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The Role of the Monocyte–Macrophage System in the Pathogenesis of Acute Pancreatitis: A Review

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Abstract: Acute pancreatitis (AP) is an inflammatory disease of the pancreas characterized by premature activation of digestive enzymes and acinar cell damage, leading to local and systemic inflammation. Recent studies have highlighted the crucial role of the monocyte–macrophage system in the pathogenesis of AP.

Keywords: acute pancreatitis, macrophages, monocytes, inflammation, TLR4, NF-κB, NLRP3 inflammasome, cytokine storm, macrophage polarization, M1/M2, immune therapy.

Introduction

Acute pancreatitis (AP) is an inflammatory disorder characterized by premature activation of intrapancreatic enzymes, acinar cell injury, and the development of a robust inflammatory response.

In recent years, growing scientific interest has been directed toward elucidating the role of innate immune cells, particularly monocytes and macrophages, in the pathogenesis of AP [71]. These cells act not only as primary effectors of the inflammatory response but also as key regulators of its dynamics, influencing both local and systemic processes of tissue injury [55]. Damage to pancreatic acinar cells and the release of damage-associated molecular patterns (DAMPs) initiate the activation of pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), expressed on the surface of macrophages [18, 29, 59]. A particularly important role in this process is played by TLR4, the activation of which triggers the NF-κB and MAPK signaling pathways, leading to the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, as well as chemokines and adhesion molecules [22, 41, 61].

Analysis of the previous researches

The relevance of studying macrophage activity in acute pancreatitis is determined by their ability to modulate inflammation through polarization into distinct phenotypes [6, 47]. Classically activated macrophages (M1) exhibit pronounced pro-inflammatory activity, exacerbating tissue damage, whereas alternatively activated macrophages (M2) are associated with anti-inflammatory and reparative mechanisms [75]. An imbalance between these macrophage subpopulations contributes to the chronicity of inflammation, fibrogenesis, and the development of multiple organ dysfunction [21].

Current evidence indicates the multifaceted involvement of macrophages in the pathogenesis of acute pancreatitis, ranging from the initiation of the inflammatory cascade to its resolution and tissue remodeling [57]. Macrophages produce reactive oxygen and nitrogen species, promote the activation of the NLRP3 inflammasome and cytokine synthesis, modulate angiogenesis, participate in the formation of neutrophil extracellular traps (NETs), and interact with

components of the adaptive immune system, thereby contributing to a coordinated and integrated immune response [40]. In severe forms of acute pancreatitis, macrophages also contribute to the development of a cytokine storm, which underlies the systemic inflammatory response and multiple organ dysfunction [15].

Thus, macrophages represent a key element in the pathogenesis of acute pancreatitis, with significant therapeutic potential. Their polarization, activation signaling pathways, and interactions with other cellular components of the inflammatory microenvironment constitute promising targets for the development of immune-targeted therapies [12]. The study of molecular mechanisms regulating macrophage function is of great importance for understanding the pathogenesis of the disease and for the development of new, effective strategies for the prevention and treatment of acute pancreatitis [6].

Monocytes and macrophages, as key cells of the innate immune system, play a crucial role in the initiation and progression of the inflammatory response, as well as in the development of complications, including systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction [64].

The monocyte–macrophage system consists of circulating blood monocytes and tissue-resident macrophages [48, 63, 69] and specialized resident cells. Under physiological conditions, these cells perform key functions such as phagocytosis of pathogens, antigen presentation, regulation of immune responses, and maintenance of tissue homeostasis. During the development of inflammation, they become active participants in innate immunity by producing a wide range of inflammatory mediators, including cytokines, chemokines, and reactive oxygen species.

Damage to acinar cells is accompanied by the release of damage-associated molecular patterns (DAMPs), which activate pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) on the surface of macrophages [28, 32, 50]. Among them, TLR4 [52, 75] plays a key role by initiating the activation of the NF-κB signaling pathway [26] and the synthesis of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6. This process forms the basis of the inflammatory cascade in acute pancreatitis.

The signaling pathways activated by TLR4 [1], initiate a cascade of intracellular events involving both the MyD88-dependent and TRIF-dependent pathways, which lead to the activation of transcription factors NF-κB [3, 72] and AP-1. In experimental models, blockade of TLR4 [4] or MyD88 has been shown to reduce the severity of the inflammatory response, confirming the critical role of these mechanisms in the pathogenesis of acute pancreatitis.

