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不同剂量乌司他汀对急性重症胆管炎大鼠肝屏障的保护作用 *

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摘要 目的:探讨不同剂量乌司他汀对急性重症胆管炎(ACST)大鼠肝屏障的保护作用。**方法:**60 只雄性 SD 大鼠通过手术造成胆总管梗阻并注射细菌内毒素造成 ACST 模型,造模 48 h 后处死,随机分成 5 组,每组 12 只,分别进行假手术(SN 组)、ACST 造模手术(ACST 组)、ACST 造模手术 + 乌司他汀治疗,依据乌司他汀浓度分为低(20000 U/kg·d)(ASCT-L 组)、中(40000 U/kg·d)(ASCT-M 组)、高(80000 U/kg·d)(ASCT-H 组)三组,采集血液进行总胆红素(TB)、谷丙转氨酶(ALT)、白细胞介素 -6(IL-6)、白细胞介素 -10(IL-10)和肿瘤坏死因子 -α(TNF-α)的检测,采集部分肝组织进行组织染色,检测肝细胞凋亡率并分析紧密连接蛋白 Occludin 和 ZO-1 基因表达水平。**结果:**与 SN 组比较,造模后各组大鼠 TB 和 ALT 水平均显著升高(均 P<0.05),乌司他汀治疗后各组大鼠 TB 和 ALT 水平随剂量增加而明显降低,各组间差异均有统计学意义(均 P<0.05);造模后大鼠 IL-6、IL-10 和 TNF-α 水平均显著升高,乌司他汀治疗后各组大鼠 IL-6 和 TNF-α 水平随剂量增加而降低,IL-10 水平随剂量增加而升高,不同剂量间差异有统计学意义(均 P<0.05);ACST 组肝细胞凋亡率显著高于 SN 组,Occludin 和 ZO-1 基因表达水平显著降低(P<0.05);乌司他汀治疗后各组大鼠肝细胞凋亡率有不同程度的降低,Occludin 和 ZO-1 基因表达水平有不同程度的升高(P<0.05)。**结论:**乌司他汀治疗 ACST 大鼠疗效显著,对肝屏障功能有良好的保护作用,其治疗效果与剂量呈现明显的相关性,其机制及合适的给药剂量值得进一步研究。

关键词:急性重症胆管炎;大鼠;肝屏障;乌司他汀

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Protective Effects of Different Dosage of Ulinastatin on Hepatic Barrier in Rats with Acute Cholangitis of Severe Type*

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ABSTRACT Objective: To explore the protective effects of different dosage of Ulinastatin on hepatic barrier in rats with acute cholangitis of severe type (ACST). **Methods:** A total of 60 male SD rats were induced by operation to cause the common bile duct obstruction and were injected with endotoxin for the ACST model. All the rats were killed 48 hours after model operation and were randomly divided into five groups with 12 rats in each group, and were treated with sham operation (SN group), ACST model operation (ACST group)and ACST model operation+Ulinastatin respectively. According to the dosage of Ulinastatin, the rats were divided into low solution(20000 U/kg·d)(ASCT-L group), middle solution(40000 U/kg·d)(ASCT-M group) and high solution(80000 U/kg·d) (ASCT-H group) respectively. Blood was collected and the levels of total bilirubin (TB), alanine transaminase (ALT), interleukin-6 (IL-6), interleukin-10 (IL-10) and tumor necrosis factor-α (TNF-α) were detected. Some hepatic tissues were collected for histological staining, the apoptosis rate of hepatocytes was detected and the expression levels of tight junction proteins Occludin and ZO-1 gene were analyzed. **Results:** Compared with SN group, the indexes of TB and ALT in the rats of each group after model operation were significantly increased (P<0.05). After treatment with Ulinastatin, the levels of TB and ALT in the rats of each group were significantly decreased with the increase of dosage, the differences were statistically significant between the groups (all P<0.05). The levels of IL-6, IL-10 and TNF-α were significantly higher in the rats after model operation. After treatment with Ulinastatin, the levels of IL-6 and TNF-α were decreased with the increase of dosage, while the levels of IL-10 were increased with the decrease of dosage, the differences were statistically significant between different dosage (all P<0.05). The apoptosis rate of hepatocytes in ACST group was significantly higher than that in SN group, the gene expression levels of Occludin and ZO-1 were decreased significantly(P<0.05). After treatment, the apoptosis rates of rats

