



1 题名：简明确切地反映论文的特定内容，鲜明而有特色，阿拉伯数字不宜开头，不用副题名，一般 20 个字。避免用“的研究”或“的观察”等非特定词。

2 作者：作者署名的次序按贡献大小排列，多作者时姓名间用逗号。英文摘要中，先名后姓，首字母大写，如：Ying-Qiu Huang, Ming Li.

3 单位：作者后写单位的全称空 1 格后再写省市及邮政编码，不同作者单位分别写出。

4 基金资助项目：可以增加省市级以上基金资助项目，并加基金号。英文摘要中翻译为准确的英文。

5 通讯作者：本刊只设一位通讯作者，不设共同通讯作者，需增加职称。

6 摘要：应包括中英文摘要，一段式非结构摘要，字数应该在 250 字内为宜。

7 关键词：应包括中英文关键词，作者应在关键词列表中提供 3-10 个关键词，来反映论文中的核心内容。请尽量使用美国国立医学图书馆编辑的最新版 *Index Medicus* 中医学主题词表 (MeSH) 内所列的词。必要时可采用惯用的自由词。每个关键词之间用“;”分隔。格式如：肠道菌群；急性胰腺炎；慢性胰腺炎；自身免疫性胰腺炎。每个英文关键词第一个字母大写。每个关键词之间用“;”分隔。

8 正文：首段为“0 引言”，末段为“结论”，中间部分根据文章划分。

9 图表：图表的数量要精选，表应有表序和表题，并有足够具有自明性的信息，使读者不查阅正文即可理解该表的内容。表内每一栏均应有表头，表内非公知通用缩写应在表注中说明，表格一律使用三线表(不用竖线)，在正文中该出现的地方应注出。图应有图序、图题和图注，以使其容易被读者理解，所有的图应在正文中该出现的地方注出。同一个主题内容的彩色图、黑白图、线条图，统一用一个注解分别叙述。如：图 1 萎缩性胃炎治疗前后病理变化。A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...。曲线图可按●、○、■、□、▲、

△顺序使用标准的符号。统计学显著性用：^a $P<0.05$ ，^b $P<0.01$ ($P>0.05$ 不注)。如同一表中另有一套 P 值，则^c $P<0.05$ ，^d $P<0.01$ ；第 3 套为^e $P<0.05$ ，^f $P<0.01$ 。

10 参考文献：本刊采用“顺序编码制”的著录方法，即以文中出现顺序用阿拉伯数字编号排序。提倡对国内同行近年已发表的相关研究论文给予充分的反映，并在文内引用处右上角加方括号注明角码。文中如列作者姓名，则需在“Pang 等”的右上角注角码号；若正文中仅引用某文献中的论述，则在该论述的句末右上角注码号。如马连生^[1]报告……，潘伯荣等^[2-5]认为……；PCR 方法敏感性高^[6-7]。文献序号作正文叙述时，用与正文同号的数字并排，如本实验方法见文献[8]。文献量达 70 条，可以参考本刊相关文献。

11 名词术语：应标准化，前后统一，如原词过长且多次出现者，可于首次出现时需要包含中英文全称，以后直接用简称。

写作格式实例

●文献综述●

Fas/FasL 在急性胰腺炎肝损伤中的作用

张晓华, 袁柏思, 朱人敏

张晓华, 袁柏思, 朱人敏, 中国人民解放军南京军区总医院消化内科 江苏省南京市 210002

作者贡献分布：本文综述由张晓华和袁柏思完成；朱人敏审校

通讯作者：朱人敏, 教授, 主任医师, 210002, 江苏省南京市, 中国人民解放军南京军区总医院消化内科。
jszhxh@sina.com

收稿日期:

修回日期:

接受日期:

在线出版日期:

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

Xiao-Hua Zhang, Bo-Si Yuan, Ren-Min Zhu

Xiao-Hua Zhang, Bo-Si Yuan, Ren-Min Zhu, Department of Gastroenterology, General Hospital of Chinese PLA, Nanjing Command, Nanjing 210002, Jiangsu Province, China

Correspondence to: Professor Xiao-Hua Zhang, Department of Gastroenterology, General Hospital of Chinese PLA, Nanjing Command, Nanjing 210002, Jiangsu Province, China. jszhxh@sina.com

Received:

Revised:

Accepted:

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

Zhang XH, Yuan BS, Zhu RM. Role of Fas/FasL in acute pancreatitis-associated liver injury. Shijie Huaren Xiaohua Zazhi 2008

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

张晓华, 袁柏思, 朱人敏. Fas/FasL 在急性胰腺炎肝损伤中的作用. 世界华人消化杂志 2008

0 引言

Fas, 即 Apo-1/CD95, 属于肿瘤坏死因子受体(tumour 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 等^[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 相对分子质量约为 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 抗原具有 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 单克隆抗体作用域, 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^[18].

