Microcirculatory Disturbances in the Pathogenesis of Acute Pancreatitis

Dirk Uhlmann

*2nd Department of Surgery, University of Leipzig
Germany*

1. Introduction

In acute pancreatitis, reductions in blood flow and alterations of microvascular integrity resulting in impaired tissue oxygenation play an important part in the progression and possibly the initiation of the disease. Independently of the initial noxa, the intra-pancreatic activation of trypsinogen to trypsin is the crucial trigger of acute pancreatitis. The central events for the further course are the release of local mediators (cytokines, vasoactive substances, free oxygen radicals) and subsequently the development of microcirculatory disturbances and the activation of leukocytes and their infiltration into the tissue. At present, the deterioration of microcirculation is seen as the most important pacemaker in the progression to a necrotizing pancreatitis. In addition to its potentiatory role, severe pancreatic ischemia can play a pathogenetic role in the initiation of acute pancreatitis. The acute edematous pancreatitis is characterized by an increased and homogeneous microperfusion. The experimental necrotizing pancreatitis shows a progredient decrease of capillary perfusion despite stable macrohemodynamics.

There is increasing evidence that ischemia alone may be the primary cause of pancreatitis or may be the exacerbating promotor for the progression from edematous to necrotizing pancreatitis. In clinical studies there was evidence, that ischemia during cardiopulmonary bypass triggered acute pancreatitis and acute pancreatitis was found in up to 25% of autopsies of patients dying after shock. In animal models severe pancreatitis could be induced by obstruction of terminal pancreatic arterioles. The study by Mithöfer et al. [1] demonstrates, that temporary hemorrhagic hypotension in rats per se initiates acute pancreatitis.

The hypothesis, that the manifestation of microvascular injury in acute pancreatitis involves ischemia/reperfusion(I/R)-associated events, is supported by the study of Menger et al. [2], who analyzed the pancreatic microcirculation of rats during postischemic reperfusion by use of intravital fluorescence microscopy (Fig. 1, 2). In this investigation, post-ischemic reperfusion was characterized by a significant reduction of functional capillary density (no-reflow) and by a marked increase of the permanently adherent leukocytes in postcapillary venules (reflow paradox) (Fig. 3). In addition, the functional and histomorphological alterations in this study were similar to the alteration seen in edematous pancreatitis. Postischemic activation of leukocytes has been reported to determine the outcome of I/R injury. Kusterer et al. [3] have demonstrated that sodium taurocholate-induced pancreatitis

is characterized by early arteriolar vasoconstriction with ischemia, followed by arteriolar vasodilation with reestablishment of blood flow (reperfusion). Increased leukocyte-endothelial cell interactions in postcapillary venules - mimicking the I/R event - were observed during vasodilation. The concept of I/R-induced pancreatitis is mostly reflected in the clinical situation of post-transplant pancreatitis. Experimental studies using the model of syngeneic pancreas transplantation in rats show microcirculatory disturbances and cellular damages similar to those seen in the beginning of an acute pancreatitis [4]. Pancreatitis after hemorrhagic shock or hypotension with hypoxia, but not complete ischemia/anoxia may also involve pathomechanisms associated with ischemia/reperfusion. A recent study demonstrates, that hemorrhagic hypotension in rats induces intermittent capillary perfusion, which is characterized by periods of normal blood flow followed by periods of complete cessation of blood flow [5]. This type of regional ischemia and reperfusion may contribute to the manifestation of pancreatitis, independent of the etiology.

2. Cell-cell interactions

By means of intravital microscopy (Fig. 1-3) in conjunction with technique of selected cell-labeling, direct impairments of pancreatic microcirculation induced by controlled haemorrhage or interruption of arterial blood supply to the pancreas in the early phase of acute pancreatitis have been observed [6], suggesting the pancreatic microcirculation being highly susceptible to ischemia [7-9]. The nature of blood cell-endothelium, especially leukocyte-endothelium, interactions as an early step in the inflammatory response has been characterized in experimental pancreas transplantation and in models of I/R-induced acute pancreatitis [4, 10].

Fig. 1. Processing of intravital microscopy of the rat pancreas.

Fig. 2. In-vivo microscopic image of pancreas microcirculation.

Fig. 3. In-vivo microscopic image of sticking platelets in a postcapillary venule of a post-ischemic rat pancreas.

2.1 Leukocytes

The neutrophils play a central part in the inflammatory process of acute pancreatitis. Their activation and that of the endothelium by cytokines (IL-6, TNF α , IL-8, IL-1b and others) and of proinflammatory mediators (platelet-activating factor (PAF), free radicals and others) will allow a narrow interaction between them that will result in a significant concentration of neutrophils activated in the interstitium [11-14]. This interaction takes place in three parts: a weak adhesion of the neutrophils to the endothelium, followed by a stronger adhesion and, finally, the neutrophil migration (Fig. 4). Three families of adhesion molecules are implicated: selectins, b2-integrins and immunoglobulins (Table 1). The selectins are surface glycoproteins implicated in weak adhesion. The L-selectin, expressed by the endothelial cells and the neutrophils, plays a part at the beginning of reperfusion. It interacts with the P-selectin on the neutrophils and a specific ligand present on the membrane of the neutrophil, the E-selectin-specific ligand-1 (ESL-1) [15]. Endothelial P-selectin will be expressed later

from the Weibel-Palade bodies after activation of the endothelium by reactive oxygen species (ROS), hypercalcaemia, complement or thrombin. Its peak of expression occurs 10–20 min after the beginning of reperfusion [14]. It interacts with P-selectin glycoprotein ligand-1 (PSGL-1) expressed by the neutrophils. These interactions are very weak, giving the neutrophils a weak, transitory, reversible adhesion known as ‘leukocyte rolling’. This phase prepares the neutrophil and the endothelium for the following stage. A more important stowing of neutrophils in the endothelium utilizes other leukocyte and endothelium proteins that have a stronger affinity for each other.

