AJPMHS GLOBAL RESEARCH NETWORK

AMERICAN Journal of Pediatric Medicine and Health Sciences
Volume 3, Issue 8, 2025 ISSN (E): 2993-2149

Key Inflammatory Mediators in Acute Pancreatitis

Alimbekova L.U., Sabirova S.A., Tursunov D.X.
Tashkent State Medical University

Abstract: Acute pancreatitis (AP) is a multifactorial inflammatory disease of the pancreas characterized by premature activation of digestive enzymes, acinar cell injury, and systemic inflammation. The pathogenesis of AP is tightly linked to the activation of key inflammatory signaling pathways and mediators that orchestrate the immune response.

Keywords: acute pancreatitis, inflammation, cytokines, NF-κB, MAPK, JAK/STAT, NLRP3 inflammasome, TNF-α, signaling pathways, macrophages.

Introduction

The pathogenesis of acute pancreatitis is accompanied by the activation of inflammatory mediators, among which interleukins, tumor necrosis factor-alpha, chemokines, and free radicals play a key role. Their excessive release leads to the formation of a cytokine storm, causing damage not only to the pancreas but also to other organs.

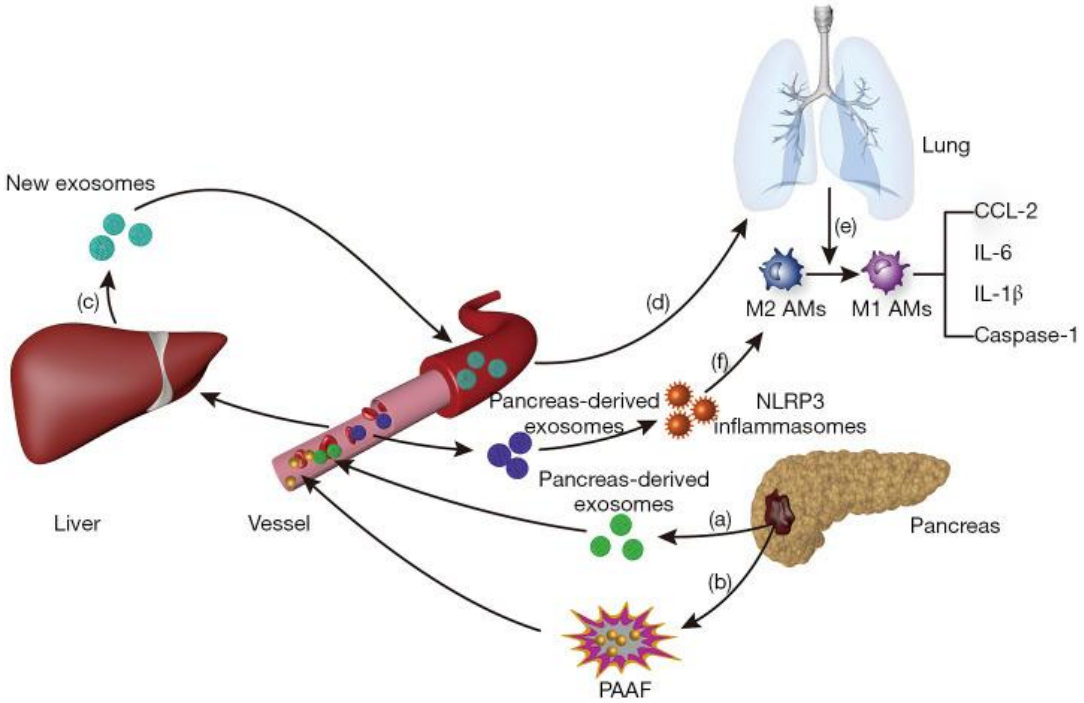

Fig. 1. A narrative review of acute pancreatitis and its diagnosis, pathogenetic mechanism, and management [53]

It is well known that cytokines such as TNF-α, IL-1β, IL-6, and IL-8 are key mediators that initiate the inflammatory response in the pancreas and other organs [6]. Early studies have demonstrated that the apoptosis of acinar cells is promoted by the release of the aforementioned

pro-inflammatory cytokines and their interaction with peripheral blood mononuclear cells (PBMCs) [17,25]. Among these pro-inflammatory cytokines, special attention should be given to TNF-α due to its potent recruitment of macrophages to inflamed regions in acute pancreatitis (AP).

