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述评 EDITORIAL

TLR4信号传导通路与胰腺炎

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Toll-like receptor 4 signaling pathway and pancreatitis

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Abstract

The pathogenesis of pancreatitis has long been a hot topic in basic and clinical research but is still not fully clarified. Toll-like receptor 4 (TLR4) recognizes the lipopolysaccharide (LPS) of Gram-negative bacteria and stimulates the synthesis and release of inflammatory cytokines through activation of the NF-κB signaling pathway, which ultimately results in inflammatory responses that involve multiple organs. Animal and clinical studies have shown that the TLR4 signal pathway plays an important role in the development of tissue injury during acute pancreatitis (AP) and up-regulation of TLR4 and the TLR4 signaling pathway contributes to the development of multiple organ dysfunction syndrome (MODS) associated with severe acute pancreatitis (SAP) by increasing proinflammatory cytokines. Therefore, further studies are required to clarify the role of the TLR 4 signaling pathway in the pathogenesis of pancreatitis to explore novel methods for treating this disease.

Key Words: Toll-like receptor 4; Acute pancreatitis; Severe acute pancreatitis

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摘要

胰腺炎的发病机制长期以来一直是基础和临床研究的一个重要课题, 然而至今尚不完全明确. 研究证实TLRs(Toll-like receptors)家族成员中TLR4可与G⁻菌内毒素脂多糖(lipopolysaccharide, LPS)结合, 通过NF-κB信号通路激发多种炎症因子的合成进而参与多种器官疾病的发病过程. 在鼠类模型和临床研究中已经显示TLR4信号通路在急性胰腺炎(acute pancreatitis, AP)的发病过程中起着重要的作用; 上调TLR4信号通路可诱导致炎细胞因子大量释放参与重症急性胰腺炎(severe acute pancreatitis, SAP)病程中多器官功能障碍综合征的形成. 因此, 进一步明确TLR4信号通路在胰腺炎发病机制的作用, 有可能通过阻断TLR4信号通路使胰腺炎获得疗效.

关键词: Toll样受体4; 急性胰腺炎; 重症急性胰腺炎

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0 引言

Toll样受体4(Toll-like receptor 4, TLR4)是Toll样受体家族(Toll-like receptors, TLRs)的成员之一, 是一种模式识别受体. TLR目前被认为是哺乳动物唯一将细胞外抗原识别信息向细胞内传递并引发炎症反应的关键跨膜蛋白, 是对病原体侵袭产生免疫应答信号通路中的一类受体[1]. TLR4主要通过与革兰阴性细菌(G⁻菌)感染后内毒素脂多糖(lipopolysaccharide, LPS)结合, 进而活化核因子-κB(nuclear factor kappa B, NF-κB)信号通路, 引起肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)等致炎细胞因子的合成, 导致多

■背景资料
TLR4是TLRs家族的成员之一. 目前研究证实G⁻菌内毒素脂多糖(LPS)作用于TLR4, 通过活化核因子-κB(NF-κB)引起致炎细胞因子的合成和释放, 参与急性胰腺炎(acute pancreatitis, AP)炎症反应.

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■创新盘点
本文首先对TLR4信号通路的结构特征、作用及调节进行了综述，然后从不同层次和角度阐述了LPS-TLR4通路在急胰腺炎发病学中的作用和机制，为胰腺炎防治开辟新方法提供了理论依据.

种炎症因子的瀑链式释放而产生生物学效应.

胰腺炎是我国消化内科的常见病, 其包括急性胰腺炎(acute pancreatitis, AP)与慢性胰腺炎(chronic pancreatitis, CP). 胰腺炎发病机制比较复杂, 至今尚未完全明了. 轻症急性胰腺炎(mild acute pancreatitis, MAP)通常呈现自限性经过, 而重型急性胰腺炎(severe acute pancreatitis, SAP)病情发展迅速, 可以在短时间内发生多器官功能衰竭, 有较高的死亡率[2]. 研究结果表明TLR4参与多种细胞因子(TNF-α、IL-1β、IL-6)的活化与SAP的发生[3-5]. TLR4的激活及其下游一系列信号分子的活化可能是SAP时全身系统性炎症反应综合征(systematic inflammatory response syndrome, SIRS)及由此引发的多器官功能障碍综合征(multiple organs dysfunction syndrome, MODS)的一个重要环节[4,6]. 近年来研究显示胰腺组织多种细胞可表达TLR4, 可能在胰腺炎发病中发挥作用[7,8]. 本文就TLR4信号通路的传导特征及其在胰腺炎发病学的作用进行综述.

