Review
https://doi.org/10.23934/2223-9022-2022-11-3-484-492

Immunopathogenesis of Acute Pancreatitis

G.V. Bulava ✉

Laboratory of Clinical Immunology
N.V. Sklifosovsky Research Institute for Emergency Medicine
3, B. Sukharevskaya Sq., Moscow, 129090, Russian Federation

✉ **Contacts:** Galina V. Bulava, Doctor of Medical Sciences, Scientific Consultant, Laboratory of Clinical Immunology, N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Health Department. Email: gbulava@mail.ru

ABSTRACT The leading positions in terms of frequency, severity of the course and high mortality belong to infectious forms of acute pancreatitis. However, not all pathophysiological mechanisms of the development of this disorder have been studied. Given that immune responses are an integral part of the pathogenesis of pancreatitis, it is extremely important to study the relationship between the mechanisms of inflammation and activation of the immune response. This review will discuss the role of various populations of innate immune cells, including macrophages, neutrophils, dendritic and mast cells, and regulatory immune cells in the pathogenesis of gland tissue destruction and the relationship between immune responses and systemic inflammatory response syndrome. Targeting innate immune cell populations and metabolite signaling pathways in acute pancreatitis may lead to a broader and ultimately more effective redirection of the treatment program towards disease resolution and improved clinical outcomes.
Keywords: acute pancreatitis, systemic inflammatory response syndrome (SIRS), innate and adaptive immune cells, cytokines
For citation Bulava GV. Immunopathogenesis of Acute Pancreatitis. *Russian Sklifosovsky Journal of Emergency Medical Care*. 2022;11(3):484–492. https://doi.org/10.23934/2223-9022-2022-11-3-484-492 (in Russ.)
Conflict of interest Author declare lack of the conflicts of interests
Acknowledgments, sponsorship The study has no sponsorship
Affiliations

Galina V. Bulava	Doctor of Medical Sciences, Scientific Consultant, Laboratory of Clinical Immunology, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0002-1244-2135, gbulava@mail.ru

AP – acute pancreatitis
APC – antigen presenting cells
DC – dendritic cells
DNA – deoxyribonucleic acid
IL – interleukin
MCP - 1–chemotactic protein of monocytes-1
MDSC – myeloid-derived suppressor cells
MAP – mild acute pancreatitis
MPO – myeloperoxidase
MF – macrophages
NF – neutrophils
NK cells – natural killer cells
SIR – systemic inflammatory response
SAP – severe acute pancreatitis
Treg cells – regulatory *T* cells

The treatment of purulent-inflammatory diseases and complications remains one of the most difficult problems of surgery, despite significant advances in understanding their pathogenesis and advances in antimicrobial therapy. One of the first places is occupied by intra-abdominal infections, complicating diseases and injuries of the abdominal organs. The leading positions in the frequency and severity of the course are occupied by infected forms of pancreatitis and widespread peritonitis. Mortality in this case does not have any tendency to decrease and varies, according to recent years, from 19 to 60% [1].

The pathogenesis of these diseases is based on the inflammatory process, which is carried out and regulated by the immune system [2–4].

Numerous data show that excessive systemic inflammation associated with acute pancreatitis (AP) is a consequence of uncontrolled or unregulated activation of the immune system [5].

In the early stage of AP, damage to pancreatic acinar cells occurs in an aseptic environment, and this leads to the release of pro-inflammatory mediators, infiltration of immune cells, and sterile inflammation [2]. Therefore, pathogen-associated molecular patterns (*PAMPs*) do not play any role in the range and activation of immune cells in the early stages of AP [6].

Necrotized pancreatic acinar cells release various types of damage-associated molecular patterns (*DAMPs*), including high mobility group 1 protein (*HMGB* 1), own DNA (deoxyribonucleic acid), and many others [7, 8]. As a result, the corresponding receptors of infiltrating immune cells are activated, the production of more inflammatory mediators increases, which, in turn, promotes greater infiltration of immune cells and exacerbates inflammation [9].

Although the pathogenesis of AP is quite complex, more and more studies show that infiltrating immune cells play a crucial role in its development and determine the severity of the disease [10]. The relative difficulty of obtaining human pancreatic tissue in pancreatitis necessitates experimental studies. Although current animal models do not capture all aspects of human disease and differences between experimental and clinical pancreatitis need to be considered, they will be used until better and more accessible models are developed [11].

Cells of the innate immune system, including macrophages (MF), neutrophils (NF), dendritic cells (DC), and labrocytes represent the majority of infiltrating cells in AP. As shown in many experimental models, within a few minutes after the onset of AP, MF [12], NF [13], DC [14], TK [15], natural killer cells (NK cells) [16], as well as adaptive immune cells such as *T* and *B* lymphocytes [17].

As a rule, infiltration by immune cells is a necessary protective mechanism for recovery. However, in some cases, pathogenic factors cannot be eliminated in a short period of time and the inflammatory response associated with the pro-inflammatory functions of immune cells will persist and intensify, which can further aggravate damage to the pancreas, provoke its necrosis and contribute to the development of systemic inflammation [18, 19].

However, about 80% of cases of AP are mild AP (MAP) [20] with only interstitial changes in the pancreas, which can usually be resolved within 2 weeks. However, patients with severe AP (SAP) rapidly develop a systemic inflammatory response (SIR) with multiorgan dysfunction leading to death [21].

It was believed that the SIR syndrome plays an important role in the progression of AP, but the specific relationship of SIR with pancreatic necrosis complicated by an infectious process remained largely unclear. In a prospective observational cohort study that included 2,130 patients with AP, the authors, using modern statistical methods, were able to prove that the duration of SIR is independently associated with pancreatic necrosis and can be used to predict persistent multiple organ failure, pancreatic infection, and mortality. These results were comparable or even exceeded the significance of such an indicator as the APACHE II severity index [22]. Thus, it is the long-term SIR syndrome that creates the prerequisites for infection of the pancreas and surrounding tissues.

