

# 高迁移率族蛋白B1在重症急性胰腺炎肠屏障损害中的作用

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## Role of high mobility group box-1 protein in gut mucosal barrier dysfunction during severe acute pancreatitis in rats

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## Abstract

**AIM:** To investigate the role of high mobility group box-1 protein (HMGB1) in gut mucosal barrier dysfunction during severe acute pancreatitis (SAP) in mice, and the mechanisms involved.

**METHODS:** A rat model of SAP was established by retrograde injection of 50 g/L sodium taurocholate into the choledochopancreatic duct. Fifty-six healthy male Wistar rats were divided randomly into three groups: control, SAP (3, 6, 12, 24 and 48 hours subgroups), and pyrrolidine dithiocarbamate (PDTC). Plasma lipopolysaccharide (LPS) and blood diamine oxidase (DAO) levels were determined. The expression of HMGB1 mRNA in the intestinal mucosa was de-

tected by reverse-transcription polymerase chain reaction (RT-PCR), and the activity of HMGB1 was determined by Western blotting.

**RESULTS:** Compared with the normal control group, HMGB1 mRNA level markedly increased in intestinal mucosa 6 hours after SAP ( $0.41 \pm 0.06$  vs  $0.26 \pm 0.03$ ,  $P < 0.01$ ), peaked at 24 hours ( $0.62 \pm 0.06$ ), and remained relatively high up to 48 hours. Meanwhile, HMGB1 mRNA expression was significantly inhibited by PDTC in the intestine 24 hours after SAP ( $0.35 \pm 0.06$  vs  $0.62 \pm 0.06$ ,  $P < 0.01$ ). PDTC alleviated the blood level of endotoxin and DAO 24 hours after SAP (LPS,  $0.433 \pm 0.120$  KEU/L vs  $0.852 \pm 0.232$  KEU/L,  $P < 0.01$ ; DAO,  $0.65 \pm 0.12$  kU/L vs  $1.36 \pm 0.22$  kU/L,  $P < 0.01$ ).

**CONCLUSION:** The expression of HMGB1 mRNA increases in the intestine during SAP. PDTC markedly inhibits HMGB1 mRNA gene expression.

**Key Words:** Severe acute pancreatitis; Intestinal mucosal barrier function; Pyrrolidine dithiocarbamate; High mobility group box-1 protein; Reverse-transcription polymerase chain reaction; Western blotting

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## 摘要

**目的:** 探讨高迁移率族蛋白B1在重症急性胰腺炎(SAP)肠屏障损害中的作用及其机制.

**方法:** 采用逆行胆胰管注射50 g/L牛磺胆酸钠制备SAP大鼠模型. 将56只Wistar大鼠随机分为正常对照组(Control组), SAP 3 h, 6 h, 12 h, 24 h, 48 h 5个亚组, 二巯代氨基甲酸吡咯烷处理组(PDTC组), 每组8只. PDTC组于建模后24 h取材. 测定血浆内毒素(LPS)、二胺氧化酶(DAO)水平, 用逆转录-聚合酶链反应(RT-PCR)方法检测肠组织高迁移率族蛋白B1(HMGB1) mRNA表达, 用Western blot法检

## 背景资料

SAP时肠黏膜屏障功能受到损害, 导致细菌和内毒素的移位, 从而引发肠源性感染和内毒素血症, 严重时可促使多器官功能衰竭发生. 最近研究表明, 高迁移率族蛋白B1相对于TNF- $\alpha$ 、IL-1 $\beta$ 等早期炎症介质分泌延迟且持续时间较长, 是一种新的“晚期”炎症介质, 能给脓毒症带来更广的“治疗窗”.

