Potential Role of Reactive Oxygen Species in Pancreatitis-Associated Multiple Organ Dysfunction

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Key Words
Reactive oxygen species · Pancreatitis · Multiple organ dysfunction · Signal

Abstract
Background: Severe acute pancreatitis is still associated with substantial morbidity and mortality. Experimental and clinical studies have demonstrated that reactive oxygen species (ROS) represent early occurring inflammatory mediators contributing to cell dysfunction, both locally in the pancreas and remote organs. Method: A systematic literature review was conducted to investigate the potential roles of intra- and intercellular, as well as interorgan signaling of ROS in the development of pancreatitis-associated multiple organ dysfunction syndrome (MODS). A text word search of the Medline, PubMed and Cochrane databases, and a manual search of the citations from these references, was performed. Results: ROS directly compromise cellular damage and regulate intercellular signals in pancreatitis-associated MODS. ROS are involved in leukocyte activation, production of cytokines, endothelial barrier dysfunction, and microcirculatory barrier dysfunction in acute pancreatitis. Beside effects on intercellular signaling, ROS also affect intracellular events and activate the transcription factor nuclear factor κ B that regulates inflammatory cytokine expression. Conclusion: ROS is a critical factor responsible for the development of pancreatitis-induced remote organ dysfunction via intercellular and interorgan signaling. The role of antioxidant treatment, included as a part of multimodal management, remains to be investigated.

Introduction
Acute pancreatitis is still associated with a substantial morbidity and mortality. In its severe form, characterized by pancreatic necrosis, mortality is about 15–25% [1, 2]. Organ dysfunction in patients with acute pancreatitis includes acute respiratory, kidney and liver failure, disturbances in the coagulation process and generalized diffuse capillary leak with water retention, hypoxia, and acid/base disturbances. Early death from severe acute pancreatitis is commonly associated with the multiple organ dysfunction syndrome (MODS). Mortality rate at the early stage of the disease is still high, with a wide variation (>30%) [1, 3–6], though some have reported on a decline in early deaths [4]. Mortality in patients with pancreatitis-associated MODS ranges up towards 100% depending on the number of failing organs [7], but also depends on severity, duration, type, combination of organ failures, and other concomitant diseases [8–10].

Increasing evidence from both experimental and clinical studies demonstrates that reactive oxygen species (ROS) play an important role in the pathogenesis of ischemia-reperfusion injury, sepsis, acute respiratory distress, and MODS [11]. For example, increased produc-
tion of ROS has been considered as a special pathophysiological condition related to the onset of MODS by affecting the rate of apoptosis in tissue cells in various organs and their respective endothelial cells [12]. Patients with severe pancreatitis had a 2- to 3-fold increase in the alveolar-arterial oxygen difference and the ratio between PaO₂ and a 40–50% decrease in the fractional concentration of inspired oxygen [13]. Deterioration of tissue oxygen supply and reduced oxygen consumption are general findings in patients with acute pancreatitis [14]. One of the pathophysiological characteristics for the severity of the disease is tissue hypoperfusion, since arteriovenous oxygen difference decreased and pulmonary right-to-left shunting increased in patients with necrotizing pancreatitis as compared to patients with acute interstitial pancreatitis [15]. The role of ROS in the pathogenesis of pancreatitis in clinical studies remains unclear due to the fact that the number of clinical studies on this issue is limited, a few patients were included in each study, and the fact that there is a lack of direct measurements of ROS. There is still a great need to clarify the existence and significance of ROS in patients with acute pancreatitis, even though a clinical study demonstrated that increased oxidative stress appeared early in the course of acute pancreatitis and lasted longer than the clinical manifestations, depending on disease severity [16]. An indirect evidence of the clinical report showed that persistent intrapancreatic oxidative stress occurred in acute pancreatitis, measured by an ‘in situ’ histochemistry [17], since ROS can hardly be detected directly. Furthermore, progressive, pancreatic tissue ischemia was shown in moderate and severe experimental pancreatitis [18]. Pancreatitis-associated arteriovenous shunting in extrapancreatic tissues was suggested to be related to the severity of tissue ischemia, leading to the development of cell injury and organ dysfunction [19]. With respect to the correlation between hypoxia and ROS, hypoxia inhibits the generation of ROS. On the other hand, it triggers the increase in mitochondrial ROS generation. Therefore, more definitive experiments are needed to provide a resolution to these differences [20]. Oxidative stress was found to be an early phenomenon in acute experimental pancreatitis [21, 22]. ROS were considered as cytoxins directly compromising cellular damage and as intercellular signals regulating the inflammatory response in pancreatitis-associated MODS [23]. The principle objective of the present paper is to evaluate the potential roles of ROS in intracellular, intercellular and interorgan signaling during the development of pancreatitis-associated MODS.

