ANTIOXIDANTS & REDOX SIGNALING
Volume 11, Number 1, 2009

DOI: 10.1089/ars.2008.2109

Comprehensive Invited Review

Role of Oxidative Stress in Pancreatic Inflammation

Po Sing Leung and Yuk Cheung Chan

Reviewing Editors: Stephen Pandol, Zoltán Rakonczay, Jr., Juan Sastre, and Roland Schmid

Abstract

Reactive oxygen and reactive nitrogen species (ROS/RNS) have been implicated in the pathogenesis of acute and chronic pancreatitis. Clinical and basic science studies have indicated that ROS/RNS formation processes are intimately linked to the development of the inflammatory disorders. The detrimental effects of highly reactive ROS/RNS are mediated by their direct actions on biomolecules (lipids, proteins, and nucleic acids) and activation of proinflammatory signal cascades, which subsequently lead to activation of immune responses. The present article summarizes the possible sources of ROS/RNS formation and the detailed signaling cascades implicated in the pathogenesis of pancreatic inflammation, as observed in acute and chronic pancreatitis. A therapeutic ROS/RNS-scavenging strategy has been advocated for decades; however, clinical studies examining such approaches have been inconsistent in their results. Emerging evidence indicates that pancreatitis-inducing ROS/RNS generation may be attenuated by targeting ROS/RNS-generating enzymes and upstream mediators. *Antioxid. Redox Signal*. 11, 135–165.

Department of Physiology, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China.

I. Introduction

Reactive species include reactive oxygen species (ROS), reactive nitrogen species (RNS), and other carbon-centered molecules, which are unstable chemicals generated in biologic systems under normal physiologic as well as pathophysiologic conditions (190). ROS include free radical intermediates, such as singlet oxygen (·O), superoxide ($\cdot O_2^-$) and hydroxyl free radical ($\cdot OH^-$), as well as nonradical molecules, such as hydrogen peroxide (H_2O_2) and hypochlorous acid (HOCl). RNS consist primarily of nitric oxide (NO), peroxynitrite, nitrogen dioxide radical ($\cdot NO_2^-$), and other nitrates, whereas carbon-centered molecules are rather complex in terms of their chemical structure and generally are produced in xenobiotic metabolism.

Ample evidence implicates ROS/RNS in many physiologic functions such as vascular tone regulation, oxygen sensing, and host-defense mechanisms (35). However, it should be emphasized that the electrophilicity of the ROS/RNS make them highly susceptible to reaction with biomolecules including lipids, proteins, and nucleic acids, which can alter the functionality of these molecules. Hence, the cellular concentration of ROS/RNS should be strictly controlled to prevent such deleterious effects. The balance between ROS/RNS-generating enzymes and scavenger enzyme systems can be disrupted in a number of pathologic conditions, such as diabetes mellitus (148, 276), endothelial dysfunction, atherosclerosis, hypertension (35), degenerative diseases (183), glomerulonephritis (271), hepatitis (184), inflammatory bowel disease (252), and pancreatitis (273). Unchecked ROS/RNS generation leads to oxidative damage and activation of reactive signaling cascades, and thus ROS-scavenging therapy has been proposed as a potential treatment for disorders related to excessive ROS/RNS generation.