TNF-α plays a particularly significant role by promoting macrophage aggregation and chemotaxis to inflamed areas of the pancreas, as well as by stimulating the secretion of endothelial adhesion factors (PECAM-1), intercellular adhesion molecule (ICAM-1), and selectins by damaged endothelial cells [30,27,35,52].

Acute pancreatitis is a polyetiological inflammatory disease of the pancreas, characterized by acinar cell injury, enzyme activation, and the initiation of a powerful systemic response [2].

It has been proven that a cascade of interconnected signaling pathways plays a key role in the pathogenesis of acute pancreatitis by regulating the expression of pro-inflammatory mediators, leukocyte chemotaxis, and the activation of innate immunity. The most significant among these pathways include NF-κB, MAPK, JAK/STAT, and the NLRP3 inflammasome [22,9].

1. NF-κB signaling pathway

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is one of the central regulators of the inflammatory response in acute pancreatitis [11,43]. Under normal conditions, NF-κB resides in the cytoplasm in an inactive complex with its inhibitor IκBα. Upon stimulation by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), Toll-like receptors (TLRs)—particularly TLR4—are activated, initiating the phosphorylation and subsequent degradation of IκBα. This process releases NF-κB dimers (p65/p50), which translocate into the nucleus and induce the expression of IL-1β, IL-6, TNF-α, iNOS, COX-2, and adhesion molecules such as ICAM-1 and VCAM-1 [34,19].

In the development of acute pancreatitis induced by L-arginine, nuclear factor NF-κB is detected in acinar cells as early as 30 minutes after induction, contributing to neutrophil recruitment, increased vascular permeability, and pancreatic tissue necrosis. This process establishes a vicious cycle of inflammation [16].

2. MAPK (mitogen-activated protein kinase) signaling pathway

The MAPK (Mitogen-Activated Protein Kinases) family includes several signaling cascades—ERK1/2, JNK (c-Jun N-terminal kinase), and p38 MAPK—which are activated through phosphorylation and mediate signal transduction across the cell membrane. In acute pancreatitis, the main activators of these pathways are oxidative stress, IL-1β, and TNF-α [26,44].

- p38 MAPK plays a key role in stabilizing the mRNA of pro-inflammatory cytokines.
- JNK is involved in the induction of apoptosis and enhances the production of nitric oxide (NO) and reactive oxygen species (ROS)
- ERK1/2 is activated by growth factor receptors and can also promote the synthesis of inflammatory mediators.

Activation of MAPK signaling in acinar cells promotes the synthesis and secretion of pro-inflammatory factors and enzymes (including trypsin), thereby exacerbating tissue damage and amplifying local inflammation [15,48].

JAK/STAT (Janus kinase/signal transducer and activator of transcription) signaling pathway. Upon binding of cytokines (such as IL-6, IFN-γ, and IL-10) to their specific receptors on the surface of immune and non-immune cells, the JAK/STAT (Janus Kinase / Signal Transducers and Activators of Transcription) pathway is activated [4].

In acute pancreatitis, activation of the IL-6/STAT3 pathway is observed both locally in the pancreas and systemically in organs such as the liver and lungs. This pathway promotes the

expression of C-reactive protein (CRP) and serum amyloid A, thereby exacerbating the acute-phase response.

In addition to its pro-inflammatory effects, STAT3 can also mediate anti-apoptotic and regenerative signals, thus playing a dual role.

Uncontrolled hyperactivation of STAT3 may contribute to the development of systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction [37,23].