**研发前沿**  
HMGB1作为晚期炎症介质在SAP肠黏膜屏障功能损害中起重要作用,通过抑制HMGB1的表达可减轻组织的炎症反应,能有效维护肠黏膜屏障功能,为预防和治疗SAP继发肠黏膜屏障损害切实可行的干预目标。

## 测肠组织HMGB1水平.

**结果:**与对照组比较, SAP 6 h组大鼠肠组织HMGB1 mRNA表达显著增高( $0.41 \pm 0.06$  vs  $0.26 \pm 0.03$ ,  $P < 0.01$ ), 12 h呈现进一步升高趋势, 24 h达峰值( $0.62 \pm 0.06$ ), 并持续至48 h. PDTC干预可显著降低肠组织HMGB1 mRNA表达( $0.35 \pm 0.06$  vs  $0.62 \pm 0.06$ ,  $P < 0.01$ ). PDTC组较SAP 24 h组肠组织HMGB1 mRNA表达, 血浆LPS和DAO显著下降(HMGB1 mRNA表达:  $0.35 \pm 0.06$  vs  $0.62 \pm 0.06$ ,  $P < 0.01$ ; LPS:  $0.433 \pm 0.120$  KEU/L vs  $0.852 \pm 0.232$  KEU/L,  $P < 0.01$ ; DAO:  $0.65 \pm 0.12$  kU/L vs  $1.36 \pm 0.22$  kU/L,  $P < 0.01$ ).

**结论:**SAP时, 肠组织内HMGB1表达上调; PDTC可以明显抑制SAP时肠组织内HMGB1表达.

**关键词:**重症急性胰腺炎; 肠黏膜屏障; 二硫代氨基甲酸吡咯烷; 高迁移率族蛋白B1; 逆转录-聚合酶链式反应; 免疫印迹

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<http://www.wjgnet.com/1009-3079/15/3173.asp>

## 0 引言

重症急性胰腺炎(severe acute pancreatitis, SAP)时肠黏膜受损伴发肠道细菌和内毒素移位是胰腺炎继发感染的根源, 严重时可导致多器官功能障碍<sup>[1-4]</sup>. 近年研究发现, 高迁移率族蛋白B1(high mobility group box-1 protein, HMGB1)作为晚期炎症介质参与疾病的病理生理过程, 其表达增加与脏器功能损害密切相关<sup>[5-9]</sup>. 我们观察SAP时肠黏膜内HMGB-1的动态变化, 探讨HMGB-1在SAP肠黏膜屏障损害中的作用.

## 1 材料和方法

**1.1 材料** 牛磺胆酸钠、二硫代氨基甲酸吡咯烷(PDTC)、DAO标准品由Sigma公司提供, 内毒素检测试剂盒购自湛江安度斯生物有限公司, RNA提取及PCR扩增试剂盒购自TaKaRa公司, PCR仪及电泳仪和凝胶扫描分析系统购自美国Kodak. 大鼠HMGB1序列(扩增片段为680 bp): 上游5'-ATGGGCAAAGGAGATCCTA-3', 下游5'-ATTTCATCATCATCTTCT-3'<sup>[10]</sup>; 大鼠GAPDH序列(扩增片段为309 bp): 上游5'-TCCCTCAAGAT

TGTCAGCAA-3', 下游5'-AGATCCACAACGGA TACATT-3'<sup>[10]</sup>. 羊抗HMGB1 mAb购自Santa Cruz公司, 辣根过氧化物酶标记的兔抗羊IgG购自深圳晶美公司, 健康成年♂ Wistar大鼠56只(体质量270-330 g), 购自中国医科大学实验动物学部.

**1.2 方法** 大鼠随机分为正常对照组(Control组,  $n = 8$ ), SAP组( $n = 40$ ), PDTC组( $n = 8$ ), SAP组分为建模后3, 6, 12, 24, 48 h共5个亚组(每亚组8只). 大鼠术前12 h禁食, 不禁饮. 20 g/L戊巴比妥钠ip麻醉(1 mL/kg), 常规消毒后, 腹部正中切口入腹腔, 找到胆胰管, 于其出肝门端以动脉夹暂时阻断胆管, 从乳头处的十二指肠壁进针, 逆行刺入胆胰管内并固定, 于胆胰管入十二指肠端用小动脉夹暂时阻断胆胰管, 以0.1 mL/min速度匀速注入50 g/L牛磺胆酸钠(1.5 mL/kg), 注射完毕后10 min去除动脉夹, 逐层关腹. PDTC组于成模后即刻ip PDTC(100 mg/kg). 术后禁食, 自由饮水, sc生理盐水40 mL/(kg·6 h)行液体复苏. 正常对照组常规麻醉后取材, SAP组分别于模型成功后3, 6, 12, 24, 48 h取材, PDTC组于模型成功后24 h取材. 于上述时间点麻醉动物, 腹主动脉采血, 离心(3000 r/min, 15 min)分离血浆, 分装冻存于-80℃待测. 组织标本严格无菌采取, 组织置于经消毒的管, 液氮速冻, -70℃贮存备用. 血浆LPS水平测定采用动态浊度法鲎试剂检测LPS水平. 所用器具经灭菌、去热源处理. 血浆二胺氧化酶(DAO)水平测定<sup>[11-12]</sup>按改良分光光度法测定.

