

JAK-STAT细胞信号转导通路与急性胰腺炎关系的研究进展

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■背景资料

急性胰腺炎(acute pancreatitis, AP)是一种常见的消化系统疾病。具有病情进展快, 并发症多, 治疗棘手等特点。目前有关其发病机制的探索一直是研究的热点。明确AP发生、发展的机制可为治疗提供保障。

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Abstract

The pathogenesis of acute pancreatitis has long been an important research topic. In acute pancreatitis, cytokines and growth factors bind to Janus kinase (JAK) related receptors, and activate JAKs. The activated JAKs phosphorylate the tyrosine residues of the receptor. The downstream signal transducers and activators of transcription (STAT) then bind to the specific site of the phosphorylated JAK receptor complexes, leading to the activation of STATs. The activated STATs detach from the receptor complexes and translocate to the nucleus to regulate the expression of *Bcl-2*, *Bcl-X(L)*, *Mcl-1* and other genes, thereby participating in the pathogenesis of pancreatitis. Such signal transduction can be terminated by the dephosphorylation of STATs. At present, more and more clinical experiments and animal studies have shown that the JAK-STAT pathway is closely related with acute pancreatitis. In this article, we will review the structure, distribution, and function of JAK-STAT signaling pathway as well as the role of JAK-STAT signaling pathway in the pathogenesis of acute pancreatitis.

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Key Words: JAK-STAT signaling pathway; Acute pancreatitis; Pathogenesis

JAK-STAT signaling pathway and acute pancreatitis

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摘要

急性胰腺炎(acute pancreatitis, AP)的发病机制长期以来是医学界研究的一个重要课题。AP时,细胞因子、生长因子等与酪氨酸蛋白激酶(Janus kinase, JAK)相关受体结合而激活JAKs,活化的JAKs使受体链酪氨酸残基磷酸化,而处于下游的信号转导-转录活化因子(signal transducers and activators of transcription, STAT)与受体复合物酪氨酸磷酸化的特异位点结合,此时JAKs接近STATs并使STATs活化,活化的STATs与受体分离,转移到细胞核内,调控调控*Bcl-2*、*Bcl-X(L)*及*Mcl-1*等基因表达,从而参与胰腺炎的发病机制,而通过STATs脱磷酸化可终止信号的转导。目前越来越多临床实验和动物研究表明JAK-STAT通路与AP有密切相关。现就JAK-STAT信号通路的结构、分布、功能及介导AP发病机制作一综述。

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关键词: JAK-STAT通路; 急性胰腺炎; 发病机制

核心提示: 急性胰腺炎(acute pancreatitis, AP)与酪氨酸蛋白激酶-信号传导和转录激活因子(janus kinase-signal transducers and activators of transcription, JAK-STAT)关系密切,其中STAT3是目前在AP分子机制中研究最多通路分子,STAT3对AP有相反的两方面作用,其具体作用机制尚未完全明确。对AP与JAK-STAT通路的研究有助于我们进一步认识AP发病机制。

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0 引言

急性胰腺炎(acute pancreatitis, AP)是临床上常见急腹症,其发病机制尚未完全明确,目前占主导地位的学说有:胰腺自身消化学说、胰腺细胞内钙超载学说、炎症介质学说、细胞凋亡学说、肠道细菌易位学说等^[1,2]。其中炎症-抗炎症因子平衡学说认为AP时机体为

保护自身健康而启动炎症反应,释放促炎细胞因子。这些促炎因子主要包括:肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、核因子 κ B(nuclear factor κ B, NF- κ B)、白介素-1 β (interleukin-1 β , IL-1 β)等。经研究证实JAK酪氨酸蛋白激酶-信号传导和转录激活因子(janus kinase-signal transducers and activators of transcription, JAK-STAT)通路与上述细胞因子有密切关系。JAK-STAT通路被认为是新的快速的经典通路之一,参与多种炎症反应,自1994年Darnell等^[3]发现以来,已证实其参与多种生理病理反应过程。JAK-STAT通路除了在细胞生长、细胞分化、细胞凋亡以及免疫等生理活动中起重要的作用外,近年还发现该通路也参与肿瘤的发生、发展、浸润和转移。目前JAK-STAT通路在AP发病机制中的相关实验研究少见详细阐述。本文就JAK-STAT通路与AP关系作一综述。