FasL 是 Fas 在体内的天然配体, 相对分子质量 31 kDa, 糖基化后相对分子质量 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、细胞凋亡与急性胰腺炎肝损伤

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, 经外界刺激应激而激活, 故又称为 MAPK 应激信号通路, 其在全身炎症反应、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 介导急性胰腺炎肝损伤

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 (APACHE II) 系统的独立指标^[35-39], 对预测 AP 临床预后尤为重要. Gallagher 等^[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, 提示雨蛙素诱导 AP 激活肝脏内凋亡前通路, 促进肝细胞损伤和死亡. 用枯否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, 枯否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, 复合物的胞内结构域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(APP), 其产物是淀粉样 β

肽(A β), A β 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 A β 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 等^[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.

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.

4 参考文献

- 1 Whiteside TL. The role of death receptor ligands in shaping tumor microenvironment. *Immunol Invest* 2007; 36:25-46 [PMID: 17190648] doi:10.1080/08820130600991893
- 2 Wesche-Soldato DE, Swan RZ, Chung CS, Ayala A. The apoptotic pathway as a therapeutic target in sepsis. *Curr Drug Targets* 2007; 8:493-500 [PMID: 17430119] doi:10.2174/138945007780362764
- 3 Massari LP, Kastelan M, Gruber F. Epidermal malignant tumors: pathogenesis, influence of UV light and apoptosis. *Coll Antropol* 2007; 31 Suppl 1: 83-85 [PMID: 17469758]
- 4 Harada T, Taniguchi F, Izawa M, Ohama Y, Takenaka Y, Tagashira Y, Ikeda A, Watanabe A, Iwabe T, Terakawa N. Apoptosis and endometriosis. *Front Biosci* 2007; 12: 3140-3151 [PMID: 17485289] doi:10.2741/2302
- 5 Suda T, Takahashi T, Golstein P, Nagata S. Molecular cloning and expression of the Fas ligand, a novel member of the tumor necrosis factor family. *Cell* 1993; 75: 1169-1178 [PMID: 7505205] doi:10.1016/0092-8674(93)90326-L
- 6 Hirsch CS, Johnson JL, Okwera A, Kanost RA, Wu M, Peters P, Muhumuza M, Mayanja Kizza H, Mugerwa RD, Mugenyi P, Ellner JJ, Toossi Z. Mechanisms of apoptosis of T cells in human tuberculosis. *J Clin Immunol* 2005; 25: 353-364 [PMID: 16133992] doi:10.1007/s10875-005-4841-4
- 7 Keckler MS. Dodging the CTL response: viral evasion of Fas and granzyme induced apoptosis. *Front Biosci* 2007; 12: 725-732 [PMID:17127333] doi:10.2741/2096
- 8 Wesche Soldato DE, Chung CS, Gregory SH, Salazar Mather TP, Ayala CA, Ayala A. CD8+ T cells promote inflammation and apoptosis in the liver after sepsis: role of Fas-FasL. *Am J Pathol* 2007; 171: 87-96 [PMID:17591956] doi:10.2353/ajpath.2007.061099

