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JAK/STAT 信号通路在急性胰腺炎疾病发生中的作用

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[摘 要] JAK/STAT信号通路广泛参与机体免疫调节、增殖、分化、迁移、凋亡等生理过程,是大多数细胞、各类因子重要的信号转导通路。JAK/STAT信号通路和炎症相关疾病关系密切,在急性胰腺炎疾病发生发展及器官损伤中起重要作用。
[关键词] JAK/STAT；急性胰腺炎；器官损伤
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Role of JAK/STAT Signal Pathway in the Development of Acute Pancreatitis

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[Abstract] JAK/STAT signal pathway is involved in many physiological processes, such as body immune regulation, proliferation, differentiation, migration and apoptosis, which is an important signal transduction pathway for most cells, and all kinds of factors. JAK/STAT signal pathway is closely related to inflammation-related diseases and plays an important role in the development of acute pancreatitis and organ damage.
[Key words] JAK/STAT; acute pancreatitis; organ damage

前言

急性胰腺炎(acute pancreatitis,AP)是指多种致病因素导致的胰酶激活,继以发生胰腺局部炎症为主,伴或不伴其他器官功能障碍的疾病,是消化系统常见疾病,随着居民生活水平的提高,发病率逐年升高,AP已成为严重危及人民健康的疾病之一。AP易继发全身炎症反应综合征(systemicinflammatoryresponsesyndrome,SIRS)和多器官功能障碍综合征(multipleorgandysfunctionsyndrome,MODS)等,导致严重的临床后果,具有病情重、预后差、并发症多、住院时间长、复发率高等特点[1-2]。急性胰腺炎的发病机制复杂,目前公认的机制主要包括胰腺胰酶自身消化学说、胰腺微循环障碍学说、白细胞过度激活学说以及肠道细菌移居胰腺继发感染学说,其最终的结果均是产生局部、全身炎症反应,大量炎症因子发生“瀑布式级联反应”,引起胰腺及多器官功能障碍[3-5]。

JAK/STAT信号传导通路主要包括酪氨酸激酶JAK及信号转导转录因子STAT两种蛋白家族。Janus激酶(Janus—activatedkinase,JAK)是一类非跨模型胞质内可溶性酪氨酸蛋白激酶,STAT代表信号转导和转录激活子(signaltransducersandactivatoroftranscriptions,STAT),JAK和STAT两个蛋白家族包括多种亚型[6]。目前公认AP炎症反应过程存在免疫系统改变,诱导抑炎和促炎信号通路的活化,JAK/STAT通路作为各种的炎症因子信号转导的通路之一,参与炎症反应的免疫调节过程,机体多种细胞、炎症因子通过激活JAK/STAT通路实现传导,进一步产生抗炎、促炎等作用,JAK/STAT在胰腺腺泡细胞中有特异性抗体[7-9]。研究还证实,JAK/STAT通路在胰腺炎导致的各种器官损伤中起重要作用,具体如下：

1 胰腺损伤

胰腺作为原发病灶,是受损最严重的器官。胰腺微循环障碍是疾病发展中重要的病理生理改变,炎症因子破坏胰腺组织血管内皮细胞引起血管痉挛、通透性增高,导致胰腺血流灌注减少、微循环障碍,严重者会发生组织坏死引起出血坏死性胰腺炎。研究发现,JAK/STAT信号通路存在于胰腺腺泡细胞内,能对IFN介导的胰腺炎症作出反应[10-11]。

JAK/STAT通路活化后对依赖STAT的免疫应答的细胞因子产生正相关作用,包括细胞间黏附分子(intercellularadhesionmolecule-1,ICAM-1),ICAM-1的表达及其引起的炎症因子积聚是AP疾病发展中很重要的细胞事件[12]。

细胞凋亡在AP的发生发展中起关键作用,胰腺腺泡细胞凋亡作为一种防御机制来防止胰腺坏死的发展。凋亡和坏死是AP时胰腺腺泡细胞死亡的两种主要方式,二者最大的区别是凋亡细胞形成凋亡小体后很快被巨噬细胞吞噬,不引起或极少引起炎症反应,AP的严重程度与坏死程度呈正相关,而与凋亡程度呈

负相关[13-14]。Bcl-2家族调控线粒体凋亡途径,是凋亡调控的关键基因,Bcl-2、Bcl-xL是JAK/STAT通路下游的靶基因,炎性因子诱导JAK/STAT通路的激活能够使Bcl-2、Bcl-xL表达改变,影响胰腺腺泡细胞凋亡、炎症修复及病情进展[15-17]。

2 颅脑损伤

在所有AP并发症中,脑组织损伤的发生率在20%左右,而死亡率却高达70%以上。胰性脑损伤发病机制复杂,主要包括胰酶的过度激活、炎症介质的参与、血脑屏障的改变、血管内皮细胞损伤及神经髓鞘损伤等方面[18-20]。研究证明,JAK/STAT通路参与了脑损伤及脑缺血发作,抑制其表达能减轻脑损伤,保护脑神经功能[21-22]。在大脑缺血再灌注损伤的研究中发现,P-STAT3能起到促进血管生成、营养神经的作用,减轻脑组织缺血再灌注损伤[23]。在外周神经损伤的研究中发现,源于施旺细胞的脑神经营养因子可通过JAK/STAT通路刺激外周神经再生与修复[24]。TNF-α,IL-6及IL-1β等炎症因子可破坏脑血管内皮细胞及基底膜,使血管通透性升高,产生脑水肿；加速血小板聚集,诱导脑血管血栓形成,进而导致脑功能障碍；刺激免疫细胞活化,介导髓鞘炎性损伤,造成髓鞘破坏,TNF-α,IL-6及IL-1β等炎症因子均可通过JAK/STAT通路导致脑损伤的发生[25-26]。