Activation of the NLRP3 [39] in macrophages is another key component of the inflammatory response. Activation of the inflammasome leads to caspase-1 activation and the release of active forms of IL-1β and IL-18, which amplify inflammation and contribute to the development of a systemic inflammatory response. Targeted blockade of NLRP3 [16, 17] may represent a promising therapeutic approach for the treatment of acute pancreatitis.

Macrophages are involved in the generation of reactive oxygen and nitrogen species, which, on the one hand, provide antimicrobial activity, but on the other hand, exacerbate tissue damage through oxidative stress—an effect that has been confirmed in several experimental models of acute pancreatitis.

Macrophage polarization [19, 74] is a determining factor in the modulation of the immune response. M1 macrophages exert pro-inflammatory effects, promoting the synthesis of cytokines and inflammatory mediators, whereas M2 macrophages are involved in tissue repair and the resolution of inflammation. In acute pancreatitis, a predominance of M1 macrophages is associated with sustained inflammation, enhanced tissue injury, and a higher risk of systemic complications [38, 74] is associated with an intensified inflammatory response and extensive tissue damage.

The balance between M1 and M2 macrophages significantly influences the outcome of the disease. Modulation of macrophage polarization [2, 24] A shift in polarization toward an M2-dominant response may serve as a potential therapeutic strategy to reduce inflammation and stimulate reparative processes in pancreatic tissue.

Macrophages actively interact with other innate immune cells, including neutrophils, contributing to the formation of neutrophil extracellular traps (NETs), which can offer protection against pathogens but also exacerbate tissue damage when excessively activated.

In addition, macrophages play a crucial role in coordinating with cells of the adaptive immune system by participating in antigen presentation and the activation of T lymphocytes, thus shaping a complex and integrated immune response in acute pancreatitis. Monocytes and macrophages also participate in the regulation of angiogenesis and extracellular matrix remodeling. Their activity is associated with the synthesis of growth factors such as VEGF and TGF-β, which can contribute both to tissue repair and to the development of fibrosis [34, 66] during chronic inflammation. Persistent activation of macrophages [8, 67] and the sustained predominance of the M1 phenotype promotes the transition from acute inflammation to a chronic process.

As part of the systemic inflammatory response, macrophages contribute to the development of a cytokine storm—a condition characterized by excessive production of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α. The cytokine storm is one of the key mechanisms underlying the development of multiple organ dysfunction [14, 49] in severe cases of acute pancreatitis. Studies have shown that blockade of key cytokines can attenuate the severity of the systemic inflammatory response, thereby reducing the risk of multiple organ dysfunction and improving clinical outcomes.