Leukocyte adhesion receptor	Endothelial ligand	Function
a4b7 (unactivated)	MadCAM-1	Rolling
a4b1 (unactivated)	VCAM-1	Rolling
PSGL-1	P-selectin	Capture, Rolling
L-selectin	P-selectin Peripheral node addressin (PNAd) E-selectin MadCAM-1	Capture Rolling
a4b7 (activated)	VCAM-1/MAdCAM-1	Firm adhesion
a4b1 (activated)	VCAM-1	Firm adhesion
CD11a /CD18 (LFA-1)	ICAM-1, ICAM-2	Firm adhesion, Emigration
CD11b/CD18 (Mac-1)	ICAM-1	Firm adhesion, Emigration
PECAM-1	PECAM-1	Emigration

Table 1. Leukocyte-endothelium interactions. Adhesion receptors and their ligands on activated endothelial cells. Modified from [17].

The ROS, PAF and leucotriene (LTB₄) stimulate the expression by neutrophils of b2-integrins from the intracellular granules. This family of membrane proteins consists of CD11a/CD18, CD11b/CD18 and CD11c/CD18 and interacts with the ICAM-1 endothelial protein whose expression is enhanced by TNF α and IL-1 [16, 17]. This interaction fastens the neutrophil to the surface of the endothelial cell and allows the next stage. ICAM-1 and PECAM-1 are adhesion molecules belonging to the superfamily of immunoglobulins which take part and orchestrate the transfer of the neutrophils towards the interstitium. The leukocyte extravasation utilizes many stages, not all of which are yet clear. Nevertheless, it seems that PECAM-1, localized at the level of the intercellular endothelial junctions, is

necessary to allow neutrophil migration [18]. This transfer is facilitated by the inflammation mediators, the connection of CD11/CD18–ICAM-1 and the ROS making the endothelial barrier receptive by decreasing the expression of cadherin and phosphorylation of vascular endothelial cadherin and catenin, components of the intercellular junctions [19, 20].

Fig. 4. Multistep adhesion cascade of leukocyte-endothelium interactions. Modified from [183].

Arriving at the interstitium, the activated neutrophil will cause considerable damage to a tissue, which has already suffered from hypoxia. These lesions are mainly related to the massive ROS production, to the release of the contents of the neutrophilic granules and to the metabolites of arachidonic acid. The last, metabolized by phospholipase A2, generates PAF and LTB4, two powerful chemoattractive components that stimulate the adhesion of neutrophils to the endothelium and their degranulation in the interstitium. The neutrophilic granules, filled with proteases, collagenases, elastases, lipooxygenases, phospholipases and myeloperoxidases, will digest and disorganize the protein network of extracellular matrix (Table 2). The proteic network of extracellular matrix is important in healing while being used to guide tissue formation. The inflammation induced by reperfusion is a major cause of the lesions observed after restoration of blood flow in an ischemic organ. The massive production of cytokines, the activation of the complement and a complex choreography of the neutrophils are the key factors and are therefore being examined in research to modulate the inflammatory reaction.

2.2 Platelets

Considerable evidence has accumulated that platelets can also contribute to I/R injury in several organs, such as the heart [21], lung [22], and pancreas [23]. Upon activation, platelets are able to generate reactive oxygen species and nitric oxide (NO) and can release pro-inflammatory mediators, such as chemokines, cytokines, growth factors, and cytotoxic proteases [24]. Therefore, platelets can potentially contribute to the manifestation of

pancreatitis after normothermic I/R injury. In the liver of a rat model, Khandoga et al. [25] have demonstrated that platelets interact with the hepatic endothelium after 90 min of warm ischemia and 20 min of reperfusion and evoke the development of hepatic microvascular and hepatocellular injury.

Leukocytes	Platelets
<i>Cytokines/chemokines</i> IL-1, IL-2, IL-6, IL-8, IL-12 IFN-a, IFN-b TNF-a, TNF-b Transforming growth factor-b Monocyte chemotactic factor-1 <i>Reactive oxygen species</i> Superoxide Hydrogen peroxide <i>Proteases</i> Cathepsin-G Elastase Collagenase <i>Oxidases</i> Myeloperoxidase <i>Lipid mediators</i> Leukotrienes B4, C4 Platelet activating factor <i>Miscellaneous</i> Cationic proteins Histamine VEGF	<i>Cytokines/chemokines</i> IL-1, IL-7, IL-8 RANTES TNF-b CD40 ligand <i>Reactive oxygen species</i> Superoxide Hydrogen peroxide <i>Growth factors</i> PDGF Transforming growth factor-b VEGF <i>Lipid mediators</i> Thromboxane A2 12-HETE <i>Procoagulants</i> Thrombin ADT and ATP Platelet factor-4 Polyphosphates

Table 2. Activation products released by leukocytes and platelets that may impair endothelial barrier function. Modified from [18].

Platelet activation was accompanied by leukocyte activation in a study of Hackert et al. [7]. An interaction between these two cell types has been demonstrated by different authors in the past [26-28]. Among others, P-selectin seems to be one of the most important adhesion molecules, which links the inflammatory and procoagulatory cascades and has the potency to activate leukocytes and platelets as the cellular elements of either pathway [27-30]. Besides their adherence to endothelial cells, activated platelets form stable aggregates with leukocytes. This results in a combined inflammatory and coagulatory contribution to thrombus formation and is also mediated by P-selectin and beta-integrins [31, 32]. Especially, the formation of microthrombotic vessel occlusion with microcirculatory perfusion failure and consequent ischemia, hypoxia, and tissue necrosis promote organ damage.