- 9 Meza Lamas E, Bollain y Goytia JJ, Ramirez Sandoval R, Sanchez Rodriguez SH, Lopez Robles E, Avalos Diaz E, Herrera Esparza R. Camptothecin induces the transit of FasL trimers to the cell surface in apoptotic HEp 2 cells. *Cell Mol Biol Lett* 2006; 11: 299-311 [PMID: 16847561] doi:10.2478/s11658-006-0025-3
- 10 Korkolopoulou P, Saetta AA, Levidou G, Gigelou F, Lazaris A, Thymara I, Scliri M, Bousboukea K, Michalopoulos NV, Apostolikas N, Konstantinidou A, Tzivras M, Patsouris E. c FLIP expression in colorectal carcinomas: association with Fas/FasL expression and prognostic implications. *Histopathology* 2007; 51: 150-156 [PMID: 17559541] doi:10.1111/j.1365-2559.2007.02723.x
- 11 Boselli D, Losana G, Bernabei P, Bosisio D, Drysdale P, Kiessling R, Gaston JS, Lammas D, Casanova JL, Kumararatne DS, Novelli F. IFN gamma regulates Fas ligand expression in human CD4+ T lymphocytes and controls their anti mycobacterial cytotoxic functions. *Eur J Immunol* 2007; 37: 2196-2204 [PMID: 17595676] doi:10.1002/eji.200636541
- 12 Zhang LJ, Zheng WD, Shi MN, Wang XZ. Effects of interleukin-10 on activation and apoptosis of hepatic stellate cells in fibrotic rat liver. *World J Gastroenterol* 2006; 12: 1918-1923 [PMID: 16609999]
- 13 Mysliwiec J, Okota M, Nikolajuk A, Gorska M. Soluble Fas, Fas ligand and Bcl-2 in autoimmune thyroid diseases: relation to humoral immune response markers. *Adv Med Sci* 2006; 51: 119-122 [PMID: 17357290]
- 14 Elsing C, Harenberg S, Stremmel W, Herrmann T. Serum levels of soluble Fas, nitric oxide and cytokines in acute decompensated cirrhotic patients. *World J Gastroenterol* 2007; 13: 421-425 [PMID: 17230612]
- 15 Yang B, Harris KP, Jain S, Nicholson ML. Caspase-7, Fas and FasL in long-term renal ischaemia/reperfusion and immunosuppressive injuries in rats. *Am J Nephrol* 2007; 27: 397-408 [PMID: 17596683] doi:10.1159/000104741
- 16 Itoh N, Yonehara S, Ishii A, Yonehara M, Mizushima S, Sameshima M, Hase A, Seto Y, Nagata S. The polypeptide encoded by the cDNA for human cell surface antigen Fas can mediate apoptosis. *Cell* 1991; 66: 233-243 [PMID: 1713127] doi:10.1016/0092-8674(91)90614-5
- 17 Contassot E, Gaide O, French LE. Death receptors and apoptosis. *Dermatol Clin* 2007; 25: 487-501 [PMID: 17903608] doi:10.1016/j.det.2007.06.010
- 18 Timmer T, de-Vries EG, de-Jong S. Fas receptor-mediated apoptosis: a clinical application? *J Pathol* 2002; 196: 125-134 [PMID: 11793363] doi:10.1002/path.1028
- 19 Mao H, Liu Q, Zhang J, Gu H, Wang L, Zhou X, Yin H, Zhang L, Xie F, Jiang G. Effects of specific antisense oligonucleotide inhibition of Fas expression on T cell apoptosis induced by Fas ligand. *Int Immunopharmacol* 2007; 7: 1714-1722 [PMID: 17996681] doi:10.1016/j.intimp.2007.09.010
- 20 Chang HW, Jeng CR, Lin CM, Liu JJ, Chang CC, Tsai YC, Chia MY, Pang VF. The involvement of Fas/FasL interaction in porcine circovirus type 2 and porcine reproductive and respiratory syndrome virus co-inoculation-associated lymphocyte apoptosis in vitro. *Vet Microbiol* 2007; 122: 72-82 [PMID: 17321702] doi:10.1016/j.vetmic.2007.01.013
- 21 Folch-Puy E. Importance of the liver in systemic complications associated with acute pancreatitis: the role of Kupffer cells. *J Pathol* 2007; 211: 383-388 [PMID: 17212343] doi:10.1002/path.2123
- 22 Wang X, Zhao X, Shi C, Börjesson A, Chen Z, Axelsson J, Zhao H, Andersson R. Potential mechanisms and significance of acute pancreatitis-associated liver injury. *Scand J Gastroenterol* 2006; 41: 604-613 [PMID: 16638705] doi:10.1080/00365520500347105
- 23 Liu HB, Cui NQ, Li DH, Chen C. Role of Kupffer cells in acute hemorrhagic necrotizing pancreatitis-associated lung injury of rats. *World J Gastroenterol* 2006; 12: 403-407 [PMID: 16489639]