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in each group were decreased in different degrees, the gene expression levels of Occludin and ZO-1 were increased in differ- ent degrees (P<0.05). **Conclusion:** Ulinastatin has significant effect in the treatment of ACST rats, and has good protective effect on hepatic barrier function. The treatment effect and dosage showed obvious correlation. Its mechanism and the appropriate dosage are worthy of further study.

Key words: ACST; Rat; Hepatic barrier; Ulinastatin

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前言

急性重症胆管炎（Acute cholangitis of severe type，ACST）是胆管系统最严重的疾病，是在完全性胆道梗阻的情况下并发的一种严重胆道感染，通常由肠道内的细菌或内毒素易位引起[1,2]。若梗阻不能及时解除将会加重病情，从而引发细菌血症或内毒素血症，激发机体产生过度炎症反应，导致患者产生免疫功能紊乱，甚至引起肝、心、肺等器官功能障碍和衰竭[3-5]。目前ACST的治疗以胆道减压和抗生素为主，但对器官的损伤无法缓解，患者常发生多器官衰竭，病死率达30%，研究显示即使抗生素已经有效控制感染，但损伤仍会继续发展，这可能与某些炎症因子水平有密切关系[6]。乌司他汀是一种广谱蛋白酶抑制剂，是内源性抗炎因子，能够抑制多种酶活性、稳定细胞膜、改善微循环[7,8]。本实验采用乌司他汀治疗ACST模型大鼠，观察不同剂量乌司他汀对ACST的治疗效果以及对大鼠肝屏障功能的影响。

1 材料与方法

1.1 实验动物

SPF级雄性SD大鼠60只，体重200-240 g，平均(225.7± 13.7)g，采用全颗粒鼠饲料进行饲养，每天给予12 h光照，室温为(25.0± 2.0)℃，湿度控制在45%~70%之间，适应性饲喂1周，期间大鼠自由摄食、取水。实验大鼠均购自上海史莱克实验动物有限公司(合格证号:201000050435)。

1.2 实验试剂

乌司他汀（广东天普生化医药股份有限公司，国药准字：H19990133，规格：50000U/支），脂多糖(Lipopolysaccharide，LPS)(L2630，源自大肠杆菌O111:B4)购自Sigma公司，生理盐水和戊巴比妥均购自北京化学试剂公司。低温高速离心机购自德国赛默飞公司，石蜡切片机、石蜡包埋机购自德国LEICA公司，光学显微镜和图像分析系统购自日本OLYMPUS公司。

1.3 动物分组和造模方法

60只SD大鼠依据是否接受造模手术及术后给药浓度分为五组，每组12只大鼠，分别为：① SN组：接受假手术，术后不给于任何药物；② ACST组：接受造模手术，术后给予生理盐水注射；③ ASCT-L组：接受造模手术，术后给予低剂量(20000 U/kg·d)的乌司他汀治疗；④ ASCT-M组：接受造模手术，术后给予中剂量(40000 U/kg·d)的乌司他汀；⑤ ASCT-H组：接受造模手术，术后给予高剂量(80000 U/kg·d)的乌司他汀。造模手术在无菌环境下进行，手术前12 h动物禁食禁水，腹腔注射3%戊巴比妥50 mg/kg，麻醉后取仰卧位，铺消毒洞巾，切口位于腹部正中线，长度小于3 cm，切口上缘距剑突0.5 cm，延肝下缘找到肝十二指肠韧带，剥离沿其表面走行的胆总管，在距其汇入左右肝管处结扎胆总管，3号针头穿刺入胆总管并注入预先配置好的LPS(10 μg/mL)1 mL/kg，1分钟内注射完毕，结扎近端胆总管，关闭腹腔，逐层缝合。SN组大鼠开腹后剥离胆总管及周围组织后，不进行任何其余操作，关腹。在手术后48 h将所有大鼠处死。

