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Review:

Mechanism of acute pancreatitis complicated with injury of intestinal mucosa barrier*

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Abstract: Acute pancreatitis (AP) is a common acute abdomen in clinic with a rapid onset and dangerous pathogenetic condition. AP can cause an injury of intestinal mucosa barrier, leading to translocation of bacteria or endotoxin through multiple routes, bacterial translocation (BT), gutorigin endotoxaemia, and secondary infection of pancreatic tissue, and then cause systemic inflammatory response syndrome (SIRS) or multiple organ dysfunction syndrome (MODS), which are important factors influencing AP's severity and mortality. Meanwhile, the injury of intestinal mucosa barrier plays a key role in AP's process. Therefore, it is clinically important to study the relationship between the injury of intestinal mucosa barrier and AP. In addition, many factors such as microcirculation disturbance, ischemical reperfusion injury, excessive release of inflammatory mediators and apoptosis may also play important roles in the damage of intestinal mucosa barrier. In this review, we summarize studies on mechanisms of AP.

Key words: Acute pancreatitis (AP), Intestinal mucosa barrier, Microcirculation disturbance, Apoptosis, Inflammatory mediators
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INTRODUCTION

Acute pancreatitis (AP) features multiple complications, high mortality and complicated pathogenesis. The secondary bacteria infection and endotoxaemia in AP are also dangerous factors to AP. In recent years, with the focus on multiple organ dysfunction syndrome (MODS), bacteria translocation, and enterogenic infection in AP, the function of intestinal mucosa barrier has gradually been recognized. Intestinal mucosa barrier can prevent intestinal harmful substances, such as malignant bacteria and toxin from penetrating the intestinal wall and maintain the stability of internal environment (Garside *et al*., 2004; Harari *et al*., 2000; Kiyono *et al*., 2001). Under stringent states, such as severe acute pancreatitis (SAP), trauma, operation, radiotherapy, chemotherapy and severe infection, the structure and function of intestinal mucosa will be damaged. Electron-microscopically manifested exuviation in microvillus of the intestinal mucosa, significantly reduced height, width and area of microvillus, damaged cell tight junction (Wu and Li, 1999; Yang and Gao, 2005), and increased apoptotic cells and other pathologic alternations. Therefore, it will lead to an increase of intestinal permeability (IP) (Wu and Li, 1999; Yang and Gao, 2005; Takahashi *et al*., 2005; Ammori *et al*., 2003; Penalva *et al*., 2004), causing translocation of bacteria and endotoxin, activation of endothelial cells, release of inflammatory mediators and cytokines, and initiation of SIRS (systemic inflammatory response syndrome) and MODS (Mole *et al*., 2005; Closa and Folch-Puy, 2004). Meanwhile, the process will further increase intestinal permeability and promote continuous invasion of intestinal bacteria and endotoxin into body to form an infernal circle. Moreover, when intestinal permeability has

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been increased to certain levels, some macromolecule substances, such as bacteria and lipopolysaccharide, can penetrate the injured intestinal mucosa to move towards multiple organs and lead to a secondary infection of pancreatic tissue (de las Heras *et al*., 2000; Kazantsev *et al*., 1994; Gloor *et al*., 2001; Schwarz *et al*., 2000), which is the main cause of deaths of AP patients (Carnovale *et al*., 2005; Furuya *et al*., 2004).

