-1(transforming growth factor- β activated kinase-1, TAK-1)等。在不同情况下,p38 MAPK被不同种类的MKK激活,如肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)的刺激、抗生素治疗及紫外线照射等。不同亚型的p38 MAPK的激酶也不相同,如在小鼠胚胎成纤维细胞中MKK3是p38 δ 的主要激活物,而当TNF- α 激活或使用茴香霉素治疗时,MKK6是p38 γ 的主要激活物^[10]。

3 p38 MAPK信号通路与炎症介质

3.1 脓毒症与细胞炎症介质的释放

当病原微生物入侵机体时,病原微生物表面的病原体相关分子模式(pathogen-associated molecular patterns, PAMPs)与免疫细胞表面的模式识别受体[如Toll样受体-2(Toll-like receptor-2, TLR-2)、TLR-4、TLR-9]^[11]结合,激活免疫防御系统。随着病情的发展,大量炎症介质释放,通过直接或间接的方式造成器官功能障碍^[11]。在脓毒症动物模型中,早期的致命性炎症反应是由一些促炎因子介导的,如TNF- α 、白细胞介素(interleukin, IL)、干扰素- γ (interferon- γ , IFN- γ)和巨噬细胞游走抑制因子(macrophage migration inhibitory factor, MIF)^[12-14]。它们通过单独或联合发挥促炎作用,使机体产生高热、中性粒细胞渗出等病理反应。高迁移率族蛋白B1(high mobility group protein box 1, HMGB1)是脓毒症晚期释放的重要炎症介质^[15],能够破坏肠黏膜的屏障功能^[16]、加重组织损伤。在中枢神经系统中, HMGB1通过释放前炎性细胞活素和兴奋性氨基酸(如谷氨酸)导致中枢神经系统功能障碍^[17]。

3.2 p38 MAPK信号通路调控炎症介质的释放

p38 MAPK信号通路是许多细胞因子产生的先决条件,但其在炎症反应中的一些精确的调控过程仍然模糊不清。有研究表明, p38 MAPK信号通路能够调节免疫细胞促炎因子的释放,如活化的p38 MAPK能够促进单核细胞释放IL-1和TNF- α ^[18],促进中性粒细胞释放IL-8^[19]等。脓毒症时, LPS诱导的p38 MAPK信号通路的激活是Th1细胞和Th2细胞表达TNF- α 所必需的^[20],在细胞质中,活化的p38 MAPK通过上调MAPK蛋白激酶2/3(MAPK-activated protein kinases 2 and 3, MK2/3)蛋白质的表达来促进TNF- α 生物合成。Blink等^[21]提出,活化的p38 MAPK在炎症反应中有着双重身份,他们使用p38 MAPK抑制剂(SB203580)对LPS诱导的脓毒血症小鼠模型进行研究,结果发现,抑制p38 MAPK活性后不同细胞的效应不同,其中在纤维母细胞、巨噬细胞和全血中炎症介质产生水平降低,而在腹膜巨噬细胞中炎症介质产生水平增高。此外, HMGB1的产生与活化也和p38 MAPK的磷酸化有关。Qin等^[22]通过对小鼠关节腔内注射内毒素和HMGB1诱导实验性关节炎证实了这一观点,他们认为, HMGB1作为糖化终产物受体(receptor for advanced glycation end products,

RAGE)的配体,通过RAGE来促进p38 MAPK的活化,从而刺激更多促炎因子的产生。

4 p38 MAPK信号通路与氧化应激损伤

4.1 脓毒症与氧化应激损伤

氧化应激损伤和钙离子超载也是发生脓毒症器官功能障碍的重要机制。严重脓毒症和脓毒症休克的患者往往存在低血压和高乳酸血症,提示患者存在微循环障碍、组织灌注不足等现象。经过积极治疗后血压逐渐升高、血流重新分布,缺血缺氧的组织器官恢复血流后易发生缺血再灌注损伤,进而引起自由基产生过多,导致氧化应激损伤的发生。发生氧化应激损伤时超氧化物歧化酶(superoxide dismutase, SOD)的活性抑制、活性氧类(reactive oxygen species, ROS)和自由基产生过多,可使线粒体功能障碍, ATP产生不足,从而导致严重的能量代谢障碍^[23]。白静等^[24]通过检测脓毒症大鼠心肌SOD及丙二醛(malondialdehyde, MDA)水平证实了脓毒症心功能障碍与心肌细胞氧化应激损伤密切相关。随着脓毒症病情的发展, MDA显著增加,氧自由基堆积, SOD活性逐渐下调;电镜下可观察到线粒体嵴消失、断裂,线粒体空泡化,心肌细胞发生能量代谢障碍,进而产生细胞内其他代谢活动的紊乱^[24]。