ROS in Pancreatitis-Associated MODS

ROS Origin

ROS can be generated by different systems in acute pancreatitis, including the inflamed hypo-oxygenated pancreatic tissue and infiltrated neutrophils within the pancreas during the initial stage of the disease [24]. Increased activities of endogenous enzymes like xanthine oxidase (XOD) together with downregulation of endogenous scavenging systems like superoxide dismutase or catalase seem to be responsible for overproduction of oxygen free radicals [22]. Such alterations depend upon the severity of ischemia/reperfusion injury and hypovolemia. On the other hand, overproduction of ROS induced by ischemia/reperfusion can induce hypovolemia and worsen tissue ischemia/reperfusion through endothelial barrier dysfunction. Beside local toxic effects, ROS are released into the circulation and activate circulating leukocytes that also contribute to overproduction of ROS and other inflammatory mediators. It is possible that cytoplasmic components, e.g. p47-phox, p67-phox and p40-phox, are translocated to the inner face of the plasma membrane to form a full active NADPH oxidase complex. ROS can be produced by the activation of the NADPH oxidase complex with the assistance of p21Rac dissociation from a GDP-dissociation inhibition factor, Rho-GDI, and translocation to the plasma membrane [25]. ROS can initiate the release of platelet-activating factor and leukotriene B₄, which result in leukocyte accumulation. It means that ROS produced during acute pancreatitis do not themselves lead to acute pancreatitis but accelerate the local tissue damage and act as leukocyte attractants [24]. Another evidence to support the ROS effect on both local and systemic cells was that ROS scavenger treatment, as indirect evidence, prevented the occurrence of local tissue damage and downregulated the activation of peripheral blood neutrophils in experimental acute pancreatitis [24]. With respect to the subcellular compartmentalization of ROS, studies of mitochondria obtained from rat lung, bovine heart, and rat heart have shown that the ubiquinone-cytochrome b complex of the inner mitochondrial membrane transport chain is a major site of intracellular O₂⁻ production in the cell [26]. Imbalance between ROS and antioxidant production is a critical factor responsible for overproduction of ROS in acute pancreatitis. For example, downregulation of γ-glutamylcysteine synthetase by L-buthionine(S,R)-sulfoximine inhibited glutathione (GSH) synthesis and depleted ROS scavengers, leading to a significant reduction of survival, increased the extent of pancreatic necrosis and secretion of amylase, and resulted in a more aggres-
sive course of experimental pancreatitis [27]. This indicates that the systemic rather than the local effects of ROS should be emphasized. A depletion of GSH and the subsequent load of oxygen free radicals could damage microtubuli, which are responsible for exocytosis, with fewer enzymes to be secreted. ROS are also involved in an early modification of intracellular proteins in acute pancreatitis, resulting in cell damage prior to lipid peroxidation of cell membranes [28]. The administration of GSH monoethyl ester increased survival in animals with acute pancreatitis [27], supporting the hypothesis that imbalance of ROS and antioxidants is involved in the development of pancreatitis-associated MODS. Taken together, the origin of ROS responsible for the pathogenesis of acute pancreatitis is rather complicated, especially in humans, and needs to be clarified.