2.3 Lymphocytes

Recent studies have implicated peripheral blood lymphocytes in Ag-independent inflammatory-mediated injury following organ reperfusion [33-36]. The contributory role of lymphocytes in I/R is likely a multifactorial one.

Evidence is mounting on the importance of T cells in mediating both short- and long-term damage during I/R injury, which in turn could explain why I/R contributes to poor late allograft function [37, 38]. The demonstration that systemic immunosuppression (CsA, FK506) attenuates hepatocellular injury following I/R implies the involvement of T lymphocytes in the pathophysiology of the injury [39, 40], data supported by Shen et al. in T-cell-deficient (nude) mice [41, 42], as well as in rats in which treatment with FTY720 prevented hepatic I/R insult in parallel with massive redistribution of recirculating T cells from host peripheral blood into the lymph node compartment [43]. The adherence of lymphocytes in hepatic sinusoids occurs early during reperfusion and impairs liver function following prolonged cold ischemic times [44]. Recent data have also shown that circulating CD4⁺ T lymphocytes may act as a cellular mediator in subacute PMN recruitment following hepatic I/R injury [38] (Table 3).

Platelet receptors	Ligand	Function
P-selectin	PSGL-1	Rolling, adhesion, RANTES deposition
PSGL-1	P-selectin	Rolling, adhesion and P/L interactions
GP1ba	vWF P-selectin Mac-1	Aggregation, rolling, adhesion and P/L interactions
GPIIb/IIIa	GPIIb/IIIa ICAM-1 (via fibrinogen) αv β3 Mac-1	Aggregation and adhesion
JAM-A	PSD95/ZO-1	Aggregation and adhesion
PECAM-1	PECAM-1	Aggregation and adhesion

Table 3. Platelet-endothelium interactions: Potential molecular determinants. Modified from [157]

JAM-A junctional adhesion molecule-A
 PECAM platelet endothelial cell adhesion molecule-1
 PSGL-1 P-Selectin glycoprotein ligand-1
 vWF von Willebrand factor
 ZO-1 zona occludens protein-1

3. Adhesion molecules

A variety of adhesion molecules are implicated in the progression of disease. Intercellular adhesion molecule, platelet endothelial cell adhesion molecule 1 and endothelial leukocyte

adhesion molecule 1 (ELAM-1) are up-regulated, expression of P- and E-selectin enhanced, and leukocytes become CD18 positive in acute pancreatitis [11].

3.1 Intercellular Adhesion Molecule-1 (ICAM-1)

ICAM-1, a single-chain transmembrane glycoprotein with a molecular weight of 80-110 kDa, consists of five Ig-like domains, a hydrophobic transmembrane domain and a short cytoplasmic C-terminal domain [45]. Its ligand includes lymphocyte function-associated antigen-1 (LFA-1) and macrophage antigen-1 (Mac-1) [46]. ICAM-1 is an immunoglobulin molecule mainly expressed in vascular endothelial cells, and plays an important role especially in the process of inflammation. Under normal circumstances, it will not be expressed or just with low expression in most vessels. However, when its expression increased, it can interact with integrin on the surface of granular cells. Therefore, it can cause leukocyte migration through capillary endothelial barriers to inflammatory regions, and then cause excessive architectonic inflammatory response [47]. Experiments show that ICAM-1 high expression may cause leukocyte adhesion through endothelial cells – leukocyte interaction, increase capillary permeability, reduce capillary blood flow velocity, cause pancreatic microcirculation disorder [48-50]. ICAM-1 expression correlates with histological severity and leukocyte infiltration [51], and can be upregulated by trypsin *in vivo* and *in vitro* [49]. This upregulation is mirrored by increased tissue infiltration of leukocytes and increased endothelium-leukocyte interaction.

Whereas the binding of endothelial ICAM is directly to CD18 on the leukocyte surface, the binding of platelets to the endothelium is possible via the following mechanism. I/R leads to fibrinogen deposition on microvascular endothelial cells and a corresponding accumulation of firmly adherent platelets. Experimental interventions (i.e., anti-fibrinogen antibody or ICAM-1 deficiency) that reduce the I/R-induced fibrinogen accumulation also blunt the accumulation of adherent platelets in both arterioles and venules, suggesting that the binding of fibrinogen to endothelial cell ICAM-1 creates a scaffold on the vessel wall onto which platelets can adhere using GPIIb/IIIa [52] (Table 3).

3.2 Platelet–endothelial cell adhesion molecule (PECAM)-1

The pancreatic circulation during acute experimental edematous pancreatitis may also be influenced by the expression of platelet-endothelial cell adhesion molecule on polymorphonuclear leukocytes. PECAM-1 expression was up-regulated in the peripheral circulation and down-regulated in the pancreatic microcirculation, suggesting that inhibition of PECAM-1 expression may improve the pathological changes associated with acute edematous pancreatitis in rats [53, 54].

3.3 P-selectin

P-selectin is normally stored in granular structures of both platelets (α -granules) and endothelial cells (Weibel–Palade bodies), from which it can be rapidly mobilized to the cell surface upon endothelial cell activation. Some vascular beds (e.g., intestine) exhibit significant basal expression of P-selectin [55], with little basal expression on inactivated circulating platelets. Several studies have addressed the contributions of platelet vs. endothelial cell P-selectin to the platelet adhesion induced by stimuli such as I/R [56, 57], [58], endotoxin [59], and TNF- α [60]. In I/R models of platelet adhesion, it appears that those models that elicit a rapid adhesion response in both venules and arterioles are entirely

dependent on endothelial P-selectin [56], while I/R models exhibiting slow, time-dependent platelet adhesion only in venules involve both platelet and endothelial cell P-selectin [57]. A blocking mAb directed against PSGL-1, a ligand for P-selectin that is expressed on leukocytes and platelets [61], is also effective in attenuating the I/R-induced platelet adhesion observed hours after reperfusion, which further supports a role for platelet-derived P-selectin [57].

