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· 文献综述 ·

重症急性胰腺炎相关肺损伤机制与治疗的研究进展

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摘要

重症急性胰腺炎(SAP)是指因胰酶异常激活对胰腺自身及周围器官产生消化作用而引起的、以胰腺局部炎性反应为主要特征,甚至可导致器官功能障碍的临床常见急腹症。SAP常并发急性肺损伤(ALI)和急性呼吸窘迫综合征(ARDS),是目前导致SAP病死率较高的主要原因之一。SAP相关ALI的发生率从15%~55%不等,其临床表现也从轻度低氧血症到ARDS各有不同。并且,ALI和ARDS是SAP腹外功能障碍最显著的表现,发病第1周病死率高达60%。近年来众多研究发现,一方面,SAP相关ALI与多种信号通路的激活密不可分;另一方面,各种炎症因子的刺激、氧化应激、细胞焦亡等也是导致SAP相关ALI的重要原因。笔者就有关SAP相关ALI的机制及治疗的最新研究进展作一综述。

关键词

胰腺炎,急性坏死性;肺损伤;呼吸窘迫综合征;综述

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Mechanism of lung injury associated with severe acute pancreatitis and its treatment: recent advances

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Abstract

Severe acute pancreatitis (SAP) is a common acute abdominal disease in clinical practice. It is caused by abnormal activation of pancreatic enzymes, which results in digestion of the pancreas itself and surrounding organs, mainly represented by local inflammatory reaction of the pancreas, and even leads to organ dysfunction. SAP is often complicated by acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), which is one of the major causes for high mortality of SAP. The incidence of SAP-associated ALI ranges from 15% to 55%, and its clinical manifestations vary from mild hypoxemia to ARDS. In addition, ALI/ARDS is the most significant manifestation of extra-abdominal organ dysfunction of SAP, with a mortality rate up to 60% within the first week of onset. In recent years, many studies have found that SAP-associated ALI is inextricably linked to the activation of a variety of

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signaling pathways, and yet, on the other hand, the stimulation of various inflammatory factors, oxidative stress and cell apoptosis are also the important causes responsible for SAP-associated ALI. Here, the authors address the latest research progress on the mechanism of SAP-associated ALI and the treatment.

Key words

Pancreatitis, Acute Necrotizing; Lung Injury; Respiratory Distress Syndrome; Review

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重症急性胰腺炎 (severe acute pancreatitis, SAP) 是一种极为危险的临床急腹症, 可引起全身炎症反应, 并迅速累及全身多个器官。急性肺损伤 (acute lung injury, ALI) 是 SAP 中最常出现的并发症, 也是 SAP 最严重的并发症之一, 且病死率超过 30%, 尤其老年患者病死率较高, 是早期 SAP 患者死亡的主要原因之一^[1-4]。目前对于 SAP 相关 ALI 的救治主要集中于胸腔穿刺、控制肺部感染、改善呼吸、吸氧等对症支持治疗。然而, SAP 相关 ALI 的具体发病机制至今尚不完全清楚, 胰腺坏死、菌血症、肠屏障功能衰竭、炎症级联激活和弥漫性肺泡损伤的串扰是导致 SAP 相关 ALI 病理机制不明确的主要原因^[5], 这也让医治临床 SAP 相关 ALI 成为现代医学的重点与难点^[6-9]。大量研究表明, SAP 相关 ALI 的发病机制与各种信号通路的激活密切相关。另外, 近年来, 抗氧化应激、抗细胞焦亡也成为治疗 SAP 及 SAP 相关 ALI 的重要研究热点之一。笔者就 SAP 相关 ALI 的机制及治疗的最新研究进展作如下综述。

1 抗炎机制

1.1 丝裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK)

MAPK 是一种由多种同工酶组成的丝氨酸/苏氨酸蛋白激酶, 包括细胞外信号调节激酶 (extracellular signal-regulated kinase, ERK)、P38MARK 和氨基末端激酶 (c-Jun N-terminal kinase, JNK), 是丝氨酸/苏氨酸激酶家族的重要组成部分, 已被证明在炎症、肿瘤发生、细胞增殖、凋亡、分化和应激反应中发挥重要作用^[10-13]。近几年来, P38MAPK 信号作为经典的蛋白激酶, 逐渐成为干预 SAP 相关 ALI 的研究热点; 大量研究证明: P38MAPK 作为一种重要的信号通路转导酶, 通过将细胞外信号转导到细胞内, 调控基因的转录、