3 肺损伤

急性肺损伤是AP最常见的并发症之一,由肺损伤导致的急性呼吸窘迫综合征(acute respiratory distress syndrome,ARDS)是AP患者死亡的重要原因[27]。AP肺损伤时肺泡毛细血管弥散受损导致肺水肿和肺不张,表现为呼吸窘迫和顽固性低氧血症,进一步发展即为ARDS。IL-6、IL-8及IL-10介导AP肺损伤,IL-6、IL-8及IL-10的表达与JAK/STAT表达成正比,JAK/STAT信号途径的激活可诱导IL-6及IL-10过度表达,加重肺组织炎性反应,导致肺泡上皮细胞、肺毛细血管内皮细胞损伤,加快了肺损伤的病理过程；AP时炎症反应介导肺泡上皮细胞功能损伤,JAK/STAT信号通路被证明有维持肺泡上皮细胞合成和分泌肺表面活性物质相关蛋白C(SP-C)的功能,进而发挥维持肺泡稳定的作用,对肺组织起到保护作用[28]。

II型肺细胞与胰腺炎相关的肺细胞凋亡关系密切。II型肺细胞可分化为I型肺细胞的前体,修复肺屏障,以及产生和释放表面因子,维持肺泡细胞的表面张力。肺泡I型上皮细胞是肺泡表面一类重要的细胞群体,其能合成和分泌肺表面活性物质相关蛋白C(SP-C),是肺泡I型上皮细胞的分化标志物,其在基因和蛋白水平表达异常可以引起肺脏功能异常,引发相关疾病。研究显示JAK/STAT信号通路能维持肺泡II型上皮细胞合成和分泌SP-C的功能,保证肺泡的稳定性,从而减轻AP时炎症反应导致肺泡功能受损[29-30]。

4 肝损伤

在AP的病程中,肝细胞膜通透性增强,肝脏的解毒作用减弱,一些内源性毒素无法在肝脏进行降解,直接进入血液循环,引起一系列炎性反应,严重影响患者疾病的治疗和恢复[31-32]。AP通过上调肝内生成的JAK的表达介导了肝细胞损伤,JAK/STAT通路可介导肝组织中高迁移率族蛋白B1(HMG B1)等多种炎性因子的表达,并与相应位点结合,促进炎症的发生以及肝脏损伤,且肝损伤的严重程度、炎性因子的释放与肝组织中JAK和STAT的磷酸化水平相关。Kuppfer细胞是产生炎性介质及细胞因子的主要细胞之一,实验表明,抑制JAK/STAT通路可下调胰弹性蛋白酶诱导的Kupffer细胞释放炎性因子,减轻胰腺炎症反应及肝损伤[33-37]。

5 肾脏损伤

AP并发肾损伤的发生率约为14%-63%,甚至可发展至急性肾功能衰竭(ARF),病死率高达80%,出现ARF后其他脏器衰竭发生率也明显升高[38]。AP引起的肾损伤的发病机制尚不明确,普遍认为细胞因子和炎症介质的过量释放在AP肾损伤中起关键作用,有效循环血容量不足和肾血流动力学异常为其发病的关键因素[39]。血管活性物质或蛋白酶等肾毒性物质可介导AP肾损害。AP时的肾功能衰竭可由免疫、毒素、应激等引起的急性肾小管细胞凋亡所致。AP相关的肾功能衰竭,其病理状态的基本认识是肾缺血引起的急性肾小管坏死[40]。

许多促炎细胞因子在AP及相关器官衰竭的病理机制中发挥重要作用,包括 TNF-a、IL-6等[41],抑制介导因子的转录和翻译,减少促炎因子的分泌,可以改善AP的炎症反应和肾功能衰竭。JAK/STAT通路是细胞因子和生长激素受体信号转导所必需的多效级联,参与了许多细胞因子的免疫应答,抑制JAK2/STAT3通路可降低AP时诱导肾损伤发生的TNF-a、IL-6表达水平[42]。

6 肠道损害

发生AP时机体处于免疫应激状态,大量的炎症因子释放引起肠道黏膜屏障受损、肠道细菌移位和肠源性内毒素血症,大量细菌和内毒素进入血液循环,启动SIRS并引发MODS。[43]AP患者肠黏膜缺血、缺氧可以导致肠黏膜上皮细胞损伤,通透性增加,细菌和内毒素可穿过肠黏膜进入组织,导致肠源性感染,甚至诱发败血症等。JAK/STAT 信号通路参与了肠黏膜屏障功能调节和炎性反应的调控,是治疗AP肠黏膜损伤的靶标[44],NF-KB是内毒素信号通路激活的靶点,启动下游基因的转录,NF-KB可通过JAK/STAT通路使内毒素炎性反应级联放大,抑制JAK/STAT通路可减轻AP导致的肠道黏膜损伤,减轻细菌移位及内毒素血症的发生。

7 结束语

综上可见,JAK/STAT通路在AP导致的各器官损伤发挥重要作用,在器官保护中担任重要靶点,许多细胞因子可通过JAK/STAT通路产生效应与对应点位进一步结合对AP产生细胞层面的影响,JAK/STAT通路为AP的治疗奠定了基础,。目前,临床上AP的治疗主要是针对病因、抑制胰酶分泌、抗生素等支持对症治疗,未来是否会针对炎症通路,使用促炎通路抑制剂等治疗AP,但许多通路及亚型在炎症反应中既扮演抗炎的角色,也起到促炎的作用,在针对炎症通路的治疗上还需谨慎。

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