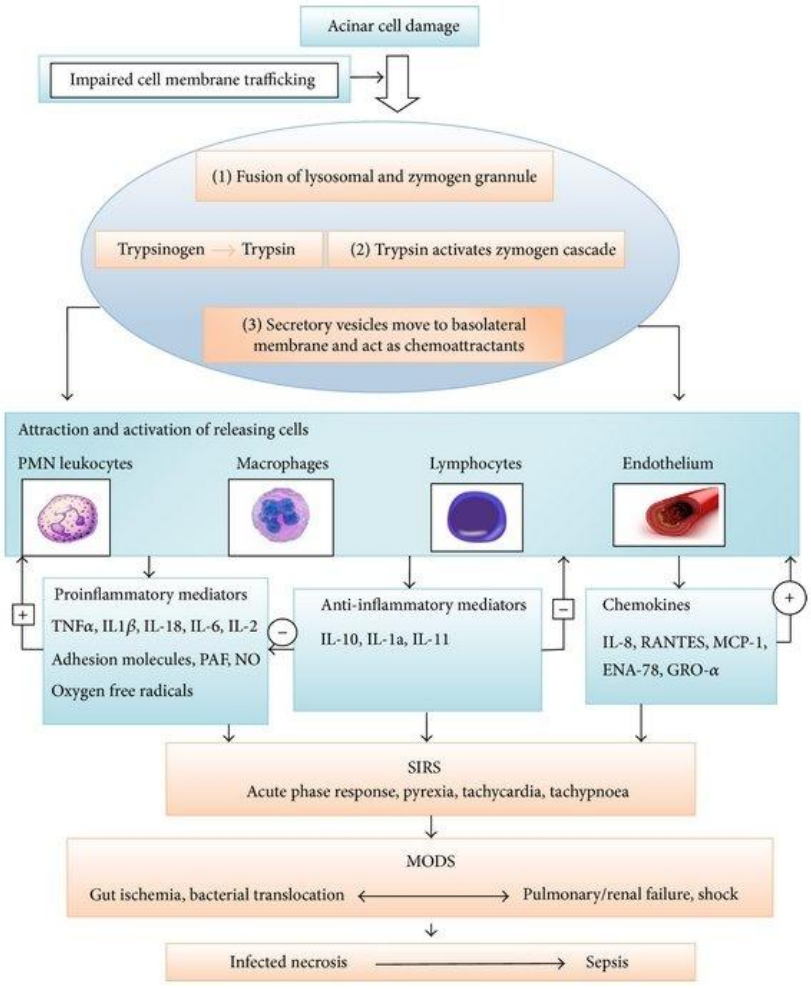

Fig. 1. Systemic model of the pathogenesis of acute pancreatitis [46]

Modern experimental models of acute pancreatitis have confirmed the relevance of macrophage-related therapeutic targets. Alcohol abuse, exposure to bile acids, and toxic agents stimulate acinar cells to increase the production of lysosomal and digestive enzymes. This is accompanied by inhibition of exocytosis and the formation of intracellular colocalization of zymogen and lysosomal granules, leading to premature fusion and activation of cathepsin B and trypsinogen within acinar cells. These events—associated with disrupted Ca^{2+} and ATP homeostasis—represent a critical step in triggering necroptosis and apoptosis pathways, including the RIP3–RIP1–MLKL cascade, ultimately resulting in necrotic changes in pancreatic tissue [74]. Toxic agents inhibit exocytosis, leading to intracellular colocalization of digestive and lysosomal enzymes and activation of cathepsin B. This, in turn, triggers cell death signaling pathways—including the RIP3–RIP1–MLKL cascade—and results in necroptosis of acinar cells, thereby exacerbating pancreatic tissue damage [9, 51].

Specifically, inhibition of TLR4 [14, 30, 45], blockade of the NLRP3 inflammasome [27, 43] and suppression of NF-κB signaling pathway activation [74] demonstrate a pronounced anti-inflammatory effect by reducing the severity of necrotic changes and the level of systemic inflammatory response. These findings provide a strong rationale for considering macrophages as a promising therapeutic target in the pharmacological treatment of acute pancreatitis.

Promising therapeutic approaches may include drugs that promote the shift of macrophage polarization [36, 60] toward the M2 phenotype, modulation of specific anti-inflammatory cytokine production, as well as gene and cell-based technologies aimed at regulating macrophage activity [37, 75]. In addition, the study of biomarkers of macrophage [53] may contribute to early diagnosis and prediction of disease severity in acute pancreatitis. Modern experimental and clinical studies are focused on identifying therapeutic agents capable of targeting key molecular mediators of macrophage activation. Among the most promising targets is TLR4 [71], NLRP3 [35, 42], caspases, the JAK/STAT signaling pathways, as well as NF-κB [25] and AP-1. Inhibitors of these pathways have demonstrated the ability to reduce the intensity of the inflammatory response, decrease the extent of necrosis, and prevent the development of systemic complications.

In the future, combined targeting of multiple pathways may play an important role—for example, the use of TLR4 [11, 54, 65], which may provide a more pronounced therapeutic effect and reduce the risk of systemic complications. Conducting clinical studies in this area appears to be both relevant and promising. Thus, an in-depth understanding of the molecular mechanisms regulating macrophage activity provide [5, 73], will enable the development of effective targeted drugs capable of preventing the progression to severe forms of pancreatitis and its complications, including multiple organ failure [62, 74] and chronic inflammation. Effective regulation of the macrophage system may become the key to successful treatment of this disease.

An important component of the pathogenesis of acute pancreatitis is the involvement of macrophages in the development of the systemic inflammatory response, which is often accompanied by multiple organ dysfunction [33]. The systemic inflammatory response is characterized by an excessive release of pro-inflammatory cytokines—TNF-α, IL-1β, and IL-6—and the activation of cascades that lead to increased vascular permeability, hypotension, and impaired microcirculation in vital organs.

A particularly important role in this process is played by the synergistic interaction between monocytes and macrophages [23, 44, 73] with endothelial cells, which contributes to the disruption of vascular wall integrity and promotes neutrophil migration into tissues. The cytokine storm in acute pancreatitis, induced by macrophages, is one of the key factors in the development of severe forms of the disease, including septic shock and multiple organ dysfunction.

From an experimental standpoint, it has been demonstrated that macrophages activated under conditions of hypoxia and oxidative stress exhibit increased expression of genes responsible for the synthesis of pro-inflammatory cytokines and genes associated with inflammasome activation.