**ROS and Cell Injury**

Oxygen-derived free radicals, defined as a species containing unpaired electrons, are paramagnetic [29]. ROS are generated under physiological conditions at various stages of aerobic cellular metabolism as important mediators of the body’s defense against infection and noninfectious inflammation, and characterized by very short half-lives. ROS overproduction via XOD was noted at an early stage of arginine-induced pancreatitis and proposed to play an important role in the development of tissue injury indirectly shown by the levels of malonyldialdehyde [30]. ROS induce leukocyte activation, production of cytokines, endothelial barrier dysfunction, and microcirculatory failure in all forms of acute pancreatitis [31]. These multiple effects are due to the oxidizing properties of the oxygen molecule, which bind electrons and are used by the cellular cytochrome system. The complete (tetra-valent) reduction of oxygen to water is utilized for the production of ATP. During this reaction, the superoxide anion (O$_2^-$) and the hydroxyl radical (\(\cdot\)OH) develop and are able to degrade hyaluronic acid and collagen. ROS can directly damage the cell membranes through peroxidation of structurally important polyunsaturated fatty acids within the phospholipid structure of the membrane itself [31]. One of the characteristics of free radical reactivity is the tendency to generate a chain reaction of radical species production, which results in amplification of the ultimate destructive effect [25]. Membrane damage of lysosomes results in release of lysosomal enzymes that could extend the role of ROS-induced cellular damage. A number of biological events contribute to the cytotoxic effect of ROS on extrapancreatic cells and tissue damage in acute pancreatitis, including initiation of lipid peroxidation, direct inhibition of membrane Na\(^+/\)K\(^+\) ATPase activity, inactivation of membrane sodium channels, other oxidative protein modification, DNA strand breaks, and activation of the nuclear enzyme poly-ADP ribosyl synthetase, like in other diseases [32]. ROS probably play a major role in any disease process that involves hyperoxygenation, ischemia (particularly ischemia followed by reperfusion), or tissue inflammation. Natural defense mechanisms against ROS and their potentially toxic effect are scavengers, such as GSH and vitamins C and E. Special elements of the cytoskeleton, microtubules and -filaments, play important roles in the transport and exocytosis of enzymes. Such structural proteins, e.g. actin and \(\beta\)-tubulin, can be degraded during acute pancreatitis [33]. Experimental studies indicate that ROS may have more local and direct toxic effects on cells, since H$_2$O$_2$ perfusion induced acute edematous pancreatitis with marked histopathological changes and increased pancreatic duct permeability, while intra-arterial H$_2$O$_2$ infusion had no effect on permeability of the main pancreatic duct and morphology of the pancreas [34]. Of interest would be to investigate the response of extrapancreatic organs/tissues to systemic administration of ROS.

The fact that cytosolic Ca\(^{2+}\) synergized with ROS-induced alterations in ultrastructure and energy metabolism of acinar cells during the early stages of acute pancreatitis [35] also contributes to cellular changes in extrapancreatic organs. ROS oxidize polyunsaturated phospholipid-bound fatty acids and protein sulphydryl groups causing morphological alterations of membranes and enzyme systems. Although these changes may lead to biochemical and functional alterations at many different sites, mitochondria appear to represent major targets of ROS attack [35]. Depending on the severity of mitochondrial alterations, cellular energy metabolism can be impaired by ROS, resulting in disturbances of essential energy-dependent processes in endothelial cells [36]. Pathologically, enhanced ROS levels can increase cytosolic calcium (Ca\(^{2+}\)), a ubiquitous intracellular messenger, leading to dysregulation of various cellular functions, and finally to cell injury and death [37, 38]. It has been reported that after uncoupling of oxidative phosphorylation, isolated pancreatic acinar cells were rapidly injured by extracellular trypsin, whereas untreated cells showed a profound resistance against the proteases [39]. Prolonged elevation of Ca\(^{2+}\) may pose deleterious effects on protein kinases and phosphatases and an activation of degradative Ca\(^{2+}\)-dependent proteases and phospholipas-
es may be induced, possibly leading to cytoskeletal disruption and membrane damage, followed by a variety of cellular dysfunctions. Using the phospholipase A$_2$ inhibitor dibucaine, alterations of mitochondrial membranes and mitochondrial enzymes were partially prevented indicating that Ca$^{2+}$-dependent phospholipase A$_2$ plays a role in ROS-mediated cell injury [40].