1.4 检测指标

大鼠处死前通过腹主动脉抽血6 mL，分别保存于抗凝管中和普通采血管中，抗凝管中血液采用日立7600全自动生化分析仪检测血液样本中的总胆红素(Total bilirubin, TB)和谷丙转氨酶(Alanine aminotransferase, ALT)，普通采血管中的血液用3000 rpm离心10 min，取血清分装后保存于-80℃中，待所有标本收集齐全后，用酶联免疫吸附法(ELISA)检测血清中的白细胞介素-6（Interleukin-6，IL-6）、白细胞介素-10(Interleukin-10, IL-10）和肿瘤坏死因子-α（Tumor necrosis factor, TNF-α)水平，试剂盒均购自美国R&D公司，操作严格按照说明书进行。大鼠处死后，取少量肝脏组织，35%甲醛溶液固定后，HE染色，采用原位末端转移酶标记技术(TUNEL)检测肝细胞凋亡率，采用组织匀浆法提取肝组织中的RNA，采用逆转录-聚合酶链式反应(RT-PCR)分析紧密连接蛋白Occludin和ZO-1基因表达水平。

1.5 统计学分析

采用SPSS17.0进行统计分析，肝功能指标、炎症因子水平等计量资料以均数± 标准差($\bar{x}$± s)表示，多组间比较采用单因素方差分析，两两比较采用SNK法，以α=0.05为检验标准。

2 结果

2.1 肝脏组织病理改变

肉眼观察SN组大鼠胆管及肝脏均无明显改变，造模后各组大鼠均出现胆管扩张，肝叶出现充血肿大，显微镜下观察可见肝细胞水肿、胞浆疏松、肝窦受压变形、肝索排列不齐等变化，并可见点状肝细胞坏死灶，汇管区可见中性粒细胞和巨噬细胞浸润，ACST组大鼠最严重，接受乌司他汀治疗后大鼠损伤减轻，尤其以ASCT-H组大鼠损伤改善最为显著(P<0.05)。

2.2 肝功能指标比较

与SN组比较，造模后各组大鼠TB和ALT水平均显著升高(均P<0.05)，乌司他汀治疗后TB和ALT水平明显降低，且随剂量增加，TB和ALT水平降低，各组间差异均有统计学意义(均P<0.05)。详见表1。

2.3 炎症因子水平比较

与SN组相比，造模后大鼠IL-6和TNF-α水平显著升高，乌司他汀治疗后，各组大鼠IL-6和TNF-α水平随剂量增加而

降低，各组间差异均具有统计学意义（均 P<0.05）。与 SN 组相比，造模后大鼠 IL-10 水平均显著升高，乌司他汀治疗后，各组大鼠 IL-10 水平随剂量增加而上升，各组间差异具有统计学意义（均 P<0.05）。详见表 2。

表 1 各组大鼠肝功能指标比较（$\bar{x}\pm s$）

Table 1 Comparison of liver function indexes of rats in each group ($\bar{x}\pm s$)

Groups	n	TB（μmmol/L）	ALT（U/L）
SN group	12	9.14± 0.658	5.13± 0.43
ACST group	12	88.25± 5.63*	107.26± 6.82*
ACST-L group	12	66.72± 2.53*#	42.81± 2.42*#
ACST-M group	12	45.48± 1.96*#△	31.35± 2.64*#△
ACST-H group	12	31.73± 2.27*#△ *	20.57± 2.43*#△ *
F	-	37.526	43.527
P	-	0.000	0.000

Note: compared with SN group, *P<0.05, compared with ACST group, #P<0.05, compared with ACST-L group, △P<0.05, compared with ACST-H-M group, *P<0.05.

