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文献综述 REVIEW

# Fas/FasL在急性胰腺炎肝损伤中的作用

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## Role of Fas/FasL in acute pancreatitis-associated liver injury

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## Abstract
Fas/FasL-mediated apoptosis is involved acute pancreatitis-associated liver injury. It up-regulates proapoptotic pathways in the liver and promotes hepatocytic injury as well as hepatocytic apoptosis during acute pancreatitis. The signal of the production of FasL and the expression of FasL were up-regulated in kupffer cells during acute pancreatitis. Then, FasL activates Fas-associated death domain (FADD) and unmasks its death effector domain (DED) followed by subsequent activation of the Caspase cascade and downstream effector Caspases, ultimately resulting in DNA cleavage and hepatocytic apoptosis. This review aimed to elucidate the construction, distribution and function of Fas/FasL, and to highlight mechanism of acute pancreatitis-associated liver injury mediated by Fas/FasL.

Key Words: Fas/FasL; Acute pancreatitis; Liver injury; Apoptosis

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## 摘要
Fas/FasL介导的凋亡参与急性胰腺炎肝损伤的发生发展, 急性胰腺炎上调肝内的促凋亡通路并且促使肝细胞损伤和肝细胞凋亡. 急性胰腺炎时通过上调Kupffer细胞内FasL生成的信号使FasL表达增加, FasL激活Fas相关的死亡域和暴露死亡效应结构域, 随后活化Caspase级联反应和下游的效应Caspases, 最终导致DNA裂解和肝细胞凋亡, 从而介导肝损伤. 本文就Fas/FasL结构、分布、功能及介导急性胰腺炎肝损伤的机制作一综述.

**关键词:** Fas/Fas配体; 急性胰腺炎; 肝损伤; 凋亡

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■背景资料
肝损伤是急性胰腺炎(AP)病情严重程度判断及预后的重要指标, 已有研究表明AP时枯否细胞生成的细胞因子TNF介导肝细胞损伤, 而Fas配体(FasL)是TNF家族成员之一, FasL介导的凋亡在肝细胞凋亡中起重要作用.

## 0 引言
Fas, 即Apo-1/CD95, 属于肿瘤坏死因子受体(tumor necrosis factor receptor, TNFR)家族的一种细胞表面蛋白, 自1989年发现以来, 已证实他参与多种病理生理过程[1-4]. 1993年Suda *et al*[5]从细胞毒T细胞杂交瘤分离到Fas/Apo-1配体(Fas/Apo-1ligand, Fas/Apo-1L), 属于TNF家族的成员之一, 由激活的淋巴细胞(如T细胞和NK细胞)产生, 其功能是作为这些细胞毒细胞的效应子来清除被病毒及细菌感染的细胞或新生物细胞. FasL与Fas阳性靶细胞结合时可诱导细胞凋亡[6-8]. 有报道表明FasL介导的凋亡在肝病、急性肾衰竭和甲状腺炎的实质细胞损伤中起重要的作用[9-15]. 但是有关急性胰腺炎(acute pancreatitis, AP)时Kupffer细胞中FasL表达及其在肝细胞损伤中的作用却少见详细阐述. 本文就Fas/FasL介导AP肝损伤的机制作一综述.

## 1 Fas/FasL结构、分布及功能
Fas和FasL分子均是由胞外区、跨膜区、胞内区三个部分所组成. Fas分子质量约为36 kDa. Fas蛋白属于Ⅰ型跨膜糖蛋白, 其N端在膜外, C端在膜内. 跨膜区由17个aa组成, 胞内区为145个aa, 其

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■研发前沿
AP肝损伤的发病机制中FasL/Fas介导的肝细胞凋亡致肝损伤是热点研究问题, 需要更进一步的实验和临床研究去阐明其机制.

中含有70个aa的保守序列, 在细胞凋亡的过程中发挥信号传导的作用, 称为死亡结构域(death domain, DD)[16-17]. Fas抗原有4个重要区域与死亡信号传导有关: 胞外2个, 即死亡信号激发域和诱导程序性细胞死亡的抗Fas mAb作用域, 前者是特异性FasL与Fas抗原结合并诱导程序性细胞死亡的部位; 胞内2个, 即死亡抑制域和死亡域, 死亡域氨基酸发生突变就阻止凋亡信号传导. Fas分布于多种细胞上, 如胸腺细胞, 外周活化T、B淋巴细胞、NK细胞, 内皮细胞, 某些组织在一定条件下也可诱导Fas表达. Fas主要以膜受体的形式存在, 当编码细胞膜Fas(membrane-binding Fas, mFas)跨膜区的DNA外显子缺失突变时, 改变的mRNA选择性剪接可产生可溶形式的Fas(soluble Fas, sFas), 存在于外周血中. sFas与FasL有很高的亲和力, 可通过与mFas分子竞争结合FasL而阻断Fas介导的细胞凋亡[13].