3. NLRP3 inflammasome

The inflammasome is a multiprotein complex of the innate immune system that is activated in response to cellular stress, reactive oxygen species (ROS), ATP, cholesterol crystals, or disturbances in ion balance. The NLRP3 inflammasome consists of the sensor protein NLRP3, the adaptor ASC, and the effector caspase-1 [7].

In the context of acute pancreatitis, acinar cell injury and mitochondrial dysfunction initiate the activation of the NLRP3 inflammasome.

This leads to the activation of caspase-1, which cleaves pro-IL-1β and pro-IL-18 into their active forms.

IL-1β promotes enhanced infiltration of macrophages and neutrophils, while IL-18 amplifies the Th1 immune response and contributes to tissue damage. Activation of the inflammasome in severe pancreatitis correlates with extensive necrosis and the development of a systemic inflammatory response. Inhibition of NLRP3 or caspase-1 is considered a promising therapeutic approach [24,39].

All of the signaling pathways described above do not operate in isolation but represent interconnected components of a unified inflammatory network. Their cross-activation amplifies the intensity of the inflammatory response and contributes to the progression of acute pancreatitis [45,12]:

The NF-κB signaling pathway not only initiates the transcription of key pro-inflammatory mediators but also induces the expression of NLRP3 inflammasome components and pro-IL-1β, thereby establishing a molecular platform for the subsequent activation of caspase-1 and the release of active IL-1β [33,38,50].

The MAPK cascades (particularly p38 and JNK) and the JAK/STAT pathway (notably STAT3) can enhance the transcriptional activity of NF-κB, as well as directly regulate the production of pro-inflammatory cytokines such as IL-6 and TNF-α, thereby synergistically sustaining the systemic inflammatory response [21,40,46].

Damage to pancreatic acinar cells is accompanied by the accumulation of reactive oxygen species (ROS), driven by mitochondrial stress and lipid peroxidation. These molecules play a critical role in ROS-dependent activation of the NLRP3 inflammasome, leading to the cascade activation of the inflammatory response [8,29].

Thus, in the setting of acute pancreatitis, a self-sustaining inflammatory cascade is formed, in which molecular signaling pathways mutually amplify one another. This leads to massive local inflammation, acinar tissue destruction, the development of necrosis, and the progression of a systemic inflammatory response with a high risk of multiple organ failure.

Thus, an inflammatory cascade is formed in which various pathways reinforce each other, leading to massive inflammation, tissue necrosis, and systemic pathology.

Synergism and Cross-Regulation of Inflammatory Signaling Pathways in Acute Pancreatitis

One of the key aspects of the pathogenesis of acute pancreatitis (AP) is the interaction between multiple inflammatory signaling pathways, such as TLR4/NF-κB, NLRP3 inflammasome,

JAK/STAT, and MAPK. These pathways do not function in isolation but form a complex network, where their activation can be interdependent, mutually enhancing, or, in some contexts, regulatory and limiting. [47].

1. Interaction between TLR4 and the NLRP3 inflammasome

Activation of TLR4 typically occurs in response to DAMPs (damage-associated molecular patterns) released from injured acinar cells [51]. Activation of the TLR4 receptor initiates the MyD88-dependent pathway, leading to the transcription of the pro-IL-1β gene and NLRP3 inflammasome components through NF-κB activation [20]. However, full activation of the inflammasome requires an additional "second signal," such as ROS, potassium efflux, or mitochondrial damage [41]. This indicates a two-step model of NLRP3 activation, in which the TLR4/NF-κB pathway provides the priming signal—preparing the cells for subsequent NLRP3 inflammasome activation [28].

2. Synergy Between NF-κB and JAK/STAT

Cytokines induced via the NF-κB pathway (such as IL-6) subsequently activate the JAK/STAT signaling pathway in both autocrine and paracrine manners. Specifically, IL-6 binds to its receptor IL-6R, which triggers the phosphorylation of JAK1/2 and STAT3 [Heink S, Yogev N, Garbers C, Herwerth M, Aly L, Gasperi C, Husterer V, Scholz CJ, Niess JH, Reindl M, Krug A, Waisman A, Müller W, Rose-John S, Becher B. Trans-presentation of IL-6 by dendritic cells is required for the priming of pathogenic TH17 cells. Nat Immunol. 2017;18(1):74–85STAT3 then translocates to the nucleus and enhances the expression of genes involved in inflammation and cell survival. In this way, NF-κB and JAK/STAT form a positive feedback loop, amplifying the production of pro-inflammatory mediators [36].