表 2 各组大鼠炎症因子水平比较（$\bar{x}\pm s$）

Table 2 Comparison of inflammatory factors of rats in each group ($\bar{x}\pm s$)

Groups	n	IL-6（pg/mL）	IL-10（pg/mL）	TNF-α（pg/mL）
SN group	12	11.48± 2.03	15.13± 0.43	11.37± 1.92
ACST group	12	49.32± 4.69*	52.24± 3.72*	34.72± 3.29*
ACST-L group	12	37.94± 3.67*#	72.81± 6.52*#	25.91± 2.88*#
ACST-M group	12	26.02± 2.46*#△	80.62± 7.98*#△	19.56± 2.15*#△
ACST-H group	12	22.77± 3.31*#△ *	92.57± 8.46*#△ *	16.32± 1.98*#△ *
F	-	28.352	34.628	25.379
P	-	0.000	0.000	0.000

Note: compared with SN group, *P<0.05, compared with ACST group, #P<0.05, compared with ACST-L group, △P<0.05, compared with ACST-H-M group, *P<0.05.

2.4 肝组织细胞凋亡率和紧密连接蛋白表达水平比较

与 SN 组比较，造模后各组大鼠凋亡率显著升高，Occludin 和 ZO-1 基因表达水平显著降低（P<0.05），乌司他汀治疗后各组大鼠凋亡率表现不同程度的降低，Occludin 和 ZO-1 基因表达水平表现不同程度的上升（P<0.05）。详见表 3。

表 3 各组大鼠干细胞凋亡率和紧密连接蛋白基因表达水平比较（$\bar{x}\pm s$）

Table 3 Comparison of stem cell apoptosis rate and expression level of tight junction protein gene of rats in each group（$\bar{x}\pm s$）

Groups	n	Apoptosis rate (%)	Occludin	ZO-1
SN group	12	1.13± 0.24	1.40± 0.25	16.35± 0.31
ACST group	12	5.83± 0.39*	0.08± 0.02*	3.46± 0.89*
ACST-L group	12	3.28± 0.43*#	0.79± 0.09*#	5.43± 0.34*#
ACST-M group	12	2.12± 0.14*#△	0.99± 0.25*#△	6.55± 1.42*#△
ACST-H group	12	1.58± 0.46*#△ *	1.18± 0.04*#△ *	8.42± 1.53*#△ *
F	-	26.238	23.126	24.362
P	-	0.000	0.000	0.000

Note: compared with SN group, *P<0.05, compared with ACST group, #P<0.05, compared with ACST-L group, △P<0.05, compared with ACST-H-M group, *P<0.05.

3 讨论

ACST 是胆道最严重的一种疾病，病情若得不到控制，胆红素、细菌和内毒素可进入体循环，内毒素是革兰氏阴性细菌细胞壁中的一种 LPS，细胞壁被破坏时才会释放出来，LPS 进入循环系统或脏器后，激活单核吞噬细胞过度分泌具有不同生物活性的炎症因子，导致多器官功能障碍（MODS）甚至衰竭[9-11]。ACST 具有起病急骤、进展迅速、并发症多、病死率高等特点，近年来治疗一直以缓解梗阻和抗感染为主，但是对于 ACST 引起的 MODS 和器官衰竭没有较好的预防和治疗方法，病

死率仍然居高不下[12,13]。本研究采用胆总管结扎的方法造成胆管梗阻,再通过注射 LPS 的方法模拟内毒素如血的过程,造成 ACST 模型大鼠,病理观察结果显示,造模后大鼠胆管和肝脏组织出现不同程度的损伤,肝功能检测也表明大鼠肝脏受到严重损伤,提示该动物模型构建成功。