**1.2.1 RT-PCR方法检测肠组织HMGB1 mRNA表达** 取小肠组织80 mg, 采用TaKaRa公司RNA提取试剂盒提取总RNA, 用紫外分光光度计测定 $A_{260} : A_{280}$ 比值, 该值稳定于1.8-2.0. 按试剂盒说明合成cDNA后取反转录产物, 加入PCR反应体系, 扩增目的基因. 以三磷酸甘油醛脱氢酶(GAPDH)作为内参对照, 扩增产物经15 g/L琼脂糖凝胶电泳检测, 凝胶用美国Kodak凝胶扫描分析系统测定积分光密度值, 通过目的基因与内参对照的积分光密度比值表示mRNA表达的相对含量.

**1.2.2 Western blot法检测肠组织HMGB1水平** 取肠组织约0.2 g, 4℃匀浆, 加入蛋白提取液, 12 000 r/min离心20 min, 取上清液, 以考马斯亮蓝法进行蛋白定量. 再将提取的蛋白等量加样, 经SDS-PAGE电泳分离样品(40 μg)后电转移至硝酸纤维膜上. 转膜后的硝酸纤维膜经漂

表 1 SAP大鼠LPS, DAO及HMGB1 mRNA、HMGB1的变化(mean  $\pm$  SD)

分组	h	血浆		肠组织	
		LPS( kEU/L)	DAO( kU/L)	HMGB1 mRNA	HMGB1
Control	-	0.106 $\pm$ 0.008	0.32 $\pm$ 0.02	0.26 $\pm$ 0.03	26.3 $\pm$ 4.3
SAP	3	0.121 $\pm$ 0.103	0.35 $\pm$ 0.03	0.32 $\pm$ 0.05	30.5 $\pm$ 5.2
	6 <sup>b</sup>	0.447 $\pm$ 0.153	0.68 $\pm$ 0.14	0.41 $\pm$ 0.06	68.4 $\pm$ 7.4
	12 <sup>b</sup>	0.614 $\pm$ 0.204	0.94 $\pm$ 0.17	0.56 $\pm$ 0.12	84.1 $\pm$ 12.6
	24 <sup>b</sup>	0.852 $\pm$ 0.232	1.36 $\pm$ 0.22	0.62 $\pm$ 0.06	132.6 $\pm$ 32.5
	48 <sup>b</sup>	0.627 $\pm$ 0.145	0.88 $\pm$ 0.16	0.54 $\pm$ 0.05	107.6 $\pm$ 26.4
PDTC	24 <sup>bd</sup>	0.433 $\pm$ 0.120	0.65 $\pm$ 0.12	0.35 $\pm$ 0.06	70.2 $\pm$ 9.3

<sup>b</sup> $P < 0.01$  vs Control; <sup>d</sup> $P < 0.01$  vs SAP 24h.

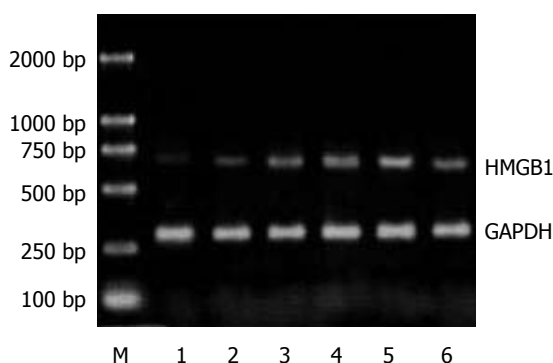


图 1 SAP大鼠肠组织HMGB1 mRNA的表达. M: Marker; 1: 对照组; 2-6: SAP 3, 6, 12, 24, 48 h组.