翻译, 主要参与炎症疾病发病机制中炎性细胞因子和介质的释放; 有实验证明, 通过抑制 P38MAPK/NF- κ B 信号通路可改善小鼠 SAP 相关 ALI, 减轻炎症反应, 改善氧化应激和自噬^[14]; Zhou 等^[15]发现 SB203580 (MAPK 抑制剂) 预处理可明显降低妊娠期急性胰腺炎 (acute pancreatitis in pregnancy, APIP) 诱导的肺组织中肿瘤坏死因子 (TNF- α)、白细胞介素 1 β (IL-1 β)、白细胞介素 6 (IL-6) 的上调表达, 并改善肺组织病理损伤。并且 SB203580 预处理标本肺组织中中性粒细胞及巨噬细胞强度降低; 提示 SB203580 可能通过抑制中性粒细胞和巨噬细胞的活化来发挥 APIP 后的抗炎和肺保护功能。

1.2 脂氧素 A4 (lipoxin A4)

作为最重要的生理性脂氧素之一, lipoxin A4 是炎症反应开始时由花生四烯酸产生的内源性抗炎分子家族的成员, 已在越来越多的炎症相关疾病模型中得到广泛研究; 研究^[16]表明, lipoxin A4 能显著降低 SAP 大鼠肺组织中肿瘤坏死因子-R1 抗体 (TNF-R1)、肿瘤坏死因子受体相关死亡域蛋白 (TRADD)、肿瘤坏死因子受体相关因子 2 (TRAF2) 的表达, 从而有效抑制促炎细胞因子的释放, 从而减轻局部和全身炎症反应, 并且 lipoxin A4 可缓解 SAP 胰腺和肺的病理改变, 降低血清促炎介质水平、细胞间黏附分子 1 (ICAM-1) 表达、抑制 NF- κ B 活化。另外, Yu 等^[17]发现 lipoxin A4 以“TNF- α ”为中心, 通过下调 TNF-R1 信号通路相关蛋白肿瘤坏死因子受体相关死亡域蛋白 (TRADD)、肿瘤坏死因子受体相关因子 2 (TRAF2) 的表达; 从而抑制 NF- κ B 通路和 MAPK 通路的活性, 进而抑制 SAP 胰腺炎症损伤及相关肺损伤。

1.3 Janus 激酶/信号传感器和转录激活因子 (JAK/STAT) 通路

此通路之前已被证明在肿瘤发生中发挥作用,

肿瘤相关淋巴分泌的配体趋化因子配体21 (CCL21) 可与口腔鳞状细胞癌 (oral squamous cell carcinoma, OSCC) 细胞的 C-C 驱化因子受体7 (CCR7) 相互作用, 从而诱导上皮-间充质转化 (EMT), 促进肿瘤细胞的干细胞性激活 JAK2/STAT3 信号通路^[18-19]。IL-6 作为一种促炎因子, 优先激活 STAT3, 在启动和加剧炎症进程中发挥重要作用; SAP 可激活 IL-6 进而激活 JAK2/STAT3 通路, 导致 ICAM-1 活化, 促进 NF- κ B 表达上调, 进而诱导 ALI 的发生发展^[18, 20]; 细胞因子信号抑制因子 (SOCS3) 过表达后, TNF- α 、IL-6、IL-18 表达显著下降, SAP 相关 ALI、肺水肿、出血、严重炎症反应、肺泡充血、细胞损伤症状显著改善^[21-23]。LI 等^[24]也发现 JAK/STAT 信号通路广泛参与炎症反应 JAK2 通过细胞因子受体与 STAT3 结合, 激活细胞因子信号级联, 而 TNF- α 在胰腺损伤中激活 JAK2 和 STAT3, 阻断 JAK2/STAT3 信号通路, 防止过度系统性炎症反应在 SAP 中的致命作用。Piao 等^[25]也发现 JAK2 和 STAT3 磷酸化的失活显著抑制炎症和氧化应激, 从而改善小鼠急性胰腺炎相关肺组织损伤。通过瑞香素处理的小鼠中, TNF- α 、IL-6、淀粉酶和脂肪酶水平显著降低, 已证明能有效减轻胰腺本身即全身炎症^[26]。Han 等^[20]发现, ICAM-1 和 JAK/STAT 信号中间体以及包括 MAPK 信号通路在内的其他急性炎症信号通路的组分可能是 SAP 相关 ALI 患者治疗的重要干预靶点; 另外, 通过下调 ICAM-1-JAK2/STAT3 信号级联能够减弱炎症反应, 促进炎症过程中的白细胞运输。大量研究^[26-28]也相继发现, 瑞香素, 地塞米松, 垂盆草提取物等药物能抑制 JAK-STAT 通路的激活, 从而抑制 SAP 相关 ALI 的发生, 相反, JAK2/STAT3 信号通路的激活可诱导 IL-6 及 IL-18 过度表达, 可能加重 SAP 时的炎症反应和肺损伤。