1 JAK-STAT结构、分布及功能

1.1 JAKs家族 JAKs家族是一类非受体酪氨酸激酶,分子量约120-140 kDa,主要由C端和N端组成。C端由两个精密联系的酪氨酸激酶活性结构域组成,而N端可能在JAK激酶与其他信号蛋白分子结合过程中起独特作用。JAKs依其结构和调节方式不同分为JAK1、JAK2、JAK3及TYK2。JAK3主要表达于造血细胞、淋巴细胞、肿瘤细胞,而JAK1、JAK2和TYK2几乎在所有细胞内有表达^[4,5]。当干扰素、白介素等物质作用于效应细胞时,上述配体与相应受体结合而激活JAKs,激活的JAKs使相应STATs磷酸化,磷酸化的STATs二聚化后转位到细胞核,最终启动*Bcl-2*、*Bcl-X(L)*及*Mcl-1*等基因表达。研究显示一个细胞因子能同时激活多个JAK激酶,而同一个JAK酶同时被多个细胞因子激活^[6]。

1.2 STATs家族 STAT是JAKs的靶蛋白,约由750-850个氨基酸组成,可分为7个类型:STAT1、STAT2、STAT3、STAT4、STAT5a、STAT5b和STAT6。STATs有7个结构域,各个结构域功能概括如下:(1)羧基末端转录活化结构域调控基因表达和转录;(2)螺旋-螺旋结构域、DNA结合结构域参与物质在细胞核和细胞质之间运输;(3)连接结构域涉及STATs与DNA结合,调控STATs在细胞核和细胞质之间进出;(4)酪氨酸磷酸化位点结构域参与STATs与JAKs结合以及STATs结构改变;(5)SH2结构

■研究前沿

至今JAK酪氨酸蛋白激酶-信号传导和转录激活因子(janus kinase-signal transducers and activators of transcription, JAK-STAT)信号通路如何参与AP的发病机制尚未被完全认识。后续展望有更多关于该通路与炎症因子和促炎因子关系、各通路之间联系以及通路与靶基因关系等方面的进一步研究。为了解AP病分子机制奠定基础。

■相关报道

细胞因子激活JAK-STAT通路同时,又可通过STAT途径诱导SOCS蛋白表达,进而使JAK-STAT通路受到特异性抑制。目前研究显示SOCS与JAKs结合后可抑制JAKs活化。另外在癌细胞的研究中发现,SOCS蛋白的过表达,可以抑制STATs的活性,从而诱导细胞凋亡。

■ 创新亮点

目前对JAK-STAT信号通路参与AP的发病机制研究不断增加, 但与有关综述报道较少. 本文从JAK-STAT通路的机构、信号转导途径以及该通路与AP之间存在的联系作一综述, 为明确AP的分子机制为提供了较为全面的理论依据.

域使STATs转化成激活状态; (6)氨基末端结构域参与STATs失活和激活状态相互转换^[7]. 各种配体和靶细胞受体结合导致JAKs磷酸化, 磷酸化JAKs使STATs激活, 活化STATs转移到细胞核内调节基因的表达^[8-10]. JAK-STAT通路影响细胞发育、生长及其存活, 并参与机体免疫和多种肿瘤的发生、发展以及转移^[11-13].