Using experimental models of AP, the immune mechanisms involved in its pathogenesis have been studied. It has been shown that the first cells rushing to the focus of inflammation are NF [23]. NFs are important effector cells and are known as powerful pathogen scavengers and inactivators due to the action of bactericidal substances found in cytoplasmic granules: myeloperoxidase (MPO), acid phosphatase, alkaline phosphatase, lysozyme, and defensins.

The main function of NF was considered to be the maintenance of immune surveillance, i.e., effectively limiting the spread of infection by clearing pathogens and preventing the development of sepsis [24]. However, in recent years, more and more evidence indicates that NFs also play an important role in sterile inflammation, they are necessary to clear the "cellular debris" formed during tissue damage in order to restore cellular homeostasis [23, 25, 26].

The two classic functions of NF, clearance of pathogens and cell fragments by phagocytosis and degranulation, are not the only ones. In 2004, Brinkmann first reported that NFs can perform these functions by forming extracellular traps (networks) [27]. Networks are structures released by activated NF into the extracellular space with DNA as a scaffold, into which histones, MPO, NF elastase, cathepsin G , calreticulin, protease 3, HMGB 1 (a nuclear protein secreted by activated cells as a cytokine mediator and also released with necrosis of cells and tissues) and others. After release from cells, HMGB 1 can bind to the innate immunity receptor TLR 4, which leads to the secretion of MF cytokines and subsequent inflammatory response [27–30]. Since the formation of networks is usually accompanied by the death of NF, this process is also called netosis [31]. Initially, it was believed that networks are the mechanism by which NF clear tissues from pathogenic microorganisms, for example, Staphylococcus aureus, Salmonella, Streptococcus, Shigella flexneri, etc. [27, 32–34]. However, studies of the last decade have convincingly shown that NFs not only have effector functions of the innate immune response, but are also able to modulate the adaptive immune response through direct interaction with cytokines or through their production and influence on DCs and lymphocytes [35].

Even more importantly, the formation of networks promotes trypsinogen activation by phosphorylation of one of the mediator proteins that provide a cell response to signals coming through the interleukin (IL) and growth factor (STAT 3) receptors, which leads to block of the pancreatic ducts due to the formation of aggregates and even greater infiltration by NF cells [36]. In addition, during AP, damaged pancreatic acinar cells release various types of damage-associated molecular patterns (DAMPs), which leads to the recruitment and activation of NF and MF [37]. Thus, NF infiltration is a double-edged sword, since the lack of a tendency to resolve or persistent local inflammation can lead to a more aggressive NF response, often accompanied by overproduction of pro-inflammatory cytokines, destruction of normal tissues, and leads to the development of uncontrolled systemic inflammation [38].

MF play an equally important role in the pathogenesis of the inflammatory process. Like NF, MF are also the main innate immune cells that penetrate the pancreas at an early stage of AP and contribute to the development of inflammation, while trypsinogen activation under the influence of NF and MF is accompanied by necrosis and increased inflammation [10, 39, 40–42]. In addition, MF activation is accompanied by their pyroptosis, a rapid programmed cell necrosis characterized by cell swelling, membrane destruction, and the release of pro-inflammatory cytokines such as IL- 1β, IL-18, and HMGB 1 [43, 44].

The functions of MF are in many respects similar to those of NF: they can clear pathogenic microorganisms, tissue debris, necrotic and apoptotic cells through their efficient phagocytosis, playing an important role in infectious and sterile inflammation [45]. They are not only an important component of innate immunity, but also participate in the regulation of the adaptive immune response as antigen presenting cells (APCs) [46].

The high plasticity is a feature of MF. MF polarization is a phenotypic and functional change in response to changes in the microenvironment [47, 48]. MFs typically exist in two distinct subsets, including classically activated (M1) and alternatively activated (M2) cells. M1 are usually polarized by Th1 cytokines IFN-γ , TNF-α and, secreting IL-1β , IL-6, IL-12 and tumor necrosis factor (TNF-α), initiate and enhance inflammation, while M2 are induced by Th2 cytokines IL-4, IL-13 and play an anti-inflammatory, immunoregulatory and pro-fibrotic role by secreting IL-4, IL-10, IL-13 and transforming growth factor-β (TGF-β) [45-47] .

The disbalance of MF polarization and especially the type where M1 to M2 increases significantly, is one of the mechanisms underlying the exacerbation of many inflammatory diseases, including autoimmune myocarditis [49], ischemic brain injury [50], acute lung injury [51], AP [52], ischemic/reperfusion injury of the intestine [53] and others.

MF polarization also occurs under the influence of other stimuli, for example, components of ascitic fluid that accumulates in the abdominal cavity during SAP. Therefore, the therapeutic effect of paracentesis drainage of the abdominal cavity is partially achieved by stimulating the polarization of M2 macrophages and inhibiting the polarization of M1, which reduces the activity of the inflammatory process and destruction of the pancreas [54].

A recent study showed that the inflamed pancreas releases exosomes containing various signaling molecules, resulting in damage to distant organs, such as the lungs, through activation of inflammation and subsequent pyroptosis in alveolar MFs. Inhibition of exosome release or uptake by GW 4869 or Enoxaparin significantly reduced alveolar MF pyroptosis and alleviated SAP-induced lung injury [55]. These studies suggest that targeting infiltrating MF to pyroptosis may be a novel and effective strategy for the treatment of AP.

Other innate immune cells involved in the pathogenesis of AP are DC, which originate from bone marrow hematopoietic stem cells and are the most potent APCs. They can phagocytize and destroy pathogens and foreign antigens in the course of innate immune functions. In addition, DCs can activate *T* and *B* cells through antigen presentation and regulate immune responses by secreting various cytokines. Therefore, DCs are the link between innate and adaptive immunity [56].

