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文献综述 REVIEW

MAPK信号通路在炎症性肠病中的研究进展

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Role of MAPK signaling pathways in inflammatory bowel disease

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Abstract

Mitogen-activated protein kinases (MAPKs) are a group of highly conserved serine protein kinases which are distributed in the cytoplasm. MAPK signal transduction pathways play a major role in inflammatory reactions and have a close relation with inflammatory bowel disease (IBD). They could be involved in the regulation of inflammatory mediators as well as IBD-associated genes. This paper reviews the role of MAPK signaling pathways in the pathogenesis of IBD, aiming at providing a new method for the treatment of IBD.

Key Words: Mitogen-activated protein kinases; Signal transduction pathways; Inflammatory bowel disease

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摘要

促分裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)是细胞浆内一类高度保守的丝氨酸蛋白激酶, 其介导的信号转导通路在机体的炎性反应中发挥重大作用. 他与炎症性肠病(inflammatory bowel diseases, IBD)关系密切, 不仅参与IBD炎性介质的调节, 还参与调控IBD发病发展相关基因. 本文综述了MAPK信号通路在IBD发病机制中的作用, 旨在为IBD的诊治研究提供新的思路.

关键词: 促分裂原活化蛋白激酶; 信号转导通路; 炎症性肠病

核心提示: 本文主要介绍促分裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)信号转导通路对炎症介质、炎症性肠病(inflammatory bowel diseases, IBD)发病发展相关基因的调节, 更深入的认识MAPK通路在IBD发病中的作用.

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0 引言

炎症性肠病(inflammatory bowel diseases, IBD)

■背景资料
炎症性肠病(inflammatory bowel diseases, IBD)是一类慢性非特异性肠道炎症疾病, 发病机制尚未明确, 但多数学者认为其发病与环境、免疫、遗传等因素有关. 近年来, 对促分裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)通路的深入研究发现其可参与调节炎症信号通路, 且给予IBD患者通路抑制剂治疗可改善临床症状, 提示MAPK信号通路在其发病中的重要作用.

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c-Jun氨基末端激酶(c-Jun N-terminal kinases, JNKs)、p38MAPK是与炎症信号通路有关的MAPKs家族的两大类, 近些年已成为炎症相关研究的热点.

是一种慢性非特异性肠道炎症疾病, 主要包括溃疡性结肠炎(ulcerative colitis, UC)和克罗恩病(Crohn's disease, CD), 目前认为其发病与肠道环境、机体免疫、遗传基因等因素有关, 但具体机制尚未明确[1]. 近年来, 促分裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)信号通路成为IBD发病机制研究的热点之一. 现就MAPK信号通路在IBD中的作用予以综述.

1 MAPK信号通路的概述

MAPK是一类存在于真核细胞中高度保守的信号转导模块, 是连接细胞内外反应的重要成员, 可介导胞外信号刺激传入胞内, 调节细胞生长、细胞分化、细胞迁移、炎症等细胞过程[2,3]. 在哺乳动物中, MAPKs家族主要分为三大类, 即细胞外信号调节激酶(extracellular signal-regulated kinases, ERKs)、c-Jun氨基末端激酶(c-Jun N-terminal kinases, JNKs)和p38MAPK激酶. 多种胞外刺激因素可激活MAPK通路, 包括炎性细胞因子、生长因子、细胞应激等. 特异性刺激因素激活下游的丝裂原活化蛋白激酶激酶激酶(MAP kinase kinase kinases, MAP3Ks), 活化的MAP3Ks磷酸化Ser和Thr而激活丝裂原活化蛋白激酶激酶(MAP kinase kinases, MAP2Ks), 活化的MAP2Ks进一步对Thr和Tyr双磷酸化激活MAPKs, 最终磷酸化和活化MAPKAPs, 调节基因转录、蛋白质合成等多种细胞生理病理过程.

2 MAPK信号通路与IBD

目前, 关于MAPK通路对IBD发病的影响有两种观点. Waetzig等[4]、Hommes等[5]研究认为MAPK对IBD的发病有着重要作用, 其研究发现IBD患者炎性结肠黏膜的p38a、JNK1/2及ERK1/2活化增强, 给予重度CD患者JNK、p38MAPK抑制剂CNI-1493进行治疗, 可改善患者的临床症状, 降低疾病活动指数, 对CD患者有益. 在动物DSS结肠炎模型中, 使用JNK通路抑制剂SP600125[6]和p38MAPK通路抑制剂SB203580[7]对缓解结肠炎有益. 然而Malamut等[8]持相反观点, 认为在IBD患者中p38MAPK和JNK的活化与正常人相似, 且动物TNBS结肠炎模型中p38MAPK通路的作用甚小, 这种现象可能是与疾病的炎症程度、动物实验结肠炎造模方法的不同有关. 基于前者观点, 本文将从MAPK通路对炎性介质的调节及其与IBD相关基因的关系两个方面重点阐述.