INFLUENCE OF INTESTINAL MICROCIRCULATION DISTURBANCE ON INJURY OF INTESTINAL MUCOSA BARRIER

Microcirculation disturbance is one of the main causes of injuries of the pancreas and other organs during AP (Zou *et al*., 2001; Foitzik *et al*., 2000), whereas the gastrointestinal tract is one of the most frequently affected organs (Rahman *et al*., 2003; Foitzik *et al*., 2002). During AP, plasma protein and histone will be decomposed by high concentrations of activated protease to generate many macromolecules carrying positive charges that will attract the negatively charged blood cell surfaces, leading to cell aggregations. Meanwhile, the fluidity of cell membrane will be directly harmed by many oxygen free radicals (Nordback and Cameron, 1993). In addition, the increased generation of acute phase reactive proteins and fibrinogen, exosmosis of massive body fluid, and the escalated plasma protein concentrations and plasma viscosity will cause abnormal hemorheology. As a systemic pathological change, abnormal hemorheology cannot only influence pancreatic microcirculation, but also cause microcirculation disturbance of non-pancreas organs, especially the intestine. On the other hand, microcirculation disturbance may be directly or indirectly caused by a number of cytokines and vasoactive substances induced by activation of elastinase and excessive inflammatory reactions. Microcirculation disturbance includes decreases of regional blood flow and blood flow rate, increases of leucocyte adhesion and capillary permeability, and a functional decrease of capillary density, etc. (Sunamura *et al*., 1998; Jaworek *et al*., 2000).

Wang *et al*.(2000) reported that there were significant hemorheological changes during SAP, featuring increased plasma viscosity and blood flow viscosity under high and low shear rates, slower blood sedimentation and significantly reduced fibrinogen. These changes will result in a decrease of intestinal blood flow and microcirculation perfusion, and formation of capillary congestion and microthrombus, leading to a damage of the intestinal mucosa. Moreover, the microcirculations of pancreas and non-pancreas organs such as the intestinal tract will be significantly influenced by a number of inflammatory mediators such as thromboxane A_2 (TXA_2) and prostacyclin I_2 (PGI_2) that are metabolites of arachidonic acid, platelet activating factor (PAF), phospholipase A_2 (PLA_2), nitrogen monoxidum (NO) and oxygen free radicals (OFR) that are released into blood during AP. Zhang *et al*.(2003) found that intestinal blood flow significantly decreased at early stages of SAP and a decrease of perfusion volume of intestinal blood capillary (Hotz *et al*., 1998). The histological injury of intestinal mucosa may also occur due possibly to a sudden drop of intestinal blood flow caused by a redistribution of visceral blood flow, as a result of a series of neuroendocrine system changes under some severe stress states. The intestinal mucosa is quite sensitive to ischemia and hypoxia. As the disease progresses accompanied with further reduced circulation volume, excessive activation of inflammatory mediators (Shames *et al*., 2002) and more decrease of intestinal blood flow (Hotz *et al*., 1998), the injury of intestinal mucosa will be further aggravated, resulting in an infernal circle. Therefore, microcirculation disturbance is one of important causes of functionary injury of intestinal mucosa barrier during AP.

INFLUENCE OF ISCHEMIA-REPERFUSION INJURY ON INJURY OF INTESTINAL MUCOSA BARRIER

Ischemia-reperfusion (IR) injury is also a common cause of function injury of intestinal mucosa barrier (Yang and Lin, 2002; Su, 1998). Ischemia may cause various levels of local tissue injuries, while reperfusion will further aggravate tissue injuries. The xanthine oxidase and hypoxanthine will be accumulated in tissues during ischemia. After perfusion, oxygen molecule will sharply increase to produce enormous OFR, which cause peroxidation of plasma

membrane and injure structures and functions of cells. Apoptosis may be caused by the disturbance of cell transmembrane ion transportation, overloading of calcium ion and camp increase (Fukuyama *et al*., 2001; Cheng and Jin, 1998). Local changes of endothelium factors will increase the permeability of local capillaries and induce the adhesion and transmigration of neutrophil leukocytes. And the injury of intestinal mucosa may be caused by neutrophil leukocytes through release of protease and free radicals. In addition, the enormous PLA_2 and interleukin-1β (IL-1β) release during AP will stimulate each other. They will cause vasospasm, aggregations of leucocytes and platelets, thrombosis and damage of endothelial cells of blood vessels through inflammatory mediators such as TXA_2, PAF and endothelin-1 (ET-1), resulting in the aggravation of intestinal ischemia. Intestinal ischemia and succeeded reperfusion injury will then lead to injury of tissues and cells to release inflammatory mediators including PLA_2 and IL-1β. The cascade reaction will result in the injury of functions of intestinal mucosa barrier (Liu and McHowat, 1998). Therefore, ischemia-reperfusion injury might be a main cause of function injury of intestinal mucosa barrier during AP.

