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Aurora-A 激酶对急性胰腺炎大鼠肺脏损伤的修复作用研究 *

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摘要 目的：探讨与研究 Aurora-A 激酶对急性胰腺炎大鼠肺脏损伤的修复作用。**方法**：36 只雄性 SD 大鼠均分为三组：对照组、模型组与 Aurora-A 组。对照组进行假手术操作，模型组建立急性胰腺炎模型后给予注射等量生理盐水治疗，Aurora-A 组建立急性胰腺炎模型后给予阴茎背静脉注射鼠 Aurora-A 类因子 -MLN8054 10 mg/kg 治疗，记录大鼠肺脏损伤的修复情况。**结果**：造模过程中无大鼠死亡情况发生，模型组与 Aurora-A 组造模后 2 w 与 4 w 的肺组织病理评分、血清中性粒细胞弹性蛋白酶(neutrophil elastase，NE)与髓过氧化物酶(myeloperoxidase，MPO)含量、肺组织 W/D、肺组织蛋白激酶 B(AKT)、细胞外信号调节激酶 1(ERK1)蛋白相对表达水平都高于对照组（P<0.05），Aurora-A 组少于模型组（P<0.05）。**结论**：Aurora-A 激酶在急性胰腺炎大鼠的应用能抑制 Akt/ERK 信号通路激活，减少血清 NE 与 MPO 的表达，从而促进肺脏损伤修复。

关键词：Aurora-A 激酶；急性胰腺炎；肺脏损伤；髓过氧化物酶；细胞外信号调节激酶 1

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Study on the Repairing Effect of Aurora-A Kinase on Lung Injury in Rats with Acute Pancreatitis*

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ABSTRACT Objective: To explore and study the repair effect of Aurora-A kinase on lung injury in rats with acute pancreatitis. **Methods:** 36 cases of male SD rats were equally divided into three groups-control group, model group and Aurora-A group. The control group were given underwent sham operation, the model group were treated with the same amount of normal saline after the acute pancreatitis model were established, and the Aurora-A group were treated with the mouse Aurora-A factor-MLN8054 10 mg/kg after the acute pancreatitis model were established. Recorded the repair effects of rat lung injury. **Results:** There were no rats died during the modeling process. The lung tissue pathology scores, serum neutrophil elastase (NE) and myeloperoxidase(MPO), lung tissue W/D, lung tissue protein kinase B (AKT), and extracellular signal-regulated kinase 1 (ERK1) protein in the model group and Aurora-A group at 2 weeks and 4 weeks after modeling were higher than those in the control group (P<0.05), the Aurora -A group were less than the model group (P<0.05). **Conclusion:** The application of Aurora-A kinase in acute pancreatitis rats can inhibit the activation of Akt/ERK signaling pathway, reduce the expression of serum NE and MPO, and promote lung injury repair.

Key words: Aurora-A kinase; Acute pancreatitis; Lung injury; Myeloperoxidase; Extracellular signal-regulated kinase 1

Chinese Library Classification(CLC): R-33; R576; R322.35 Document code: A

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前言

急性胰腺炎(acute pancreatitis，AP)是常见的消化内科住院疾病之一，目前尚无有效的预防或治疗策略[1,2]。该病的发生机制还不明确，随着病情发展，很多患者可出现多器官功能障碍综合征，病死率在 6 %左右，其中重症急性胰腺炎的病死率在 20 %左右[3,4]。胰腺腺泡细胞约占据绝大部分的胰腺实质，急性胰腺炎的形态学变化是胰腺腺泡细胞正常合成和分泌的酶对腺体的消化所致[5]。现代研究表明急性胰腺炎在一定程度上可引发急性肺脏损伤，包括轻度低氧血症与急性呼吸窘迫综合征[6-8]。有丝分裂激酶是协调细胞有丝分裂精确过程的主要蛋白质，其中参与人类有丝分裂的 Aurora 激酶家族由高度保守的苏氨酸

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-丝氨酸酶组成[9,10]。Aurora-A 激酶是该 Aurora 激酶家族的重要成员之一，可调节细胞迁移和粘附、双极纺锤体形成和细胞分裂，在干细胞自我更新、重新编程和分化中也发挥重要作用[11,12]。Aurora-A 激酶也可抑制 BRCA1 和 BRCA2 基因的表达，被认为是多种恶性肿瘤的潜在治疗靶标[13,14]。本文具体探讨了 Aurora-A 激酶对急性胰腺炎大鼠肺脏损伤的修复作用，以明确抑制 Aurora-A 激酶表达的价值。现总结报道如下。