Influenced Paramter	Treatment	Effect	References
Leukocytes	Neutrophil depletion	+	[57]
	Diannexin	+	[42]
	Tacrolimus	+	[158, 7]
	Anti-fibrinogen antibody		[159]
	Erythropoietin		[160, 161]
Platelets	Platelet depletion, anti-platelet serum	+	[162]
Lymphocytes	FTY720	+	[43, 163, 33]
	Tacrolimus	+	[158, 7]
ICAM-1	Anti-ICAM-1 antibody	+	[51, 164, 165]
	ICAM-1-deficiency	+	[52]
	Phloretin	+	[166]
	Erythropoietin		[160, 161]
P-selectin	CP-96,345	+	[167]
	Statins	+	[168-170]
ET	ET _A receptor antagonist	+	[79, 171-173]
NO	L-arginine	+	[174-176]
	Sodium nitroprusside		
TNF- α	Receptor antagonist	+	[177]
	Knockout mice	+	[178]
	Polyclonal antibody	+	[90]
IL-1	Receptor antagonist	+	[177]
	Knockout mice	+	[178]
IL-10	IL-10 administration	+	[108, 109].
PAF	PAF antagonist	+	[179], [180], [111]
Serotonin	5HT ₂ receptor antagonists	+	[119], [118]
Bradykinin	Bradykinin B ₂ receptor antagonist	++	[181], [132]
TXA ₂	TXA ₂ receptor blocker	+	[182]
VEGF	tyrosinekinase inhibitor PTK787/ZK222584	+	[146]
COX2	Inhibition, depletion	+	[136, 137]

Table 4. Therapeutic approaches to prevent or treat microcirculatory disturbances in acute pancreatitis.

The platelet adhesion elicited by bacterial endotoxin also appears to involve endothelial P-selectin [59]. However, glycoprotein (GP) Iba is the platelet ligand that appears to mediate this interaction. This glycoprotein and PSGL-1 are two platelet ligands that have been

implicated in P-selectin-mediated platelet interactions (primarily rolling) with venular endothelial cells. Platelet GPIb α also exhibits the capacity to bind to endothelial cells in a P-selectin-independent manner. vWF, which is released from Weibel-Palade bodies during endothelial cell activation, can bind to GPIb α . vWF-GPIb α interactions have been implicated in the platelet recruitment in mouse mesenteric venules stimulated with either calcium ionophore, A23187, or histamine [62, 63].

4. Vasoactive mediators

4.1 Endothelin

Endothelin-1 (ET-1) is a potent vasoconstrictor of the pancreatic microcirculation mainly produced by endothelial cells. The intact microvasculature is balanced by the constricting action of ET-1 and the dilating features of nitric oxide (NO), made constitutively by endothelial nitric oxide synthase (eNOS). It has been shown that ET-1 production is controlled at the transcriptional level. Up-regulation of prepro-ET-1 mRNA can be induced by numerous factors such as cytokines, angiotensin, thrombin, and TGF- β [64]. Released from endothelial cells, ET-1 mediates transient vasodilation followed by a profound and longlasting vasoconstriction. Furthermore, ET-1 is able to induce an inflammatory response in human vascular smooth muscle cells by stimulating the synthesis and release of pro-inflammatory cytokines such as interleukin-6 [65]. ET-1 does not only mediate local injury, but also systemic disease.

ET affects microcirculation by:

- constriction of arterioles and venules [66, 67]
- release of prostaglandine E2, IL-6 and IL-8 from monocytes [68]
- stimulation of phospholipase A2 [69]
- reinforced formation of free oxygen radicals in neutrophils [70]
- expression of adhesion molecules [71, 72]
- stimulation of catecholamine release [73]

Beside its vasoconstrictive effects endothelin as multifunctional cytokine modulates the motility and secretion of the intestine, stimulates mitogenesis and acts as a growth factor. Several investigators have shown that the pancreas is especially susceptible to ET-1 [74], [75]. The study of Hildebrand et al. showed that the rat pancreatic acini possess ET_A and ET_B receptors [76]. At doses of 100 to 1000 pmol/kg via intravenous injection, endothelins cause sustained reduction in pancreatic blood flow in the rabbit and dog of up to 80 % [75, 77]. In a study in rats, intravenous infusion of endothelin-1 or alcohol significantly reduced pancreatic capillary blood flow. The deterioration of capillary blood flow was more pronounced when alcohol and ET-1 were combined [78]. Liu et al. observed a decrease of pancreatic blood flow and a reinforcement of morphological changes after application of endothelin to rats with cerulein-induced edematous pancreatitis [47]. Foitzik et al. found in transgenic rats with an overexpression of endothelin receptors a more severe course of a necrotizing pancreatitis, which could be moderated by the application of a selective ET_A receptor antagonist [79]. Plusczyk et al. showed that topical ET-1 application leads to a decrease in blood flow in the pancreas [80]. In intravital microscopy a strong heterogeneity of erythrocyte velocity, a decrease in the number of perfused capillaries and a reduction of the capillary width were seen. This group suggests that high local ET concentrations can cause complex microcirculatory disturbances, leading to acinar cell necrosis and therefore to the development of necrotizing pancreatitis [80]. There is some evidence that endothelins

also increase pancreatic capillary permeability [74, 81], though this might be explained by the resulting portal venous vasoconstriction.