2 JAK-STAT信号转导途径

JAK-STAT是与炎症反应的一组信号分子, 当IL-1、IL-6等配体与JAKs受体结合时, 受体单位会发生同源或异源寡聚化进而激活JAKs, 同时受体胞浆段酪氨酸磷酸化, 形成JAK与STATs的SH2结合位点. JAKs通过SH2结构域与STATs结合, 并使STATs羟基酪氨酸磷酸化, 磷酸化的STATs形成同源或异源二聚体, 进入细胞核内调节基因表达, 影响AP发展^[14]. JAK-STAT通路的负调节因子研究较多, 蛋白酪氨酸磷酸酶(protein tyrosine phosphatase, PTP)、细胞因子信号通路抑制因子、转录活性抑制蛋白是其主要的负调控因子. 而JAK-STAT通路正性调节反应有: (1)细胞因子级联反应; (2)通过*IFN-γ3*、*IFN*基因诱导磷酸化可加强JAK-STAT通路传导; 另外下调非特异性抑制因子可使该通路传导加强; (3)STATs分子翻译后修饰可使转录活性加强^[15-17].

3 JAK-STAT信号通路与AP

3.1 JAK-STAT相关的炎症因子 JAK-STAT通路中STAT1主要参与IFNs反应, STAT2参与INF-α/β和INF-λs激活, STAT3参与IL-6、IL-10、INF-α/β活化; STAT4则可被IL-12、IL-23、INF-α激活; 生长激素、表皮生长因子、IL-2、IL-4及IL-7等都可激活STAT5; IL-4、IL-13、INF-α可以激活STAT6, 目前STAT1和STAT3与AP的研究较多. 尽管多数AP患者属轻症, 但约22.7%AP患者会并发呼吸窘迫综合征和多器官衰竭, 死亡率较高. 研究认为重症胰腺炎与IL-6、IL-10、NF-κB和TNF-α等炎症因子密切相关. 这些炎症因子会募集中性粒细胞、单核巨噬细胞等炎症细胞, 导致胰腺细胞损伤以及各种炎症反应^[18-20]. 随着科技不断进步, 越来越多研究表明JAK-STAT通路激活与AP的发生发展有着密切联系.

3.2 JAK-STAT在AP中的作用

3.2.1 JAK2和STAT1活化加重AP病情: JAK2参

与多种生理过程, 如细胞生长、分化, 肿瘤发生、发展, 以及免疫免疫功能等. JAK2能被胰蛋白酶原激活肽(trypsinogen activation peptide, TAP)等炎症因子激活, 起加重胰腺炎作用. 而细胞因子信号抑制物3(suppressor of cytokine signaling 3, SOCS3)、还原型辅酶II抑制剂(NADPH oxidase inhibitor diphenyleneiodonium, DPI)和垂盆草提取物(sedum sarmentosum bunge extraction, SSBE)等能抑制JAK2活化, 减少TNF-α等炎症因子表达, 起到治疗AP作用^[21-23]. Ju等^[21]研究报道雨蛙素刺激AR42J后TGF-β1表达增加, PSTAT3(phosphorylated STAT3, pSTAT3)、JAK2活性以及STAT3-DNA结合活性增加, 而给予DPI后上述物质活性下降, 推断DPI与AG490作用类似, 能抑制JAK2激活, 并推测TGF-β1表达受JAK2以及STAT3影响. Fractalkine是胰腺表达的一种趋化因子, 有调节β细胞功能, 减少β细胞凋亡, 以及减少TNF-α损伤等作用^[24]. Huang等^[25]研究发现Fractalkine与JAK2有关, 预先给予AG490的AR42J细胞中Jak2磷酸化程度明显减少, 此外STAT1、3磷酸化程度也减少, 推断Fractalkine通过JAK2激活STAT1、3, 参与加重AP机制.