肝脏是 ACST 发生时最易受到累及的器官之一,因为胆管阻塞时胆汁不能正常进入肠道,缺乏胆盐的抑制,肠道细菌过度繁殖,内毒素吸收增加,并可易位到肝脾等相邻脏器,此外肝门最先接受来自肠道的含菌或内毒素的血液,因此也最容易发生损伤[14-16]。本研究结果显示,造模 48h 后大鼠血液内 TB 和 ALT 均显著升高,提示肝脏受损严重,也证实肝脏是 ACST 发展过程中首先损害的器官之一。过度炎症反应是内毒素介导的另一个严重损伤过程 [17]。本研究结果显示发生 ACST 后大鼠 IL-6、IL-10 和 TNF-α 水平均显著升高。IL-6 和 TNF-α 是重要的炎症因子，可引起多种促炎因子的释放，造成细胞凋亡，IL-10 是体内重要的抗炎因子，对几乎所有的单核巨噬细胞都有抑制作用,可控制炎症反应[18,19]。大鼠给予不同剂量的乌司他汀后，血清中 IL-6 和 TNF-α 表现不同程度的降低,IL-10 继续升高,且均表现出剂量 - 效应关系。提示乌司他汀能够有效调节体内的炎症反应水平,降低促炎因子的分泌,促进抗炎因子的分泌,避免过度炎症反应造成器官损伤[20-22]。

肝屏障包括细胞 - 血液屏障和血液 - 胆汁屏障，其中血液 - 胆汁屏障由紧密连接蛋白 Occludin 和 ZO-1 构成，这些紧密连接将毛细胆管与肝脏窦状隙细胞的表面分隔开,形成胆汁与血液间的屏障,使胆汁只能在胆管中循环而不会进入血液[23-25]。造模后,检测肝脏组织中凋亡细胞和紧密连接蛋白基因表达水平发现,细胞凋亡率显著增加,而 Occludin 和 ZO-1 基因表达水平显著下降，提示除了造成肝功能损伤外,ACST 对肝屏障功能也造成了严重损伤[26]。而给予了乌司他汀治疗的大鼠在检测时肝屏障功能得到修复,紧密连接蛋白基因表达水平显著升高,特别是 ACST-H 组,Occludin 基因表达水平接近正常大鼠。乌司他汀是从成人尿液中分离纯化的一种蛋白，分子量约 67000D,是一种蛋白酶抑制剂,能够对多种蛋白酶的活性产生抑制作用,还能提高溶酶体膜的稳定性,抑制炎症因子释放,清除氧自由基,减轻各种水解酶和炎症反应对组织的损伤,常用与急性胰腺炎和慢性复发性胰腺炎的治疗[27,28]。此外乌司他汀也被用于急性循环衰竭的抢救，其可有效控制炎症因子的水平,维持肝组织微结构的稳定,这是治疗大鼠 ACST 和保护肝屏障的关键机制[29,30]。

综上所述,乌司他汀治疗 ACST 大鼠疗效显著,对肝屏障功能有良好的保护功能，其治疗效力与剂量呈现明显的相关性,其机制及合适的给药剂量值得进一步研究。

参 考 文 献(References)

[1] Manterola C, Otzen T. Cholangiohydatidosis: an Infrequent Cause of Obstructive Jaundice and Acute Cholangitis [J]. Ann Hepatol, 2017, 16(3): 436-441

[2] Kozakai F, Kanno Y, Ito K, et al. Endoscopic-ultrasonography-guided biliary drainage for repetitive acute cholangitis of the accessory hepatic duct obstructed by clipping during laparoscopic cholecystectomy[J]. Nihon Shokakibyo Gakkai Zasshi, 2017, 114(4): 683-690