- 24 Cuenda A, Rousseau S. p38 MAP-kinases pathway regulation, function and role in human diseases. *Biochim Biophys Acta* 2007; 1773: 1358-1375 [PMID: 17481747]
- 25 Su Q, Chen J, Fang Q. Modulation of the p38MAPK pathway in failing human myocardium secondary to rheumatic heart disease. *J Heart Valve Dis* 2007; 16: 683-689 [PMID: 18095520]
- 26 Nold MF, Nold-Petry CA, Fischer D, Richter B, Blaheta R, Pfeilschifter J, Muhl H, Schranz D, Veldman A. Activated protein C downregulates p38 mitogen-activated protein kinase and improves clinical parameters in an in-vivo model of septic shock. *Thromb Haemost* 2007; 98: 1118-1126 [PMID: 18000619]
- 27 Gahring LC, Osborne-Hereford AV, Vasquez-Opazo GA, Rogers SW. Tumor necrosis factor alpha enhances nicotinic receptor up-regulation via a p38MAPK-dependent pathway. *J Biol Chem* 2008; 283: 693-699 [PMID: 17977823] doi:10.1074/jbc.M707330200
- 28 Hirai H, Shibata T, Aoyama T, Yoshiyama M, Omura T, Suehiro S. Activation of mitogen activated protein kinases, activator protein 1, and nuclear factor kappaB during acute rejection after heterotopic heart transplantation in rats. *Osaka City Med J* 2006; 52: 9-19 [PMID: 16986359]
- 29 Guilloton F, Jean C, de Thonel A, Laurent G, Quillet-Mary A. Granzyme B induction signalling pathway in acute myeloid leukemia cell lines stimulated by tumor necrosis factor alpha and Fas ligand. *Cell Signal* 2007; 19: 1132-1140 [PMID: 17258890] doi:10.1016/j.cellsig.2006.12.005
- 30 Guilloton F, Jean C, de Thonel A, Laurent G, Quillet Mary A. Granzyme B induction signalling pathway in acute myeloid leukemia cell lines stimulated by tumor necrosis factor alpha and Fas ligand. *Cell Signal* 2007; 19: 1132-1140 [PMID: 17258890] doi:10.1016/j.cellsig.2006.12.005
- 31 Ubol S, Kasisith J, Pitidhamabhorn D, Tepsumethanol V. Screening of pro-apoptotic genes upregulated in an experimental street rabies virus-infected neonatal mouse brain. *Microbiol Immunol* 2005; 49: 423-431 [PMID: 15905604]
- 32 Tanaka N, Kamanaka M, Enslen H, Dong C, Wysk M, Davis RJ, Flavell RA. Differential involvement of p38 mitogen-activated protein kinase kinases MKK3 and MKK6 in T-cell apoptosis. *EMBO Rep* 2002; 3: 785-791 [PMID: 12151339] doi:10.1093/embo-reports/kvf153
- 33 Bai YP, Liu YH, Chen J, Song T, You Y, Tang ZY, Li YJ, Zhang GG. Rosiglitazone attenuates NF kappaB dependent ICAM 1 and TNF alpha production caused by homocysteine via inhibiting ERK1/2/p38MAPK activation. *Biochem Biophys Res Commun* 2007; 360: 20-26 [PMID: 17583675] doi:10.1016/j.bbrc.2007.05.222
- 34 Ma X, Jia YT, Qiu DK. Inhibition of p38 mitogen-activated protein kinase attenuates experimental autoimmune hepatitis: involvement of nuclear factor kappa B. *World J Gastroenterol* 2007; 13: 4249-4254 [PMID: 17696256]