STAT1是在对INF作用研究中发现的, STAT1能JAK-STAT通过信号转导过程, 参与病毒、细菌、寄生虫等病原体感染的炎症反应, 在自然免疫起重要作用. AG490和Ad5/F35-PIAS1分别是JAK2和STAT1特异性抑制剂, 研究发现AP时STAT1和PSTAT1表达随时间推移逐渐上升, 且与金属蛋白酶-9、细胞间黏附分子-1、TNF-α、IL-1β、NF-κB和IL-6变化趋势一致, 加入AG490和Ad5/F35-PIAS1后上述物质活性下降, 胰腺炎炎症程度以及肺损伤程度减轻, 患者生存率增高^[26,27]. Hao等^[28]报告重症胰腺炎小鼠使用罗格列酮后STAT1、血清淀粉酶、TNF-α等表达降低. 罗格列酮能明显抑制JAK1, 减少TNF-α表达以及阻止炎症瀑布反应发生, 起到减轻AP作用. 另外单核细胞能影响STAT1活化, 罗格列酮抑制STAT1作用是否与单核细胞有关需待进一步研究^[29]. 目前关于JAK2和STAT1研究较少, 对其作进一步研究有助于了解AP的发病机制.

3.2.2 STAT3活化对AP有双重作用: 目前活化STAT3诱导物研究主要集中在IL-6, 被IL-6激活的STAT3能加重AP以及并发急性肺损伤^[30]. 脂类诱导的AP中扮演着重要的角色. 临床发现

12%-38%的AP患者伴有血脂的异常升高,在反复发作或暴发性AP患者常见有高血脂症。所以,高脂血症既是AP的病因,又是AP代谢紊乱的常见并发症,二者形成恶性循环^[31]。Pini等^[32]发现,1 d时肥胖组野生型小鼠pSTAT3水平比正常体质量野生型小鼠高,而正常体质量野生型小鼠pSTAT3水平明显比敲除IL-6基因小鼠高。7 d时除了肥胖野生型小鼠外,其余各组pSTAT3都恢复到正常水平。另外脂质也能激活STAT3。推断肥胖能通过IL-6诱导STAT3活化, JAK-STAT通路参与脂质AP炎症因子的表达。此外Ramnath等^[33]报告P物质也能活化STAT3、NF- κ B以及活化蛋白-1(activator protein-1, AP-1)。而丝氨酸家族激酶抑制剂(Src family kinases inhibitor, PP2)则能减少P物质对上述物质活化过程。但P物质是否直接诱导STAT3活化仍需进一步研究。

STAT3是一个有争议的蛋白,在炎症时STAT3具有两面性。STAT3能正性调控JAK-STAT通路预防或控制肺损伤发生,但其过度表达又会引起炎症性关节炎的自发发生,同时在炎症性肠病中却起的是促进炎症的作用^[34-36]。STAT3的两面性作用在AP中也有类似的报道。胰腺炎相关蛋白(pancreatitis associated protein, PAP)能减轻AP。PAP是科学家在小鼠胰液内发现的一种新蛋白质,包括3个亚型PAP1、PAP2、PAP3^[37-39]。其中AP早期PAP1有着快速且高表达,恢复期则回到低水平。目前研究显示PAP1与JAK-STAT通路有相互促进作用:细胞因子和JAK-STAT通路能诱导PAP1表达,增加炎症因子表达及炎症细胞浸润等,而PAP1也能同时激活MAPK以及JAK/STAT3通路^[40-42]。Folch-Puy^[43]研究显示PAP1能阻止NF- κ B转移到细胞核,而给予JAK拮抗剂后抑制得以恢复。另外受PAP1刺激的STAT3存在于细胞核,而没有受PAP1刺激的STAT3存在于细胞质。上述结果提示, PAP1能调节STAT3和NF- κ B活性,抑制NF- κ B进入细胞核,在AP过程中起保护作用。T细胞蛋白酪氨酸磷酸酶(T-cell protein tyrosine phosphatase, TCPTP)是JAK-STAT通路作用底物,能加重炎症反应。敲除TCPTP基因的AP小鼠体内脂肪酶、淀粉酶、TNF- α 、IL-6以及IL-1 β 含量减少,而STAT3磷酸化程度明显增高,推测缺少TCPTP能增加STAT3磷酸化,缓解AP病情^[44]。除PAP1和TCPTP外,研究^[29,45,46]发现胰腺炎患者淋巴细胞pSTAT3荧光强度和pSTAT3阳性细胞比例明显比正常人强度高。而单核细胞