INFLUENCE OF EXCESSIVE RELEASE OF INFLAMMATORY MEDIATORS ON INJURY OF INTESTINAL MUCOSA BARRIER

The excessive release of inflammatory mediators during AP is a main cause of intestinal mucosa injury. Wang *et al*.(2003) found that there were more inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and IL-1β in the intestinal mucosa at early stage of SAP of rats than those in sham operation group, indicating that a number of inflammatory mediators had been synthesized at early stage of SAP.

First of all, polymorphonuclear granulocyte activated through an increase of TNF-α leads to releasing manifold injuring substances, such as oxydant and proteolytic enzyme, and causes injury of intestinal mucosa. Meanwhile, TNF-α will interact with other cytokines and inflammatory transmitters, and cause a cascade reaction of manifold injuring factors. The intestinal inflammatory reaction and microcirculation disturbance may be aggravated by TNF-α that can induce the genetic expression of IL-1β, IL-6, etc., activate PLA_2, lead to decomposition of arachidonic acid, and generate inflammatory transmitters like PAF, LT (leukotriene), PGE (prostaglandins E) and TXA_2. In addition, TNF-α activates the complement system aggravating the tissue injury through the cytotoxic action.

Secondly, nuclear factor-κB (NF-κB) has played a key role in the excessive release of inflammatory mediators. NF-κB remains inactive in cytoplasm of silent cells. When AP occurs, the inflammatory mediators (TNF-α and IL-1β), endotoxin, hemolytic phosphatidylcholine, oxidative products, metabolites and some pancreatin in local pancreas are potent excitomotors of NF-κB (Ji *et al*., 2000). They will reach the intestinal tract through microcirculation to activate the NF-κB in the effector cell of intestinal tract. After activation, nucleus translocation of NF-κB will occur. NF-κB will bind the κB site on promoter or enhancer of target genes to promote or enhance the expressions of corresponding cytokines in cell nucleus, adhesion molecules and chemotactic factors (Izumi *et al*., 2001; Antonelli *et al*., 2001; Ginis *et al*., 2002; Wright *et al*., 2002; Lakshminarayanan *et al*., 2001; Moine *et al*., 2000; Valen *et al*., 2001; Omoya *et al*., 2001), and to regulate inflammation and immunological reactions (Neurath *et al*., 1998). Although the massive production of inflammatory mediators in local intestinal tract is a defense reaction to the invasion of intestinal bacteria and toxin, it will cause injury of intestinal mucosa (Wang *et al*., 2002; Theuer *et al*., 2002). The levels of inflammatory mediators increase with the progression of SAP. On one hand, the vascular endothelial cells of intestinal mucosa will be activated to express ICAM-1 (intercellular adhesion molecule 1) and let it interact with L-selectin expressed by PMN (polymorphnuclear neutrophil**)**, promoting the roll effect of PMN along the vessel wall. On the other hand, the integrin receptor on PMN surface will be activated to increase the expression of lymphocyte function-associated antigen-1 (LFA-1) on PMN surface. Thus, PMN will rapidly adhere to endothelial cells through the interaction of integrin receptor and ligand (ICAM-1 on endothelial cell surface) leading to intestinal mucosa injury. In addition, as injury changes occur to the small intestine mucosa during SAP, the level of

lipopolysaccharide (LPS) in plasma will significantly increase. The ICAM-1 expression of small intestine mucosa is positively correlated with LPS level in plasma.

In addition, as an important inflammation promoting cytokine, IL-1β plays its role in prompting the adhesion and aggregation of leucocytes on the surface of vascular endothelial cells and activating other inflammatory mediators. Tissues will be injured by PLA_2 through damaging the lipid cell membrane to cause cell necrosis. PLA_2 and IL-1β stimulate each other. The inflammatory mediators such as TXA_2, PAF and ET-1 regulated by PLA_2 and IL-1β will cause vasospasm, aggregations of leucocytes and platelets, thrombosis and injury of vascular endothelial cells, resulting in the aggravation of intestinal ischemia. Intestinal ischemia and succeeded reperfusion injury will lead to injuries of tissues and cells to release inflammatory mediators including PLA_2 and IL-1β. This cascade reaction will result in the functional injury of intestinal mucosa barrier (Liu and McHowat, 1998).