1 TLR4的结构、功能及传导通路

1.1 TLRs家族中TLR4与其配体的结构特征 TLR家族是一类由天然免疫细胞表达的跨膜蛋白, 他可以识别外来微生物的侵袭, 由此激活免疫及炎症反应信号通路以破坏外源微生物. 在哺乳动物中, TLRs存在11个家族成员. 最近, TLR12和TLR13在鼠类细胞中被发现, 但有关他们的作用尚不明确. TLRs的不同成员分别识别不同的配体, 配体包括细菌细胞壁的组成成分, 双链RNA病毒, 小分子逆转录病毒及免疫调节复合物等[9,10].

在人体中, TLR1, 2, 4, 5和6属于膜外受体, 并且主要针对细菌表面的病原相关分子模式(pathogen-associated molecular patterns, PAMPs)作出应答. 另一组成员TLR3, 7, 8和9是在包涵体上被发现, 他们主要针对病毒及细菌的核酸PAMPs作出应答[9,11]. 在TLRs家族中, 除了TLR3, TLR7, TLR8这3种病毒特异性受体外, 其余TLRs均参与对细菌的防御过程. 革兰阳性细菌及革兰阴性细菌表面有不同的PAMPs, 其与相应的TLR结合. 其中, G^-菌感染后细菌内毒素-脂多糖(lipopolysaccharide, LPS)通过与TLR4结合, 激活信号通路进而活化NF-κB, 引起TNF-α等炎症因子参与炎症的形成[9,12].

TLR4属于I型跨膜蛋白, 其胞外区含有1个高度保守的富含亮氨酸的重复序列, 借此识别PAMPs并与其辅助受体结合形成受体复合物, 激发下游信号通路将识别的抗原信息向细胞内传递, 引发炎症反应[13]. 目前已经确认的可作为TLR4结合的配体依据来源分为2类: 即外源性和内源性, LPS是TLR4的主要外源性配体, 而热休克蛋白(heat shock protein, HSP)、纤维连接蛋白中的EDA(extra domain A)片段及透明质酸(hyaluronic acid, HA)的寡糖等则为内源性配体[14,15].

1.2 TLR4的分布及功能 人类TLR4基因定位于9号染色体上的q32、q33. TLR4属于泛生型, 在体内广泛分布于各类与免疫相关的细胞如中性粒细胞、单核细胞和树突状细胞等, 此外, 还分布于人体其他组织细胞如肝脏的枯否氏细胞、肝细胞、肝星状细胞, 胰腺的巨噬细胞、腺泡细胞和胰腺星状细胞等[8]. TLR4的主要功能是当G^-菌感染后内毒素LPS与其结合, 活化NF-κB转录因子的结合活性, 诱导包括TNF-α等致炎细胞因子的合成和释放, 引起组织的炎症反应.

1.3 TLR4的信号传导通路 近年来的研究显示TLR4与其配体G^-菌内毒素LPS结合后, 可以激活髓样分化蛋白88(myeloid differentiation factor 88, MyD88)依赖性和MyD88非依赖性信号途径. MyD88依赖性信号通路主要介导NF-κB活化和致炎细胞因子产生. 其基本过程如下: TIR域衔接器蛋白(TIR-domain containing adaptor protein, TIRAP)将TLR4与MyD88桥接, 进而诱导IL-1受体相关激酶(interleukin-1 receptor-associated kinase, IRAK)磷酸化并与MyD88分离, 磷酸化的IRAK与肿瘤坏死因子受体相关因子6(TNF receptor-associated factor 6, TRAF6)、转化生长因子β激酶1(TGF-β activate kinase 1, TAK1)形成多蛋白复合物, 然后TRAF6被泛素化和降解, 分别使下游的IkB激酶(IkB kinase, IKK)复合物和有丝分裂原激活的蛋白激酶(mitogen-activated protein kinase, MAPK)活化. 含有IKKα、IKKβ及NEMO的复合物形成后可诱导IkBα泛素化和降解, 使转录因子NF-κB从胞浆转移至细胞核, 活化的MAPKs包括c-Jun氨基末端激酶(c-Jun N-terminal kinase, JNK)和p38 MAPK(p38)可激活转录因子AP-1. 这些活化的转录因子进而可诱导致炎细胞因子如TNF-α、IL-6、IL-1β等的转录, 参与组织的炎症反应[16-18].