4.2 Nitric oxide

Nitric oxide (NO) is synthesized through NO synthases from the amino acid L-arginine. For the first time, this pathway was described in endothelial cells [82], but it is also found in platelets, macrophages and in cells of the pancreas [68, 69]. NO causes a relaxation of vascular smooth muscle cells, depression of platelet aggregation and adhesion and reduces the leukocyte activation in vitro [72, 83]. Reduced NO formation reinforces leukocyte adhesion and migration [84-87]. These effects are regulated by the activation of the soluble guanylatcylase which leads to increased concentrations of cGMP in the effector cells [86]. NO may also act as scavenger of oxygen free radicals [88]. However, also cytotoxic effects are described [89]. The overproduction of NO by inducible NO synthetase is an important factor in the hemodynamic disturbances of several inflammatory states.

5. Cytokines

During acute pancreatitis, some inflammatory cells and pancreatic tissues release inflammatory mediators and cytokines, which influence the whole process of inflammation. The most important cytokines are tumor necrosis factor- α (TNF- α), interleukins (IL) and transforming growth factor (TGF).

5.1 TNF- α

Lipsett [90] and Hirota et al. [91] independently proved that the levels of inflammatory cytokines always increase during acute pancreatitis and that the degree of the increase is closely linked to the severity of the disease. Many other studies have reported that self-tissue injured with over-activated neutrophil leucocytes is an important causal factor of systemic complications [92-94]. One proposal is that the neutrophilic granulocyte may generate and release inflammatory cytokines such as TNF- α following inflammatory stimulation [95, 96]. TNF- α is an important species of inflammatory cytokines that participates in the pathomechanism during pancreatitis. Hughes et al. [97] found that injecting TNF- α antibody into rats can markedly improve the state and survival of rats with necrotizing pancreatitis, thereby indicating the important role of TNF- α in the onset and progression of the disease. A number of mechanisms have been proposed for TNF- α -induced pancreatic injury. TNF- α can directly injure pancreatic duct cells and cause microthrombus, pancreatic acinus ischemia, hemorrhage, necrosis, inflammation and edema [6]. When the quantity of produced TNF- α exceeds that of the tissue TNF receptor, the excessive free TNF- α will enter the blood circulation, activate neutrophilic granulocytes and cause their aggregation. It then stimulates the release of cytokines, such as IL-1b, IL-8 and IL-6 [98], causing a cytokine cascade reaction that promotes the local and systemic injury. The continuous existence of TNF- α may enhance the expression of endothelium adhesion molecules, which is necessary for the aggregation of inflammatory cells. Numerous granulocytes invade the pancreatic and renal tissues, increase granulocyte phagocytosis and degranulation, generate oxygen-derived free radicals, lysosomes, elastin enzyme, among others, and cause cell metabolic disturbances and renal failure [99].

5.2 IL-1

Interleukin (IL) IL-1 is a pro-inflammatory cytokine generated by the pancreas that plays an important role in the early stage of severe acute pancreatitis. In a animal model, the IL-1 receptor antagonist (IL-1r) has been found to decrease case fatality by 30% [100]; in addition, the IL-1 receptor can markedly lower the concentrations of IL-6 and TNF- α [101]. Fink et al. [102] administered the IL-1 receptor antagonist before inducing the pancreatitis model and found that the IL-1 receptor block markedly lowered the release of amylpsin and pancreatic necrosis in a dose-dependent manner.

The generation of IL-1 β formed from IL-1 through the mediation of IL-1 convertase (ICE). IL-1 β and TNF- α have many of the same biological activities, including pyrogen functions, the promotion of cell catabolism, the production of protein in the acute reaction period, effecting the secretion of PGI₂ by epithelial cells and platelet activating factor, among others, that will cause the expansion of the inflammation area and increase the levels of inflammatory mediators, destructive enzymes and ROS secretion. IL-1 β can interact with TNF- α to induce or aggravate organ injury. It also has chemotaxis and activating effects on granulocyte and can stimulate the production of other inflammatory mediators, such as IL-8, IL-6 and other inflammatory cytokines, through autocrine or paracrine mechanisms.

5.3 IL-6

IL-6 is mainly generated by mononuclear macrophages, which have extensive inflammation-promoting effects, such as promoting the activation and proliferation of B cells and their final differentiation into plasmocytes, increasing immunoglobulin synthesis, promoting T cell differentiation and proliferation, promoting the acute period reaction and injuring tissue. The level of IL-6 in the serum can reflect the state of necrotizing acute pancreatitis. There are marked differences between acute pancreatitis patients without complications and severe acute pancreatitis patients with complications in terms of IL-6 levels. When present at levels of over 40 μ l, IL-6 is considered to be an indication index of severe acute pancreatitis [103]. Relevant data show that IL-1 and IL-6 can act on endothelial cells, causing them to lower their thrombomodulin activity, aggravate renal ischemia, form thrombus [104] and activate inflammatory cells to release NO and ROS to directly cause renal injury.

5.4 IL-8

IL-8 is a potent neutrophilic granulocyte chemotatic factor and activating factor that is mainly generated by neutrophilic granulocytes. Generated by mononuclear/ macrophages and endothelial cells, it can activate and induce T and B cell differentiation, enhance NK cells for killing target cells, promote phagocytosis and play an important role in tissue injury mediated by neutrophilic granulocytes. It is currently believed that most inflammatory reactions induced by TNF- α , IL-1 and IL-6 are realized by inducing the generation of chemotactic factors, mainly IL-8. Studies have shown that during necrotizing acute pancreatitis the levels of IL-6 and IL-8 always increase concurrently and that these positively correlate with the state of severe acute pancreatitis [105].