1.4 NOD样受体蛋白3炎症小体(NLRP3)

NLRP3 是一种结点样受体, 是炎症的关键组织损伤激活剂, 可以被不同的损伤相关分子模式 (DAMPs) 激活, 如活性氧类物质 (ROS)、线粒体 DNA (mtDNA)、三磷酸腺苷, 从而产生 IL-6、TNF- α 等炎症因子; 而 NF- κ B 信号通路作为转录因子核因子, 启动过程中 Toll 样受体识别危险相关的分子模式或病原体相关的分子模式, 从而激活 NF- κ B、诱导 IL-1 β 和增加 NLRP3 的合成。作为经典的促炎途径, 具有传统的作用模式, 而且由于在 NLRP3 激活的初始步骤中的关键作用; NLRP3 和 NF- κ B 通路都是引起细胞损伤的促炎通路; 有证据表明

大黄素、地塞米松可能通过抑制 NLRP3 炎症小体介导的中性粒细胞募集和减弱 NF- κ B 信号通路的激活, 从而达到抑制 SAP 相关 ALI 的作用^[29-31]; 不难看出, NF- κ B 信号通路是启动 NLRP3 激活的重要起始步骤, 以此介导的炎症产生的 ROS 也是激活 NLRP3 的危险信号; 而 Yu 等^[32]发现, 表面活性蛋白 D 作为抑制剂对 NLRP3 和 NF- κ B 信号通路均有抑制作用, 降低了 SAP 模型中细胞因子 IL-1 β 、IL-6 和趋化因子 MCP-1 的表达, 从而降低了 SAP 相关 ALI 的炎症程度。

2 氧化应激机制

有研究表明核因子 E2 相关因子 2 (Nrf2) 是一种氧化还原敏感的转录因子, 可以通过转运到细胞核诱导抗氧化应激酶 HO-1 的表达, 已有多项研究^[33-35]证实 Nrf2-HO-1 信号通路的激活对恶性肿瘤的血管生成、脊髓损伤和缺血性卒中等产生影响。近年来, Nrf2 作为经典通路的关键因子, 在炎症中的重要作用越来越引起关注; 有研究表明, Nrf2 是人类抗氧化反应元件 (ARE) 的正调节因子, 驱动抗氧化酶的表达。Kelch 样环氧氯丙烷相关蛋白-1 (Keap1) 是一种固定在细胞骨架上的 Nrf2 结合蛋白, 在基础条件下, Nrf2 作为细胞的一个组成部分存在于细胞质中, 并与 Keap1 结合, 最终降解 Keap1, 它的发现揭示了 Keap1/Nrf2 复合物作为细胞“氧化应激传感器”的功能^[36]; 西格列汀通过激活 SAP 相关 ALI 中 p62-Keap1-Nrf2 途径, 促进 Nrf2 核转位, 最终发挥保护作用, 从而抑制氧化应激、控制炎症、减少 ROS 生成和过度自噬, 从而抑制 SAP 相关 ALI^[37]。