2.1 MAPK信号通路对IBD炎性介质的调节

IBD的发病普遍认为是由免疫功能失调、炎症介质释放引起的强烈炎症反应. 发病时, 病灶部位肠黏膜组织产生大量炎性介质, 包括血管活性胺、花生四烯酸代谢产物、细胞因子、一氧化氮等细胞释放的炎性介质及补体系统. 以下将具体阐明MAPK通路对上述炎性介质的调节.

2.1.1 血管活性胺类炎症介质: 血管活性胺类炎性介质包括组胺和5-羟色胺(5-hydroxy tryptamine, 5-HT)两大类, 其中5-HT是一种自体活性物质, 约90%合成和分布于肠嗜铬细胞(enterochromaffin cell, EC细胞). 研究表明MAPK信号通路可通过调节色氨酸羟化酶-1(tryptophan hydroxylase-1, TPH-1)和囊泡单胺转运体1(vesicle monoamine transporter 1, VMAT1)间接对5-HT的合成和分泌进行调节. 具体机制表现为EC细胞表面表达腺苷受体ADORA2B, 机械性的刺激可诱导A2B的激活, 随后又可激活蛋白激酶A(protein kinase A, PKA)、磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase, PI3K)、MAPK信号通路调节TPH-1的转录, 对5-HT进行合成, 又可通过PKA/cAMP通路调节5-HT的分泌, 这些效应在CD患者结肠炎症部位黏膜分离的EC细胞中被放大[9]. 在低氧环境下, 由IBD患者肠黏膜分离的EC细胞也可激活胞外腺苷信号通路, 使EC细胞通过表面ADORA2B受体调节MAPK的活性, 进而调节TPH-1的磷酸化和5-HT的分泌[10].

2.1.2 花生四烯酸代谢产物: 花生四烯酸代谢产物前列腺素(prostaglandins, PGs)和白三烯类(leukotrienes, LTs)在促炎过程中起重要作用. 环氧化酶(cyclooxygenase, COX)是PGs合成的限速酶, 经典抗炎药物水杨酸类通过抑制其活性减少PG的产生, 抑制炎症反应. 在血管内皮生长因子(vascular endothelial growth factor, VEGF)介导的原代人肠微血管内皮细胞(human intestinal microvascular endothelial cells, HIMECs)血管生成的过程中, JNK、p38、p44/42MAPK通路均参与COX-2的表达[11]. 此外, 对于药物抗炎机制的研究, 也发现其可通过MAPK通路下调COX-2发挥作用. Camacho-Barquero等[12]在研究姜黄素对实验性结肠炎动物的作用中, 发现姜黄素可作用于p38MAPK通路调节COX-2和iNOS表达. González-Mauraza等[13]研究发现利比亚豆科植物*Retama monosperma*对急性溃疡性结肠炎大鼠的抗炎作用可能是通过p38MAPK和核因子-κB(nuclear factor-κB, NF-κB)信号通路下调

COX-2和iNOS发挥效应的. 然而, 也有研究表明MAPK通路不参与LPS诱导的肠上皮细胞系IEC18表达COX-2[14].