5.5 Transforming growth factor (TGF)

Kimura et al. [106] studied the expression of TGF- β 1 by means of immune electron microscopy and found that a marked effusion of the polymorphonuclear leukocyte and deposition of fibronectin and TGF- β 1 among pancreatic lobules and inside lobules within

12–24 h after inducing pancreatitis. They therefore believed that this kind of change at the early stage of pancreatitis is related to the generation of fibronectin and type III collagen in the extracellular matrix during the reparative process of pancreatic tissues. Konturek et al. [107] proposed that TGF- β can induce non-inflammatory apoptosis to repair injured pancreatic tissues.

5.6 IL-10

Interleukin-10 (IL-10) is an anti-inflammatory cytokine. Its plasma levels are elevated in animal models of endotoxemia and inhibit the release of pro-inflammatory cytokines (i.e. IL-1 β , IL-6 and TNF- α) from monocytes/macrophages thus preventing subsequent tissue damage. IL-10 also stimulates production of naturally occurring IL-1 receptor antagonist (IL-1ra) and release of soluble p75 TNF receptor [108]. IL-10 is believed to have a protective role in acute pancreatitis. Administration of IL-10 in experimental acute pancreatitis reduces the local inflammatory response and subsequent mortality [108, 109].

Fig. 5. Interaction between cytokines and oxidative stress in the inflammatory response in acute pancreatitis (IL-1 β : interleukin-1 β ; IL-10: interleukin 10; MnSOD: Mn-superoxide dismutase; PAP-I: pancreatitis-associated protein I; TNF-: tumor necrosis factor α ; NF- κ B: nuclear factor kappaB; ERK: extracellular signal regulated kinases; JNK: c-jun N-terminal kinases; p38: p38 kinase). Modified from [184].

6. Other mediators

6.1 Platelet activating factor (PAF)

PAF, 1-O-octadecyl-2-acetyl-sn-glycero-3-phosphocholine, is a potent inflammatory mediator produced by endothelial cells, platelets, monocytes, neutrophils, and basophils. It is considered to be the key inflammatory mediator in severe acute pancreatitis external secretion and local/systemic inflammatory reactions [110].

PAF has been shown to be released into the peritoneal fluid as well as the bloodstream and the lung after the induction of acute experimental pancreatitis. Locally, PAF acts on microvascular diameter, permeability and platelet and leukocyte rolling, adhesion and migration through different mechanisms, including synthesis and release of NO and arachidonic acid metabolites, and up-regulated expressions of ICAM-1 and CD11/CD18. Secondary actions include the elevation of adhesion factor b2-integrin, changes in the endothelial cell skeleton, increases in capillary permeability, massive effusion of plasma, increase in blood viscosity and a slowdown of blood flow. It also participates in I/R injury and stimulates other vasoactive substances, including the generation of cytokine and inflammatory mediators. In acute pancreatitis, PAF levels rise due to the cytokine cascade reaction activated by elevated levels of TNF- α [98]. On the one hand, PAF promotes granulocyte aggregation and aggravates inflammatory reactions; on the other hand, it increases capillary permeability and aggravates renal tubule injury. The imbalance between PAF and vasoactive substances can initiate a vicious cycle that leads to a series of chain reactions and amplifying reactions—the cascade reaction. This reaction can increase tissue and organ injury, cause systemic inflammatory reaction syndrome (SIRS) and, eventually, multiple organ dysfunction syndrome (MODS) and/or multiple organ failure (MOF), or even death [98], [48]. Clinical studies have found that PAF antagonist Lexipafant has clear treatment effects on multiple organ failure of severe acute pancreatitis patients and also lowers the serum levels of inflammatory mediators such as IL-8 and IL-6 [111].

6.2 Activation of complement

I/R activates the complement and the formation of many inflammatory mediators, including the anaphylatoxins C3a, C4a and C5a. These recruit and stimulate the inflammatory cells and increase the expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), ICAM-1, E-selectin and P-selectin on the surface of the endothelium and the neutrophils [112, 113]. C5a is a chemotactic factor that directly stimulates the synthesis and the leucocyte secretion of cytokines such as IL-1 and 6, the monocytes chemo-attractive protein-1 (MCP-1) and TNF α . The iC3b takes part in the adhesion of the neutrophils on the endothelium. C5b-9, known as the 'final cytolytic membrane attack complex complement', is a powerful chemotactic agent, which causes direct lesions to the endothelial cells, stimulates the endothelial production of IL-8, MCP-1 and ROS and inhibits endothelium-dependent vasodilatation [13, 113, 114].

6.3 Serotonin

Platelet serotonin (hydroxytryptamine; p-5HT) is an index of platelet activation [115, 116]. Furthermore, the administration of human pancreatic fluid caused the release of 5HT in parallel with platelet activation [117]. Several studies showed that the production of 5HT can induce further platelet aggregation and 5HT release [118, 119], a positive feedback that may lead to thrombus formation [120]. Furthermore, 5HT is also a potent vasoconstrictor

[116]. Thus, these proprieties may mean that this bioamine is an aggravating factor for acute pancreatitis. The release of serotonin is considered to be the “gold standard” assay for the detection of platelet activation [121].

