Research Progress on Intestinal Barrier Dysfunction and Treatment of Severe Acute Pancreatitis

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Abstract: Severe acute pancreatitis (SAP) often leads to intestinal epithelial cell damage, disrupts intestinal epithelial cell structure, increases intestinal mucosal permeability, and leads to intestinal barrier dysfunction (IBD). IBD is prone to cause intestinal toxin and bacterial translocation, further accelerating the course of severe pancreatitis, leading to systemic inflammatory response or multiple organ failure, and even death. It can be seen that IBD plays a key role in the development of pancreatic tissue necrosis infection and severe pancreatitis. Intestinal barriers, ie, chemical, physical, immune, and biological barriers, can interact and promote positive feedback. Factors such as intestinal ischemia, inflammatory factors, intestinal flora, immune damage, intestinal nutrition and motility lead to IBD disease. Therefore, the assessment and protection of intestinal barrier function is essential for the treatment of severe pancreatitis. This article reviews the pathogenesis and treatment of IBD disease.

Keywords: Severe Acute Pancreatitis; Intestinal Barrier Dysfunction; Pathogenesis; Ischemia Reperfusion; Intestinal Flora; Immunity; Treatment

Severe Acute Pancreatitis(Sever, Acute, Pancreatitis , SAP) is an inflammatory disease of pancreas, which can cause local pancreatic damage, systemic inflammatory response syndrome and organ failure. It is a dangerous disease development, the mortality rate is as high as 20% to 30%, and it is a common digestive system diseases worldwide [1]. The intestinal tract as one of the targeted organs of SAP, will cause changes in intestinal mucosal structure, increase intestinal permeability, and further cause intestinal barrier dysfunction(IBD). Complete intestinal barrier includes physical barrier, chemical barrier, biological barrier and immune barrier, jointly resist pathogenic bacteria. However, the occurrence of IBD, aggravates pancreatic and peripancreatic necrosis, can also cause persistent organ failure. The pathogenesis of SAP, IBD and SAP is still unclear, and it can be roughly divided into intestinal ischemia and hypoxia and ischemia reperfusion, stimulation of inflammatory mediators and cytokines, immune deficiency, flora imbalance and intestinal mucosal nutrition disorders.

Intestinal Ischemia, Hypoxia and Reperfusion

SAP is characterized by microcirculatory disturbance. Potential mechanisms include increased vascular permeability, intestinal vasoconstriction, shunt, hypoperfusion and increased coagulation function [2]. At the same time, the body fluid begins to enter the third gap, causing a simultaneous decrease in the effective circulating blood volume of the whole body, and the activation of the neuro-endocrine system causes the intestinal tract to redistribute blood flow to the most important organs in the case of severe blood loss or low blood volume, including the heart and brain. [3] Previous studies have confirmed that [4] SAP and Decrease of organ perfusion in the process, can cause damage to intestinal mucosal structure. Research shows that [5], it is often accompanied by lung tissue damage, in the pathogenesis of SAP, resulting in decrease of blood oxygen saturation combined with decrease of intestinal blood flow, resulting in Ischemia

and Hypoxia of Intestinal Tissue. While sap increased intra-abdominal pressure, increased intestinal mucosal ischemia due to the production of peritoneal effusion, when intestinal ischemia is further aggravated and leads to intestinal necro sis, can lead to severe inflammatory reaction, septicemia and shock [6].

Rehydration therapy when the intestinal blood supply is seriously insufficient causes intestinal reperfusion injury, while intestinal ischemia reperfusion is the earlies, and the most serious damage is the mechanical barrier composed of intestinal epithelial cells [7]. On the one hand, research shows that it can produce xanthine oxidase and hypoxanthine when intestinal ischemia can release superoxide ions [8], which further forms oxygen free radicals, and lipid peroxidation reaction by oxygen free radicals, can damage intestinal epithelial cells, and destroy tight and adhesive connections between cells. Besides, the oxygen radicals generated can stimulate the activation of neutrophils and romote the release of inflammatory factors [9]. At the same time [10-13], during intestinal reperfusion, loss of large amount of calcium pump function in cells, causing calcium overload. Calcium ions entering mitochondria can cause the function of cytochrome oxidase and manganese - superoxide dismutase(SOD) to decline, to further increase intracellular reactive oxygen species, and promote each other with calcium overload, to accelerate apoptosis of intestinal epithelial cells.