TLR4亦可激活MyD88非依赖性信号通路, 即TRIF(toll-interleukin-1R domain-containing adapter inducing IFN-β, TRIF)依赖性信号通路.

■同行评价
急性胰腺炎发病机制中TLR4作用是近5年研究的新认识, 对于急性胰腺炎发病机制的研究有参考意义.

当TLR4与另1个衔接器分子TRAM连接, 随即从细胞膜进入胞浆与TRIF相互作用, TRIF进而与TRAF3和TRAF6联合, 激活TANK结合激酶1(TANK-binding kinase 1, TBK1)与IKKε, 引起转录因子IRF3活化, 诱导IFN-β的转录. TRIF依赖性信号通路亦可经由TRAF6通过RIP1诱导NF-kB和MAPK晚期激活, 诱导致炎细胞因子合成和释放[16,18-20]. 此外, 近来研究表明: CD180作为TLR4的类似物亦可调节MyD88非依赖途径[21]. 脂联素和血红素氧合酶-1可抑制鼠类暴露乙醇后肝脏枯否氏细胞MyD88非依赖的TLR4信号通路产生致炎细胞因子[22].

1.4 TLR4信号传导通路的调节 TLR4/NF-κB信号通路存在相关调节因子. 研究证实IL-4可下调TLRs的表达, 受体相互作用蛋白-1(receptor interacting protein 1, RIP-1)可以介导TRIF(Toll/IL-1R domain-containing adaptor inducing IFN-β)诱导的NF-κB活化, 而RIP-3能在RIP-1诱导的NF-κB通路中起负性调节作用[23]. Toll相互作用蛋白(Toll interacting protein, Tollip)可抑制TLR2和TLR4通路中IL-1R的自身磷酸化[24]. IFN-α可以增强TLR信号通路中MyD88及其调节分子和激酶的表达[25].

2 TLR4信号通路与胰腺炎

2.1 TLR4在正常胰腺组织中的分布 在正常人体胰腺组织中, TLR4在主胰管上皮细胞及胰腺血管内皮细胞可有表达, 胰岛为弥散较强型表达, 胰腺腺泡细胞为均匀分布、相对较弱的表达[7]. TLR4在胰腺导管上皮的表达可能与其识别入侵的病原菌, 诱导天然与获得性免疫功能, 最终清除病原菌防止胰腺感染有关. 胰腺血管内皮细胞及其细胞间隙通常构成胰腺与血管的屏障, 研究发现胰腺组织血管内皮可表达TLR4, 提示其在参与局部免疫炎症反应及维持内环境稳定过程中有可能发挥作用[7].

2.2 TLR4在急性胰腺炎的作用 动物实验和人体研究结果表明AP肠腔细菌增殖, 肠黏膜屏障破坏, 肠壁通透性增加[26-28]. 肠壁通透性增加可使肠腔内的细菌和内毒素易位(bacterial translocation)至肠系膜淋巴结或其他肠外器官[26,27]. 此外, AP患者和动物的血液中LPS水平明显升高[5,26], 这就为LPS-TLR4通路在AP发病过程的作用提供了间接证据.

目前研究证实TLRs/NF-κB通路在AP炎症发生发展中起重要的作用. TLR4通过识别G$^-$细菌表面的PAMPs活化抗原呈递细胞, 增加细胞因子的表达, 启动获得性免疫应答, TLR4基因的上调与AP器官损伤的发生、发展相关[6,29,30]. 在AP的发病过程中, TLR4可以和许多内源性及外源性配体结合[31]. 研究发现TLR4信号通路的活化需要4种接头蛋白的调节, 即MyD88、MyD88接头蛋白、Toll样受体相关的干扰素活化子(TRIF接头蛋白)和TRIF相关的接头分子(TRIF-related adaptor molecule, TRAM). TLR4受体复合物可以将信号传递给TIR结构域, 进而激活NF-κB. NF-κB发挥“信使”作用对多种炎症介质和细胞因子的表达进行调控. 在AP发病初期, NF-κB介导多种炎性细胞因子引起局部炎症, 随着病情进展这些致炎因子逐渐扩散至全身组织器官而导致SIRS的发生[6,32].