NF- κ B和pSTAT3和pSTAT6阳性细胞比例比正常人低, STAT5磷酸化水平正常。由此推断IL-6能激活STAT3以及T淋巴细胞,在AP中起保护作用。单核细胞能影响NF- κ B和STAT3、6激活,增加二重感染可能性,加重胰腺炎病情。其次,在STAT3活化加重AP方面,国外研究报告高迁移率蛋白B1(high mobility group box 1, HMGB1)能增加胰腺腺泡细胞JAK2、STAT3、TNF- α 及IL-1的mRNA和蛋白表达。考虑HMGB1通过诱导JAK-STAT通路活化来加重AP以及急性肺损伤^[47]。地塞米松和SSBE对AP有一定治疗作用。徐志红等^[23]和Yubero等^[48]发现地塞米松和SSBE治疗后MAPK、NF- κ B、pJAK2以及pSTAT3蛋白表达较SAP组少,上述改变与病理检测胰腺和肺的结果相一致,推断地塞米松和SSBE对SAP及并发肺损伤起治疗作用,其机制可能通过抑制STAT3激活,降低促炎细胞因子水平有关。

3.2.3 JAK-STAT通路抑制物: 为避免过度刺激,机体会严密控制细胞因子诱导的信号转导。当各种炎症因子刺激后, JAK-STAT途径诱导细胞因子SOCS3基因表达,与此同时不断增多的SOCS3又能特异性地抑制JAK-STAT信号转导通路,构成一负反馈调节环路,从而使机体处于动态平衡^[49,50]。Chen^[51]研究显示, SOCS3主要通过干扰JAK与受体结合,抑制STAT磷酸化,抑制JAK激酶活性以及降解JAK-STAT等信号蛋白而起抑制JAK-STAT通路作用。而刘瑾^[22]研究则具体指出SOCS3能抑制JAK中JAK2和STAT中STAT3活化,起减轻AP作用。IFN- γ 也能抑制胰腺腺泡细胞JAK2和STAT3产生以及TNF- α 、IL-1、IL-6和胰酶释放,减轻胰腺炎炎症反应^[52]。

4 结论

参与AP发病的细胞信号转导通路很多,而JAK-STAT通路是其中一条简洁的炎症反应通路,促炎症因子和抗炎因子通过JAK-TAT通路参与AP发病机制,药物能通过JAK-STAT通路对AP起治疗作用。如果对AP时JAK-STAT通路与抗炎症因子和促炎因子关系、各通路之间联系以及通路与靶基因关系三者作进一步研究,将有助于了解AP的发病机制,为AP的治疗以及开发安全有效的靶向药物提供新的思路。

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应用要点

JAK-STAT信号通路与AP存在着密切的相关性,但其具体作用机制尚未被完全认识,需要我们进一步探索。展望针对该通路治疗新药物的开发,为AP治疗奠定基础。

■ 名词解释

STAT3: T细胞分化通路上的一个关键因子, 当有炎症发生时, STAT3被活化, 启动Th17细胞的分化。既往研究表明AP大鼠时STAT3表达较对照组增高, 而pSTAT3是胞浆蛋白, 作为转录激活因子在不同类型的免疫和炎症应答中起了重要的调节作用。

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同行评价

JAK-STAT通路是细胞信号转导中及其重要的通道, 其对于多种炎症反应的过程都有影响. 作者从这一角度出发, 有助于阐明AP早期作为一种无菌性的SIRS反应这一本质, 并对疾病的诊治有启发作用, 具有一定的创新性.

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