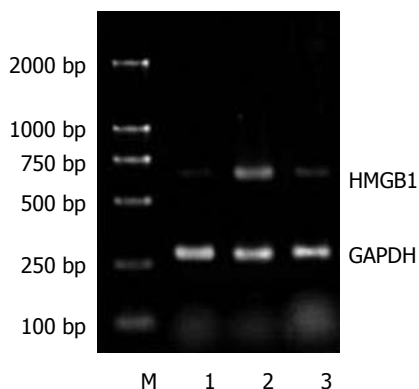


图 2 SAP大鼠肠组织HMGB1 mRNA的表达. M: Marker; 1: 对照组; 2: SAP 24 h组; 3: PDTC.

洗后用50 g/L脱脂奶粉阻断非特异性结合, 然后加入一抗(羊抗HMGB1mAb, Santa Cruz, 浓度1:400)4℃孵育过夜, 加入标记二抗(辣根过氧化物酶标记的兔抗羊IgG, 深圳晶美, 浓度1:1000)37℃孵育1 h, ECL浸膜显色. 在图像分析仪上对胶片进行扫描, 测定各条带的吸光度值.

**统计学处理** 所有数据均以mean  $\pm$  SD表示, 采用单因素方差分析, 经SPSS11.0统计分析软件对数据进行处理.

## 应用要点

本文研究结果表明, HMGB1在SAP肠组织中表达较晚, 持续时间较长, 说明HMGB1在SAP肠黏膜损害中起重要作用. 应用PDTC可下调HMGB1表达水平, 能够减轻肠黏膜屏障损害, 为SAP肠黏膜屏障损害的防治提供新的思路.

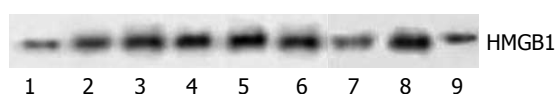


图 3 SAP大鼠肠组织HMGB1的表达. 1: 对照组; 2-6: SAP 3, 6, 12, 24, 48 h组; 7: 对照组; 8: SAP 24 h组; 9: PDTC组.

## 2 结果

**2.1 血浆LPS含量和DAO水平变化** 与正常对照组相比, SAP组发病后6 h, 大鼠血浆中LPS含量上升, 24 h达峰值, 48 h仍显著高于正常对照组( $P < 0.01$ ). PDTC干预后, 大鼠血浆LPS含量显著降低( $P < 0.01$ , 表1). 在SAP组3 h时血浆DAO水平较正常对照组无明显变化, 在SAP建模后6 h时血浆DAO水平明显上升, 24 h达峰, 48 h仍显著高于对照组( $P < 0.01$ ). PDTC组较SAP 24 h组血浆DAO水平明显下降( $P < 0.01$ , 表1).

**2.2 肠组织HMGB1 mRNA和HMGB1的变化** 正常对照组大鼠肠组织中HMGB1 mRNA表达微弱. SAP建模后6 h, 大鼠肠组织中HMGB1 mRNA转录水平较正常对照组增高, 12 h显著升高, 24 h达峰值并持续至48 h( $P < 0.01$ , 表1, 图1). 应用PDTC干预后, PDTC组大鼠肠组织中HMGB1 mRNA转录水平显著低于SAP 24 h组( $P < 0.01$ , 表1, 图2). 正常情况下大鼠肠组织中有少量的HMGB1表达. SAP模型制成6 h后, 大鼠肠组织中HMGB1表达开始增高, 较对照组差异显著( $P < 0.01$ ); 12 h呈现进一步升高趋势, 24 h达峰值, 至48 h仍维持在较高水平( $P < 0.01$ ). 给予PDTC处理后, 与SAP 24 h组相比, PDTC组大鼠肠组织中HMGB1表达明显下降( $P < 0.01$ , 表1, 图3).