The results of studies of AP on experimental models have shown conflicting results. Infiltrating DC in some cases play a protective role [14, 56, 57], while DC activity's block limits NF infiltration and tissue damage during inflammation [58]. But sometimes they can aggravate the severity of AP [59, 60]. It was also shown that the number of DCs, represented by a phenotype secreting IL-6, monocyte chemoattractant protein-1 (MCP -1) and TNF-a, increased 100-fold in the pancreas of mice with SAP, induced by cerulein or *L*-arginine. The addition of the probiotic *Clostridium butyricum* to the therapeutic complex can alleviate tissue damage and inflammation by reducing DC infiltration into the tissue of the inflamed pancreas [61].

A recent study reported an interesting phenomenon that in AP, pancreatic acinar cells undergo an acinar transition to DC, which in turn promotes the differentiation of naive *CD* 4+ *T* cells into *CD*4+/*IFN*-γ+*Th*1 and

CD4^{+}*/IL-17A+Th17* cells, thereby exacerbating local inflammation and tissue damage [59]. Thus, DCs play both a pro- and anti-inflammatory role in AP, but its full understanding in the pathogenesis of AP requires further research.

In AP, not only abnormal accumulation of labrocytes in the pancreatic tissue was noted, but also their activation and degranulation [15, 62]. In a process known as degranulation, labrocytes release cytoplasmic granules including histamine, serotonin, proteases, cytokines, and chemokines. The treatment with ketotifen [63], as well as intraperitoneal administration of other labrocytes inhibitors such as cromolyn or sodium cromoglycate, has been shown to significantly reduce histamine release, reduce prostate tissue damage, and reduce plasma exudation in the prostate, colon, and lungs, suggesting that labrocytes activation is involved in the development of endothelial dysfunction in the pancreas and other distant organs in AP, which can lead to multiple organ dysfunction [15, 64]. Given that activated infiltrating labrocytes secrete IL-33 and histamine, which cause inflammation of the pancreas [65], scopoletin administration reduced the severity of pancreatic injury and associated lung damage by reducing labrocytes activation and corresponding levels of IL-33 [66]. Thus, it has been indirectly shown that labrocytes play a certain role in the pathogenesis of AP and can be promising targets for its treatment.

The understanding the role of natural killer cells (NK cells) in the pathogenesis of AP is currently limited by the paucity of studies. Some of them reported that NK cells penetrated into the inflamed pancreas from the second day, reaching a maximum on the 4th day and remaining up to 28 days, in the model of AP provoked by an adenovirus vector, however, their role in the pathogenesis of pancreatic inflammation is unclear [16].

The main function of NK cells is the destruction of tumor or virus-infected cells [67]. Apparently, this is why it was possible to fix the infiltration of gland tissues with NK cells on the model of pancreatitis caused by a viral infection. In addition, they are involved in maintaining immune homeostasis and regulating inflammation. A number of researchers focused on changes in NK cells in the peripheral blood and showed that their number in patients with AP was lower than in healthy people who made up the control group [68, 69].

The activity of NK cells and their antibody-dependent cell-mediated cytotoxicity were significantly reduced in some patients with SAP compared with MAP, while a significant decrease in the number of peripheral blood NK cells was maintained from an early date for 30 days. It is believed that the immunosuppressive state, accompanied by the depletion of peripheral leukocytes and NK cells, is responsible for the infectious complications of AP [70, 71]. However, additional studies are needed to confirm the pathogenetic role of NK cells in AP.

Hyperactivation of the immune system and uncontrolled inflammation are undesirable consequences of many pathological conditions, since they lead to tissue damage, immune depletion and increased pathological changes. But there are immune regulatory cells in the immune system that can limit overactivation and inflammation. It is currently believed that myeloid-derived suppressor cells (MDSC) can suppress specific and non-specific immune responses through various mechanisms. One of these mechanisms is the secretion of a large amount of anti-inflammatory ILs, such as IL-10 [72].

However, excessive activation of anti-inflammatory immune responses is associated with undesirable consequences in the form of septic complications. The spread of MDSC is promoted by infection with Staphylococcus aureus (*S. aureus*) as a result of inhibition of specific *T* -cell responses against this pathogen [73]. In *S. aureus*-infected mice, MDSC inhibited monocyte/macrophage-mediated antibacterial immunity by secreting IL-10, which excess concentration promotes infection persistence [74].

Clearly, MDSC is an important population of immunoregulatory cells that is activated mainly during infectious inflammation. The secretion of a large number of immunoregulatory cytokines IL-10 and TGF-β is considered the main mechanism by which MDSC can reduce the activity of immune responses . It is important to understand that IL-10 can directly inhibit immune responses by upregulating cell membrane suppressor molecules such as PD-1 and PD-L1 on MDSC. This, in turn, can suppress the activation of the immune response through direct cross-talk with neighboring immune cells at the site of inflammation. On the other hand, IL-10 can indirectly suppress immune responses by switching inflammatory immune responses to anti-inflammatory ones, suppressing the maturation and activation of innate immune cells such as labrocytes, MF and NK cells, while simultaneously causing the expansion of regulatory T cells (Treg cells).

Interest in the role of T cells in the regulation of the inflammatory process has recently increased greatly. Most of the research focuses on how mediators that promote recovery after acute inflammation affect the functional activity of T cells. For example, lipoxins and cellular protectin D1 of T-helper type 2 (Th2) suppress T-cell pro-inflammatory cytokines and infiltration into inflammatory foci [75].

Conversely, the pro-inflammatory leukotriene B4 (LTB4) has been shown to dose-dependently reduce the differentiation of naive T cells into Treg cells, promoting the formation of Th 17 cells instead [76]. The role of Treg cells is very important, since they secrete IL-10 and amphiregulin, which promote tissue repair [77, 78].