6.4 Bradykinin

The neuropeptide bradykinin is well known for its actions as an endothelium-dependent vasodilator. Bradykinin induces relaxation of vascular smooth muscle via stimulation of B2 receptors, which in turn stimulates constitutively expressed endothelial nitric oxide (NO) synthase (eNOS) to produce NO, induces cyclooxygenase-dependent production of prostacyclin and other prostanoids, as well as superoxide, activates charybdotoxin-sensitive K⁺ channels, and induces the formation of epoxyeicosatrienoic acids by cytochrome P-450 epoxygenase [122-124]. In addition to its actions on arterial and arteriolar vascular smooth muscle, bradykinin also exerts powerful pro-inflammatory effects in postcapillary venules. For example, it generates the release of endothelium-derived mediators from cultured endothelial cells that are chemotactic for neutrophils, eosinophils, monocytes, and pulmonary alveolar macrophages; induces the expression of endothelial adhesion molecules; and provokes leukocyte and platelet adherence to endothelial monolayers and postcapillary venules [125-129].

The specific mechanisms of bradykinin in the pancreas can be listed as follows: bradykinin can promote the synthesis and release of NO, bradykinin influences the pancreatic microcirculation by stimulating the formation of reactive oxygen species, PAF, ET, and different inflammatory mediators.

6.5 Thromboxane A₂ (TXA₂)

TXA₂ is a potent capillary vasoconstrictor substance and platelet aggregation promoter that is able to induce platelet release and secretion, cause local and/or systemic disturbance of hemorrhage blood coagulation and destroy the cell-protection mechanism [130, 131]. Effected by increased phospholipase during acute pancreatitis condition, the cell membrane phospholipids decompose arachidonic acid, evoke TXA₂ increase, lead to platelet aggregation, thrombosis, induce platelet deformation, adhesion, result in coagulation dysfunction, precipitate pancreatic ischemia and microcirculation, and increase pancreatic pathology injury [132]. In addition, it can promote neutrophil cell activation, release ROS, injure capillary endothelial cells, result in increased capillary permeability, and plasma extravasation [133].

6.6 Cyclooxygenase (COX)

COX, the key enzyme for prostaglandin synthesis, exists in two isoforms as COX-1 and COX-2. COX-1 is constitutively expressed in most tissues and has been suggested to mediate the synthesis of prostaglandins required for physiological functions and maintenance of organ integrity. COX-2 is undetectable in most tissues in normal condition, but is highly inducible by cytokines, mitogens, and endotoxins, and is responsible for an increased production of prostaglandins during inflammation [134, 135]. The role of COX-2 in pancreatic pathology is unclear. Studies performed by Song et al. [136], and Ethridge et al. [137], with mice have shown that pharmacological inhibition of COX-2 or COX-2 gene disruption reduces the severity of pancreatitis and pancreatitis-associated lung injury.

Furthermore, Foitzik et al. [138], found some beneficial systemic effects of COX-2 inhibition on acute pancreatitis, such as an improvement of renal and respiratory function, but they have not observed any significant effect of COX-2 inhibition on histological score of pancreatic damage or plasma level of trypsinogen activation peptides. Warzecha et al. [135] investigated the role of the blockade of COX-1 or COX-2 and found a significantly reduction of serum lipase and serum poly-C ribonuclease activity, as well as decreased pancreatic edema and inflammatory infiltration in morphological features in animals with cerulein-induced pancreatitis.

6.7 Prostaglandin I₂ (PGI₂)

PGI₂ is also one of the arachidonic acid metabolites with a strong vasodilator effect. The main influence on pancreatic microcirculation in pancreatitis can be listed as follows: expansion of the pancreatic bed to increase pancreatic blood supply, improvement of pancreatic microcirculation, and increase of pancreatic blood flow by inhibiting platelet aggregation, adhesion and deformation. Furthermore, PGI₂ can also stabilize lysosomal membrane to prevent cytokine release and attenuate inflammatory response [139], [140].

6.8 Nuclear factor-kappa B (NF-kappa B)

NF-kappa B is a multi-purpose nuclear transcription factor, mainly involved in the regulation of expression referring to immune and inflammatory molecules [141]. Under the normal physiological circumstances, the NF-kappa B exists in the cytoplasm of other cells in the form of inactivity. When it is activated, it will promote a variety of cytokines gene transcription, and it plays an important role in cytokine-mediated infection, inflammation, oxidative stress, cell proliferation and apoptosis, the process of microcirculation and so on. Shi et al. showed that NF-kappa B activation can aggravate acute pancreatitis microcirculation disorder and gradually reduce the amplitude of pancreatic blood flow, and slow down blood flow velocity with the gradual increase of NF-kappa B P65 expression. The possible acting mechanism of NF-kappa B is that the excessive expression of NF-kappa B induces inflammatory cells' excessive secretion of nitric oxide, and then causes dysfunction of endothelial cells and smooth muscle cells, and capillary tension disorders, and leads to capillary pathological expansion, increase in capillary permeability due to endothelial cell injury, and plasma extravasation, which eventually leads to reduction of effective blood volume, pancreatic tissue hypoperfusion, and induces increases microcirculation disorder [142].

6.9 Vascular endothelial growth factor (VEGF)

VEGFs are endogenous vascular peptides that result in angiogenesis, vasodilatation and increased microvascular permeability in vivo [143]. Induction of VEGF mainly occurs in response to hypoxia [144]. Warzecha et al. found an increase in the immunohistochemical expression of VEGF even in the early course of I/R-induced acute pancreatitis [145]. Using the novel tyrosinekinase inhibitor PTK787/ZK222584, von Dobschuetz et al. observed a significant decrease of macromolecular permeability and a slightly increased functional capillary density with reduced leukocyte-endothelium interactions in the treatment group supporting a beneficial effect of this approach [146].