On the other hand, some studies have shown that [14-15] 30 minutes after intestinal ischemia and reperfusion, intestinal villus tip epithelial cell apoptosis begins to accelerate. Firstly, in the early stage of reperfusion, endothelial cell intercellular adhesion molecule-1 (ICAM-1) expression is enhanced, accompanied by neutrophils entering the damaged villus tip, and activated neutrophils release localized antibacterial proteins, including myelin. Oxidase, leading to the formation of reactive oxygen species. Secondly, the inflammatory response is accompanied by activation of complement, which is manifested by the deposition of C3 activated in the complement activation cascade in damaged luminal epithelial cells. At the same time, because complement activation is chemotactic, it can induce the production of chemokines and cytokines. Third, increased expression of pro-inflammatory mRNA was observed 30 minutes after reperfusion, and IL-6, IL-8 and tumor necrosis factor-α (TNF-α), arteriovenous blood IL-6 and IL- were also increased simultaneously. 8 concentration difference increased.

The above two aspects of ischemia-reperfusion accelerate the edema, hyperemia, shedding and apoptosis of intestinal epithelial cells, increase intestinal mucosal permeability, and initially induce IBD. It has also been reported that ischemia-reperfusion also activates inducible nitric oxide synthase, causing destruction of intracellular scaffolds, resulting in the loss of intestinal epithelial cells. Recent studies have found that [16], the loss of filamentous actin in SAP, causing destruction of the intercellular junction structure and increasing intestinal mucosal permeability. Impaired systemic and intestinal microcirculation leads to ischemia-reperfusion injury and release of free oxygen free radicals, leading to intestinal barrier failure.

Under the above mechanism, when the permeability of the intestinal mucosa increases to a certain level, bacteria and endotoxin parasitic in the intestinal tract can cross the intestinal mucosal barrier, invade the mesenteric lymph nodes, thoracic ducts and systemic circulation, causing bacteria and Endotoxin is translocated to form enterogenous endotoxemia and bacteremia [17]. Wang *et al.* [18] considered that the intestinal tract is the release point of inflammatory factors in the inflammatory response axis of the intestinal-liver-lung in SAP. The liver protects and promotes the two-way regulation of inflammatory factors. It has also been suggested that [19-20], bacterial translocation due to increased permeability of the intestinal wall is thought to stimulate intestinal-associated lymphoid tissue (GALT) through the interaction between polymorphonuclear leukocytes and endothelial cells, reticular Impaired endothelial system function leads to excessive release of local cytokines and other mediators, thereby promoting intestinal inflammation. This may result in a stronger SIRS response and MODS.

2. Stimulation of Inflammatory Mediators and Cytokines

In the early days of SAP, the production of large amounts of oxygen free radicals stimulates the mononuclear macrophage system and activates neutrophils and other inflammatory mediators. Studies have shown that [21], nuclear factor-κB (NF-κB) plays a regulatory role in inflammatory injury of SAP. These inflammatory mediators and cytokines can induce, stimulate and activate each other, causing linkage and amplification effects, forming positive feedback and causing waterfall responses. Studies have shown that [22], TNF-α has a function of regulating the tight junction of intes-

tinal epithelial cells. TNF-α induces NF-κB activation, which leads to down-regulation of ZO-1 protein and changes in junction sites, and increases myosin light chain. Kinase (MLCK) expression increases intestinal mucosal permeability. In addition, TNF-α can also stimulate neutrophils, causing a local inflammatory response. Early studies have shown that IL-1, IL-6, TNF-α, and endotoxin are involved in the regulation of intestinal barrier protection and inflammatory response in SAP patients [23]. In recent years, Surbatovic et al [24] believe that TNF-α can be used to assess the severity and prognosis of SAP. Recent studies suggest that phospholipase A2 (PLA2) also plays a role in the inflammatory process and can be used as an early inflammatory marker for the detection of SAP. PLA2 is released under the control of TNF-α, promotes the release of PAF, and enhances the effect of endothelial cells and neutrophils on tissue damage around the pancreas [25].

IL-1 Increase intestinal permeability by activating MLCK gene activity. Studies have shown

[26-27] that in the mouse colitis model, IL-1 produced by intestinal epithelial cells is the main driving factor of inflammation, and IL-1 deficient mice can significantly improve the survival rate after intestinal epithelial injury.

IL-1 is exposed to the surface of cells undergoing oxidative or metabolic stress and in turn activates itself. Thus, the initial IL-1-IL-1R1 signaling initiates a sustained and self-sustaining inflammatory cycle leading to extensive tissue damage until IL-1R1 signaling is depleted or inhibited.

IL-6, which has been considered to be a typical pro-inflammatory cytokine, is involved in the development of inflammatory diseases through the homodimerization of gpl30, which activates the Janus kinase (JAK)/STAT signal transduction pathway. However, a number of studies have shown that IL-6 not only binds to its soluble receptor (trans signaling pathway) but also mediates ischemia-reperfusion injury, and can also bind to its membrane-bound receptor (classical signaling pathway) to mediate regeneration and anti-inflammatory. And other protective effects [28].