- 35 Murr MM, Yang J, Fier A, Gallagher SF, Carter G, Gower WR Jr, Norman JG. Regulation of Kupffer cell TNF gene expression during experimental acute pancreatitis: the role of p38-MAPK, ERK1/2, SAPK/JNK, and NF-kappaB. *J Gastrointest Surg* 2003; 7: 20-25 [PMID: 12559181] doi:10.1016/S1091-255X(02)00053-7
- 36 Kaya E, Dervisoglu A, Polat C. Evaluation of diagnostic findings and scoring systems in outcome prediction in acute pancreatitis. *World J Gastroenterol.* 2007;13: 3090-3094 [PMID: 17589925]
- 37 Göçmen E, Klc YA, Yoldaş O, Ertan T, Karaköse N, Koç M, Tez M. Comparison and validation of scoring systems in a cohort of patients treated for biliary acute pancreatitis. *Pancreas* 2007; 34: 66-69 [PMID: 17198185] doi:10.1097/01.mpa.0000246667.53622.e3
- 38 Yeung YP, Lam BY, Yip AW. APACHE system is better than Ranson system in the prediction of severity of acute pancreatitis. *Hepatobiliary Pancreat Dis Int* 2006; 5: 294-299 [PMID: 16698595]
- 39 Taylor SL, Morgan DL, Denson KD, Lane MM, Pennington LR. A comparison of the Ranson, Glasgow, and APACHE II scoring systems to a multiple organ system score in predicting patient outcome in pancreatitis. *Am J Surg.* 2005; 189: 219-222 [PMID: 15720995] doi:10.1016/j.amjsurg.2004.11.010
- 40 Khan AA, Parekh D, Cho Y, Ruiz R, Selby RR, Jabbour N, Genyk YS, Mateo R. Improved prediction of outcome in patients with severe acute pancreatitis by the APACHE II score at 48 hours after hospital admission compared with the APACHE II score at admission. *Acute Physiology and Chronic Health Evaluation. Arch Surg* 2002; 137: 1136-1140 [PMID: 12361419] doi:10.1001/archsurg.137.10.1136
- 41 Gallagher SF, Yang J, Baksh K, Haines K, Carpenter H, Epling-Burnette PK, Peng Y, Norman J, Murr MM. Acute pancreatitis induces FasL gene expression and apoptosis in the liver. *J Surg Res* 2004; 122: 201-209 [PMID: 15555619] doi:10.1016/j.jss.2004.05.019
- 42 Yang J, Gallagher SF, Haines K, Epling-Burnette PK, Bai F, Gower WR Jr; Mastorides S, Norman JG, Murr MM. Kupffer cell-derived Fas ligand plays a role in liver injury and hepatocyte death. *J Gastrointest Surg* 2004; 8: 166-174 [PMID: 15036192] doi:10.1016/j.gassur.2003.10.016
- 43 Gallagher SF, Peng Y, Haines K, Baksh K, Epling-Burnette PK, Yang J, Murr MM. Fas/FasL play a central role in pancreatitis-induced hepatocyte apoptosis. *J Gastrointest Surg* 2005; 9: 467-474 [PMID: 15797225] doi:10.1016/j.gassur.2004.12.008
- 44 Peng Y, Gallagher SF, Landmann R, Haines K, Murr MM. The role of p65 NF-kappaB/RelA in pancreatitis-induced Kupffer cell apoptosis. *J Gastrointest Surg* 2006; 10: 837-847.[PMID: 16769540]
- 45 Denault JB, Salvesen GS. Apoptotic caspase activation and activity. *Methods Mol Biol.* 2008; 414: 191-220 [PMID: 18175821]
- 46 Hatano E Tumor necrosis factor signaling in hepatocyte apoptosis. *J Gastroenterol Hepatol.* 2007; 22 Suppl 1: S43-44 [PMID: 17567463] doi:10.1111/j.1440-1746.2006.04645.x
- 47 Yin XM, Ding WX. Death receptor activation-induced hepatocyte apoptosis and liver injury. *Curr Mol Med* 2003; 3: 491-508 [PMID: 14527081] doi:10.2174/1566524033479555
- 48 Estève MA, Carré M, Braguer D. Microtubules in apoptosis induction: are they necessary? *Curr Cancer Drug Targets* 2007; 7: 713-729 [PMID: 18220532] doi:10.2174/156800907783220480
- 49 Orrenius S. Reactive oxygen species in mitochondria-mediated cell death. *Drug Metab Rev* 2007; 39: 443-455 [PMID: 17786631] doi:10.1080/03602530701468516
- 50 Wesche-Soldato DE, Swan RZ, Chung CS, Ayala A. The apoptotic pathway as a therapeutic target in sepsis. *Curr Drug Targets* 2007; 8: 493-500 [PMID: 17430119] doi:10.2174/138945007780362764