3 抗细胞焦亡机制

目前认为焦亡是一种程序性细胞坏死, 其特征是细胞肿胀、破裂, 并释放促炎内容物; 焦亡包括 caspase-1 依赖的经典炎症小体途径和 caspase-4/5/11 依赖的非经典炎症小体途径。近年来, caspase-1 依赖的经典炎症小体受到广泛关注; 已有研究证明, 在肝损伤与肝纤维化中, NLRP3 炎症小体激活后, 小鼠和人的原发性肝细胞可发生焦死, 随后释放 NLRP3 炎症小体蛋白, 放大和延续炎症小体驱动的纤维化; 另外, Gaul 等^[38]发现通过阻断 caspase-1 和消皮素 D (Gasdermin D) 的激活,

可抑制焦亡；因此肝细胞焦亡和炎性小体成分的释放是一种新的机制传播肝损伤和肝纤维化的发展；Fan等^[39]发现细胞焦亡与SAP及相关ALI中起着关键作用；螾蜞菊内酯（Wed）通过抑制焦亡和铁死亡来保护AP和相关的肺损伤，并表示可能与激活或上调GPX4水平有关；Gao等^[40]提出，在体内和体外，去除焦亡相关因子NLRP3、caspase-1或焦孔素（Gsdmd）可以有效地减少腺泡细胞死亡和胰腺组织与肺组织的坏死程度。

4 现状与展望

SAP相关ALI在临床上被认为是一个复杂且棘手的临床疾病，在过去的几十年里，有大量动物实验证明，SAP可导致ALI中各种信号通路的持续激活，通过抑制相关信号通路，可以减少促炎因子的分泌，减轻肺损伤，达到一定的治疗效果。近10年来，如间充质干细胞（MSCs）、腹腔穿刺引流（APD）、腹腔灌洗等治疗SAP及SAP相关ALI的方式也开始被陆续报道。然而，准确有效的靶向抑制剂的发现仍依赖于通路中涉及的基因和蛋白质的研究，而炎症疾病的诊断基因和蛋白质组学的研究目前仍处于初级阶段。在今后的研究中，需要注重分析各种蛋白质、基因及信号通路之间的相互作用，以此加深对SAP相关ALI的机制的理解，望能早日为有效诊断和治疗提供实验依据。