3. MAPK and Its Cross-Activation

The MAPK pathway (particularly p38 and JNK) can also be activated through TLR4 and is involved in enhancing the transcription of pro-inflammatory genes [Jiménez-Castro MB, Cornide-Petronio ME, Gracia-Sancho J, Casillas-Ramírez A, Peralta C. Mitogen Activated Protein Kinases in Steatotic and Non-Steatotic Livers Submitted to Ischemia-Reperfusion. Int J Mol Sci. 2019 Apr 10;20(7):1785]. Interestingly, p38 MAPK is capable of stabilizing the mRNA of cytokines induced by NF-κB, such as TNF-α, thereby prolonging their biological activity [1]. In certain models of pancreatitis, it has been shown that inhibition of p38 MAPK leads to a reduction in TNF-α expression even in the presence of active NF-κB [13,10].

4. Joint Involvement in the Initiation and Amplification of Inflammation

These pathways synergize at multiple levels [3,54,31,32]:

- At the transcriptional level: NF-κB and AP-1 (a downstream product of the MAPK pathway) can cooperatively activate the promoters of the same target genes.
- At the secretion level: IL-1β, activated via the NLRP3 inflammasome, can enhance TLR4 expression and increase cellular sensitivity to DAMPs.
- At the level of cellular polarization: Combined activation of these pathways promotes a predominance of the M1 macrophage phenotype, sustaining the inflammatory response.

5. Mechanisms of Self-Sustaining Inflammation

These signaling axes also form mechanisms of self-sustaining inflammation: the production of IL-6 and IL-1β enhances the expression of TLR4 and STAT3, which in turn amplify the inflammatory response. Additionally, ROS generated as a result of inflammation activate both the NLRP3 and MAPK pathways, creating a vicious cycle of inflammation [42,49].

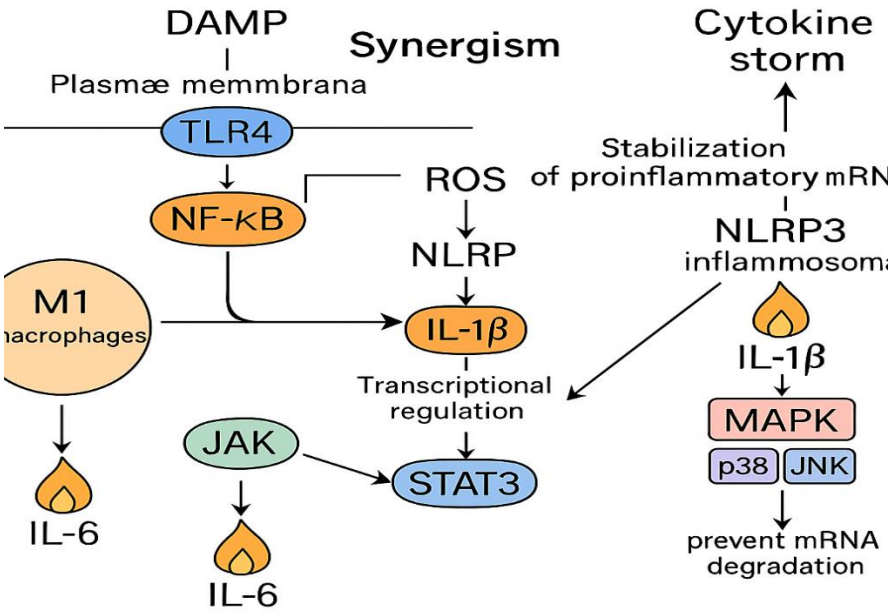

Fig.2. Cross-regulation and synergistic interactions between key inflammatory signaling pathways (TLR4/NF-κB, NLRP3 inflammasome, MAPK, and JAK/STAT) in the pathogenesis of acute pancreatitis.