- 51 Majors BS, Betenbaugh MJ, Chiang GG. Links between metabolism and apoptosis in mammalian cells: applications for anti-apoptosis engineering. *Metab Eng* 2007; 9: 317-326 [PMID: 17611135]
doi:10.1016/j.ymben.2007.05.003
- 52 Bodmer JL, Holler N, Reynard S, Vinciguerra P, Schneider P, Juo P, Blenis J, Tschopp J. TRAIL receptor-2 signals apoptosis through FADD and caspase-8. *Nat Cell Biol* 2000; 2: 241-243 [PMID: 10783243]
doi:10.1038/35008667
- 53 Sprick MR, Weigand MA, Rieser E, Rauch CT, Juo P, Blenis J, Krammer PH, Walczak H. FADD/MORT1 and caspase-8 are recruited to TRAIL receptors 1 and 2 and are essential for apoptosis mediated by TRAIL receptor 2. *Immunity* 2000; 12: 599-609 [PMID: 10894160] doi:10.1016/S1074-7613(00)80211-3
- 54 Kischkel FC, Lawrence DA, Chuntharapai A, Schow P, Kim KJ, Ashkenazi A. Apo2L/TRAIL-dependent recruitment of endogenous FADD and caspase-8 to death receptors 4 and 5. *Immunity* 2000; 12: 611-620 [PMID: 10894161] doi:10.1016/S1074-7613(00)80212-5
- 55 Garrido C, Galluzzi L, Brunet M, Puig PE, Didelot C, Kroemer G. Mechanisms of cytochrome c release from mitochondria. *Cell Death Differ* 2006; 13: 1423-1433 [PMID: 16676004] doi:10.1038/sj.cdd.4401950
- 56 Cain K. Chemical-induced apoptosis: formation of the Apaf-1 apoptosome. *Drug Metab Rev* 2003; 35: 337-363 [PMID: 14705865] doi:10.1081/DMR-120026497
- 57 Ferrer I, Planas AM. Signaling of cell death and cell survival following focal cerebral ischemia: life and death struggle in the penumbra. *J Neuropathol Exp Neurol* 2003 ; 62: 329-339 [PMID: 12722825]
- 58 Mazumder S, Plesca D, Almasan A. Caspase-3 activation is a critical determinant of genotoxic stress-induced apoptosis. *Methods Mol Biol* 2008; 414: 13-21 [PMID: 18175808]
- 59 Mehmet H. Caspases find a new place to hide. *Nature* 2000; 403: 29-30 [PMID: 10638735]
- Nakagawa T, Zhu H, Morishima N, Li E, Xu J, Yankner BA, Yuan J. Caspase-12 mediates endoplasmic-reticulum-specific apoptosis and cytotoxicity by amyloid-beta. *Nature* 2000; 403: 98-103 [PMID: 10638761]
- 60 Fischer R, Baumert T, Blum HE. Hepatitis C virus infection and apoptosis. *World J Gastroenterol.* 2007; 13: 4865-4872 [PMID: 17828818]
- 61 Lapierre P, Béland K, Alvarez F. Pathogenesis of autoimmune hepatitis: from break of tolerance to immune-mediated hepatocyte apoptosis. *Transl Res* 2007; 149: 107-113 [PMID: 17320796]
doi:10.1016/j.trsl.2006.11.010
- 62 Reinehr R, Häussinger D. CD95 activation in the liver: ion fluxes and oxidative signaling. *Arch Biochem Biophys* 2007; 462: 124-131 [PMID: 17258167] doi:10.1016/j.abb.2006.12.019
- 63 Sastre J, Serviddio G, Pereda J, Minana JB, Arduini A, Vendemiale G, Poli G, Pallardo FV, Vina J. Mitochondrial function in liver disease. *Front Biosci* 2007; 12: 1200-1209 [PMID: 17127373]
doi:10.2741/2138
- 64 Chen J, Delannoy M, Odwin S, He P, Trush MA, Yager JD. Enhanced mitochondrial gene transcript, ATP, bcl-2 protein levels, and altered glutathione distribution in ethinyl estradiol-treated cultured female rat hepatocytes. *Toxicol Sci* 2003; 75: 271-278 [PMID: 12857939] doi:10.1093/toxsci/kfg183
- 65 Guha M, Kumar S, Choubey V, Maity P, Bandyopadhyay U. Apoptosis in liver during malaria: role of oxidative stress and implication of mitochondrial pathway. *FASEB J* 2006; 20: 1224-1226 [PMID: 16603602]
doi:10.1096/fj.05-5338fje

- 66 Huang DC, Hahne M, Schroeter M, Frei K, Fontana A, Villunger A, Newton K, Tschopp J, Strasser A. Activation of Fas by FasL induces apoptosis by a mechanism that cannot be blocked by Bcl-2 or cl-x(L). *Proc Natl Acad Sci USA* 1999; 96: 14871-14876 [PMID: 10611305] doi:10.1073/pnas.96.26.14871
- 67 Imao M, Nagaki M, Imose M, Moriwaki H. Differential caspase-9-dependent signaling pathway between tumor necrosis factor receptor- and Fas-mediated hepatocyte apoptosis in mice. *Liver Int* 2006; 26: 137-146 [PMID: 16420519] doi:10.1111/j.1478-3231.2005.01195.x