1 材料与方法

1.1 研究材料

清洁级健康成年雄性 SD 大鼠购自凯学生物科技(上海)有限公司(n=36，体重 180~220 g)，饲养于本实验动物中心。饲养条件完全符合伦理要求，也得到了医院伦理委员会的批准，先于标准实验环境下饲养 1 w，然后进行实验。雨蛙素、MLN8054 购自美国 Sigma 公司，血清学检测试剂盒购自南京建成生物工程研究所，蛋白一抗购于 Abcam 公司，二抗购于武汉三鹰公司。

1.2 动物分组与处理

所有大鼠随机分为三组 - 对照组、模型组与 Aurora-A 组，每组 12 只。对照组：常规麻醉后开腹，仅翻动胰腺后关腹；模型组：建立急性胰腺炎模型后给予注射等量生理盐水治疗；Aurora-A 组：建立急性胰腺炎模型后给予阴茎背静脉注射鼠 Aurora-A 类因子 -MLN8054 10 mg/kg 治疗。所有大鼠清醒后自由饮水并饮食。

大鼠急性胰腺炎模型的建立：建模前 1 d 大鼠禁食，每 250 g 体重大鼠每次注射时给予 100 μL 体积的 1× 雨蛙素，注射部位为右中下腹部，注射时避开腹腔内脏器官和大血管的位置，动作尽量轻柔，每隔 1 h 注射 1 次，共注射 8 次。

三组大鼠在造模后 2 w 与 4 w 各处死 6 只大鼠进行后续实验。

1.3 观察指标

(1)肺组织病理评分：处死大鼠后将心脏向两侧拨开，暴露肺叶后进行切除，制成病理切片并采用 HE 染色。在光镜下依据肺间质水肿、肺泡出血、肺泡水肿、细胞浸润的无、轻、中、重程度都分别以 0、1、2、3 分评分。(2)取处死大鼠的心脏血液 1~2 mL，静置 1 h 左右，离心(3000 r/min)5 min 分离血清，采用酶联免疫检测血清中性粒细胞弹性蛋白酶 (neutrophil elastase，NE)与髓过氧化物酶(myeloperoxidase，MPO)含量。(3)取处死大鼠的右肺下叶，用生理盐水洗净后在滤纸上吸干水分并称重，此为湿肺重量。然后在 60℃电热恒温干燥箱中烘烤 72 h，此时称重为干肺重量，计算湿重与干重之比(W/D)。(4)取肺组织，研磨后进行 Western blot 检验，记录蛋白激酶 B(AKT)与细胞外信号调节激酶 1(ERK1)蛋白相对表达水平，以β-actin 作为内标。

1.4 统计方法

统计方法应用 SPSS 25.00 软件，计量数据以均数± 标准差表示，多组数据间比较采用单因素方差分析进行统计，两组间比较采用 t 检验，检验水准为α=0.05，P<0.05 表示有统计学意义。

2 结果

2.1 造模情况

造模过程中无大鼠死亡情况发生，对照组为正常肺脏组织。模型组肺脏标本可见紫褐色肺不张区，肺泡腔及支气管中可见渗出下，胰腺炎组肺脏组织可见肺泡隔明显增宽。Aurora-A 组较模型组明显好转，仍有炎性细胞浸润，肺泡间隔部分增宽，肺泡及支气管中渗出、出血减少。

2.2 三组肺组织病理评分对比

模型组与 Aurora-A 组造模后 2 w 与 4 w 的肺组织病理评分都高于对照组，Aurora-A 组少于模型组，组间对比均有统计学意义(P<0.05)，见表 1。

表 1 三组造模后不同时间点的肺组织病理评分对比(分，$\bar{x}\pm s$)

Table 1 Comparison of lung tissue pathological scores at different time points after the three groups of models (min, $\bar{x}\pm s$)

Groups	n	2 weeks after molding	4 weeks after molding
Control group	6	0.88± 0.05	0.89± 0.06
Model group	6	9.22± 0.14*	9.89± 0.22*
Aurora-A group	6	3.44± 0.21*#	3.15± 0.18*#
F		29.842	31.482
P		0.000	0.000

Note: Compared with the control group, *P<0.05; compared with the model group, #P<0.05.