Recent studies have shown that [29], IL-10 is mainly secreted by T cells, and activated IL-10 is considered to be an important anti-inflammatory cytokine. By reducing the expression of MHNC2 molecules expressed by dendritic cells and macrophages, it can reduce antigen presentation, inhibit T cell proliferation, inhibit cellular immunity and reduce other pro-inflammatory factors such as IL-1, TNF-α, etc. to reduce inflammation.

Studies have shown that [30], high mobility group box-1 protein (HMGB1), which is actively

released by mononuclear macrophages and passively released in necrotic tissue, is considered to be an important late-stage inflammatory cytokine. Andersson et al. [31] found that extracellular HMGB1 acts through the RAGE-receptor-mediated endocytosis to the endolysosomal region while attaching to other extracellular pro-inflammatory molecules. Chen et al [32] also found that blocking the expression of HMGB1 can effectively protect the intestinal mucosal barrier. In short, the release of inflammatory mediators and cytokines increases intestinal mucosal permeability and aggravates the displacement of bacteria and endotoxin, while enterogenous endotoxemia reverses the release of inflammatory mediators and forms a vicious circle.

Immunodeficiency

The intestinal immune barrier consists of two components, one consisting of three parts: the intestinal lymphoid tissue and various immune cells and secreted immunoglobulin (sIgA) secreted by them. It can not only resist the invasion of bacteria and endotoxin, but also monitor and remove it, called acquired immunity [33]. The other is congenital immunity consisting of intestinal microbes, which stimulates the body to produce self-limiting body fluid mucosal immunity [34]. Experimental studies have found that [35], sIgA plays a central role in the intestinal immune response, on the one hand, prevents the binding of pathogenic bacteria to intestinal epithelial cells, and on the other hand, combines with bacteria to form antigen-antibody complexes, which are presented to macrophages. cell. The sIgA in the cecal feces of SAP rats decreased significantly at 24, 48, and 72 h, suggesting that humoral immunity was impaired, as well as CD3+, CD4+, CD4+/CD8+ T lymphocytes, and mature T lymphocytes, ie, cellular immunity suffered from damage.

Therefore, intestinal epithelial cells maintain a dynamic balance between intestinal immunity and human immunity by constructing a mucosal barrier, secreting various immune mediators, and delivering bacterial antigens. Studies have shown that IL-17 and IL-22 produced by Th17 cells or type 3 intrinsic lymphocytes (ILC3) upregulate intestinal epithelial cells to secrete AMPS and ReG3 family proteins. Proinflammatory cytokines, such as tumor necrosis factor (TNF) and interferon (IFN), inhibit epithelial cell proliferation by inhibiting T cell factor signaling. IL-13 promotes

apoptosis of intestinal epithelial cells, leading to mucosal barrier disorder [36-37].

In SAP, intestinal epithelial cells are reduced by the production of thymic stromal lymphopoietin (TSLP), and the loss of Th2 immune response leads to easy bacterial infection. MUC2 produced by goblet cells inhibits the immunogenicity of intestinal antigens by transmitting tolerance signals to dendritic cells. Intestinal epithelial cells can also promote intestinal adaptive immune responses by delivering antigen to intestinal immune cells [38].

Recently, more and more clinical trials have proved that immunosuppressive agents can effectively restore the immune function of SAP patients. Wang Haiyan *et al* [39] confirmed that the application of immunosuppressive agents can significantly increase the number of peripheral blood T lymphocyte subsets (CD3+, CD4+, CD8+, CD4+/CD8+) and immunoglobulins (IgA, IgG, IgM), suggesting early Enteral nutrition restores intestinal immune function and protects the intestinal mucosal barrier.

4. Flora imbalance

The mucous layer formed by the secretion of mucus by intestinal epithelial cells is the first barrier to prevent bacterial invasion. Intestinal inflammation causes the mucus layer to become thinner or disappear, and bacteria and its metabolites can pass through the mucus layer and invade the intestinal epithelial cells, directly or indirectly damaging the intercellular connections, resulting in a decrease in intestinal mechanical barrier function.

However, the interaction between the flora, especially the commensal bacteria (such as bifidobacteria), adheres to the intestinal mucosal epithelial cells and resists the erosion of other pathogenic bacteria (such as Escherichia coli, Shigella, etc.). ① Stimulate the proliferation of intestinal epithelial cells by stimulating Toll-like receptors (TLRs), strengthen the tight junction of intestinal epithelial cells, reduce the damage of pathogenic bacteria to intestinal mucosa, reduce the migration of bacteria and its products into the intestinal circulation, and the intestinal flora is driven. The TLR4/MyD88 signal regulates the production of antibacterial molecules by Paneth cells. ② The short-chain fatty acids produced by the metabolism of intestinal flora are the main source of energy for intestinal epithelial cells. Bile salts help colonization of probiotics in the intestine, promote mucosal growth and repair, induce cell proliferation in intestinal wall, and up-regulate heat shock proteins (Hsp72), the gene expression level encoding cytoskeletal anchoring protein, Occludin protein and tubulin, and the tight junction structure of intestinal epithelium is enhanced. ③ Intestinal flora can stimulate the intestinal epithelial goblet cells to secrete mucin proteins Muc-1, Muc-2, Muc-3, so that the mucus layer can be restored to prevent adhesion and contact between pathogenic bacteria and intestinal mucosa. It can stimulate the intestinal tract to strengthen the peristalsis and discharge the intestinal pathogenic bacteria [40].