## 3 讨论

重症急性胰腺炎(severe acute pancreatitis, SAP)发病凶险, 并发症多, 可在短时间内损伤多个脏

### 名词解释

HMGB1: 是一大类高度保守的蛋白质, 是细胞核内含量丰富的非组蛋白染色质蛋白, 分子量较低(30 kDa), 因其在聚丙烯酰胺凝胶电泳中迁移迅速而得名, 可参与DNA复制、细胞分化及基因表达等多种细胞生命活动。与TNF- $\alpha$ 和IL-1 $\beta$ 等早期细胞因子相比, HMGB1出现较晚且持续时间更长, 可能成为脓毒症防治切实可行的干预目标。

器。近年来其救治成功率有所提高, 但病死率仍为12%-15%。有并发症者可高达50%, 而其中80%的死亡原因与SAP患者肠道屏障功能受继发感染有关<sup>[13-15]</sup>。SAP时肠黏膜遭到破坏, 肠绒毛萎缩, 尖端坏死, 微绒毛脱落, 肠道屏障作用的削弱使肠道内细菌及其毒素易于穿透受损的黏膜上皮向肠外移位, 成为继发性感染的根源<sup>[16-20]</sup>。HMGB1是细胞核内一种含量丰富的非组蛋白, 广泛地存在于真核细胞核中, 因在电泳时快速迁移而得名, 他与DNA复制、细胞增殖分化及基因转录等多种生命活动有关。研究发现, HMGB1可分泌到细胞外发挥致炎效应, 其产生明显晚于TNF- $\alpha$ , IL-1等早期炎性介质, 且持续时间较长, 与严重全身炎症反应综合征及多器官功能障碍等病理过程密切相关<sup>[21-24]</sup>。阻断HMGB1的表达或抑制HMGB1的活性可明显减轻炎症反应和组织损伤<sup>[25]</sup>。新近研究表明, 严重创伤或感染时, 组织HMGB1基因表达上调, HMGB1可介导肠屏障功能不全<sup>[21,26-28]</sup>。

本研究结果显示, SAP时大鼠肠组织中HMGB1表达在建模后数小时内无明显变化, 于建模后6 h即上升, 24 h达峰值, 48 h仍高于正常, 提示HMGB1对肠组织有直接损伤作用, HMGB1可能参与SAP肠组织损伤的病理生理过程。PDTC能够选择性地抑制NF- $\kappa$ B的活化<sup>[29]</sup>, 使用PDTC抑制NF- $\kappa$ B通路后, SAP大鼠肠组织中HMGB1表达明显下调, 提示NF- $\kappa$ B可能直接或间接参与HMGB1诱生的细胞信号转导过程<sup>[30-32]</sup>。我们观察到, SAP大鼠肠组织HMGB1表达延迟并持续增高的同时, 血浆LPS、DAO等反映肠黏膜屏障功能的指标也不同程度的升高。SAP建模后6 h, 大鼠血浆中LPS含量与DAO水平明显上升, 24 h达峰值, 48 h仍显著高于正常对照组, 说明HMGB1作为晚期炎症介质可使肠黏膜损伤加重, 肠黏膜通透性持续增加。给予PDTC干预后, HMGB1表达下调, 同时SAP大鼠血浆LPS含量与DAO水平明显下降, 说明肠黏膜屏障功能得到明显改善, 其机制可能为SAP大鼠应用PDTC抑制NF- $\kappa$ B活化后, 肠组织HMGB1表达受到抑制, HMGB1对肠组织的直接损伤作用减轻<sup>[26]</sup>。HMGB1与TNF- $\alpha$ , IL-1等早期炎性介质可相互诱导<sup>[33]</sup>, NF- $\kappa$ B活性受抑后TNF- $\alpha$ , IL-1, iNOS及黏附分子等早期炎性介质表达下调进而阻断HMGB1与早期炎性介质的相互诱导, 从而改善肠黏膜屏障功

能。肠道细菌移位是SAP并发感染的主要原因, HMGB1作为晚期炎症介质在SAP肠黏膜屏障功能损害中起重要作用<sup>[34]</sup>。通过应用PDTC可下调HMGB1水平, 能有效维护肠黏膜屏障功能, 为预防和治疗SAP继发肠黏膜屏障损害提供新途径。

### 4 参考文献

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同行评价  
本文立意较为新颖, 实验目的明确, 紧扣SAP这一研究热点, 实验设计较为严密, 动物模型成熟, 统计方法选择合理, 有一定的可读性。

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