This contributes to the development of a severe inflammatory cascade even in the presence of limited primary pancreatic tissue injury.

Fibrosis of pancreatic tissue, as one of the late complications of acute pancreatitis, is closely associated with chronic macrophage activation [20] and their interaction with fibroblasts. M2-polarized macrophages produce a range of growth factors, including TGF-β, which is a key mediator of fibrogenesis. This leads to enhanced collagen synthesis, remodeling of the extracellular matrix, and the formation of fibrotic scar tissue.

Consequently, chronic activation of macrophages [58] promotes the transition from acute inflammation to chronic pancreatitis. Effective modulation of macrophage activity [10] may become the key to preventing the progression of fibrosis [31, 68] and preserving the functional activity of the pancreas.

In several models of acute pancreatitis, the use of anti-TNF-α agents, IL-1β blockers, and TLR4 inhibitors has been associated with a significant reduction in systemic inflammation and decreased mortality. These findings highlight the high therapeutic potential of immuno-targeted approaches [56], were accompanied by a marked reduction in systemic inflammation and decreased mortality. These findings underscore the high therapeutic potential of immuno-targeted approaches.

The development of personalized medicine focused on the assessment of macrophage activation markers may serve as a foundation for predicting the severity of acute pancreatitis and selecting the most effective therapy. The use of biomarkers will enable the evaluation of monocyte–macrophage system activation and help predict the risk of systemic complications. A comprehensive investigation of macrophage [73] A comprehensive investigation of macrophage interactions with other immune cells, their polarization, involvement in tissue remodeling, and contribution to the systemic inflammatory response is a necessary step toward the development of effective therapeutic strategies for acute pancreatitis. This area remains highly relevant for both fundamental and clinical research.

Conclusion

Thus, the involvement of the monocyte–macrophage system in the pathogenesis of acute pancreatitis is multifaceted. These cells not only initiate the inflammatory response but also actively regulate its course, contributing to the development of systemic complications, multiple organ dysfunction, and chronic disease progression through tissue fibrosis.

Current research is opening new therapeutic perspectives aimed at modulating macrophage activity and suppressing key inflammatory pathways, which may significantly improve treatment outcomes in patients with acute pancreatitis.

References

1. Aney KJ, Jeong WJ, Vallejo AF, Burdziak C, Chen E, Wang A, Koak P, Wise K, Jensen K, Pe'er D, Dougan SK, Martelotto L, Nissim S. Novel Approach for Pancreas Transcriptomics Reveals the Cellular Landscape in Homeostasis and Acute Pancreatitis. Gastroenterology. 2024 Jun;166(6):1100-1113;
2. Bahram Yazdroudi F, Malek A. Reducing M2 macrophage in lung fibrosis by controlling anti-M1 agent. Sci Rep. 2025 Feb 3;15(1):4120;
3. Baldan J, Camacho-Roda J, Ballester M, Høj K, Kurilla A, Maurer HC, Arcila-Barrera S, Lin X, Pan Z, Castro JL, Mayorca-Guiliani AE, Rift CV, Hasselby J, Bouwens L, Lefebvre V, David CJ, Parnas O, DelGiorno KE, Erler JT, Rooman I, Arnes L. Resolution of Acinar Dedifferentiation Regulates Tissue Remodeling in Pancreatic Injury and Cancer Initiation. Gastroenterology. 2024 Sep;167(4):718-732.e18;