4.2 p38 MAPK信号通路在氧化应激损伤中的作用

脓毒症时组织细胞处于应激状态, p38 MAPK信号通路易被炎症介质、热休克及ROS激活, ROS能通过耦联生长因子受体结合蛋白2(growth factor receptor binding protein 2, Grb2)激活下游细胞因子^[25],参与p38 MAPK信号通路的活化。但这一过程的始动机制并不明确,目前主要存在以下两种猜想: (1) ROS通过修饰表皮生长因子受体(epidermal growth factor receptor, EGFR)上的半胱氨酸残基,模拟表皮生长因子(epidermal growth factor, EGF)与EGFR结合^[26]; (2) ROS使磷酸酶失活,从而抑制了EGFR的去磷酸化反应^[27]。EGF与EGFR的结合能够诱导EGFR上的酪氨酸激酶发生二聚化作用、自身磷酸化和反式激活,从而产生各种各样的蛋白结合位点,激活下游信号通路,例如磷酸酪氨酸992位点(pY992)能够提供一个磷脂酶C- γ (phospholipase C- γ , PLC- γ)的结合模体,启动下游信号因子,包括蛋白激酶C(protein kinase C, PKC)的激活以及细胞外信号调节激酶(ERK)的活化^[28]。ROS包括超氧阴离子、羟自由基和过氧化氢

(H₂O₂)等。Ushio-Fukio等^[29]证实, 200 μmol/L H₂O₂能够在短时间内引起p38 MAPK的快速磷酸化(小于2 min), 并能持续作用15 min。Dong等^[30]通过氢醌诱导的猪近曲小管上皮细胞发生氧化应激损伤模型证实了H₂O₂通过大量诱导EGFR上的Y992位点发生酪氨酸磷酸化激活p38 MAPK信号通路, 进而影响热休克蛋白27(heat shock proteins 27, HSP27)及组蛋白3(histones 3, H3)的活化促进细胞凋亡的发生。

5 p38 MAPK信号通路与细胞凋亡

5.1 脓毒症与细胞过度凋亡

炎症因子、ROS和细胞内Ca²⁺浓度升高促进了细胞凋亡, 过度的细胞凋亡加速了器官功能障碍的发生。例如, ROS通过上调Bax蛋白、下调B淋巴细胞瘤-2(B-cell lymphoma-2, Bcl-2)的表达, 加速肠柱状上皮细胞的凋亡, 导致肠黏膜屏障功能破坏, 肠道细菌移位使感染更加难以控制^[31]; TNF-α诱导血管内皮细胞过度凋亡, 导致血管内凝血功能紊乱、组织器官缺血再灌注损伤的发生^[32]。此外, 免疫系统也存在细胞过度凋亡的现象, 脓毒症早期固有免疫系统过度激活, 产生大量的促炎因子、细胞因子及炎症介质, 而脓毒症晚期则表现为大量免疫活性细胞丢失的免疫抑制状态, 被称为代偿性抗免疫反应综合征^[33], 这一过程与淋巴细胞的过度凋亡有关。脓毒症发生时, TNF-α以及人凋亡相关因子配体(human factors associated with apoptosis ligand, FASL)激活含半胱氨酸的天冬氨酸蛋白水解酶-8(cysteiny aspartate specific proteinase-8, Caspase-8)启动外在凋亡途径促进淋巴细胞凋亡^[34], 同时属于Bcl-2家族的BH3结构域凋亡诱导蛋白(BH3 interacting domain death agonist, BID)启动线粒体途径促进凋亡的发生^[35]。这一过程在对脓毒症患者的脾脏进行免疫组化分析时被证实^[36]。

5.2 p38 MAPK信号通路在细胞凋亡中的作用

p38 MAPK信号通路激活后作用于下游激活物, 调控细胞因子的转录, 进而调节细胞凋亡的发生, 如组蛋白、p53、CCAAT增强子结合蛋白(CCAAT/enhancer binding protein homologous protein, CHOP)、活化T细胞核因子(nuclear factor of activated T cell, NFAT)等。然而, 细胞的存活或凋亡不是取决于一种蛋白的表达增多或减少, 而是抗凋亡蛋白和促凋亡蛋白表达之间的平衡^[37]。p38 MAPK通过使下游