利益冲突：所有作者均声明不存在利益冲突。

参考文献

- [1] Zerem E. Treatment of severe acute pancreatitis and its complications[J]. *World J Gastroenterol*, 2014, 20(38): 13879-13892. doi: 10.3748/wjg.v20.i38.13879.
- [2] Guo H, Suo DW, Zhu HP, et al. Early blood purification therapy of severe acute pancreatitis complicated by acute lung injury[J]. *Eur Rev Med Pharmacol Sci*, 2016, 20(5):873-878.
- [3] Surbatović M, Jovanović K, Radaković S, et al. Pathophysiological aspects of severe acute pancreatitis-associated lung injury[J]. *Srp Arh Celok Lek*, 2005, 133(1/2):76-81. doi: 10.2298/sarh0502076s.
- [4] Ge P, Luo YL, Okoye CS, et al. Intestinal barrier damage, systemic inflammatory response syndrome, and acute lung injury: a troublesome trio for acute pancreatitis[J]. *Biomed Pharmacother*, 2020, 132:110770. doi: 10.1016/j.biopha.2020.110770.
- [5] Iyer H, Elhence A, Mittal S, et al. Pulmonary complications of acute pancreatitis[J]. *Expert Rev Respir Med*, 2020, 14(2): 209-217. doi: 10.1080/17476348.2020.1698951.
- [6] Zhou JL, Zhou PC, Zhang YY, et al. Signal pathways and markers involved in acute lung injury induced by acute pancreatitis[J]. *Dis Markers*, 2021, 2021:9947047. doi: 10.1155/2021/9947047.
- [7] Iyer H, Elhence A, Mittal S, et al. Pulmonary complications of acute pancreatitis[J]. *Expert Rev Respir Med*, 2020, 14(2): 209-217. doi: 10.1080/17476348.2020.1698951.
- [8] Huang L, Wang MH, Yang XN, et al. Acute lung injury in patients with severe acute pancreatitis[J]. *Turk J Gastroenterol*, 2013, 24(6): 502-507. doi: 10.4318/tjg.2013.0544.
- [9] Elder ASF, Saccone GTP, Dixon DL. Lung injury in acute pancreatitis: mechanisms underlying augmented secondary injury[J]. *Pancreatology*, 2012, 12(1): 49-56. doi: 10.1016/j.pan.2011.12.012.
- [10] Cha SM, Cha JD, Jang EJ, et al. Sophoraflavanone G prevents *Streptococcus mutans* surface antigen I/II-induced production of NO and PGE2 by inhibiting MAPK-mediated pathways in RAW 264.7 macrophages[J]. *Arch Oral Biol*, 2016, 68: 97-104. doi: 10.1016/j.archoralbio.2016.04.001.
- [11] Hung YC, Hsu CC, Chung CH, et al. The disintegrin, trimucrin, suppresses LPS-induced activation of phagocytes primarily through blockade of NF- κ B and MAPK activation[J]. *Naunyn Schmiedebergs Arch Pharmacol*, 2016, 389(7): 723-737. doi: 10.1007/s00210-016-1233-7.
- [12] Kong GQ, Huang X, Wang LP, et al. Astilbin alleviates LPS-induced ARDS by suppressing MAPK signaling pathway and protecting pulmonary endothelial glycocalyx[J]. *Int Immunopharmacol*, 2016, 36: 51-58. doi: 10.1016/j.intimp.2016.03.039.
- [13] Cornell TT, Fleszar A, McHugh W, et al. Mitogen-activated protein kinase phosphatase 2, MKP-2, regulates early inflammation in acute lung injury[J]. *Am J Physiol Lung Cell Mol Physiol*, 2012, 303(3):L251-258. doi: 10.1152/ajplung.00063.2012.
- [14] Chen C, Wang YL, Zhang ZZ, et al. Toll-like receptor 4 regulates heme oxygenase-1 expression after hemorrhagic shock induced acute lung injury in mice: requirement of p38 mitogen-activated protein kinase activation[J]. *Shock*, 2009, 31(5): 486-492. doi: 10.1097/SHK.0b013e318188f7e1.
- [15] Zhou Y, Xia HM, Zhao L, et al. SB203580 attenuates acute lung injury and inflammation in rats with acute pancreatitis in pregnancy[J]. *Inflammopharmacology*, 2019, 27(1): 99-107. doi: 10.1007/s10787-018-0522-9.
- [16] Ye W, Zheng CL, Yu DL, et al. Lipoxin A4 ameliorates acute pancreatitis-associated acute lung injury through the antioxidative and anti-inflammatory effects of the Nrf2 pathway[J]. *Oxid Med Cell Longev*, 2019, 2019:2197017. doi: 10.1155/2019/2197017.
- [17] Yu SH, Xie JM, Xiang YK, et al. Downregulation of TNF- α /TNF-R1 signals by AT-lipoxin A4 may be a significant mechanism of attenuation in SAP-associated lung injury[J]. *Mediat Inflamm*, 2019, 2019:9019404. doi: 10.1155/2019/9019404.
- [18] Chatterjee PK, Al-Abed Y, Sherry B, et al. Cholinergic agonists regulate JAK2/STAT3 signaling to suppress endothelial cell