Conclusion

Thus, the TLR4/NF-κB, NLRP3, MAPK, and JAK/STAT signaling pathways are not merely activated in parallel during acute pancreatitis (AP), but rather form a tightly interconnected network, in which cross-regulation and synergism amplify the inflammatory response. Targeting these interactions may represent a key approach to modifying the course of the disease, particularly in severe forms of AP.

References

1. Barker KH, Higham JP, Pattison LA, Taylor TS, Chessell IP, Welsh F, Smith ESJ, Bulmer DC. Sensitization of colonic nociceptors by TNFα is dependent on TNFR1 expression and p38 MAPK activity. J Physiol. 2022 Aug;600(16):3819-3836
2. Baron TH, DiMaio CJ, Wang AY, Morgan KA. American Gastroenterological Association Clinical Practice Update: Management of Pancreatic Necrosis. Gastroenterology. 2020 Jan;158(1):67-75.e1
3. Chen Y, Ye X, Escames G, Lei W, Zhang X, Li M, Jing T, Yao Y, Qiu Z, Wang Z, Acuña-Castroviejo D, Yang Y. The NLRP3 inflammasome: contributions to inflammation-related diseases. Cell Mol Biol Lett. 2023 Jun 27;28(1):51;
4. Chen Z, Zheng R, Jiang H, Zhang X, Peng M, Jiang T, Zhang X, Shang H. Therapeutic efficacy of Xuebijing injection in treating severe acute pancreatitis and its mechanisms of action: A comprehensive survey. Phytomedicine. 2025 May; 140:156629
5. Druszczyńska M, Godkowicz M, Kulesza J, Wawrocki S, Fol M. Cytokine Receptors-Regulators of Antimycobacterial Immune Response. Int J Mol Sci. 2022 Jan 20;23(3):1112;
6. Duan P-Y, Ma Y, Li X-N, et al. (2019). Inhibition of RIPK1-dependent regulated acinar cell necrosis provides protection against acute pancreatitis via the RIPK1/NF-κB/AQP8 pathway. Exp Mol Med 51:1–17
7. Ferrero-Andrés A, Panisello-Roselló A, Roselló-Catafau J, Folch-Puy E. NLRP3 Inflammasome-Mediated Inflammation in Acute Pancreatitis. Int J Mol Sci. 2020 Jul 29;21(15):5386;

8. Gao L, Chong E, Pendharkar S, Hong J, Windsor JA, Ke L, Li W, Phillips A. The Effects of NLRP3 Inflammasome Inhibition in Experimental Acute Pancreatitis: A Systematic Review and Meta-Analysis. Pancreas. 2022 Jan 1;51(1):13-24;

9. Gukovskaya AS, Gukovsky I, Algül H, Habtezion A. Autophagy, Inflammation, and Immune Dysfunction in the Pathogenesis of Pancreatitis. Gastroenterology. 2017 Nov;153(5):1212-1226

10. Gukovskaya AS, Gukovsky I, Zaninovic V, Song M, Sandoval D, Gukovsky S, Pandol SJ. Activation of p38 mitogen-activated protein kinase is required for TNF-α upregulation and NF-κB activation in cerulein pancreatitis in mice. Gastroenterology. 2002;122(4): 1004–1017

11. Guo Q, Jin Y, Chen X, Ye X, Shen X, Lin M, Zeng C, Zhou T, Zhang J. NF-κB in biology and targeted therapy: new insights and translational implications. Signal Transduct Target Ther. 2024 Mar 4;9(1):53;

12. Habtezion A, Gukovskaya AS, Pandol SJ. Acute Pancreatitis: A Multifaceted Set of Organelle and Cellular Interactions. Gastroenterology. 2019 May;156(7):1941-1950