**ROS and Adhesion Molecules**

Acute pancreatitis is a disease with multiple stages, where the pathological events at the acinar cell level are paralleled by both an exaggerated local and systemic inflammatory response. Excessive release of ROS and destructive enzymes by activated leukocytes aggravate both the local injury and pancreatitis-associated MODS. The recruitment of leukocytes to inflammatory sites is mediated by the ‘adhesion cascade’ of cellular adhesion molecules (CAMs) [41]. Selectins are responsible for the initial leukocyte rolling along the vessel walls. The firm adhesion of leukocytes is predominantly a result of interactions between leukocyte integrins and the constitutively expressed, or newly synthesized, endothelial intercellular adhesion molecule-1 (ICAM-1). A requirement for the transmigration of leukocytes is the involvement of platelet endothelial cell adhesion molecule-1 [42] and vascular cell adhesion molecule-1 (VCAM-1) [43]. The behavior of inducible CAMs in relation to pancreatic oxidative stress was investigated using a method based on the novel modification of cerium capture histochemistry combined with reflectance confocal laser scanning microscopy, allowing the histological codemonstration of in vivo ROS production, immunolabeled CAMs, or nuclear transcription factor-κB (NF-κB) [44]. The early acinar oxidative stress is colocalized with NF-κB activation, and P-selectin, and ICAM upregulation in acute pancreatitis. Subsequently, adherent, activated leukocytes become the major source of ROS, contributing to tissue damage. It demonstrated that the local and systemic oxidative stress exert a similar effect via NF-κB activation [44]. The potential pathogenic role of ROS for the induction of the exaggerated inflammatory response is supported by observations on the pronounced upregulation of CAM expression colocalized with oxidative stress. The initial acinar ROS production can play an important role in the induction of the inflammatory reaction by mobilizing P-selectin and, in parallel, by activating the genes of several cytokines and adhesion molecules through NF-κB [44]. It is possible that early pancreatic acinar oxidative stress plays an important role in the rapid and extensive activation of the proinflammatory response in acute pancreatitis. Acinar-cell-derived ROS can promote the activation of proinflammatory factors and induce production of certain adhesion molecules (e.g. ICAM-1, VCAM, P- and E-selectin) and cytokines via NF-κB [44]. ROS generated by XOD could affect the infiltration of neutrophils by facilitating the adhesion of neutrophils to the endothelium, since it is known that superoxide anion mediates the expression of selectins on the surface of endothelial cells [45].

During acute pancreatitis, P-selectin and ICAM-1 are upregulated on the pulmonary endothelium and represent key determinants of leukocyte recruitment into the lungs. The increased expression of P-selectin is triggered by a mechanism dependent on free radicals generated by XOD, released by the damaged pancreas [46]. Release of xanthine and XOD from the pancreas into the bloodstream plays an essential role in the pathogenesis of systemic complications of pancreatitis, including ROS and neutrophil infiltration into the lungs. It was demonstrated in vivo that XOS-derived ROS promoted neutrophil-endothelial cell interactions through ICAM-1 and P-selectin ligation [45]. With respect to the intraparenchymal histopathological changes, anti-ICAM-1 and superoxide dismutase/catalase application significantly limited the extent of acinar cell damage and inflammatory cell infiltration [47]. ROS and neutrophils seem to be potent and important regulatory mechanisms for nitric oxide (NO) synthase activity and NO-mediated toxicity but imply only a second role for NO in local injury in pancreatitis. NO is a double-edged sword that lies at the crossroads between cytotoxicity and cytoprotection [47]. It means that the potential NO responsibility for the pathogenesis of acute pancreatitis is still a complicated and controversial issue. NO is involved in cellular signal transduction via the stimulation of guanylate cyclase-mediated cGMP synthesis. In addition, the endogenous production of NO plays a vital role in the regulation of blood vessel tone, microvascular permeability, host defense, inflammation, immunity and apoptosis [48]. Moreover, the vascular system, with subsequent microcirculatory and hemodynamic disturbances, seems to be the predominant target of NO-mediated toxicity [47].