- activation[J]. *Am J Physiol Cell Physiol*, 2009, 297(5): C1294–1306. doi: [10.1152/ajpcell.00160.2009](https://doi.org/10.1152/ajpcell.00160.2009).
- [19] Chen Y, Shao Z, Jiang EH, et al. CCL21/CCR7 interaction promotes EMT and enhances the stemness of OSCC via a JAK2/STAT3 signaling pathway[J]. *J Cell Physiol*, 2020, 235(9): 5995–6009. doi: [10.1002/jcp.29525](https://doi.org/10.1002/jcp.29525).
- [20] Han X, Wang YX, Chen HL, et al. Enhancement of ICAM-1 via the JAK2/STAT3 signaling pathway in a rat model of severe acute pancreatitis-associated lung injury[J]. *Exp Ther Med*, 2016, 11(3): 788–796. doi: [10.3892/etm.2016.2988](https://doi.org/10.3892/etm.2016.2988).
- [21] Qin MZ, Qin MB, Liang ZH, et al. Effect of SOCS3 on lung injury in rats with severe acute pancreatitis through regulating JAK2/STAT3 signaling pathway[J]. *Eur Rev Med Pharmacol Sci*, 2019, 23(22):10123–10131. doi: [10.26355/eurrev_201911_19582](https://doi.org/10.26355/eurrev_201911_19582).
- [22] Kershaw NJ, Murphy JM, Liao NP, et al. SOCS3 binds specific receptor-JAK complexes to control cytokine signaling by direct kinase inhibition[J]. *Nat Struct Mol Biol*, 2013, 20(4): 469–476. doi: [10.1038/nsmb.2519](https://doi.org/10.1038/nsmb.2519).
- [23] Karki P, Ke YB, Zhang CO, et al. SOCS3-microtubule interaction via CLIP-170 and CLASP2 is critical for modulation of endothelial inflammation and lung injury[J]. *J Biol Chem*, 2021, 296: 100239. doi: [10.1074/jbc.RA120.014232](https://doi.org/10.1074/jbc.RA120.014232).
- [24] Li S, Cui HZ, Xu CM, et al. RUNX3 protects against acute lung injury by inhibiting the JAK2/STAT3 pathway in rats with severe acute pancreatitis[J]. *Eur Rev Med Pharmacol Sci*, 2019, 23(12): 5382–5391. doi: [10.26355/eurrev_201906_18207](https://doi.org/10.26355/eurrev_201906_18207).
- [25] Piao XH, Zou YP, Sui XD, et al. Hydrostatin-SN10 ameliorates pancreatitis-induced lung injury by affecting IL-6-induced JAK2/STAT3-associated inflammation and oxidative stress[J]. *Oxid Med Cell Longev*, 2019, 2019:9659757. doi: [10.1155/2019/9659757](https://doi.org/10.1155/2019/9659757).
- [26] Yang SJ, Song YD, Wang QF, et al. Daphnetin ameliorates acute lung injury in mice with severe acute pancreatitis by inhibiting the JAK2-STAT3 pathway[J]. *Sci Rep*, 2021, 11(1): 11491. doi: [10.1038/s41598-021-91008-6](https://doi.org/10.1038/s41598-021-91008-6).
- [27] Ramudo L, Yubero S, Manso MA, et al. Effects of dexamethasone on intercellular adhesion molecule 1 expression and inflammatory response in necrotizing acute pancreatitis in rats[J]. *Pancreas*, 2010, 39(7):1057–1063. doi: [10.1097/MPA.0b013e3181da0f3e](https://doi.org/10.1097/MPA.0b013e3181da0f3e).
- [28] 徐志红, 白永愉, 黄新策, 等. 垂盆草提取物经JAK2/STAT3信号通路途径改善大鼠重症急性胰腺炎肺损伤的研究[J]. *肝胆胰外科杂志*, 2014, 26(5): 398–402. doi: [10.13709/j.cnki.1007-1954.2014.05.013](https://doi.org/10.13709/j.cnki.1007-1954.2014.05.013).
- Xu ZH, Bai YY, Huang XC, et al. Study of sedum sarmentosum bunge extraction attenuates on severe acute pancreatitis-associated acute lung injury in rats model via JAK2/STAT3 signaling pathway[J]. *Journal of Hepatopancreatobiliary Surgery*, 2014, 26(5): 398–402. doi: [10.13709/j.cnki.1007-1954.2014.05.013](https://doi.org/10.13709/j.cnki.1007-1954.2014.05.013).