13. Haque M, Kaminsky L, Abdulqadir R, Engers J, Kovtunov E, Rawat M, Al-Sadi R, Ma TY. Lactobacillus acidophilus inhibits the TNF-α-induced increase in intestinal epithelial tight junction permeability via a TLR-2 and PI3K-dependent inhibition of NF-κB activation. Front Immunol. 2024 Jul 16;15:1348010;

14. Hey-Hadavi J, Velisetty P, Mhatre S. Trends and recent developments in pharmacotherapy of acute pancreatitis. Postgrad Med. 2023 May;135(4):334-344

15. Huang H, Wang M, Guo Z, Wu D, Wang H, Jia Y, Liu H, Ding J, Peng J. Rutaecarpine alleviates acute pancreatitis in mice and AR42J cells by suppressing the MAPK and NF-κB signaling pathways via calcitonin gene-related peptide. Phytother Res. 2021 Nov;35(11):6472-6485;

16. Jakkampudi A, Jangala R, Reddy BR, Mitnala S, Nageshwar Reddy D, Talukdar R. NF-κB in acute pancreatitis: Mechanisms and therapeutic potential. Pancreatology. 2016 Jul-Aug;16(4):477-88;

17. Jakkampudi A, Jangala R, Reddy R, Mitnala S, Rao GV, Pradeep R, Reddy DN, Talukdar R. Acinar injury and early cytokine response in human acute biliary pancreatitis. Sci Rep. 2017 Nov 10;7(1):15276;

18. Jiménez-Castro MB, Cornide-Petronio ME, Gracia-Sancho J, Casillas-Ramírez A, Peralta C. Mitogen Activated Protein Kinases in Steatotic and Non-Steatotic Livers Submitted to Ischemia-Reperfusion. Int J Mol Sci. 2019 Apr 10;20(7):1785

19. Kang MH, Oh SC, Lee HJ, Kang HN, Kim JL, Kim JS, Yoo YA. Metastatic function of BMP-2 in gastric cancer cells: the role of PI3K/AKT, MAPK, the NF-κB pathway, and MMP-9 expression. Exp Cell Res. 2011 Jul 15;317(12):1746-62

20. Kang R, Chen R, Zhang Q, Hou W, Wu S, Cao L, Huang J, Yu Y, Fan XG, Yan Z, Sun X, Wang H, Wang Q, Tsung A, Billiar TR, Zeh HJ, Lotze MT, Tang D. HMGB1 in health and disease. Mol Aspects Med. 2014; 40:1–116.

21. Komar HM, Serpa G, Kerscher C, Schwoegl E, Mace TA, Jin M, Yang MC, Chen CS, Bloomston M, Ostrowski MC, Hart PA, Conwell DL, Lesinski GB. Inhibition of Jak/STAT signaling reduces the activation of pancreatic stellate cells in vitro and limits caerulein-induced chronic pancreatitis in vivo. Sci Rep. 2017 May 11;7(1):1787;

22. Li L, Tan Q, Wu X, Mou X, Lin Z, Liu T, Huang W, Deng L, Jin T, Xia Q. Coagulopathy and acute pancreatitis: pathophysiology and clinical treatment. Front Immunol. 2024 Oct 31;15:1477160;

23. Li M, Zhang X, Wang B, Xu X, Wu X, Guo M, Wang F. Effect of JAK2/STAT3 signaling pathway on liver injury associated with severe acute pancreatitis in rats. Exp Ther Med. 2018 Sep;16(3):2013-2021

24. Li X, He C, Li N, Ding L, Chen H, Wan J, Yang X, Xia L, He W, Xiong H, Shu X, Zhu Y, Lu N. The interplay between the gut microbiota and NLRP3 activation affects the severity of acute pancreatitis in mice. Gut Microbes. 2020 Nov 1;11(6):1774-1789;

25. Li Y, Li G, Suo L, Zhang J. Recent advances in studies of molecular hydrogen in the treatment of pancreatitis. Life Sci. 2021 Jan 1; 264:118641