2.1.3 细胞因子: 大量的研究表明在IBD患者病灶部位促炎细胞因子的分泌增多, 导致促炎与抑炎平衡破坏, 引起炎症. MAPK通路可通过磷酸化级联反应激活下游的转录因子促进或抑制基因的转录来调节细胞因子的分泌, 进而参与炎症反应. 在体内实验研究中, 给予SB203580(p38通路抑制剂)治疗DSS诱导的溃疡性结肠炎小鼠, 与模型组相比, 其可显著性下调促炎因子肿瘤坏死因子-α(tumor necrosis factor alpha, TNF-α)、干扰素-γ(interferon γ, IFN-γ)、白介素-12 p35亚基(interleukin 12 p35, IL-12p35)、IL-18的表达[7], 同样, 给予XG-102、SP600125(JNK通路抑制剂)可保护TNBS/DSS诱导的结肠炎, TNF-α、IL-6、IFN-γ与模型组相比显著下调[6,15]. 在体外实验研究中, 由IBD患者肠黏膜活检分离出的固有层单核细胞体外培养, 给予p38a的抑制剂后, TNF-α、IL-1β、IL-6分泌均得到抑制[16]; Waetzig等[4]研究也表明p38抑制剂SB203580可抑制CD患者黏膜活检体外培养中TNF-α的分泌; p42/44MAPK通路依赖的NF-κB和AP-1的激活可介导IL-1β和TNF-α刺激活动期UC患者肠黏膜分离的结肠上皮下肌成纤维细胞(human colonic subepithelial myofibroblasts, SEMFs)高表达IL-33 mRNA[17]; p38MAPK和ERK1/2通路的激活可调节DSS诱导小鼠的腹腔巨噬细胞分泌IL-1β[18]; ERK和p38MAPK可调节IL-17诱导SEMFs分泌IL-6、IL-8和MCP-1[19]; p38、ERK1/2、JNK MAPK通路均参与IL-1诱导的肠上皮细胞caco-2分泌IL-6和IL-8[20]. 对于趋化因子的调节, 研究表明Ras/MAPK/AP-1通路可调节脆弱类杆菌肠毒素诱导肠上皮细胞分泌IL-8和趋化因子MCP-1[21]. Sunil等[22]发现p38通路参与IL-1β诱导的caco-2细胞和HT-29细胞对CXCL8和CXCL10的调节, 同时其也参与TNF-α诱导人的结肠肌成纤维细胞的CCL2和CXCL10的表达[23].

2.1.4 补体系统: 补体系统是抵抗病原微生物的天然和过继免疫的重要因子, 其可通过经典途径、替代途径、凝集素途径激活, 其中C3激活是最重要的一步. 研究[22]表明, 活动期的UC、CD患者的IL-17和补体系统C3 mRNA的表达显著提高, 用IL-17刺激SEMFs, 补体系统C3的mRNA和蛋白分泌呈时间、剂量依赖性, 且p42/44 MAPK和p38MAPK均参与其调控.

2.2 MAPK与IBD相关基因

2.2.1 *TL1A*/*TNFSF15*: *TL1A*/*TNFSF15*(TNF超家族成员15)是2005年日本学者发现, 现已被确认和证实为IBD相关基因[24], 其基因的多态性与IBD疾病发展的严重程度有关[25-27]. TL1A可调节细胞的增殖、活化和免疫细胞的分化, TL1A/死亡受体3(death receptor 3, DR3)信号通路参与调节Th1、Th2、Th17介导的免疫反应, 且TL1A与DR3结合可诱导TRADD募集TRAF2、RIP1形成信号复合物激活MAPK通路[28], 同时该通路可放大模式识别受体(pattern-recognition receptor, PRR)诱导的MAPK/NF-kb/PI3K信号通路和细胞因子的分泌[29]. 对于TL1A/DR3信号通路, 不仅其可调节MAPK通路, 而MAPK通路也可调节TL1A mRNA和蛋白的表达. Gonsky等[30]对*TNFSF15*基因研究, 发现JNK可通过活化转录因子c-jun作用于启动子元件AP-1位点部分介导*TNFSF15*基因的反式激活. Shih等[31]发现p38MAPK可通过其活化转录因子ATF-2参与大肠杆菌刺激的单核细胞和树突状细胞中TL1A的表达.

2.2.2 蛋白酪氨酸磷酸酶非受体型2(*PTPN2*): *PTPN2*为全基因组关联研究中确认的IBD相关基因[32,33], 其通过对免疫系统、炎症反应及肠上皮细胞功能的调节来参与IBD的发病[34-36]. 在*PTPN2*的功能研究中, 发现此基因可调节MAPK通路抑制炎症. van Vliet等[37]早期研究中发现该基因通过与衔接蛋白TRAF2相互作用、抑制Src家族酪氨酸激酶活性来抑制TNF诱导的ERK1/2信号通路的激活和IL-6的分泌. 近期研究中[38]发现, *PTPN2*基因敲除可促进IFN-γ诱导的THP-1细胞STATs、p38MAPK的磷酸化及IL-6、MCP-1的分泌, 且对TNF-α诱导肠上皮T84细胞中也有着相似的作用, 其敲除可促进ERK1/2、p38MAPK信号通路的激活和促炎介质IL-6、IL-8和iNOS的表达[39].