4. Chen F, Xu K, Han Y, Ding J, Ren J, Wang Y, Ma Z, Cao F. Mitochondrial dysfunction in pancreatic acinar cells: mechanisms and therapeutic strategies in acute pancreatitis. Front Immunol. 2024 Dec 24; 15:1503087;
5. Chen S, Saeed AFUH, Liu Q, Jiang Q, Xu H, Xiao GG, Rao L, Duo Y. Macrophages in immunoregulation and therapeutics. Signal Transduct Target Ther. 2023 May 22;8(1):207;
6. Chávez-Castillo M, Ortega Á, Cudris-Torres L, Duran P, Rojas M, Manzano A, Garrido B, Salazar J, Silva A, Rojas-Gomez DM, De Sanctis JB, Bermúdez V. Specialized Pro-Resolving Lipid Mediators: The Future of Chronic Pain Therapy? Int J Mol Sci. 2021 Sep 26;22(19):10370;
7. Deng L, Jian Z, Xu T, Li F, Deng H, Zhou Y, Lai S, Xu Z, Zhu L. Macrophage Polarization: An Important Candidate Regulator for Lung Diseases. Molecules. 2023 Mar 4;28(5):2379;
8. Diakopoulos KN, Lesina M, Wörmann SM, et al. Cell death in pancreatic diseases: apoptosis, necrosis and beyond. Pancreatology. 2021;21(2):173-184;
9. Dong Y, Wang T, Wu H. Heterogeneity of macrophage activation syndrome and treatment progression. Front Immunol. 2024 Apr 26;15:1389710;
10. Du Q, Dickinson A, Nakuleswaran P, Maghami S, Alagoda S, Hook AL, Ghaemmaghami AM. Targeting Macrophage Polarization for Reinstating Homeostasis following Tissue Damage. Int J Mol Sci. 2024 Jul 2;25(13):7278;
11. Du Q, Dickinson A, Nakuleswaran P, Maghami S, Alagoda S, Hook AL, Ghaemmaghami AM. Targeting Macrophage Polarization for Reinstating Homeostasis following Tissue Damage. Int J Mol Sci. 2024;25(13):7278;
12. Fajgenbaum DC, June CH. Cytokine Storm. N Engl J Med. 2020 Dec 3;383(23):2255-2273;
13. Feng M, Xu S. Global insights and knowledge mapping of immunity and inflammation in acute pancreatitis: A bibliometric and visual analysis. Medicine (Baltimore). 2025 Jun 13;104(24):e42898;
14. 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;
15. Gaman L, Dragos D, Vlad A, Robu GC, Radoi MP, Stroica L, Badea M, Gilca M. Phytoceuticals in Acute Pancreatitis: Targeting the Balance between Apoptosis and Necrosis. Evid Based Complement Alternat Med. 2018 Mar 4; 2018:5264592
16. Ge Z, Chen Y, Ma L, Hu F, Xie L. Macrophage polarization and its impact on idiopathic pulmonary fibrosis. Front Immunol. 2024 Jul 26;15:1444964;
17. Geiß C, Salas E, Guevara-Coto J, Régnier-Vigouroux A, Mora-Rodríguez RA. Multistability in Macrophage Activation Pathways and Metabolic Implications. Cells. 2022 Jan 25;11(3):404;
18. Geiß C, Salas E, Guevara-Coto J, Régnier-Vigouroux A, Mora-Rodríguez RA. Multistability in Macrophage Activation Pathways and Metabolic Implications. Cells. 2022;11(3):404;
19. He J, Liu MW, Wang ZY, Shi RJ. Protective effects of the notoginsenoside R1 on acute lung injury by regulating the miR-128-2-5p/Tollip signaling pathway in rats with severe acute pancreatitis. Innate Immun. 2022 Jan;28(1):19-36;
20. He L, Jhong JH, Chen Q, Huang KY, Strittmatter K, Kreuzer J, DeRan M, Wu X, Lee TY, Slavov N, Haas W, Marneros AG. Global characterization of macrophage polarization mechanisms and identification of M2-type polarization inhibitors. Cell Rep. 2021 Nov 2;37(5):109955;

21. Horiba S, Kawamoto M, Tobita R, Kami R, Ogura Y, Hosoi J. M1/M2 Macrophage Skewing is Related to Reduction in Types I, V, and VI Collagens with Aging in Sun-Exposed Human Skin. JID Innov. 2023 Aug 12;3(6):100222;

22. Hu Q, Bian Q, Rong D, Wang L, Song J, Huang HS, Zeng J, Mei J, Wang PY. JAK/STAT pathway: Extracellular signals, diseases, immunity, and therapeutic regimens. Front Bioeng Biotechnol. 2023 Feb 23; 11:1110765;

23. Huber W, Algül H, Lahmer T, Mayr U, Lehmann M, Schmid RM, Faltlhauser A. Pancreatitis cytosorbents (CytoSorb) inflammatory cytokine removal: A Prospective Study (PACIFIC). Medicine (Baltimore). 2019 Jan;98(4):e13044;

24. Jalali AM, Mitchell KJ, Pompoco C, Poludasu S, Tran S, Ramana KV. Therapeutic Significance of NLRP3 Inflammasome in Cancer: Friend or Foe? Int J Mol Sci. 2024 Dec 21;25(24):13689;

25. Jia YC, Ding YX, Mei WT, Wang YT, Zheng Z, Qu YX, Liang K, Li J, Cao F, Li F. Extracellular vesicles and pancreatitis: mechanisms, status and perspectives. Int J Biol Sci. 2021 Jan 11;17(2):549-561;