In terms of immunity, recent studies have shown that metabolites produced by some commensal bacteria can directly affect the T cell immune response to affect the intestinal barrier. ATP from commensal bacteria promotes Th17 differentiation by activation of CD70high. In terms of ATP-dependent Th17 cell differentiation, intestinal epithelial cells regulate the ATP concentration in the intestinal lumen by controlling the expression of ATP-degrading enzymes, such as nucleoside diphosphate hydrolase 7, thereby regulating Th17 cell overactivation [41]. For example, the segmental filamentous fungus (SFB) in the intestine is a commensal bacterium found in the intestine of mice, most of which is attached to the ileal intestinal epithelial cells, and promotes the differentiation of Th17 cells by inducing serum amyloid A (SAA). At the same time, SFB stimulates IL-23 receptor-dependent IL-22 by activating ILC3. Escherichia coli and the like stimulate the TLR5/Myd88 signal to promote the production of IL-8 by intestinal epithelial cells, and aggregate neutrophils into the lamina propria. IL-33 released from damaged intestinal epithelial cells produces IL-5 and IL-13 by activating ILC2, thereby promoting Th2 responses [42].

Therefore, many scholars now believe that the early application of probiotics and other microecological preparations to adjuvant treatment of SAP can effectively regulate the intestinal microflora balance, reduce SAP intestinal mucosal damage, protect the intestinal barrier function, and thus improve its disease course and prognosis [43].

Intestinal Mucosal Dystrophy

As a systemic inflammatory response, SAP is generally under stress, resulting in a negative nitrogen balance, plus the necessary fasting water, total parenteral nutrition, gastrointestinal decompression, and ischemic hypoxia in the early stages of infection. The state causes a decrease in the supply of intestinal nutrition, atrophy of the intestinal mucosa,

separation and widening of the tight junction between the intestinal epithelial cells, and decreased protein and DNA content in the intestinal mucosal cell population and intestinal epithelial cells. Intestinal mucosal permeability, destroying the intestinal mechanical barrier [44]. At the same time, the immune response carried out by SAP severely consumes the energy and nutrients of the immune cells, and the number of lymphocytes and their secretions sIgA in the lamina propria of the intestinal mucosa is reduced, and the immune barrier is damaged [3]. Not only that, fasting water, total parenteral nutrition, the gastrointestinal tract is at zero load, so that the secretion of intestinal digestive juice (such as gastric acid, bile, lysozyme, mucopolysaccharide, hydrolase) is reduced, causing intestinal tract The killing of the bacteria has been weakened, and the intestinal chemical barrier has also been damaged.

Glutamine (GIN), as a intestinal mucosal substrate, has been widely used to enhance the proliferation of intestinal epithelial cells through various mechanisms. Oxidation of 1Gln provides ATP to support intestinal ion transport, cell growth and migration, and maintain intestinal integrity; 2Gln is a precursor for the synthesis of purine and pyrimidine nucleotides, which is essential for DNA synthesis and cell proliferation; 3Gln Is the main substrate for the production of glutathione, glutathione is an antioxidant in the cellular environment; 4Gln up-regulates the expression of ornithine decarboxylase, ornithine decarboxylase converts ornithine into DNA and protein The key enzymes for the synthesis of the desired polyamines; 5Gln stimulates the expression of heat shock proteins to promote cell survival and reduce apoptosis; 6GLN regulates cell signaling pathways for cell proliferation; 7Gln promotes expression of mitogen genes and proteins activated by intestinal barrier function Kinases, including ERK1/2 and JNK, which leads to the activation of AP1-dependent gene transcription, which promotes cell proliferation [45].

5. Conclusion

Severe SAP intestinal barrier dysfunction can be caused by a variety of factors, mutual stimulation. A good understanding of the mechanism of IBD can effectively prevent the occurrence of complications, and can further guide clinical treatment. Although the current understanding of the pathogenesis of SAP has made great progress and a variety of new treatment methods have emerged, more specific and in-depth research is still needed to guide the treatment of clinical patients and further improve the prognosis of patients.

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