[3] 黄书明,陈圣开,樊大明,等.腹腔镜和胆道镜及十二指肠镜联合治疗急性梗阻性化脓性胆管炎的临床研究 [J]. 现代生物医学进展, 2015, 15(23): 4525-4527, 4531
Huang Shu-ming, Chen Sheng-kai, Fan Da-ming, et al. Clinical Research of Combination of Laparoscope, Choledochoscope and Duodenoscope for Acute Obstructive Suppurative Cholangitis[J]. Progress in Modern Biomedicine, 2015, 15(23): 4525-4527, 4531

[4] 李荣霖,张大鹏,钟玉川.急性重症胆管炎患者手术前后血清炎性因子的变化及意义[J].中国实验诊断学, 2015, 19(10): 1705-1707
Li Rong-lin, Zhang Da-peng, Zhong Yu-chuan. The changes of serum inflammatory factors of patients with acute cholangitis of severe type before and after operation[J]. Chinese Journal of Laboratory Diagnosis, 2015, 19(10): 1705-1707

[5] Gomi H, Takada T, Hwang TL, et al. Updated comprehensive epidemiology, microbiology, and outcomes among patients with acute cholangitis[J]. J Hepatobiliary Pancreat Sci, 2017, 24(6): 310-318

[6] Yang J, Lu B. Establishment of a novel rat model of severe acute cholangitis[J]. Iran J Basic Med Sci, 2015, 18(11): 1124-1129

[7] Tao Z, Hu FQ, Li CF, et al. Effect of ulinastatin,a human urinary protease inhibitor, on heatstroke-induced apoptosis and inflammatory responses in rats[J]. Exp Ther Med, 2017, 13(1): 335-341

[8] 周玉坤,李刚强.乌司他丁对急性重症胆管炎所致肝屏障损伤的作用和影响[J].肝胆胰外科杂志, 2015, 27(3): 209-213
Zhou Yu-kun, Li Gang-qiang. Effects of Ulinastatin on hepatic barrier in experimental acute cholangitis of severe type [J]. Journal of Hepatopancreatobiliary Surgery, 2015, 27(3): 209-213

[9] 刘思义,朱革非.急性重症胆管炎致死因素分析[J].中国现代医学杂志, 2015, 25(14): 93-96
Liu Si-yi, Zhu Ge-fei. Lethal factors of acute cholangitis of severe type[J]. China Journal of Modern Medicine, 2015, 25(14): 93-96

[10] Lee JM, Lee SH, Chung KH, et al. Risk factors of organ failure in cholangitis with bacteriobilia[J]. World J Gastroenterol, 2015, 21(24): 7506-7513

[11] 鲁葆春,杨建辉.新型大鼠急性重症胆管炎模型的建立[J].中国中西医结合外科杂志, 2015, 21(1): 45-48
Lu Bao-chun, Yang Jian-hui. Establishment of a Novel Rat Model of Severe Acute Cholangitis[J]. Chinese Journal of Surgery of Integrated Traditional and Western Medicine, 2015, 21(1): 45-48

[12] Umefune G, Kogure H, Hamada T, et al. Procalcitonin is a useful biomarker to predict severe acute cholangitis: a single-center prospective study[J]. J Gastroenterol, 2017, 52(6): 734-745

[13] Kim H, Kong T, Chung SP, et al. Usefulness of the Delta Neutrophil Index as a Promising Prognostic Marker of Acute Cholangitis in Emergency Departments[J]. Shock, 2017, 47(3): 303-312

[14] Schwed AC, Boggs MM, Pham XD, et al. Association of Admission Laboratory Values and the Timing of Endoscopic Retrograde Cholangiopancreatography With Clinical Outcomes in Acute Cholangitis[J]. JAMA Surg, 2016, 151(11): 1039-1045

[15] Sadowska-Krłpa E, Kłapcińska B, Jagsz S, et al. High-dose testosterone enanthate supplementation boosts oxidative stress, but exerts little effect on the antioxidant barrier in sedentary adolescent male rat liver[J]. Pharmacol Rep, 2017, 69(4): 673-678