26. Jiang W, Li X, Zhang Y, Zhou W. Natural Compounds for the Treatment of Acute Pancreatitis: Novel Anti-Inflammatory Therapies. Biomolecules. 2024 Sep 2;14(9):1101;

27. Jiang X, Zheng YW, Bao S, Zhang H, Chen R, Yao Q, Kou L. Drug discovery and formulation development for acute pancreatitis. Drug Deliv. 2020 Dec;27(1):1562-1580;

28. Kwak Y, Daly CWP, Fogarty EA, Grimson A, Kwak H. Dynamic and widespread control of poly(A) tail length during macrophage activation. RNA. 2022 Jul;28(7):947-971;

29. Lan WP, Guo W, Zhou X, Li Z. Research trends on traditional Chinese medicine and acute pancreatitis: A bibliometric analysis from 2007 to mid-2023. Heliyon. 2024 Feb 15;10(5):e25659;

30. Li W, Yuan Q, Li M, He X, Shen C, Luo Y, Tai Y, Li Y, Deng Z, Luo Y. Research advances on signaling pathways regulating the polarization of tumor-associated macrophages in lung cancer microenvironment. Front Immunol. 2024 Jul 31; 15:1452078

31. Li Y, You J, Zou Z, Sun G, Shi Y, Sun Y, Xu S, Zhang X. Decoding the Tumor Microenvironment: Exosome-Mediated Macrophage Polarization and Therapeutic Frontiers. Int J Biol Sci. 2025 Jun 20;21(9):4187-4214;

32. Lin R, Yu Y, Du L, Ding Z, Wang Z, Wei J, Guo Z. Active ingredients of traditional Chinese medicine inhibit NOD-like receptor protein 3 inflammasome: a novel strategy for preventing and treating heart failure. Front Immunol. 2025 Jan 24;16:1520482;

33. Liu J, Niu Z, Zhang R, Peng Z, Wang L, Liu Z, Gao Y, Pei H, Pan L. MALAT1 shuttled by extracellular vesicles promotes M1 polarization of macrophages to induce acute pancreatitis via miR-181a-5p/HMGB1 axis. J Cell Mol Med. 2021 Oct;25(19):9241-9254;

34. Liu J, Yan W, Chen S, Sun Y, Zhang F, Yang Y, Jin L. TLR3 Agonist Amplifies the Anti-Inflammatory Potency of ADSCs via IL-10-Mediated Macrophage Polarization in Acute Pancreatitis. Stem Cells Int. 2024 Mar 21;2024:5579228;

35. Liu Q, Sun Y, Zhang T, Lin W, Zhang J, Zhang H, Zheng W, Xu H, Zhou F. GNA15 predicts poor outcomes as a novel biomarker related to M2 macrophage infiltration in ovarian cancer. Front Immunol. 2025 Feb 7; 16:1512086;

36. Liu S, Szatmary P, Lin JW, Wang Q, Sutton R, Chen L, Liu T, Huang W, Xia Q. Circulating monocytes in acute pancreatitis. Front Immunol. 2022 Dec 12; 13:1062849;

37. Liu X, Dou B, Zhu Q, Liu C. Targeting the programmed cell death signaling mechanism with natural products for the treatment of acute pancreatitis: a review. Front Pharmacol. 2025 May 30; 16:1567552;

38. Lu Y, Cheng L, Xiong Y, Huang C, Liu Z, Shen C, Wang H, Qiu Y, Yang SB, Wu M, Zhang X. NLRP3 Inflammasome in Vascular Dementia: Regulatory Mechanisms, Functions, and Therapeutic Implications: A Comprehensive Review. CNS Neurosci Ther. 2025 May;31(5):e70403;

39. Luo L, Zhuang X, Fu L, Dong Z, Yi S, Wang K, Jiang Y, Zhao J, Yang X, Hei F. The role of the interplay between macrophage glycolytic reprogramming and NLRP3 inflammasome activation in acute lung injury/acute respiratory distress syndrome. Clin Transl Med. 2024 Dec;14(12):e70098;

40. Luo M, Zhao F, Cheng H, Su M, Wang Y. Macrophage polarization: an important role in inflammatory diseases. Front Immunol. 2024 Apr 10;15:1352946;

41. Mattke J, Darden CM, Lawrence MC, Kuncha J, Shah YA, Kane RR, Naziruddin B. Toll-like receptor 4 in pancreatic damage and immune infiltration in acute pancreatitis. Front Immunol. 2024 Mar 22;15:1362727;