It has been shown that both in vitro and in vivo Treg cells, producing IL-13, include the induction of IL-10 synthesis in MF. IL-10 through the autocrine-paracrine pathway helps MF to carry out efferocytosis (uptake of apoptotic cells) during the inflammation resolution reaction [79, 80]. In accordance with the role of efferocytosis in resolving the consequences of inflammation, Treg cells can also change the MF phenotype and reprogram their metabolism in such a way that their anti-inflammatory and restorative functions are activated [78, 80].

In addition, data from an experimental model suggest that Treg cells play an important role in the clearance of apoptotic cells during the resolution phase of zymosan-induced peritonitis [81]. It has also been shown that, as in peritonitis, Treg cells contribute to efferocytosis in acute lung injury provoked by bacterial lipopolysaccharide, and this process is independent of B cells and effector T cells [77, 82]. These results reveal a specific role for Treg cells in inflammation resolution and tissue repair.

In recent years, studies have appeared confirming that Treg cells releasing IL-10 are activated under the influence of probiotics. After oral administration, probiotic bacteria interact with intestinal epithelial cells or lamina propria immune cells through Toll-like receptors and induce the production of various cytokines or chemokines. Macrophage MCP-1, produced by epithelial cells, activates intestinal immune cells, which is accompanied by an increase in the production of immunoglobulin A and activation of T cells.

In addition, probiotics strengthen the intestinal barrier by increasing the amount of mucins, tight junction proteins, and goblet and paneth cells, limiting the translocation of the intestinal microflora [83]. Another suggested mechanism of action for probiotics is to modulate intestinal microbiota by maintaining balance and inhibiting the growth of potential pathogenic bacteria in the intestinal tract. It has been shown that probiotic bacteria and their cell walls have an important immunoregulatory effect on the immune system of the mucous membranes without changing the homeostatic environment, but with an increase in the number of cells producing immunoglobulin *A* (IgA) and innate immunity cells (MF), thereby improving the functioning of the immune system. MF and DC play an important role in this immune response, without causing an inflammatory process, but only slightly increasing the cell infiltration of the lamina propria [84].

Thus, probiotics, affecting the microbiome and intestinal permeability, affect the activity of the inflammatory process in the pancreas, preventing the activation of the infectious process caused by the translocation of microflora.

NK cells, in the pathogenesis of AP has become increasingly clear and significant. While promoting damage to the pancreas, these innate immune cells also interact with each other and adaptive immune cells to form a vast regulatory network. Starting with abnormal trypsinogen activation and self-digestion, some patients experience a transition from local inflammation of the pancreas to systemic inflammation with multiple organ dysfunction and sepsis.

Unfortunately, the current understanding of the pathogenesis of AP is still far from an accurate idea of how long it takes from the onset of the disease and which parts of the immune system should be affected in order to interrupt the chain of life-threatening immune responses.

At the same time, it has been shown that with the help of pharmacological preparations, it was possible to alleviate the course of AP and, in some cases, prevent the development of fatal complications [10].

CONCLUSION

The pathophysiological processes underlying acute pancreatitis are quite complex, but more and more research shows that infiltrating cells of the innate immune system, including macrophages, neutrophils, dendritic cells and labrocytes, play a critical role in its pathogenesis and determine the severity of the disease. Establishing the relationship between inflammatory, immune responses and signaling pathways is becoming an important factor in understanding the development and progression of pancreatitis. It is likely that, based on the knowledge of these mechanisms, targeted therapies targeting immune cells and their associated inflammatory mediators will be proposed in the future, which can either stop or reverse the progression of the disease and improve prognosis. Among other things, it is assumed that the use of immunomodulatory drugs will help alleviate the course of acute pancreatitis and, in some cases, prevent the development of fatal complications [10].