FasL是Fas在体内的天然配体, 分子质量31 kDa, 糖基化后分子质量36-43 kDa, 分子C端位于胞膜外, 与TNF家族蛋白很相似, 是典型的Ⅱ型膜蛋白, 属于TNF家族成员. FasL以膜结合蛋白和可溶性蛋白两种形式存在, 在人体的分布相当局限, 只有睾丸组织基质细胞、角膜、虹膜和视网膜上皮细胞持续表达FasL, 静息的T淋巴细胞不表达, 受抗原或丝裂原刺激后活化的T淋巴细胞快速表达Fas, 通过Fas/FasL结合而介导细胞凋亡[8,13,18-20]. 可溶性FasL(sFasL)分子是通过金属蛋白酶介导的FasL胞外段蛋白溶解而从细胞表面释放, 并以三聚体形式存在, 能诱导细胞凋亡, sFasL三体能与1个Fas单体结合, 也能与3个Fas单体交叉联结.

## 2 Fas/FasL、细胞凋亡与AP肝损伤

2.1 Kupffer细胞FasL生成的信号调节 AP时释放的炎症介质经血液循环到达肝脏, 通过Kupffer细胞内信号转导通路的激活来介导一系列生物学效应[21-23]. 丝裂原活化蛋白激酶(mitogen activated protein kinases, MAPKs)是一类存在于大多数真核细胞内, 转导胞外信号引起细胞反应的丝/苏氨酸蛋白激酶, 是细胞内一类重要信号系统. 其中, p38MAPK信号通路是MAPKs家族的重要组成部分, 他经外界刺激应激而激活, 故又称为MAPK应激信号通路, 其在全身炎性反应、细胞分化及凋亡等方面具有十分重要的作用[24-28], 被认为是细胞信息传递的交汇点和共同通路. 细胞受到刺激后通过下述信号传导路线激活p38MAPK: 胞外信号→MEKK5→MKK3/MKK6→p38MAPK, p38MAPK受到磷酸化激活后通过级联反应作用于下游的转录因子而使FasL mRNA表达上调和FasL蛋白增加[29-31]. NF-κB是由MAPK超家族的应激调节蛋白激酶激活的, 这些上游的NF-κB调节物质包括p38MAPK、ERK1/2和SAPK/JNK, 受到不同的胞外刺激导致磷酸化, 激发级联反应调节多种转录因子作用于NF-κB[32-33]. 胰弹性蛋白酶作用于Kupffer细胞介导p38MAPK、ERK1/2和SAPK/JNK的磷酸化和激活NF-κB, 这些物质的活化都是时间依赖性的; Kupffer细胞抑制剂氯化钆能通过减弱NF-κB和上游的调节物质(ERK1/2和SAPK/JNK)的激活来抑制胰弹性蛋白酶介导的FasL mRNA的上调, 提示FasL来源于Kupffer细胞并且FasL和NF-κB的活化是通过MAPK的各条不相互依赖的通路激活的[34].

2.2 FasL介导AP肝损伤 肝损伤是AP进程中全身炎症反应的临床表现之一, 肝功能损害已成为评估AP严重程度的Ranson评分和急性生理和慢性健康评估Ⅱ(APACHEⅡ)系统的独立指标[35-39], 对预测AP临床预后尤为重要. Gallagher *et al*[40]体内实验研究表明, 雨蛙素诱导小鼠AP后, 肝损伤的标志物-血清AST、LDH水平随时间依赖性的增高, 并和血清FasL水平增高相平行, 同时小鼠肝脏中FasL mRNA及其蛋白表达亦同时上调; 而且FasL表达增加与肝脏凋亡通路中重要的调节酶p38MAPK磷酸化和Caspase-3激活相关, 提示雨蛙肽诱导AP激活肝脏内凋亡前通路, 促进肝细胞损伤和死亡. 用Kupffer细胞抑制剂氯化钆预处理能够降低预期升高的AP小鼠血清FasL水平及肝脏中FasL mRNA及FasL的表达. 类似的结果同样出现在体外试验中, Kupffer细胞和肝细胞共同培养时, 胰弹性蛋白酶(其在体外能够模拟AP的体内效应)处理的Kupffer细胞培养液中肝细胞损伤的标志酶AST、LDH呈时间依赖性的明显增加, 并使肝细胞的存活力明显下降; 同时胰弹性蛋白酶也上调Kupffer细胞内FasL基因及其蛋白表达, 并明显增加上清液中FasL水平, 而且Kupffer细胞中Fas也在同一时间里上调, 这些物质的上调都呈时间依赖性, 而用氯化钆处理后则明显降低上述各物质的水平, 并且减少p38MAPK磷酸化和Caspases-3的活化. 用FasL单独作用于肝细胞能够降低肝细胞存活力和明显增加肝细胞的凋亡数目, 并增加p38MAPK的磷酸化和Caspase-3的活化, 而FasL

mAb能减弱FasL介导的对肝细胞的上述作用[41]. 另有研究表明[42]: 胆碱缺乏的乙硫氨酸饮食诱导的小鼠AP肝脏FasL、Fas和p38MAPK表达明显上调, 从而诱导肝细胞凋亡, 而在FasL和Fas基因缺陷小鼠的肝脏p38MAPK表达明显减少, 并减少肝细胞凋亡. 上述研究均表明, AP通过上调Kupffer细胞产生Fas/FasL导致肝损伤, FasL在肝细胞凋亡中起着关键性作用. 最近研究表明, AP相关性肝损伤的严重程度取决于Kupffer细胞上调Fas/FasL表达与其自身凋亡之间的平衡[43].