6.10 Role of endotoxin

Endotoxin, which is mainly produced by Gram-negative bacteria, is a component of the lipopolysaccharide present in cell walls. Clinical studies show that endotoxemia occurs in acute pancreatitis and particularly in severe acute pancreatitis, and that it is closely related to the onset, progression and complication of multiple organ failure in severe acute pancreatitis. Windsor et al.'s [147] study demonstrated the link between endotoxin and the state of pancreatitis. Other researchers studying the relation between plasma endotoxin levels of acute pancreatitis patients and multiple organ injury have found that endotoxin has an important promoting effect during the progression of multiple organ injury. As the most potent stimulant of endothelin, endotoxin can elevate the endothelin level in vivo and in blood, potentially contracting medium-sized arteries and arterioles. Increased endothelin levels will also aggravate ischemia in other tissues, enhance bacterial translocation, raise blood endotoxin and renin-angiotensin levels and form a vicious cycle chain of tissue ischemia and endothelin that aggravates tissue ischemia endlessly [148].

6.11 Influence of reactive oxygen species (ROS)

The ROS is an oxygen-containing chemical group with high chemical reaction activities, mainly those involving the peroxide anion-free radical (O_2^-) and the hydroxy radical ($OH^\bullet$). By causing lipid oxidation, it can increase mucosa permeability, further enhance phagocyte activity, generate more ROS and finally cause histiocyte injury. Scott et al. [149] demonstrated that in the pathological state, excessive ROS can cause tissue and cell injury. ROS can also participate in the formation of acute pancreatitis pancreatic edema and, possibly, in pancreatic necrosis and mediate leukocytes and platelets activated by $TNF-\alpha$ in all organs to

6.12 Toll-like receptor-4 (TLR4)

In the early stage, acute pancreatitis mainly manifests as a chemical inflammation, which is a pancreatic nonspecific inflammatory process resulting from the action of a variety of factors. This inflammatory process is an inflammatory cascade reaction dominated by the body's innate immune system. Toll-like receptors are a kind of protein that can trigger this inflammatory cascade reaction. It is currently thought that TLRs might play a central role in the recognition of endogenous or exogenous antigen in the immune system and in the initiation of signal transduction in the process of inflammatory reaction during acute pancreatitis. Therefore, investigating the tissue-specific expression of TLRs (mainly TLR4) in pancreas and exploring their roles have great significance for understanding the pathogenesis of acute pancreatitis. A report has indicated that in the early stage of acute pancreatitis, the expression levels of TLR4, $TNF-\alpha$, and IL-6 in pancreas of acute pancreatitis patients are significantly higher than those in the control ones, the level of plasma $TNF-\alpha$ in acute pancreatitis patients increases subsequently, and the increase of plasma $TNF-\alpha$ level is positively correlated with the expression of TLR4, suggesting that the up-regulation of TLR4 expression on the surface of peripheral blood monocytes in patients with early acute pancreatitis might be associated with the activation of the innate immune system in the early stage of the disease [150]. Results of animal experiments have shown that TLR4 messenger RNA is also up-regulated in the pancreas of rats with cerulein-induced edematous pancreatitis in the early stage, the serum levels of cytokines such as $TNF-\alpha$ are subsequently elevated, and the two phenomena are correlated [151].

Some researchers believe that TLR4 may play an important role in the synthesis and release of pro-inflammatory cytokines, and the up-regulation of the TLR4 gene may be related with the development and progression of organ injury during acute pancreatitis [152, 153]. Some studies have indicated that when severe acute pancreatitis is stimulated by LPS, the expressions of cytokines and cell adhesion molecules are significantly up-regulated in pancreas, thereby promoting the accumulation of excessive neutrophils in inflammatory region and leading to the injury of pancreas and other organs [154, 155]. Although it has been known that the translocation of intestinal bacteria and endotoxins is a key to secondary bacterial infection in necrotic pancreatic tissue, the mechanism of how multiple organ failure develops during pancreatitis has not yet been fully clarified [156].

7. Conclusions

Recent advances in experimental research have helped witness the pathophysiology of acute pancreatitis. The phenomena of microcirculatory changes observed in acute experimental pancreatitis during the past few years gradually underlie the disturbance of the local microcirculation in acute pancreatitis, but several challenges remain. Still some questions remain unexplained concerning the mechanisms: (1) Which is the first event in the pathogenesis of acute pancreatitis? (2) Which factor determines the edematous or necrotizing pancreatitis in a given experimental or clinical situation? (3) What is the role of impaired distribution of blood supply in early steps of acute pancreatitis? The potential mediators responsible for the progression of the disease severity and suggestions for therapeutic intervention have largely remained subjecting to speculation and debate.

Further research may help to find sufficient therapeutic approaches, eventually by affecting microcirculatory mechanisms, to influence development and progression of this disease.

8. References

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Acute Pancreatitis

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Acute Pancreatitis (AP) in approximately 80% of cases, occurs as a secondary complication related to gallstone disease and alcohol misuse. However there are several other different causes that produce it such as metabolism, genetics, autoimmunity, post-ERCP, and trauma for example... This disease is commonly associated with the sudden onset of upper abdominal pain that is usually severe enough to warrant the patient seeking urgent medical attention. Overall, 10-25% of AP episodes are classified as severe. This leads to an associated mortality rate of 7-30% that has not changed in recent years. Treatment is conservative and generally performed by experienced teams often in ICUs. Although most cases of acute pancreatitis are uncomplicated and resolve spontaneously, the presence of complications has a significant prognostic importance. Necrosis, hemorrhage, and infection convey up to 25%, 50%, and 80% mortality, respectively. Other complications such as pseudocyst formation, pseudo-aneurysm formation, or venous thrombosis, increase morbidity and mortality to a lesser degree. The presence of pancreatic infection must be avoided.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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