26. Liu H, Xu X, Li J, Liu Z, Xiong Y, Yue M, Liu P. Overexpression of Plakophilin2 Mitigates Capillary Leak Syndrome in Severe Acute Pancreatitis by Activating the p38/MAPK Signaling Pathway. J Inflamm Res. 2024 Jun 26;17:4129-4149;

27. Liu Y, Zhou D, Long FW, Chen KL, Yang HW, Lv ZY, Zhou B, Peng ZH, Sun XF, Li Y, Zhou ZG. Resolvin D1 protects against inflammation in experimental acute pancreatitis and associated lung injury. Am J Physiol Gastrointest Liver Physiol. 2016 Mar 1;310(5):G303-9;

28. Lu HF, Zhou YC, Hu TY, Yang DH, Wang XJ, Luo DD, Qiu SQ, Cheng BH, Zeng XH. Unraveling the role of NLRP3 inflammasome in allergic inflammation: implications for novel therapies. Front Immunol. 2024 Jul 26;15:1435892

29. Lyu S, Liu S, Guo X, Zhang Y, Liu Z, Shi S, Li W, Pei J, Fan Y, Sun H. hP-MSCs attenuate severe acute pancreatitis in mice via inhibiting NLRP3 inflammasome-mediated acinar cell pyroptosis. Apoptosis. 2024 Jun;29(5-6):920-933

30. Malleo G, Mazzon E, Siriwardena AK, et al. (2007). TNF-alpha as a therapeutic target in acute pancreatitis-lessons from experimental models. Scientific World J 7:431–48;

31. Medzhitov R. Origin and physiological roles of inflammation. Nature. 2008;454(7203):428–435;

32. Murray PJ. Macrophage polarization. Annu Rev Physiol. 2017;79:541–566.

33. Papantoniou K, Aggeletopoulou I, Michailides C, Pastras P, Triantos C. Understanding the Role of NLRP3 Inflammasome in Acute Pancreatitis. Biology (Basel). 2024 Nov 18;13(11):945;

34. Patrad E, Khalighfard S, Amiriani T, Khori V, Alizadeh AM. Molecular mechanisms underlying the action of carcinogens in gastric cancer with a glimpse into targeted therapy. Cell Oncol (Dordr). 2022 Dec;45(6):1073-1117;

35. Pocino K, Carnazzo V, Stefanile A, Basile V, Guerriero C, Marino M, Rigante D, Basile U. Tumor Necrosis Factor-Alpha: Ally and Enemy in Protean Cutaneous Sceneries. Int J Mol Sci. 2024 Jul 16;25(14):7762;

36. Pogozheva ID, Cherepanov S, Park SJ, Raghavan M, Im W, Lomize AL. Structural Modeling of Cytokine-Receptor-JAK2 Signaling Complexes Using AlphaFold Multimer. J Chem Inf Model. 2023 Sep 25;63(18):5874-5895

37. Qiu Z, Xu F, Wang Z, Yang P, Bu Z, Cheng F, Jiang H, Li L, Zhang F. Blockade of JAK2 signaling produces immunomodulatory effect to preserve pancreatic homeostasis in severe acute pancreatitis. Biochem Biophys Rep. 2021 Sep 17;28:101133;

38. Rong J, Han C, Huang Y, Wang Y, Qiu Q, Wang M, Wang S, Wang R, Yang J, Li X, Hu C, Chen Z, Deng L, Huang W, Xia Q, Du D. Inhibition of xanthine oxidase alleviated pancreatic necrosis via HIF-1α-regulated LDHA and NLRP3 signaling pathway in acute pancreatitis. Acta Pharm Sin B. 2024 Aug;14(8):3591-3604;

39. Sendler M, van den Brandt C, Glaubitz J, Wilden A, Golchert J, Weiss FU, Homuth G, De Freitas Chama LL, Mishra N, Mahajan UM, Bossaller L, Völker U, Bröker BM, Mayerle J,