Through the intercellular signaling, ROS can initiate intracellular signaling and production of intracellular cytokines by activating adhesion molecules in acute pancreatitis [49]. Production and release of ROS highly depend upon the activation and location of leukocytes and correlate with the development of pancreatitis-associated
distant organ dysfunction. One of the potential roles of ROS in pancreatitis-associated MODS is that ROS activate leukocyte-endothelial cell interactions and compromise endothelial barrier function by increasing the expression of CAMs, since ROS directly contribute to the activation of NF-κB and the expression of endothelial surface CAMs, leading to an increase in leukocyte-endothelial cell interaction [50, 51]. The role of ROS and CAMs as intra- and intercellular signal substances may depend on the type of challenge, but a common response seems to exist in critical illness leading to secondary organ injury.

ROS and MODS

ROS is considered to be a pathogenic factor for pancreatitis-associated MODS and extrapancreatic tissue injury [52]. Several studies have demonstrated that the depletion of antioxidants and the oxidative damage of lipids and proteins by ROS are involved in the pathogenesis of pancreatic tissue injury in experimental acute pancreatitis [53–56]. A compromised pancreas as a source of ROS could release XOS into the circulation, the liver and possibly other tissues [57], leading to increased lipid peroxidation and decreased protein sulphydryl in extrapancreatic organs/tissues [21]. These results indicate that ROS can function as an interorgan signal substance responsible for the development of pancreatitis-associated MODS. Although the correlation between severity of pancreatic injury and survival rates as compared with the degree of ROS in extrapancreatic tissues is not clear, a closer analysis of oxidative changes in the lungs, liver, and kidneys was performed in acute pancreatitis induced by different concentrations of sodium taurocholate [58]. Overproduction of extrapancreatic ROS was related to the severity of pancreatitis, since pancreatitis induced by the infusion of 5% taurocholate resulted in alterations of proteins from lung tissue by the aldehydic product of lipid peroxidation 4-hydroxynonenal, but not following 3% taurocholate. 4-hydroxynonenal could interact with isoforms of the c-Jun amino-terminal kinase, leading to their nuclear translocation and activation and eliciting a c-Jun amino-terminal kinase/c-Jun/AP1 pathway [59]. This demonstrates that 4-hydroxynonenal could modulate signal transduction pathways and transcription in distant organs during pancreatitis.

It still needs to be further investigated whether ROS could act as the pathogenic factor of pancreatitis-associated MODS, although it has been suggested that ROS might be involved in the pathogenesis of pancreatitis-associated MODS [58]. It was hypothesized that ROS generated by XOD derived from the liver [57] might be released into the circulation and act as an interorgan messenger to initiate extrapancreatic organ compromises during pancreatitis with a special preference to lung injury [58]. The question is whether ROS derived from the liver could be transported into the distant organs, since the short half-life of ROS may limit distances that they reach. Another possibility is that overproduction of ROS in compromised pancreas may activate circulating leukocytes to produce ROS, or pancreatic resident inflammatory cells to release secondary mediators responsible for interorgan communication. It is also possible that resident inflammatory cells in the distant organs are activated to produce ROS responsible for extrapancreatic organ dysfunction, since the levels of malonyldialdehyde in the liver, lungs, and kidneys were elevated 1 h after induction of acute pancreatitis [58]. Another candidate of ROS as an interorgan messenger may be H$_2$O$_2$, which is uncharged and sufficiently stable to diffuse from one cell to another and could cause surrounding cell and tissue injury in acute pancreatitis [60]. The magnitude of the subsequently developing inflammatory reaction in extrapancreatic organs may be a determinant for outcome and survival of patients with severe acute pancreatitis [61].