REFERENCES

1. Abakumov MM, Bagnenko SF, Beloborodov VB, Belotserkovsky BZ, Belyaev AM, Burnevich SZ, et al. *Abdominal'and surgical infection* . Moscow; 2011. (in Russian.)
2. Watanabe T, Kudo M, Strober W. Immunopathogenesis of pancreatitis. *Mucosal Immunol* . 2017;10(2):283–298. PMID: 27848953 https://doi.org/10.1038/mi.2016.101
3. by Till JWO, by Veen SQ, by Ruler O, Lamb B, Rubber DJ, Mayor MA. The innate immune response to secondary peritonitis. *Shock* . 2007;28(5):504–517. PMID: 17589378 https://doi.org/10.1097/shk.0b013e318063e6ca
4. Liu M, Silva-Sanchez A, Randall TD, Meza-Perez S. Specialized immune responses in the peritoneal cavity and omentum. *J Leukoc Biol*. 2021;109(4):717–729. PMID: 32881077 https://doi.org/10.1002/JLB.5MIR0720-271RR
5. Gukovsky I, Li N, Todoric J, Gukovskaya A, Karin M. Inflammation, autophagy, and obesity: common features in the pathogenesis of pancreatitis and pancreatic cancer. *Gastroenterology*. 2013;144(6):1199–1209. PMID: 23622129 https://doi.org/10.1053/j.gastro.2013.02.007
6. Mayerle J, Sendler M, Hegyi E, Beyer G, Lerch MM, Sahin-Tóth M. Genetics, Cell Biology, and Pathophysiology of Pancreatitis. *Gastroenterology*. 2019;156(7):1951–1968. PMID: 30660731 https://doi.org/10.1053/j.gastro.2018.11.081
7. Hoque R, Malik AF, Gorelick F, Mehal WZ. Sterile inflammatory response in acute pancreatitis. *Pancreas*. 2012;41(3):353–357. PMID: 22415665 https://doi.org/10.1097/MPA.0b013e3182321500
8. Kang R, Zhang Q, Hou W, Yan Z, Chen R, Bonaroti J, et al. Intracellular Hmgb1 inhibits inflammatory nucleosome release and limits acute pancreatitis in mice. *Gastroenterology*. 2014;146(4):1097–1107. PMID: 24361123 https://doi.org/10.1053/j.gastro.2013.12.015
9. Sarhan M, Land WG, Tonnus W, Hugo CP, Linkermann A. Origin and Consequences of Necroinflammation. *Physiol Rev*. 2018;98(2):727–780. PMID: 29465288 https://doi.org/10.1152/physrev.00041.2016
10. Peng C, Li Z, Yu X. The Role of Pancreatic Infiltrating Innate Immune Cells in Acute Pancreatitis. *Int J Med Sci*. 2021;18(2):534–545. PMID: 33390823 https://doi.org/10.7150/ijms.51618
11. Xue J, Sharma V, Habtezion A. Immune cells and immune-based therapy in pancreatitis. *Immunol Res*. 2014;58(2–3):378–386. PMID: 24710635 https://doi.org/10.1007/s12026-014-8504-5
12. Antonucci L, Fagman JB, Kim JY, Todoric J, Gukovsky I, Mackey M, et al. Basal autophagy maintains pancreatic acinar cell homeostasis and protein synthesis and prevents ER stress. *Proc Natl Acad Sci USA*. 2015;112(45):E6166–6174. PMID: 26512112 https://doi.org/10.1073/pnas.1519384112
13. Wan J, Yang X, Ren Y, Li X, Zhu Y, Haddock AN, et al. Inhibition of miR-155 reduces impaired autophagy and improves prognosis in an experimental pancreatitis mouse model. *Cell Death Dis*. 2019;10(4):303. PMID: 30944299 https://doi.org/10.1038/s41419-019-1545-x
14. Bedrosian AS, Nguyen AH, Hackman M, Connolly MK, Malhotra A, Ibrahim J, et al. Dendritic cells promote pancreatic viability in mice with acute pancreatitis. *Gastroenterology*. 2011;141(5):1915–1926. PMID: 21801698 https://doi.org/10.1053/j.gastro.2011.07.033
15. Lopez-Font I, Gea-Sorlí S, de-Madaria E, Gutiérrez LM, Pérez-Mateo M, Closa D. Pancreatic and pulmonary mast cells activation during experimental acute pancreatitis. *World J Gastroenterol*. 2010;16(27):3411–3417. PMID: 20632444 https://doi.org/10.3748/wjg.v16.i27.3411
16. Shifrin AL, Chirmule N, Gao GP, Wilson JM, Raper SE. Innate immune responses to adenoviral vector-mediated acute pancreatitis. *Pancreas*. 2005;30(2):122–129. PMID: 15714134 https://doi.org/10.1097/01.mpa.0000151578.99413.88
17. Son A, Ahuja M, Schwartz DM, Varga A, Swaim W, Kang N, et al. Ca(2+) Influx Channel Inhibitor SARAF Protects Mice From Acute Pancreatitis. *Gastroenterology*. 2019;157(6):1660–1672. PMID: 31493399 https://doi.org/10.1053/j.gastro.2019.08.042
18. Sendler M, Dummer A, Weiss FU, Krüger B, Wartmann T, Scharffetter-Kochanek K, et al. Tumour necrosis factor α secretion induces protease activation and acinar cell necrosis in acute experimental pancreatitis in mice. *Gut*. 2013;62(3):430–439. PMID: 22490516 https://doi.org/10.1136/gutjnl-2011-300771
19. Sendler M, Weiss FU, Golchert J, Homuth G, van den Brandt C, Mahajan UM, et al. Cathepsin B-Mediated Activation of Trypsinogen in Endocytosing Macrophages Increases Severity of Pancreatitis in Mice. *Gastroenterology*. 2018;154(3):704–718. PMID: 29079517 https://doi.org/10.1053/j.gastro.2017.10.018
20. van Dijk SM, Hallensleben NDL, van Santvoort HC, Fockens P, van Goor H, Bruno MJ, et al. Acute pancreatitis: recent advances through randomised trials. Gut. 2017;66(11):2024–2032. PMID: 28838972 https://doi.org/10.1136/gutjnl-2016-313595
21. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62(1):102–111. PMID: 23100216 https://doi.org/10.1136/gutjnl-2012-302779
22. Tan C, Yang L, Shi F, Hu J, Zhang X, Wang Y, et al. Early Systemic Inflammatory Response Syndrome Duration Predicts Infected Pancreatic Necrosis. *J Gastrointest Surg*. 2020;24(3):590–597. PMID: 30891659 https://doi.org/10.1007/s11605-019-04149-5
23. Castanheira FVS, Kubes P. Neutrophils and NETs in modulating acute and chronic inflammation. *Blood*. 2019;133(20):2178–2185. PMID: 30898862 https://doi.org/10.1182/blood-2018-11-844530
24. Sônego F, Castanheira FV, Ferreira RG, Kanashiro A, Leite CA, Nascimento DC, et al. Paradoxical Roles of the Neutrophil in Sepsis: Protective and Deleterious. *Front Immunol*. 2016;7:155. PMID: 27199981 https://doi.org/10.3389/fimmu.2016.00155
25. Jorch SK and Kubes P. An emerging role for neutrophil extracellular traps in noninfectious disease. *Nat Med*. 2017;23(3):279–287. PMID: 28267716 https://doi.org/10.1038/nm.4294
26. Huang H, Tohme S, Al-Khafaji AB, Tai S, Loughran P, Chen L, et al. Damage-associated molecular pattern-activated neutrophil extracellular trap exacerbates sterile inflammatory liver injury. *Hepatology*. 2015;62(2):600–614. PMID: 25855125 https://doi.org/10.1002/hep.27841
27. Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, et al. Neutrophil extracellular traps kill bacteria. *Science*. 2004;303(5663):1532–1535. PMID: 15001782 https://doi.org/10.1126/science.1092385
28. Zha C, Meng X, Li L, Mi S, Qian D, Li Z, et al. Neutrophil extracellular traps mediate the crosstalk between glioma progression and the tumor microenvironment via the HMGB1/RAGE/IL-8 axis. *Cancer Biol Med*. 2020;17(1):154–168. PMID: 32296583 https://doi.org/10.20892/j.issn.2095-3941.2019.0353
29. Rada B. Neutrophil Extracellular Traps. *Methods Mol Biol*. 2019;1982:517–528. PMID: 31172493 https://doi.org/10.1007/978-1-4939-9424-3_31
30. Vorobjeva NV, Pinegin BV. Neutrophil Extracellular Traps: Mechanisms of Formation and Role in Health and Disease. *Biochemistry (Moscow)*. 2014; 79(12):1286–1296.
31. Steinberg BE, Grinstein S. Unconventional roles of the NADPH oxidase: signaling, ion homeostasis, and cell death. *Sci STKE*. 2007;2007(379): pe11. PMID: 17392241 https://doi.org/10.1126/stke.3792007pe11
32. Beiter K, Wartha F, Albiger B, Normark S, Zychlinsky A, Henriques-Normark B. An endonuclease allows Streptococcus pneumoniae to escape from neutrophil extracellular traps. *Curr Biol*. 2006;16(4):401–407. PMID: 16488875 https://doi.org/10.1016/j.cub.2006.01.056