2.2.3 核苷酸结合寡聚域2/胱冬酶吸引域家族成员15(*NOD2*/*CARD15*): *NOD2*/*CARD15*是第一个被发现的人类CD易感基因, 他可以通过识别细菌细胞壁的肽聚糖及其裂解产物胞壁酰二肽参与宿主对病原体的免疫应答[40]. 胞壁酰二肽(muramyl dipeptide, MDP)刺激细胞可引起NOD2构相改变从而结合并激活蛋白激酶RIP2, 而NOD2-RIP2复合物又可激活NF-κB、MAPK通路, 诱导促炎细胞因子、趋化因子的表达及适应性免疫和辅助性Th2型免疫应答[41,42]. 研究

■相关报道

自从2002年Hommes等将p38MAPK抑制剂用于治疗CD患者, 现已有许多研究报道其通路抑制剂在IBD体内、体外实验中的调节作用.

■创新盘点
本文与其他报道的不同之处在于更深入的从MAPK通路对炎性介质、IBD相关基因的调节两个方面进行综述, 有利于更具体的了解此通路在IBD发病的作用.

表明多种因素参与调节MDP/NOD2/MAPK通路, 相关研究[43-46]发现IL-18RAP与IL-18R1介导的IL-18信号通路、共刺激分子ICOSL信号通路、干扰素调节因子5(IFN regulatory factor 5, *IRF5*)基因及IL-1β均可调节NOD2诱导的MAPK、NF-κB信号通路的激活. Spalinger等[47]发现*PTPN22*基因也参与该通路的调节, 其基因敲除可增强MDP诱导的THP-1细胞激活p38/JNK MAPK及NF-κB通路和细胞因子IL-6、IL-8、TNF的分泌.

2.2.4 蛋白酪氨酸磷酸酶非受体型22(PTPN22): *PTPN22*基因参与T细胞活化的负性调节, 在免疫稳态中发挥着重要作用. 研究发现PTPN22单核苷酸多态性与丹麦[48]、加拿大[49]、突尼斯[50]IBD人群的易感性相关, 也有研究认为其与西班牙[51]、英国[52]IBD人群的易感性关系很小, 提示此基因与IBD易感性关系可能与种族差异有关. 对于PTPN22功能的研究, Spalinger研究小组[47,53]发现PTPN22敲除可加剧IFN-γ诱导的THP-1细胞p38MAPK的活化, 增加炎性因子IL-6和IL-17的分泌; 其也参与MDP/NOD2/MAPK通路的调节. Cao等[54]研究抗中性粒细胞胞浆抗体(anti-neutrophil cytoplasmic antibody, ANCA)相关性血管炎患者发现PTPN22功能突变可加强其基底活性, 负性调节ERK通路, 进而影响抑炎因子IL-10的分泌.

2.2.5 自噬相关16样1(ATG16L1): *ATG16L1*基因主要表达于肠上皮细胞和$CD4^+$、$CD8^+$、$CD19^+$淋巴细胞, 是一种涉及处理细胞内细菌的自噬小体代谢途径的蛋白, 对自噬过程至关重要, 其突变与CD显著相关[55]. 研究[56]表明ATG16L1可调控IL-1β信号通路, 在IL-1β刺激下, 其与受体IL-1RI结合, 随之结合IL-1RI受体相关蛋白, 依次募集MyD88、IRAK1、TRAF6, 进而引起下游NF-κB和MAPKs的活化引发炎症反应, Lee等[56]发现对于*ATG16L1*基因的敲除使选择性自噬受体p62水平升高, 升高的p62可促进TRAF6的寡聚化和激活, 导致下游的NF-κB和MAPKs的过度激活引起较强炎症反应. Choe等[57]用尿酸钠结晶刺激巨噬细胞引起蛋白酶体降解受损, p62水平升高, p62进而作用于ERK/JNK通路和Capase1调节IL-1β的合成, *ATG16L1*基因敲除使p62水平升高, 可放大尿酸钠结晶引起的炎症反应.

3 结论

MAPK信号的活化在IBD发生、发展中起重要作用, 涉及机体内致炎因子和抗炎因子的平衡及致病基因的活化等多种病理过程. 在IBD疾病中深入研究MAPK信号及其下游信号转导通路, 可以为减轻肠道炎症, 延缓IBD病变进程, 寻找更好抑制剂治疗提供理论依据.

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■应用要点
在IBD疾病中深入研究MAPK信号及其下游信号转导通路, 为认识IBD发病机制、寻找更好的抑制剂或药物治疗提供理论依据.

■同行评价
本文立题有依据，研究内容集中，论点明确，结果可信，文章简洁，对IBD的发病机制研究和临床诊治有参考意义.

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• 消息 •

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