[16] 王建,陈卫东,刘兴洲,等.利胆汤对大鼠急性重症胆管炎所致的肝

损伤的作用机制[J].临床与病理杂志, 2017, 37(2): 353-358
Wang Jian, Chen Wei-dong, Liu Xing-zhou, et al. Lidantang attenuates severe acute cholangitis induced hepatic injury [J]. Journal of Pathology and Clinical Medicine, 2017, 37(2): 353-358

[17] 冼健元. 胆管引流术对急性重症胆管炎患者血清促炎因子的影响[J].医学综述, 2015, 21(2): 353-354
Xian Jian-yuan. Influence of Endoscopic Naso-biliary Drainage on Serum Cytokines in Patients with Acute Severe Cholangitis[J]. Medical Recapitulate, 2015, 21(2): 353-354

[18] Murayama KM. Acute Cholangitis Management: Prevention of Organ Failure and Death[J]. JAMA Surg, 2016, 151(11): 1045

[19] Wannhoff A, Rupp C, Friedrich K, et al. Inflammation But Not Biliary Obstruction Is Associated With Carbohydrate Antigen 19-9 Levels in Patients With Primary Sclerosing Cholangitis [J]. Clin Gastroenterol Hepatol, 2015, 13(13): 2372-2379

[20] Wang LZ, Luo MY, Zhang JS, et al. Effect of ulinastatin on serum inflammatory factors in Asian patients with acute pancreatitis before and after treatment: a meta-analysis [J]. Int J Clin Pharmacol Ther, 2016, 54(11): 890-898

[21] Zhang C, Wang Y, Fu W, et al. A Meta-analysis on the Effect of Ulinastatin on Serum Levels of C-Reactive Protein,Interleukin 6, and Tumor Necrosis Factor Alpha in Asian Patients with Acute Pancreatitis [J]. Genet Test Mol Biomarkers, 2016, 20(3): 118-124

[22] 范志勇,李晖,孙中杰,等.损伤控制在重症胆管炎合并多脏器功能不全治疗中的应用[J].实用医学杂志, 2016, 32(7): 1139-1141
Fan Zhi-yong, Li Hui, Sun Zhong-jie, et al. Application of damage control in the treatment of severe cholangitis complicated with multiple organ dysfunction syndrome [J]. Journal of Practical Medicine, 2016, 32(7): 1139-1141

[23] 曹才文,何旋,李莉,等.重症中暑早期肠黏膜屏障功能损害与全身炎症反应的相关性研究 [J]. 中华危重病急救医学, 2016, 28(4): 303-307
Cao Cai-wen, He Xuan, Li Li, et al. The correlation analysis of intestinal mucosal barrier function damage with systemic inflammation reaction during severe heatstroke [J]. Chinese Critical Care Medicine, 2016, 28(4): 303-307

[24] Ma CL, Wang LP, Qiao S, et al. Risk Factors for Death of Elderly Patients with Acute Obstructive Suppurative Cholangitis[J]. West Indian Med J, 2015, 65(2): 316-319

[25] Eto K, Kawakami H, Haba S, et al. Single-stage endoscopic treatment for mild to moderate acute cholangitis associated with choledocholithiasis: a multicenter, non-randomized,open-label and exploratory clinical trial[J]. J Hepatobiliary Pancreat Sci, 2015, 22(12): 825-830

[26] Tabibian JH, Yang JD, Baron TH, et al. Weekend Admission for Acute Cholangitis Does Not Adversely Impact Clinical or Endoscopic Outcomes[J]. Dig Dis Sci, 2016, 61(1): 53-61

[27] Luo Y, Che W, Zhao M. Ulinastatin post-treatment attenuates lipopolysaccharide-induced acute lung injury in rats and human alveolar epithelial cells[J]. Int J Mol Med, 2017, 39(2): 297-306

[28] Tao Z, Hu FQ, Li CF, et al. Effect of ulinastatin,a human urinary protease inhibitor, on heatstroke-induced apoptosis and inflammatory responses in rats[J]. Exp Ther Med, 2017, 13(1): 335-341