2.3 三组血清 NE 与 MPO 含量对比

模型组与 Aurora-A 组造模后 2 w 与 4 w 的血清 NE 与 MPO 含量都高于对照组，Aurora-A 组少于模型组，组间对比均有统计学意义(P<0.05)，见表 2。

2.4 三组肺组织 W/D 对比

模型组与 Aurora-A 组造模后 2 w 与 4 w 的肺组织 W/D 对比高于对照组，Aurora-A 组少于模型组，组间对比均有统计学意义(P<0.05)，见表 3。

2.5 三组肺组织 AKT 与 ERK1 蛋白相对表达水平对比

模型组与 Aurora-A 组造模后 2 w 与 4 w 的肺组织 AKT 与 ERK1 蛋白相对表达水平高于对照组 (P<0.05)，Aurora-A 组少于模型组，组间对比均有统计学意义(P<0.05)，见表 4。

3 讨论

急性胰腺炎的发病人数逐年增加，也是院内患者死亡的重要原因。酗酒和胆石症占急性胰腺炎总发病率的 60 %左右，逆行胰胆管造影、药物、脂质代谢紊乱、感染也可引起该病的发生[15]。其中 20 %左右的急性胰腺炎患者伴有局部或全身并发症

表 2 三组造模后不同时间点的血清 NE 与 MPO 含量对比($\bar{x}\pm s$)

Table 2 Comparison of serum NE and MPO contents at different time points after three groups of models ($\bar{x}\pm s$)

Groups	n	NE(ng/mL)		MPO(U/g)	
		2 weeks after molding	4 weeks after molding	2 weeks after molding	4 weeks after molding
Control group	6	52.22± 6.10	52.81± 4.59	0.94± 0.09	0.96± 0.11
Model group	6	187.00± 14.58*	191.09± 15.60*	4.59± 0.14*	5.33± 0.28*
Aurora-A group	6	78.89± 5.33*#	72.72± 5.02*#	1.56± 0.22*#	1.46± 0.18*#
F		18.032	15.838	11.022	14.053
P		0.000	0.000	0.000	0.000

表 3 三组造模后不同时间点的肺组织 W/D 对比($\bar{x}\pm s$)

Table 3 Comparison of W/D of lung tissue at different time points after three groups of models ($\bar{x}\pm s$)

Groups	n	2 weeks after molding	4 weeks after molding
Control group	6	3.56± 0.10	3.61± 0.14
Model group	6	8.65± 0.11*	9.09± 0.18*
Aurora-A group	6	6.22± 0.18*#	5.89± 0.17*#
F		9.133	10.372
P		0.002	0.001

表 4 三组造模后不同时间点的肺组织 AKT 与 ERK1 蛋白相对表达水平对比(%,$\bar{x}\pm s$)

Table 4 Comparison of the relative expression levels of AKT and ERK1 proteins in lung tissues at different time points after the three groups of models (%, $\bar{x}\pm s$)

Groups	n	AKT		ERK1	
		2 weeks after molding	4 weeks after molding	2 weeks after molding	4 weeks after molding
Control group	6	1.09± 0.03	1.02± 0.12	1.67± 0.11	1.68± 0.15
Model group	6	4.52± 0.11*	4.98± 0.24*	7.63± 0.19*	8.44± 0.25*
Aurora-A group	6	2.98± 0.22*#	2.56± 0.17*#	3.21± 0.11*#	2.87± 0.18*#
F		10.033	13.024	14.055	16.783
P		0.000	0.000	0.000	0.000

和器官衰竭等，具有比较高的死亡率[16,17]。肺脏是急性胰腺炎机体长期受累的器官，也是受循环中炎性介质影响最大的器官之一[18]。本研究显示模型组与 Aurora-A 组造模后 2 w 与 4 w 的肺组织病理评分、肺组织 W/D 都高于对照组，Aurora-A 组少于模型组，表明急性胰腺炎大鼠伴随有明显的肺组织损伤，而 Aurora-A 激酶的应用有一定的治疗作用。