- [29] Jiang N, Li ZX, Luo YL, et al. Emodin ameliorates acute pancreatitis-induced lung injury by suppressing NLRP3 inflammasome-mediated neutrophil recruitment[J]. *Exp Ther Med*, 2021, 22(2):857. doi: [10.3892/etm.2021.10289](https://doi.org/10.3892/etm.2021.10289).
- [30] Gao ZM, Sui JD, Fan R, et al. Emodin protects against acute pancreatitis-associated lung injury by inhibiting NLRP3 inflammasome activation via Nrf2/HO-1 signaling[J]. *Drug Des Devel Ther*, 2020, 14:1971–1982. doi: [10.2147/DDDT.S247103](https://doi.org/10.2147/DDDT.S247103).
- [31] Zhang XP, Zhang L, Chen LJ, et al. Influence of dexamethasone on inflammatory mediators and NF-kappaB expression in multiple organs of rats with severe acute pancreatitis[J]. *World J Gastroenterol*, 2007, 13(4):548–556. doi: [10.3748/wjg.v13.i4.548](https://doi.org/10.3748/wjg.v13.i4.548).
- [32] Yu J, Ni L, Zhang XY, et al. Surfactant protein D dampens lung injury by suppressing NLRP3 inflammasome activation and NF-κB signaling in acute pancreatitis[J]. *Shock*, 2019, 51(5):557–568. doi: [10.1097/SHK.0000000000001244](https://doi.org/10.1097/SHK.0000000000001244).
- [33] Huang YN, Yang YY, Xu YY, et al. Nrf2/HO-1 axis regulates the angiogenesis of gastric cancer via targeting VEGF[J]. *Cancer Manag Res*, 2021, 13:3155–3169. doi: [10.2147/CMAR.S292461](https://doi.org/10.2147/CMAR.S292461).
- [34] Zhang Z, Yang K, Mao R, et al. Ginsenoside Rg1 inhibits oxidative stress and inflammation in rats with spinal cord injury via Nrf2/HO-1 signaling pathway[J]. *Neuroreport*, 2022, 33(2): 81–89. doi: [10.1097/WNR.0000000000001757](https://doi.org/10.1097/WNR.0000000000001757).
- [35] Lv CM, Maharjan S, Wang QQ, et al. A -lipoic acid promotes neurological recovery after ischemic stroke by activating the Nrf2/HO-1 pathway to attenuate oxidative damage[J]. *Cell Physiol Biochem*, 2017, 43(3): 1273–1287. doi: [10.1159/000481840](https://doi.org/10.1159/000481840).
- [36] Bellezza I, Giambanco I, Minelli A, et al. Nrf2-Keap1 signaling in oxidative and reductive stress[J]. *Biochim Biophys Acta Mol Cell Res*, 2018, 1865(5):721–733. doi: [10.1016/j.bbamcr.2018.02.010](https://doi.org/10.1016/j.bbamcr.2018.02.010).
- [37] Kong LM, Deng J, Zhou X, et al. Sitagliptin activates the p62-Keap1-Nrf2 signalling pathway to alleviate oxidative stress and excessive autophagy in severe acute pancreatitis-related acute lung injury[J]. *Cell Death Dis*, 2021, 12(10):928. doi: [10.1038/s41419-021-04227-0](https://doi.org/10.1038/s41419-021-04227-0).
- [38] Gaul S, Leszczynska A, Alegre F, et al. Hepatocyte pyroptosis and release of inflammasome particles induce stellate cell activation and liver fibrosis[J]. *J Hepatol*, 2021, 74(1):156–167. doi: [10.1016/j.jhep.2020.07.041](https://doi.org/10.1016/j.jhep.2020.07.041).
- [39] Fan R, Sui JD, Dong XP, et al. Wedelolactone alleviates acute pancreatitis and associated lung injury via GPX4 mediated suppression of pyroptosis and ferroptosis[J]. *Free Radic Biol Med*, 2021, 173:29–40. doi: [10.1016/j.freeradbiomed.2021.07.009](https://doi.org/10.1016/j.freeradbiomed.2021.07.009).
- [40] Gao L, Dong XW, Gong WJ, et al. Acinar cell NLRP3 inflammasome and gasdermin D (GSDMD) activation mediates pyroptosis and systemic inflammation in acute pancreatitis[J]. *Br J Pharmacol*, 2021, 178(17):3533–3552. doi: [10.1111/bph.15499](https://doi.org/10.1111/bph.15499).

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