2.3 Caspases级联反应介导肝细胞凋亡 Caspases级联反应是细胞凋亡执行的重要步骤[44-46]. 凋亡信号传导途径有两条: 一条是死亡受体传导途径, 另一条是线粒体传导途径[47-50]. 细胞膜表面存在死亡受体超家族, 当Fas和相应的配体FasL结合后将引起受体聚集, Fas和FasL结合形成死亡诱导信号复合物, 复合物的胞内结构将和胞质中的结合器分子-Fas相关死亡结构域(fas-associated death domain, FADD)结合, FADD末端的死亡效应器结构域(death effector domain, DED)再和Caspase-8前体结合, 使Caspase-8前体水解活化, 再作用于下游底物Caspase-3前体, 将其水解成活性Caspase-3并最终引起细胞凋亡[51-53]. 当细胞外和细胞内的损害信号传导到线粒体上后, 在线粒体表面存在由对凋亡起相反作用的蛋白因子组成的Bcl-2家族, 他们竞争调节细胞色素C的释放, 如果促使凋亡的一方大于另一方, 线粒体将释放细胞色素C[54], 后者和胞质中的凋亡激活因子1(Apaf-1)及Caspase-9前体结合形成凋亡酶体(apoptosome), 使Caspase-9前体水解活化, 再进一步水解Caspase-3前体而最终诱发凋亡[55-56]. 以上两条途径是经典的凋亡传导途径, 其中Caspase-8和Caspase-9作为起始Caspase, 而Caspase-3作为效应器Caspase[57]. Caspase-3的作用底物是β-淀粉样前体蛋白(amyloid precursor protein, APP), 其产物是淀粉样β肽(Aβ), Aβ将最终触发凋亡[58]. 有研究发现, 内质网可能是凋亡的新途径, 参与此途径的是Caspase-12, 内质网在应激作用下将Caspase-12前体激活, Caspase-12是否直接触发凋亡尚不清楚, 但Aβ引起凋亡必须有Caspase-12的参与, 目前此途径的具体细节有待进一步研究[59].

许多研究表明, 肝细胞凋亡是通过线粒体传导途径[60-65]. 通过转基因小鼠对Fas信号研究显示: FADD和Caspase-8是介导凋亡所必需, 而Bcl-2或Bcl-x(L)并不能阻滞FasL介导的肝细胞凋亡, 提示Fas诱导的细胞死亡信号和Bcl-2家族对凋亡调节的通路是不同的[66]. 最近Imao *et al*[67]研究表明, Fas可能依赖Caspase-8(外部途径)和线粒体(内部途径)两条途径激活Caspase-3, 如果线粒体依赖途径被阻滞, 另一途径能够代偿; 而TNFR则主要单独通过线粒体介导的Caspase-9激活途径, 进而激活Caspase-3, 导致肝细胞凋亡.

■**创新盘点**
本文从FasL/Fas介导的肝细胞凋亡来阐明AP肝损伤的发病机制, 对AP的治疗具有潜在的临床意义.

## 3 结论

Fas/FasL系统介导的肝细胞凋亡在AP相关的肝损伤中发挥着重要作用, 他参与AP肝损伤的发生发展过程. AP上调肝内促凋亡通路并且促使肝细胞损伤和肝细胞凋亡, 即通过活化的TNFR受体家族成员Fas, FasL激活Fas相关的死亡域和暴露死亡效应结构域, 随后活化Caspase级联反应和下游的效应Caspases, 最终导致DNA裂解和肝细胞凋亡, 从而介导肝损伤. 因此, 以Fas/FasL为靶目标, 阐明其在AP肝细胞损伤中的作用机制, 将为AP临床治疗提供理论和实验依据. 由此提示我们如果能抑制枯否细胞Fas/FasL的表达, 或是用相应的抗体中和其作用, 或是通过RNA干扰技术干扰Fas/FasL的表达, 将有可能达到防治AP肝损伤的目的.

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■应用要点
通过抑制FasL/Fas的表达, 从而抑制肝细胞凋亡通路进而达到保护作用, 有望成为控制AP发生发展及保护肝脏的新措施.

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**■同行评价**
本文内容全面, 语言流畅, 可读性好, 但学术价值一般.

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