An increase in XOD activity in plasma paralleled with the development of pancreatitis, generating superoxide radicals involved in the decrease of reduced GSH levels in plasma and liver [57]. XOD inhibition prevented the infiltration of neutrophils into the lungs. It indicates that ROS generated by xanthine and XOD and released into the bloodstream are involved in the development of pancreatitis-associated systemic manifestations and MODS by the conversion of xanthine dehydrogenase (XDH) to XOD as has been described in different experimental models of pancreatitis [62]. The XOD released by the damaged pancreas could act as a source of ROS to the liver during the early stages of acute pancreatitis. Total XDH plus XOD activity in plasma significantly increased and conversion of XDH to XOD occurred during pancreatitis, probably by the action of proteolytic enzymes (particularly trypsin) activated as a consequence of cell disruption. Inhibition of XOD was associated with a recovery of reduced GSH levels after induction of acute pancreatitis [62], indicating that the enzyme in plasma may be the main source of ROS-induced damage, e.g. in the liver, during the early stages of acute pancreatitis. It is possible that ROS generated by XOD could activate the liver to generate systemic levels of proinflammatory signals.
mediators, leading to the development of pancreatitis-associated lung injury. Active ROS generated through the XOD system induce DNA damage in microcirculatory endothelial barrier dysfunction in severe acute experimental pancreatitis [52]. ROS act as an important promoter of tissue damage in the development of pancreatitis-associated MODS. Although XOD is a putative source of ROS generation, other potential sources, such as an enhanced cytochrome P450 enzyme system, should be considered.

Although it is still unclear whether ROS is an initiating event or a mediator of tissue damage [22], it has been found as an important factor in the pathogenesis and progression of acute pancreatitis. Representing highly reactive biochemical species, ROS exert their pathophysiological effects by directly attacking liquids and proteins in the biological membranes at the local site of generation and result in cellular dysfunction [63, 64]. Indirectly, they act on the arachidonic acid cascade by two mechanisms: to increase the production of thromboxane inducing tissue microcirculatory dysfunction by potent platelet-aggregating and vasoconstricting effects [65], and/or to enhance the production of leukotriene B₄ promoting the activation of leukocytes [66] and the discharge of lysosomal enzymes [67]. These changes contribute to secondary cell damage in the development of pancreatitis-associated MODS. Another hypothesis is that GSH depletion is responsible for the mitochondrial and cellular damage associated with acute pancreatitis, since pentoxifylline, also acting as a TNF-α antagonist, ameliorates interstitial edema, the inflammatory infiltrate, GSH depletion, and systemic levels of inflammatory mediators [68]. On the other hand, the link between ROS and pancreatitis-associated hepatic dysfunction is unclear [69]. Pretreatment with a ROS scavenger prevented alterations within the pancreas and pancreatitis-associated multiple organ dysfunction [70]. Inhibition of other substances besides ROS may exert similar effects in acute pancreatitis-associated MODS in rats.

In contrast, some studies indicated that ROS had little effect on acute pancreatitis. For example, oxygen radicals produced during acute pancreatitis do not lead to acute pancreatitis, but increase the local tissue damage and act as PMN attractants [24]. Moreover, ROS play a minor role in the pathogenesis at an intermediate stage of experimental acute pancreatitis, which explains the lack of clinical effect of antioxidants in fulminant pancreatitis [71]. In ERCP-induced acute pancreatitis, the prophylactic use of a scavenger sodium selenite did not show any beneficial effect on the clinical outcome [72]. In a recent and extensive review, the available data on oxidative stress in acute pancreatitis from experimental models and from clinical studies have been compared. Free radicals seem to be involved, although efficient antioxidant treatment in established acute pancreatitis has proven useless [48]. This indicates that the complexity of underlying pathophysiological mechanisms in acute pancreatitis, especially when complicated by MODS, is profound.