42. Meher, Susanta & Mishra, Tushar & Sasmal, Prakash & Rath, Satyajit & Sharma, Rakesh & Rout, Bikram & Sahu, Manoj.Role of Biomarkers in Diagnosis and Prognostic Evaluation of Acute Pancreatitis. journal of biomarkers – 2015- Journal of Biomarkers Volume 2015, Article ID 519534, 13 pages;

43. Mihoc T, Latcu SC, Secasan CC, Dema V, Cumpanas AA, Selaru M, Pirvu CA, Valceanu AP, Zara F, Dumitru CS, Novacescu D, Pantea S. Pancreatic Morphology, Immunology, and the Pathogenesis of Acute Pancreatitis. Biomedicines. 2024 Nov 17;12(11):2627;

44. Mititelu A, Grama A, Colceriu MC, Pop TL. Overview of the cellular and immune mechanisms involved in acute pancreatitis: In search of new prognosis biomarkers. Expert Rev Mol Med. 2025 Jan 6; 27:e9;

45. Nazerian Y, Ghasemi M, Yassaghi Y, Nazerian A, Hashemi SM. Role of SARS-CoV-2-induced cytokine storm in multi-organ failure: Molecular pathways and potential therapeutic options. Int Immunopharmacol. 2022 Dec;113(Pt B):109428;

46. Otsuka Y, Hara A, Minaga K, Sekai I, Kurimoto M, Masuta Y, Takada R, Yoshikawa T, Kamata K, Kudo M, Watanabe T. Leucine-rich repeat kinase 2 promotes the development of experimental severe acute pancreatitis. Clin Exp Immunol. 2023 Dec 12;214(2):182-196;

47. Park W, Wei S, Kim BS, Kim B, Bae SJ, Chae YC, Ryu D, Ha KT. Diversity and complexity of cell death: a historical review. Exp Mol Med. 2023 Aug;55(8):1573-1594;

48. Patel HR, Diaz Almanzar VM, LaComb JF, Ju J, Bialkowska AB. The Role of MicroRNAs in Pancreatitis Development and Progression. Int J Mol Sci. 2023 Jan 5;24(2):1057;

49. Peng C, Tu G, Yu L, Wu P, Zhang X, Li Z, Li Z, Yu X. Murine Chronic Pancreatitis Model Induced by Partial Ligation of the Pancreatic Duct Encapsulates the Profile of Macrophage in Human Chronic Pancreatitis. Front Immunol. 2022 Apr 1; 13:840887;

50. Peng Y, Zhou M, Yang H, Qu R, Qiu Y, Hao J, Bi H, Guo D. Regulatory Mechanism of M1/M2 Macrophage Polarization in the Development of Autoimmune Diseases. Mediators Inflamm. 2023 Jun 8; 2023:8821610;

51. Qiang R, Li Y, Dai X, Lv W. NLRP3 inflammasome in digestive diseases: From mechanism to therapy. Front Immunol. 2022 Oct 26; 13:978190;

52. Shen Q, Wang S, Wu K, Wang L, Gong W, Lu G, Chen W, Yuan C, Tu B, Li W, Wang Y, Yang W. Identification of Grb2 protein as a potential mediator of macrophage activation in

acute pancreatitis based on bioinformatics and experimental verification. Front Immunol. 2025;16:1575880;