Lerch MM. NLRP3 Inflammasome Regulates Development of Systemic Inflammatory Response and Compensatory Anti-Inflammatory Response Syndromes in Mice With Acute Pancreatitis. Gastroenterology. 2020 Jan;158(1):253-269.e14

40. Sun C, Li B, Duan H, Tao B, Zhao C, Li W, Pang Y, Fan B, Feng S. Cytokine expressions of spinal cord injury treated by neurotropin and nafamostat mesylate. Ann Transl Med. 2021 Mar;9(6):489;
41. Swanson KV, Deng M, Ting JP. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. Nat Rev Immunol. 2019;19(8):477–489
42. Tan C, Li S, Zhang H, Yang H, Gao Y, Shi W. The Role of NLRP3 Inflammasome in Inflammatory Pancreatic Diseases. Front Pharmacol. 2021;12:752193;
43. Thapa R, Afzal O, Gupta G, Bhat AA, Almalki WH, Alzarea SI, Kazmi I, Altamimi ASA, Subramaniyan V, Thangavelu L, Singh SK, Dua K. Unveiling the connection: Long-chain non-coding RNAs and critical signaling pathways in breast cancer. Pathol Res Pract. 2023 Sep; 249:154736.
44. Wan L, Lin KT, Rahman MA, Ishigami Y, Wang Z, Jensen MA, Wilkinson JE, Park Y, Tuveson DA, Krainer AR. Splicing Factor SRSF1 Promotes Pancreatitis and KRASG12D-Mediated Pancreatic Cancer. Cancer Discov. 2023 Jul 7;13(7):1678-1695
45. Wiley MB, Mehrotra K, Bauer J, Yazici C, Bialkowska AB, Jung B. Acute Pancreatitis: Current Clinical Approaches, Molecular Pathophysiology, and Potential Therapeutics. Pancreas. 2023 Jul 1;52(6):e335-e343;
46. Yang X, Geng H, You L, Yuan L, Meng J, Ma Y, Gu X, Lei M. Rhein Protects Against Severe Acute Pancreatitis In vitro and In vivo by Regulating the JAK2/STAT3 Pathway. Front Pharmacol. 2022 Mar 17; 13:778221
47. Yu J, Wang C, Su L, Li Y, Liu Y, Guo Y. Crosstalk of TLR4/NF-κB, NLRP3 inflammasome, MAPK and JAK/STAT pathways in acute pancreatitis: From molecular mechanisms to potential therapeutic targets. Int Immunopharmacol. 2023;117:109983.
48. Zhang J, Mei F, Zhao L, Zuo T, Hong Y, Li M, Yu J, Wang W. Inhibition of the p38 MAPK pathway attenuates renal injury in pregnant rats with acute necrotizing pancreatitis. Immunol Res. 2021 Jun;69(3):295-306
49. Zhang W, Xu W, Xiong S. Blockade of TLR4 alleviates cerulein-induced acute pancreatitis in mice via inhibiting inflammation and oxidative stress. Mol Immunol. 2020;125:92–100
50. Zhang Y, Wang Y, Lu M, Qiao X, Sun B, Zhang W, Xue D. Modular analysis of bioinformatics demonstrates a critical role for NF-κB in macrophage activation. Inflammation. 2014 Aug;37(4):1240-53
51. Zhao L, Li J, Zeng X, Wang Y, Lu G, He S. DAMPs and their interactions with pattern recognition receptors in acute pancreatitis: implications for immunotherapy. Front Immunol. 2022;13:993719
52. Zhao R, Wang Y, Zhou Y, Fan W, Yin H. Tumor necrosis factor-α polymorphism and risk of primary nephrotic syndrome: A case-control study and meta-analysis. Immun Inflamm Dis. 2024 Jun;12(6):e1278
53. Zheng Z, Ding YX, Qu YX, Cao F, Li F. A narrative review of acute pancreatitis and its diagnosis, pathogenetic mechanism, and management. Annals of Translational Medicine. 2021 Jan;9(1):69
54. Zhou R, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in NLRP3 inflammasome activation. Nature. 2011;469(7329):221–225;