33. Berends ET, Horswill AR, Haste NM, Monestier M, Nizet V, von Köckritz-Blickwede M. Nuclease expression by Staphylococcus aureus facilitates escape from neutrophil extracellular traps. *J Innate Immun*. 2010;2(6):576–586. PMID: 20829609 https://doi.org/10.1159/000319909
34. Thammavongsa V, Missiakas DM, Schneewind O. Staphylococcus aureus degrades neutrophil extracellular traps to promote immune cell death. Science. 2013;342(6160):863–866. PMID: 24233725 https://doi.org/10.1126/science.1242255
35. Rosales C. Neutrophils at the crossroads of innate and adaptive immunity. *J Leukoc Biol*. 2020;108(1):377–396. PMID: 32202340 https://doi.org/10.1002/JLB.4MIR0220-574RR
36. Hines OJ, Pandol SJ. Management of severe acute pancreatitis. *BMJ*. 2019;367:l6227. PMID: 31791953 https://doi.org/10.1136/bmj.l6227
37. Gukovskaya AS, Gukovsky I, Algül H, Habtezion A. Autophagy, Inflammation, and Immune Dysfunction in the Pathogenesis of Pancreatitis. *Gastroenterology*. 2017;153(5):1212–1226. PMID: 28918190 https://doi.org/10.1053/j.gastro.2017.08.071
38. Kovtun A, Messerer DAC, Scharffetter-Kochanek K, Huber-Lang M, Ignatius A. Neutrophils in Tissue Trauma of the Skin, Bone, and Lung: Two Sides of the Same Coin. *J Immunol Res*. 2018;2018:8173983. PMID: 29850639 https://doi.org/10.1155/2018/8173983
39. Han X, Ni J, Wu Z, Wu J, Li B, Ye X, et al. Myeloid-specific dopamine D2 receptor signalling controls inflammation in acute pancreatitis via inhibiting M1 macrophage. *Br J Pharmacol*. 2020;177(13):2991–3008. PMID: 32060901 https://doi.org/10.1111/bph.15026
40. Zhao Q, Wei Y, Pandol SJ, Li L, Habtezion A. STING Signaling Promotes Inflammation in Experimental Acute Pancreatitis. *Gastroenterology*. 2018;154(6):1822–1835. PMID: 29425920 https://doi.org/10.1053/j.gastro.2018.01.065
41. Makhija R, Kingsnorth AN. Cytokine storm in acute pancreatitis. *J Hepatobiliary Pancreat Surg*. 2002;9(4):401–410. PMID: 12483260 https://doi.org/10.1007/s005340200049
42. Roch AM, Maatman TK, Cook TG, Wu HH, Merfeld-Clauss S, Traktuev DO, et al. Therapeutic Use of Adipose-Derived Stromal Cells in a Murine Model of Acute Pancreatitis. *J Gastrointest Surg*. 2020;24(1):67–75. PMID: 31745900 https://doi.org/10.1007/s11605-019-04411-w
43. Frank D, Vince JE. Pyroptosis versus necroptosis: similarities, differences, and crosstalk. *Cell Death Differ*. 2019;26(1):99–114. PMID: 30341423 https://doi.org/10.1038/s41418-018-0212-6
44. Shi J, Gao W, Shao F. Pyroptosis: Gasdermin-Mediated Programmed Necrotic Cell Death. *Trends Biochem Sci*. 2017;42(4):245–254. PMID: 27932073 https://doi.org/10.1016/j.tibs.2016.10.004
45. Gordon S, Martinez-Pomares L. Physiological roles of macrophages. *Pflugers Arch*. 2017;469(3–4):365–374. PMID: 28185068 https://doi.org/10.1007/s00424-017-1945-7
46. Arango Duque G and Descoteaux A. Macrophage cytokines: involvement in immunity and infectious diseases. *Front Immunol*. 2014;5:491. PMID: 25339958 https://doi.org/10.3389/fimmu.2014.00491
47. Shapouri-Moghaddam A, Mohammadian S, Vazini H, Taghadosi M, Esmaeili SA, Mardani F, et al. Macrophage plasticity, polarization, and function in health and disease. *J Cell Physiol*. 2018;233(9):6425–6440. PMID: 29319160 https://doi.org/10.1002/jcp.26429
48. Murray PJ. Macrophage Polarization. *Annu Rev Physiol*. 2017;79:541–566. PMID: 27813830 https://doi.org/10.1146/annurev-physiol-022516-034339
49. Su Z, Zhang P, Yu Y, Lu H, Liu Y, Ni P, et al. HMGB1 Facilitated Macrophage Reprogramming towards a Proinflammatory M1-like Phenotype in Experimental Autoimmune Myocarditis Development. *Sci Rep*. 2016;6:21884. PMID: 26899795 https://doi.org/10.1038/srep21884