[29] 刘彦西,高大宽,马亚玲,等.乌司他丁对大鼠脑缺血再灌注损伤后的保护作用及其机制研究 [J]. 现代生物医学进展, 2015, 15(23): 4462-4466
Liu Yan-xi, Gao Da-kuan, Ma Ya-ling, et al. A Study on the Protective Effect and Its Mechanism of Ulinastatin in Cerebral Ischemia Reperfusion Injury [J]. Progress in Modern Biomedicine, 2015, 15 (23): 4462-4466

[30] 张慧慧,蔡国龙,胡才宝,等.乌司他丁对脓毒症大鼠急性肺损伤的保护作用及其机制研究[J].中华危重症医学杂志(电子版), 2017, 10 (3): 153-158
Zhang Hui-hui, Cai Guo-long, Hu Cai-bao, et al. Protective effect of ulinastatin on acute lung injury in sepsis rats and its mechanism[J]. Chinese Journal of Critical Care Medicine (Electronic Edition), 2017, 10(3): 153-158

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[18] Song H, Zhang B, Watson MA, et al. Loss of Nkx3.1 leads to the activation of discrete downstream target genes during prostate tumorigenesis[J]. Oncogene, 2009, 28(37): 3307-3319

[19] Shi CY, Fan Y, Liu B, et al. HIF1 contributes to hypoxia-induced pancreatic cancer cells invasion via promoting QSOX1 expression[J]. Cell Physiol Biochem, 2013, 32(3): 561-568

[20] 谢维,黄天壬,李云西,等.肝癌进展过程中 QSOX-1 的动态变化及意义[J].中国热带医学, 2015, (04): 389-392
Xie Wei, Huang Tian-ren, Li Yun-xi, et al. Expression and significance of QSOX1 in a population with high risk of primary liver cancer in Guangxi[J]. China Tropical Medicine, 2015, (04): 389-392

[21] Tanaka M, Shimamura S, Kuriyama S, et al. SKAP2 Promotes Podosome Formation to Facilitate Tumor-Associated Macrophage Infiltration and Metastatic Progression[J]. Cancer Res, 2016, 76(2): 358-369

[22] Kuranami S, Yokobori T, Mogi A, et al. Src kinase-associated phosphoprotein2 expression is associated with poor prognosis in non-small cell lung cancer[J]. Anticancer Res, 2015, 35(4): 2411-2415

[23] Conti MA, Adelstein RS. Nonmuscle myosin II moves in new directions[J]. J Cell Sci, 2008, 121(Pt 1): 11-18

[24] Liu D, Zhang L, Shen Z, et al. Clinicopathological significance of NMIIA overexpression in human gastric cancer [J]. Int J Mol Sci, 2012, 13(11): 15291-15304

[25] Liang S, He L, Zhao X, et al. MicroRNA let-7f inhibits tumor invasion and metastasis by targeting MYH9 in human gastric cancer[J]. PLoS One, 2011, 6(4): e18409

[26] Ramsey KM, Yoshino J, Brace CS, et al. Circadian clock feedback cycle through NAMPT-mediated NAD+ biosynthesis [J]. Science, 2009, 324(5927): 651-654

[27] 李亮,陈锐,刘俊松,等.突变型 p53 与 Nampt 在胃癌组织中的表达及其与预后的关系[J].中国普通外科杂志, 2015, (04): 505-510
Li Liang, Chen Rui, Liu Jun-song, et al. Expressions of mutant p53 and Nampt in gastric cancer tissue and their relations with prognosis [J]. Chinese Journal of General Surgery, 2015, (04): 505-510

[28] Zhang LQ, Heruth DP, Ye SQ. Nicotinamide Phosphoribosyltransferase in Human Diseases[J]. J Bioanal Biomed, 2011, 3: 13-25