However, the general immune system formerly in pre-excitation will be activated by endotoxin due to endotoxaemia generated after injury of intestinal mucosa barrier. The monocytes/macrophages, neutrophils and endothelial cells will release a large amount of inflammatory mediators (OFR, PLA_2, PAF and TXA_2) to further injure intestinal mucosa barrier, leading to more endotoxin entering blood and forming an infernal circle (Yin *et al*., 2005; Wu *et al*., 2003).

INFLUENCE OF APOPTOSIS ON INJURY OF INTESTINAL MUCOSA BARRIER

The stability of intestinal mucosa barrier depends on the balance between proliferation and apoptosis of epithelial cells. Apoptosis is a protecting mechanism of body. However, the inhibition of apoptosis will cause proliferation and thickening of intestinal epithelium or even canceration. Excessive apoptosis is harmful to the regeneration and recovery of intestinal epithelium, causing functional disturbance.

Wang *et al*.(2001a) found that the incidence of epithelial apoptosis of intestinal mucosa increased significantly at the early stage of SAP of rats, reaching peak value at 6 h after operation, while the ratio of apoptotic and necrotic cell (A/N) reached 27.7±17. The break of the linkage between epithelial cell and cell matrix was believed to be the main cause of apoptosis. The pathological process of participation of intestinal epithelial apoptosis in functional disturbance of intestinal mucosa barrier during AP was fully revealed. The experiment has confirmed the increase of epithelial apoptosis of intestinal mucosa was accompanied with shortages of inflammatory mediators and growth factors, bacteria toxin, OFR and intestinal IR injury of rats as well as the barrier functional disturbance of intestinal mucosa (Jones and Gores, 1997; Raab *et al*., 1998). The permeability is positively correlated with apoptosis. During AP, the visceral blood flow perfusion will decrease, ischemia and hypoxia will occur to intestinal mucosa, a great deal of OFR will be generated and calcium overload will occur. OFR can damage cell DNA, attack protein and influence nuclear gene transcription. Calcium ion can split DNA and increase intracellular camp, and these factors together will cause apoptosis (Su, 1998). Meanwhile, inflammatory reaction and cytokines (TNF-α and IL-6) will be produced by slowing enterocinesia, injuring intestinal epithelial, bacteria adhesion and penetration of intestinal epithelium, and induce and regulate intestinal epithelial apoptosis (Ikeda *et al*., 1998). Besides, the linkage between epithelial cell and cell matrix will be damaged by abnormal expression of cellular adhesion molecule (Swank *et al*., 1998) while the apoptosis in vivo or in vitro will also be increased by excessive inflammatory cytokines such as TNF-α and IL-1β (Dunger *et al*., 1996; Liu *et al*., 1996).

In addition, the apoptosis of lymphocytes of intestinal Peyer's patches also participates in the function injury of intestinal mucosa barrier. Intestinal Peyer's patches are exposed in enteric cavity to receive the increase of gutorigin antigen load. The lymphocyte apoptosis will be directly or indirectly induced by the hyperkinesis and hypermetabolism at early stage of systemic inflammatory reaction (Schmidt *et al*., 1992), and production and release of regulating factors of lymphocyte apoptosis such as NO (Bzowska *et al*., 2002). The plasma cells differentiated from B lymphocytes of Peyer's patches are the main secreting source of secretory IgA (sIgA).