50. Yang J, Zhao Y, Zhang L, Fan H, Qi C, Zhang K, et al. RIPK3/MLKL-Mediated Neuronal Necroptosis Modulates the M1/M2 Polarization of Microglia/Macrophages in the Ischemic Cortex. *Cereb Cortex*. 2018;28(7):2622–2635. PMID: 29746630 https://doi.org/10.1093/cercor/bhy089
51. Wang J, Li R, Peng Z, Zhou W, Hu B, Rao X, et al. GTS-21 Reduces Inflammation in Acute Lung Injury by Regulating M1 Polarization and Function of Alveolar Macrophages. *Shock*. 2019;51(3):389–400. PMID: 29608552 https://doi.org/10.1097/SHK.0000000000001144
52. Han X, Ni J, Wu Z, Wu J, Li B, Ye X, et al. Myeloid-specific dopamine D2 receptor signalling controls inflammation in acute pancreatitis via inhibiting M1 macrophage. *Br J Pharmacol*. 2020;177(13):2991–3008. PMID: 32060901 https://doi.org/10.1111/bph.15026
53. Wen S, Li X, Ling Y, Chen S, Deng Q, Yang L, et al. HMGB1-associated necroptosis and Kupffer cells M1 polarization underlies remote liver injury induced by intestinal ischemia/reperfusion in rats. *Faseb J*. 2020;34: 4384–4402. PMID: 31961020 https://doi.org/10.1096/fj.201900817R
54. Liu RH, Wen Y, Sun HY, Liu CY, Zhang YF, Yang Y, et al. Abdominal paracentesis drainage ameliorates severe acute pancreatitis in rats by regulating the polarization of peritoneal macrophages. *World J Gastroenterol*. 2018;24(1):5131–5143. PMID: 30568390 https://doi.org/10.3748/wjg.v24.i45.5131
55. Wu XB, Sun HY, Luo ZL, Cheng L, Duan XM, Ren JD. Plasma-derived exosomes contribute to pancreatitis-associated lung injury by triggering NLRP3-dependent pyroptosis in alveolar macrophages. *Biochim Biophys Acta Mol Basis Dis*. 2020;1866(5):165685. PMID: 31953217 https://doi.org/10.1016/j.bbadis.2020.165685
56. Puhr S, Lee J, Zvezdova E, Zhou YJ and Liu K. Dendritic cell development-History, advances, and open questions. *Semin Immunol*. 2015;27(6):388–396. PMID: 27040276 https://doi.org/10.1016/j.smim.2016.03.012
57. Françozo MCS, Costa FRC, Guerra-Gomes IC, Silva JS and Sesti-Costa R. Dendritic cells and regulatory T cells expressing CCR4 provide resistance to coxsackievirus B5-induced pancreatitis. *Sci Rep*. 2019;9(1):14766. PMID: 31611578 https://doi.org/10.1038/s41598-019-51311-9
58. Del Fresno C, Saz-Leal P, Enamorado M, Wculek SK, Martínez-Cano S, Blanco-Menéndez N, et al. DNGR-1 in dendritic cells limits tissue damage by dampening neutrophil recruitment. *Science*. 2018;362(6412):351–356. PMID: 30337411 https://doi.org/10.1126/science.aan8423
59. Xu D, Xie R, Xu Z, Zhao Z, Ding M, Chen W, et al. mTOR-Myc axis drives acinar-to-dendritic cell transition and the CD4(+) T cell immune response in acute pancreatitis. *Cell Death Dis*. 2020;11(6):416. PMID: 32488108 https://doi.org/10.1038/s41419-020-2517-x
60. Ochi A, Nguyen AH, Bedrosian AS, Mushlin HM, Zarbakhsh S, Barilla R, et al. MyD88 inhibition amplifies dendritic cell capacity to promote pancreatic carcinogenesis via Th2 cells. J Exp Med. 2012;209(9):1671–1687. PMID: 22908323 https://doi.org/10.1084/jem.20111706
61. Pan LL, Niu W, Fang X, Liang W, Li H, Chen W, et al. Clostridium butyricum Strains Suppress Experimental Acute Pancreatitis by Maintaining Intestinal Homeostasis. *Mol Nutr Food Res*. 2019;e1801419. PMID: 31034143 https://doi.org/10.1002/mnfr.201801419
62. González-de-Olano D, Álvarez-Twose I. Mast Cells as Key Players in Allergy and Inflammation. *J Investig Allergol Clin Immunol*. 2018;28(6):365–378. PMID: 30530385 https://doi.org/10.18176/jiaci.0327
63. Yönetçi N, Oruç N, Ozütemiz AO, Celik HA, Yüce G. Effects of mast-cell stabilization in cerulein-induced acute pancreatitis in rats. *Int J Pancreatol*. 2001;29(3):163–171. PMID: 12067220 https://doi.org/10.1385/IJGC:29:3:163
64. Dib M, Zhao X, Wang XD, Andersson R. Role of mast cells in the development of pancreatitis-induced multiple organ dysfunction. *Br J Surg*. 2002;89(2):172–178. PMID: 11856129 https://doi.org/10.1046/j.0007-1323.2001.01991.x