53. Sipka T, Peroceschi R, Hassan-Abdi R, Groß M, Ellett F, Begon-Pescia C, Gonzalez C, Lutfalla G, Nguyen-Chi M. Damage-Induced Calcium Signaling and Reactive Oxygen Species Mediate Macrophage Activation in Zebrafish. Front Immunol. 2021 Mar 26; 12:636585
54. Spano M, Di Matteo G, Ingallina C, Ambroselli D, Carradori S, Gallorini M, Giusti AM, Salvo A, Grosso M, Mannina L. Modulatory Properties of Food and Nutraceutical Components Targeting NLRP3 Inflammasome Activation. Nutrients. 2022 Jan 23;14(3):490;
55. Stojanovic B, Jovanovic IP, Stojanovic MD, Jovanovic M, Vekic B, Milosevic B, Cvetkovic A, Spasic M, Stojanovic BS. The Emerging Roles of the Adaptive Immune Response in Acute Pancr; UEG Week 2019 Poster Presentations. United European Gastroenterol J. 2019 Oct;7(8_suppl):189-1030;
56. Tang Y, Sun M, Liu Z. Phytochemicals with protective effects against acute pancreatitis: a review of recent literature. Pharm Biol. 2022 Dec;60(1):479-490;
57. Toledo B, Zhu Chen L, Paniagua-Sancho M, Marchal JA, Perán M, Giovannetti E. Deciphering the performance of macrophages in tumour microenvironment: a call for precision immunotherapy. J Hematol Oncol. 2024 Jun 11;17(1):44;
58. Venkatesh K, Glenn H, Delaney A, Andersen CR, Sasson SC. Fire in the belly: A scoping review of the immunopathological mechanisms of acute pancreatitis. Front Immunol. 2023 Jan 11;13:1077414;
59. Venkatesh K, Glenn H, Delaney A, Andersen CR, Sasson SC. Fire in the belly: A scoping review of the immunopathological mechanisms of acute pancreatitis. Front Immunol. 2023;13:1077414;
60. Wan Z, Wang X, Fu Z, Ma Y, Dai G, Gong X, Chen G, Yang L. Toll-like receptor activation regulates the paracrine effect of adipose-derived mesenchymal stem cells on reversing osteoarthritic phenotype of chondrocytes. Mol Biol Rep. 2024 Apr 20;51(1)
61. Wang C, Ma C, Gong L, Guo Y, Fu K, Zhang Y, Zhou H, Li Y. Macrophage Polarization and Its Role in Liver Disease. Front Immunol. 2021 Dec 14;12:803037;
62. Wang C, Wang X, Zhang D, Sun X, Wu Y, Wang J, Li Q, Jiang G. The macrophage polarization by miRNAs and its potential role in the treatment of tumor and inflammation (Review). Oncol Rep. 2023 Oct;50(4):190;
63. Wang G, Jin X, Chen J. TLR4/NF-κB pathway and NLRP3 inflammasome activation in acute pancreatitis: Therapeutic targets for intervention. Front Immunol. 2021; 12:728235;
64. Wang G, Jin X, Chen J. TLR4/NF-κB pathway and NLRP3 inflammasome activation in acute pancreatitis: Therapeutic targets for intervention. Front Immunol. 2021;12:728235;
65. Wei X, Weng Z, Xu X, Yao J. Exploration of a miRNA-mRNA network shared between acute pancreatitis and Epstein-Barr virus infection by integrated bioinformatics analysis. PLoS One. 2024 Nov 15;19(11):e0311130;
66. Wei Y, Guo H, Chen S, Tang XX. Regulation of macrophage activation by lactylation in lung disease. Front Immunol. 2024 Jul 4;15:1427739;
67. Wen J, Xuan B, Liu Y, Wang L, He L, Meng X, Zhou T, Wang Y. NLRP3 inflammasome-induced pyroptosis in digestive system tumors. Front Immunol. 2023 Apr 4; 14:1074606;

68. 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;

69. Xu C, Chen J, Tan M, Tan Q. The role of macrophage polarization in ovarian cancer: from molecular mechanism to therapeutic potentials. Front Immunol. 2025 Apr 22;16:1543096 ;

70. Yang Q, Luo Y, Lan B, Dong X, Wang Z, Ge P, Zhang G, Chen H. Fighting Fire with Fire: Exosomes and Acute Pancreatitis-Associated Acute Lung Injury. Bioengineering (Basel). 2022 Oct 26;9(11):615;

71. Yu KX, Yuan WJ, Wang HZ, Li YX. Extracellular matrix stiffness and tumor-associated macrophage polarization: new fields affecting immune exclusion. Cancer Immunol Immunother. 2024 May 2;73(6):115

72. Yuan Z, Jiang D, Yang M, Tao J, Hu X, Yang X, Zeng Y. Emerging Roles of Macrophage Polarization in Osteoarthritis: Mechanisms and Therapeutic Strategies. Orthop Surg. 2024 Mar;16(3):532-550;

73. Zeng W, Li F, Jin S, Ho PC, Liu PS, Xie X. Functional polarization of tumor-associated macrophages dictated by metabolic reprogramming. J Exp Clin Cancer Res. 2023 Sep 23;42(1):245;

74. Zhang L, Wang Y, Wu G, Xiong W, Gu W, Wang CY. Macrophages: friend or foe in idiopathic pulmonary fibrosis? Respir Res. 2018 Sep 6;19(1):170;

75. Zheng Z, Ding YX, Qu YX, Cao F, Li F. A narrative review of acute pancreatitis and its diagnosis, pathogenetic mechanism, and management. Ann Transl Med. 2021 Jan;9(1):69;