的MSK1磷酸化间接活化H3, H3通过与细胞核内的DNA结合参与染色体的形成, H3过量磷酸化会使染色质凝聚、细胞周期停滞, 进而促进细胞凋亡^[38]。p38 MAPK还能够导致p53堆积超过一定的阈值而触发细胞凋亡^[39], 通过磷酸化p53的Ser15位点来促进凋亡的发生。相反, p38 MAPK下游激活物MAPK活化蛋白激酶-2(MAP kinase-activated protein kinase-2, MK-2)通过使Hsp-27磷酸化来调节肌动蛋白的聚合、亚细胞结构的稳定以及抑制细胞凋亡的发生。p38 MAPK的激活的总体效应为促进细胞凋亡。Sanchez等^[40]发现, 对化疗药物处理过的细胞使用p38 MAPK抑制剂可促进细胞生长, p53的转录激活减少, 从而抑制细胞凋亡, 从侧面证实了p38 MAPK信号通路的激活促进了细胞凋亡的发生。

6 MAPK与钙离子超载

钙离子是细胞内重要的第二信使, 参与调节细胞代谢、炎症反应等过程, 同时也是心脏收缩期形成动作电位平台期的主要离子。脓毒症发生时, 细胞发生能量代谢障碍导致细胞膜表面的Na⁺-K⁺-ATP酶活性降低, 导致细胞内Na⁺浓度升高, 加速了Na⁺-Ca²⁺交换。同时, 氧自由基堆积导致细胞膜通透性增加, 细胞外的Ca²⁺顺浓度梯度流向细胞内。此外, 细胞内Ca²⁺浓度升高进一步刺激内质网钙池释放, 加重了细胞内钙超载。近年来研究发现, 当内质网Ca²⁺耗竭时, 通过细胞内信号通路转导至细胞膜表面的钙池可控性钙离子通道SOCs(store-operated channels), 产生钙池操纵性内流^[41], 进一步加剧了细胞内Ca²⁺超载。

Dong等^[42]通过不完全结扎结肠建立结肠扩张的小鼠模型, 8 d后证实扩张的结肠平滑肌发生了Ca²⁺超载, 并且超载的Ca²⁺激活了MAPK的三个家族成员, 包括JNK、ERK和p38 MAPK。这些持续活化的MAPK信号通路可能会导致干细胞因子的减少和GDP-甘露糖4,6-脱水酶(GDP-mannose 4,6-dehydratase, GMDs)基因过度表达。

7 结语与展望

脓毒症产生机制十分复杂, 是各种信号通路相互作用共同产生一系列病理反应, 破坏细胞正常的结构和功能, 进而导致器官功能障碍。p38 MAPK信号通路通过调节氧化应激、炎症介质的释放、细

胞凋亡等病理过程来调控脓毒症病情进展, 抑制p38 MAPK信号通路的活性也许会成为治疗脓毒症新的治疗手段。目前, 研究发现, 许多药物通过抑制p38 MAPK信号通路的激活而发挥器官保护作用, 如乌司他丁通过抑制p38 MAPK信号通路的激活, 减少肺泡中性粒细胞产生TNF- α 等炎症因子, 发挥肺保护作用^[43]; 糖皮质激素与透明质酸结合治疗后, 能通过抑制p38 MAPK的磷酸化, 缓解LPS诱导产生的大鼠肺损伤, 还能改善肺泡组织的微环境^[44]; Han等^[45]用p38的特异性阻断剂有效地阻断了LPS诱导的NO合成酶(inducible nitric oxide synthase, iNOS)的表达, 为治疗休克找到了一种有效的手段。

不同的p38 MAPK异构体分布在不同的组织器官中, 通过不同的分子生物学机制发挥不同的作用, 且对其抑制剂SB203580的敏感性不同^[46]。目前针对不同异构体的分布及亚型的研究较少, 尚未有针对各组织细胞中p38 MAPK的异构体的特异性抑制剂。因此, 明确各异构体的调控基因及作用底物、研发特异性抑制剂对脓毒症器官功能保护具有十分重要的意义。

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