Intravenous administration of the hydroxyl radical scavenger dimethylsulphoxide prevented the compromised intestinal permeability and gut-absorptive capacity induced by acute pancreatitis, but did not affect the reduced arterial pressure and intestinal microcirculation [73]. Cytotoxic oxygen-derived free radicals contribute to the development of alterations in intestinal permeability and absorptive function found in the early stage of acute pancreatitis in the rat [73]. Dimethylsulphoxide does not act as a plasma expander to protect against mucosal injury by increasing the circulatory volume, and reduced intestinal blood flow by itself does not seem to be a primary factor directly affecting gut permeability and absorption [73]. A possible mechanism to explain failure of the intestinal barrier in experimental acute pancreatitis is that systemic and local ischemia-reperfusion injury reduces the mucosal microcirculation, compromises oxygen delivery and results in insufficient energy production. This reduces the regeneration of adenosine 5'-triphosphate by oxidative phosphorylation in enterocytes, which causes release of cytotoxic ROS by activated leukocytes, macrophages and/or intestinal capillary endothelial cells [74]. XDH-XOD activity exists mainly in the intestinal mucosal layer, with an increasing gradient of activity from the base to the top of the villus. Excessive production of oxygen-derived free radicals can induce alterations in intestinal permeability and absorption in acute pancreatitis by effects of lysosomal proteases and eicosanoids released by stimulated leukocytes, macrophages, dendritic cells and antigen-presenting cells in the mucosa, and by lipid peroxidation of cell membranes [75]. Extra-pancreatic endothelial barrier dysfunction characterized by increased microcirculatory endothelial permeability has been noted in the early stage of acute pancreatitis [23, 70, 73]. High concentrations of ROS generated in the early stage of pancreatitis are responsible for such an increase in endothelial permeability by promoting expression and activation of adhesion molecules on both leukocytes and endothelial cells, leading to alterations in cell signal transduction and redox-regulated transcription factors such as activator protein-1 and NF-κB. It has been found that ROS signals could compromise endothelial
barrier function by regulation of cell-to-cell interaction, cell surface adhesion molecules, the actin cytoskeleton, key protein kinase, and signal transduction events [50].

Another potential mechanism is that ROS act as activators of the transcription factor nuclear factor-B (NF-B), regulating proinflammatory cytokine gene expression [76]. Increased cytokines both locally in the pancreatic tissue and in the circulation are involved in the development of pancreatitis-associated MODS. ROS derived from neutrophils are a major contributor to cytokine production in tissue cells by directly activating oxidant-sensitive transcription factor, NF-κB, and inducing nuclear translocation of a p50, p65 NF-κB heterodimer and a p50 NF-κB homodimer, prevented by N-acetylcysteine [77].

ROS-regulated cytokine pathways should also be emphasized in pancreatitis-associated MODS, since results on potential mechanism of pancreatitis-associated lung injury demonstrated that ROS production from activated migrating and migrated leukocytes increased in parallel with elevated levels of cytokines in the lung tissue and bronchoalveolar lavage fluid. Another evidence to support the importance of ROS-regulated cytokine pathways is that pretreatment with antioxidants could downregulate the transcription of cytokine genes in pancreatitis [76]. ROS can induce cytokine synthesis and production by both intercellular and intracellular signaling, while overproduction of cytokines during inflammatory reactions also can stimulate ROS production and accelerate ROS cytotoxic effects. ROS regulate cytokine signal pathways by alterations in the dynamic ratio of GSH and its disulphide form (GSSG), induction of thioredoxin (a redox control protein), and activation of ROS-sensitive transcription factors and cofactors [78].

In summary, ROS is one of the earliest inflammatory mediators occurring during the development of acute pancreatitis. ROS has both direct and indirect biological effects resulting in cell dysfunction in the pancreas and in remote organs. Although the role of ROS in pancreatitis-associated MODS is not fully clear, experimental studies indicate that ROS is important in intracellular, inter-
cellular and interorgan signaling for the initiation and development of pancreatitis-associated MODS. ROS are involved in the pathogenesis of pancreatitis-associated MODS, e.g. by activating nuclear factor transcription to produce a number of cytokines, stimulating the expression of adhesion molecules on leukocytes and endothelial cell surfaces, initiating inflammatory reactions in extra-pancreatic organs/tissues, or compromising intracellular signaling resulting in cell dysfunction (fig. 1). The complexity of underlying pathophysiological mechanisms in acute pancreatitis, especially when complicated by MODS, is profound. Despite this, the key role of ROS makes broad acting antioxidants potentially interesting, at least as a part of a multimodal treatment therapy [79].

References