迄今有文献报道促炎细胞因子TNF-α、IL-1、IL-6等在AP发病机制中起重要作用, 致炎因子的产生可促发多种促炎细胞因子的级联反应, 导致胰腺组织受损. AP早期炎症反应主要与胰腺实质与胰腺周边浸润的巨噬细胞及中性粒细胞大量释放的TNFα等炎症细胞因子密切相关, TNF-α持续升高或长期存在可加重AP的严重程度[33], 相反, 低浓度的NO有抗炎作用, NO通过抑制TLR4基因表达, 使SAP的损伤减轻[34-36]. 由此可见, 细胞因子网络的失衡在AP的发病学中起着重要的作用.

在鼠类动物SAP模型显示组织中TLR4、ICAM-1、NF-κB和Bax蛋白水平升高与相应的组织损伤密切相关[37,38]. 细菌内毒素LPS可激活大鼠TLR4信号通路并由此介导胰腺及其器官的损伤[39,40]. TLR4缺失小鼠可下调无胆盐乙硫氨酸饲养诱导胰腺炎模型的PKC-δ、NF-κB和ERK1/2的活性, 并减轻胰腺炎继发的肝细胞凋亡[41].

目前研究已证实肠道细菌易位及内毒素是胰腺继发感染组织坏死的重要原因, 但是SAP中多器官功能衰竭的原因尚不完全明确. 一项临床动态研究显示, SAP患者外周血单核细胞表面TLR4发病后表达上调, 随后逐渐下降, 3 d左右恢复正常, 血中TNF-α与TLR4变化一致, 这项研究表明SAP早期可能通过先天性免疫门户蛋白TLR4激活单核巨噬细胞系统, 导致TNF-α等促炎细胞因子的产生和释放[42]. 在小鼠SAP出现SIRS的模型肝脏发现TLR4及其下游炎症因子TNF-α和IL-6表达明显增加, 在人SAP血浆IL-6和IL-10水平明显高于轻型AP, 提示TLR4信号通

路可能与SIRS的发生、发展密切相关[43,44]. 采用TLR4敲除小鼠制作SAP模型发现这种小鼠血清中IL-1、TNF-α水平明显减低, 肝脏和肾脏细胞的程序性死亡亦减少, 血清丙氨酸转氨酶、尿素氮、肌酐水平明显较野生型低, 而胰腺的G$^-$菌培养阳性率增高. 相反, 在TLR4野生型SAP制模后4 h, TLR4在肝、肾和小肠中的表达增加, 12 h后下降. 因此推测SAP时TLR4既可触发炎症反应, 同时对细菌感染可能有防御作用[37]. 在一项TLR4(896A>G)基因错义突变与胰腺坏死组织感染相关的研究显示, SAP患者TLR4(896A>G)基因错义突变检出率高于健康人, 携带TLR4基因错义突变的SAP患者易患G$^-$菌感染, 因此认为TLR4(896A>G)基因错义突变是胰腺坏死组织继发感染的危险因素[45].

总之, 目前对于TLR4在胰腺炎中的发病机制研究仍处在初级阶段. 然而, 越来越多的实验结果证实, 抑制TLR4信号通路的启动可能有助于胰腺炎的防治. 在临床实践中TLR4信号通路相关药物既可能有望作为胰腺炎治疗性药物, 也可作为疫苗佐剂. 今后需加强胰腺炎动物模型及临床实验研究, 以进一步明确TLR4与胰腺炎发病学的关系, 为胰腺炎的防治提供更确切的理论依据.

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• 消息 •

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本刊讯 《中国学术期刊评价研究报告-RCCSE权威、核心期刊排行榜与指南》由中国科学评价研究中心、武汉大学图书馆和信息管理学院联合研发, 采用定量评价和定性分析相结合的方法, 对我国万种期刊大致浏览、反复比较和分析研究, 得出了65个学术期刊排行榜, 其中《世界华人消化杂志》位居396种临床医学类期刊第45位. (编辑部主任: 李军亮 2010-01-08)