从机制上分析，Aurora 激酶家族是在纺锤体形成与中心体复制，在有丝分裂过程中发挥重要作用[19,20]。Aurora-A 激酶和 Aurora-B 激酶是调控有丝分裂最重要的激酶，定位于染色体 20q13.2，全长 cDNA 为 1209 kb，包括 N 端 β 链结构域和一个 C 端 α 螺旋结构域，其中 N 端是定位结构域，可将 Aurora-A 激酶以微管依赖的方式定位在中心体上，可调节中心体的成熟和纺锤体的组装[21]。当 Aurora-A 激酶表达缺少时，可使得中心体无法形成两极纺锤体，从而抑制有丝分裂。降低 Aurora-A 激酶蛋白的表达水平使细胞周期停滞在 G2 期与 M 期，导致细胞凋亡与纺锤体缺陷[22]。而激活 Aurora-A 激酶的表达可为此有助于基因组的稳定性，抑制肿瘤与其他疾病的发生，也可发挥治疗急性胰腺炎的作用[23]。与郝剑文[24]等学者的研究类似，该学者探究 Aurora 激酶 A (AURKA) 抑制剂 Alisertib 对人肝癌细胞 HepG2 DNA 损伤修复的影响，结果显示 Alisertib 可通过下调 AURKA 蛋白表达，上调 DNA 损伤标记物 p-H2A.X 蛋白表达，有效激活 DNA 损伤修复，抑制肿瘤进展。

急性胰腺炎引起的肺脏损伤发病机制复杂，目前认为中性粒细胞的过度激活，引起机体抗炎 / 促炎系统失衡，是其发病的重要原因之一[25]。本研究显示模型组与 Aurora-A 组造模后 2 w 与 4 w 的血清 NE 与 MPO 含量都高于对照组，Aurora-A 组少于模型组，目前动物研究与临床研究缺乏 Aurora-A 对急性胰腺炎血清 NE 与 MPO 含量的研究，NE 是重要的炎症介质；MPO 是中性粒细胞的功能标志和激活标志，也是一种重要的含铁溶酶体，两者的表达水平对机体产生和调节炎症反应等发生重要作用[26]。Aurora-A 激酶表达下降可导致细胞有丝分裂缺陷，激活 Aurora-A 激酶表达可诱导其构象变化，促使激酶的

磷酸化活化结构域变得更为紧凑,更加有利于促进中心体的成熟和分离,并且可抑制 p53 的降解,从而可缓解急性胰腺炎的病情[27,28]。

急性胰腺炎是胰酶引起的一种炎症反应性疾病,肺脏损伤是其常见并发症之一,多数急性胰腺炎死亡患者合并有肺脏损伤[29]。本研究显示模型组与 Aurora-A 组造模后 2 w 与 4 w 的肺组织 AKT 与 ERK1 蛋白相对表达水平高于对照组,Aurora-A 组少于模型组。从机制上分析,肺组织中炎症细胞的活化、趋化等作用与 Akt/ERK 信号通路有关,可使炎症细胞活性增强、凋亡延迟,加重肺脏损伤[30,31]。其中 ERK1 负责将细胞表面受体的丝裂原信号传递至细胞核内,激活下游蛋白的表达,从而促进炎症反应发生。Aurora-A 激酶是参与有丝分裂纺锤体和染色体分离的形成的重要激酶, 激活其表达能抑制 Akt/ERK 信号通路激活,从而减少炎症介质释放,减轻肺组织病理反应[32,33]。对于 Aurora-A 激酶的应用,目前在胰腺炎中的报道甚少,多参于肺癌、胃癌、喉癌等多种癌症[34],本研究创新性的将 Aurora-A 激酶应用于急性胰腺炎, 表明 Aurora-A 激酶在急性胰腺炎大鼠的应用能抑制 Akt/ERK 信号通路激活, 减少血清 NE 与 MPO 的表达,从而促进肺脏损伤修复,为后续的基础研究提供数据参考,给胰腺炎的治疗提供了治疗思路。但是本研究也存在一定的不足,没有分析 Aurora 激酶家族其他因子的作用,且没有进行抑制剂分析,将在后续研究中进行探讨。

综上所示,Aurora-A 激酶在急性胰腺炎大鼠的应用能抑制 Akt/ERK 信号通路激活,减少血清 NE 与 MPO 的表达,从而有助于促进肺脏损伤修复。

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(下转第 3435 页)

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