65. Kempuraj D, Twait EC, Williard DE, Yuan Z, Meyerholz DK, Samuel I. The novel cytokine interleukin-33 activates acinar cell proinflammatory pathways and induces acute pancreatic inflammation in mice. *PLoS One*. 2013;8(2):e56866. PMID: 23418608 https://doi.org/10.1371/journal.pone.0056866
66. Leema G, Tamizhselvi R. Protective Effect of Scopoletin Against Cerulein-Induced Acute Pancreatitis and Associated Lung Injury in Mice. *Pancreas*. 2018;47:577–585. PMID: 29595543 https://doi.org/10.1097/MPA.0000000000001034
67. Zitti B and Bryceson YT. Natural killer cells in inflammation and autoimmunity. *Cytokine Growth Factor Rev*. 2018;42:37–46. PMID: 30122459 https://doi.org/10.1016/j.cytogfr.2018.08.001
68. Mylona V, Koussoulas V, Tzivras D, Makrygiannis E, Georgopoulou P, Koratzanis G, et al. Changes in adaptive and innate immunity in patients with acute pancreatitis and systemic inflammatory response syndrome. *Pancreatology*. 2011; 11(5):475–481. PMID: 21997439 https://doi.org/10.1159/000329460
69. Wei X, Yao W, Li H, Qian J, Xie Y, Zhang Z, et al. B and NK Cells Closely Correlate with the Condition of Patients with Acute Pancreatitis. *Gastroenterol Res Pract*. 2019;2019:7568410. PMID: 30881449 https://doi.org/10.1155/2019/7568410
70. Ueda T, Takeyama Y, Yasuda T, Shinzeki M, Sawa H, Nakajima T, et al. Immunosuppression in patients with severe acute pancreatitis. *J Gastroenterol*. 2006;41(8):779–784. PMID: 16988767 https://doi.org/10.1007/s00535-006-1852-8
71. Dabrowski A, Osada J, Dabrowska MI, Wereszczynska-Siemiatkowska U. Monocyte subsets and natural killer cells in acute pancreatitis. *Pancreatology*. 2008;8(2):126–134. PMID: 18382098 https://doi.org/10.1159/000123605
72. Yaseen MM, Abuharfeil NM, Darmani H, Daoud A. Mechanisms of immune suppression by myeloid-derived suppressor cells: the role of interleukin-10 as a key immunoregulatory cytokine. *Open Biol*. 2020;10(9):200111. PMID: 32931721 https://doi.org/10.1098/rsob.200111
73. Goldmann O, Beineke A, Medina E. Identification of a novel subset of myeloid-derived suppressor cells during chronic staphylococcal infection that resembles immature eosinophils. *J Infect Dis*. 2017;216(11):1444–1451. PMID: 29029332 https://doi.org/10.1093/infdis/jix494
74. Heim CE, Vidlak D, Kielian T. Interleukin-10 production by myeloid-derived suppressor cells contributes to bacterial persistence during Staphylococcus aureus orthopedic biofilm infection. *J Leukoc Biol*. 2015;98(6):1003–1013. PMID: 26232453 https://doi.org/10.1189/jlb.4VMA0315-125RR
75. Buckley CD, Gilroy DW, Serhan CN. Proresolving lipid mediators and mechanisms in the resolution of acute inflammation. *Immunity*. 2014;40(3):315–327. PMID: 24656045 https://doi.org/10.1016/j.immuni.2014.02.009
76. Chen H, Qin J, Wei P, Zhang J, Li Q, Fu L, et al. Effects of leukotriene B4 and prostaglandin E2 on the differentiation of murine Foxp3+ T regulatory cells and Th17 cells. Prostaglandins Leukot. Essent. *Fatty Acids*. 2009;80(4):195–200. PMID: 19264469 https://doi.org/10.1016/j.plefa.2009.01.006
77. D'Alessio FR, Tsushima K, Aggarwal NR, West EE, Willett MH, Britos MF, et al. CD4+CD25+Foxp3+ Treg cells resolve experimental lung injury in mice and are present in humans with acute lung injury. *J Clin Invest*. 2009;119(10):2898–2913. PMID: 19770521 https://doi.org/10.1172/JCI36498
78. Arpaia N, Green JA, Moltedo B, Arvey A, Hemmers S, Yuan S, et al. A distinct function of regulatory T cells in tissue protection. *Cell* _ 2015;162(5):1078–1089. PMID: 26317471 https://doi.org/10.1016/j.cell.2015.08.021
79. Proto JD, Doran AC, Gusarova G, Yurdagul A Jr, Sozen E, Subramanian M, et al. Regulatory T Cells Promote Macrophage Efferocytosis during Inflammation Resolution. *Immunity* . 2018;49(4):666–677. PMID: 30291029 https://doi.org/10.1016/j.immune.2018.07.015
80. Ip WKE, Hoshi N, Shouval DS, Snapper S, Medzhitov R. Anti-inflammatory effect of IL-10 mediated by metabolic reprogramming of macrophages. *Science* _ 2017;356(6337):513–519. PMID: 28473584 http://doi.org/10.1126/science.al3535
81. Newson J, Stables M, Karra E, Arce-Vargas F, Quezada S, Motwani M, et al. Resolution of acute inflammation bridges the gap between innate and adaptive immunity. *Blood*. 2014;124(11):1748–1764. PMID: 25006125 https://doi.org/10.1182/blood-2014-03-562710
82. Sutmuller RP, van Duivenvoorde LM, van Elsas A, Schumacher TN, Wildenberg ME, Allison JP, et al. Synergism of cytotoxic T lymphocyte-associated antigen 4 blockade and depletion of CD25(+) regulatory T cells in antitumor therapy reveals alternative pathways for suppression of autoreactive cytotoxic T lymphocyte responses. *J Exp Med.* 2001;194(6):823–832. PMID: 11560997 https://doi.org/10.1084/jem.194.6.823
83. Galdeano CM, Cazorla SI, Lemme-Dumit JM, Vélez E, Perdigón G. Beneficial Effects of Probiotic Consumption on the Immune System. *Ann Nutr Metab*. 2019;74(2):115–124. PMID: 30673668 https://doi.org/10.1159/000496426
84. Lemme-Dumit JM, Polti MA, Perdigón G, Galdeano CM. Probiotic bacteria cell walls stimulate the activity of the intestinal epithelial cells and macrophage functionality. *Benef Microbes*. 2018;9(1):153–164. PMID: 29124968 https://doi.org/10.3920/BM2016.0220

Received on 11.04.2022
Review completed on 22.06.2022
Accepted on 29.06.2022