As the main component of mucus covering the surface of intestinal epithelial cells, sIgA plays an important role in protecting epithelial cells of the intestinal mucosa, phagocytizing bacteria and virus and preventing bacteria translocation. When receiving an increase of gutorigin antigen load, Peyer's patches may stimulate the immature B lymphocyte to differentiate plasma cells and secrete more sIgA. Meanwhile, apoptosis will occur to more B-lymphocytes, which, at the early stages of disease, will play a role of compensational secretion of sIgA. Later, this may cause excessive apoptosis of B-lymphocytes, resulting in an imbalance between the production and death of lymphocytes, a decrease or a failure of sIgA. Finally, this may lead to a functional injury of intestinal immune barrier causing translocations of intestinal bacteria and endotoxin, and initiations of SIRS and MODS.

INFLUENCE OF ENTERAL NUTRITION DEFICIENCY ON INJURY OF INTESTINAL MUCOSA BARRIER

The decline of enteral nutrition is also a cause of functional injury of intestinal barrier. The renewal of intestinal mucosa epithelial cells relies on a number of energy, with glutamine (Gln) and arginine as its main "fuel" to maintain the immune function and microecological environment and protect the mucosa barrier function of the intestinal tract (Wang *et al*., 2001b). During AP, especially SAP, body in high decomposition state needs a much greater energy demand. Nutrition deficiency or fasting during AP will cause the deficiency of Gln and arginine and less growth factors synthesized by epithelial cells of the intestinal mucosa, leading to regulating function disturbance of lymphocytes and macrophages (Foitzik *et al*., 1999; Exner *et al*., 2002) and the injury of the intestinal mucosa (Avgerinos *et al*., 2003). In addition, although sufficient energy and nitrogen source may be supplied by long-term total parenteral neruition (TPN), functional injury of the intestinal mucosa will still inevitably be caused by a shortage of nutrition required for repairing metabolism of the intestinal mucosa and digestion stimulation due to food shortage (Liu *et al*., 2001). Li (1998) have proven that the function of rat intestinal barrier will be significantly weakened after TPN supportive treatment, and 100% bacteria translocation will occur if there is a hemorrhagic shock. The early enteral nutuition (EN) might be indispensable to the protection of intestinal mucosa barrier of rats (Al-Omran *et al*., 2003; Marik and Zaloga, 2004).

OTHERS

Grady *et al*.(2000) found that PAF played an important role in the progression of pancreatitis complicated with functional disturbance of intestinal mucosa barrier. Its antagonist might be a potential therapy. As the important ligand of hyaluronic acid, the main component of extracellular matrix, CD44 is significant for maintaining the compact and integrity of epithelial structures as it can mediate the linkage between cell and cell or cell and matrix. Wang *et al*.(2001c) showed CD44 mRNA expression of the intestinal mucosa of rats with SAP was higher than that of control group. Based on the pathological changes such as intestinal mucosa injury and mucosa exuviation, it is presumed that the linkage between cell and cell or cell and matrix of the intestinal epithelium as well as the recovery of the intestinal epithelial layer were affected by a decrease of CD44 expression after SAP, while the role of growth hormone (GH) in maintaining the integrity of epithelial structures and immune functions of the intestinal mucosa might be related to the increase of CD44 mRNA expression. P substance and its receptor such as neurokinin-1 receptor (NK-1R) and neurokinin-2 receptor (NK-2R) have played important roles in the onset and progression of AP (Maa *et al*., 2000; Grady *et al*., 2000). The action of neurokinin has been disturbed and the intestinal mucosa injury has been aggravated due to the significant increase of expressions of NK-1R and NK-2R in the colon during SAP (Zheng *et al*., 2002).

SUMMARY

In conclusion, there are manifold ways to cause the function injury of intestinal mucosa barrier including excessive release of inflammatory mediators, apoptosis, microcirculation disturbance and ische-

mia-reperfusion injury during the progression of AP. In addition, these ways have formed a network reaction during AP progression to cause a synergistic intestinal injury. Reaching certain levels, injury of intestinal mucosa barrier will increase the permeability of the intestinal mucosa, cause intestinal bacteria translocation and gutorigin endotoxaemia, and result in multiple organ functional disturbance and failure. We will have a new understanding of the onset of AP, find new therapies through further studies of the mediating role of intestinal mucosa barrier during AP, and discover ways to protect its function, which plays a key role in improving the prognosis of AP patients.

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