Pancreatic inflammation occurs in two forms: acute pancreatitis (AP) and chronic pancreatitis (CP). AP is generally characterized by edema and inflammatory infiltration, and in severe cases, by necrosis and hemorrhage (38). Most CP is associated with pancreatic-head enlargement, parenchymal calcification, cystitis, pancreatic stones, fibrosis, and pancreatic exocrine and endocrine dysfunction (36). Direct insults, such as insults due to chemical exposure, autoimmune reactions, and surgical manipulations, which are thought to harm pancreatic acinar cells, result in AP. Conversely, the overactivation of pancreatic stellate cells (PSCs) has been implicated in the development of CP. Although the epidemiologies of AP and CP differ, some evidence suggests that repeated episodes of AP can result in the gradual development of CP (230). The so-called "necrosis-fibrosis theory" hypothesizes that residual pancreatic damage, in particular necrosis, may gradually lead to parenchymal destruction and fibrosis replacement (8). If so, the two clinically distinct disorders may share some common pathogenic mechanisms. Indeed, accumulated evidence from clinical and basic research suggests that the pathogenesis of both AP and CP can be associated with the presence of ROS/RNS. Abnormal ROS/RNS generation seems to be independent of the etiology of pancreatitis, because oxidative stress is observed in different experimental pancreatitis models. Induction of AP by using choline-deficient ethionine (CDE)-supplemented diet, caerulein, taurocholate, and biliopancreatic duct ligation resulted in elevated levels of malondialdehyde (MDA), a lipid peroxidation product, and depletion of reduced glutathione (GSH) (17, 222, 273). Similarly, findings from experiments with chemical-induced CP models [hyperlipidemia, repeated caerulein injections, trinitrobenzene sulfonic acid (TNBS), and dibutyltin dichloride (DBTC)] and spontaneous CP animals [Wistar Bonn/Kobori, WBN/Kob rats (227)] indicated that signs of oxidative stress were present during CP episodes (175, 228, 302, 341, 350). Radical generation has been detected directly by electron spin-resonance (ESR) spectroscopy and the spin-trapping technique in experimental AP and CP (221, 273). Clinical findings have been consistent with experimental findings. Both AP and CP patients exhibited elevated plasma lipid peroxidation, with the concomitance of depleted serum thiol (87, 259). Meanwhile, levels of circulating antioxidants such as vitamins A, C, and E were depleted in pancreatitis patients (212, 244). Furthermore, serum oxidative stress markers have been shown to correlate well with the severity of the pancreatitis (1, 259). The increased lipid peroxidation in duodenum juice of pancreatitis patients, in addition to plasma, implies that their oxidative stress originated in the pancreas (111). Taken together, this convergence of findings suggests that ROS/RNS are generated during the course of pancreatitis, leading to pancreatic oxidative stress, which subsequently produces systemic oxidative stress.

II. Effects of ROS/RNS on the Cellular Injuries and Inflammatory Cascades

A. Direct actions on biomolecules

The instability of ROS and RNS predisposes them to react with essential cellular components. Polyunsaturated fatty acids, which are abundant in the plasma membrane and also in the mitochondrial membrane, are among the most vulnerable targets of the ROS/RNS. They react with ROS, particularly hydroxyl free radicals, to form lipid peroxide, which leads to membrane disintegration and necrosis of pancreatic cells (273). ROS can also disrupt mitochondrial membrane potential ($ø_m$), leading to cytochrome *c* release and subsequent DNA fragmentation (54, 266) (see IV*(C)* on H_2O_2-induced mitochondrial damage). In addition, sulfhydryl groups (−SH) in the cysteine moieties of proteins are vulnerable to ROS oxidation, which results in protein misfolding (81). Such alternations in protein structure can affect enzyme activity, membrane-receptor function, and protein-complex assembly (110, 164, 199, 253, 278). In some cases, the protein oxidation is so severe that proteolysis takes place (79). Cofactors of functional proteins (*e.g.*, Fe^{2+} moiety in hemoglobin) can also be oxidized by selective oxidizing agents, resulting in a nonfunctional protein (*e.g.*, methemoglobin) (79). Nitric oxide, which can be synthesized within pancreatic acinar cells, can react with protein thiol groups directly or indirectly (*via* its metabolite peroxynitrite), forming nitrosylated adducts (117, 284). It has been reported that S-nitrosylation can suppress cellular respiration by inhibiting enzymatic activity of glyceraldehyde-3-phosphate dehydrogenase and GSH reductase (21). Simultaneous generation of nitric oxide and superoxide free radicals has also been shown to induce DNA fragmentation and 8-hydroxylation of guanine residues *in vitro* (136). The schematic diagram in

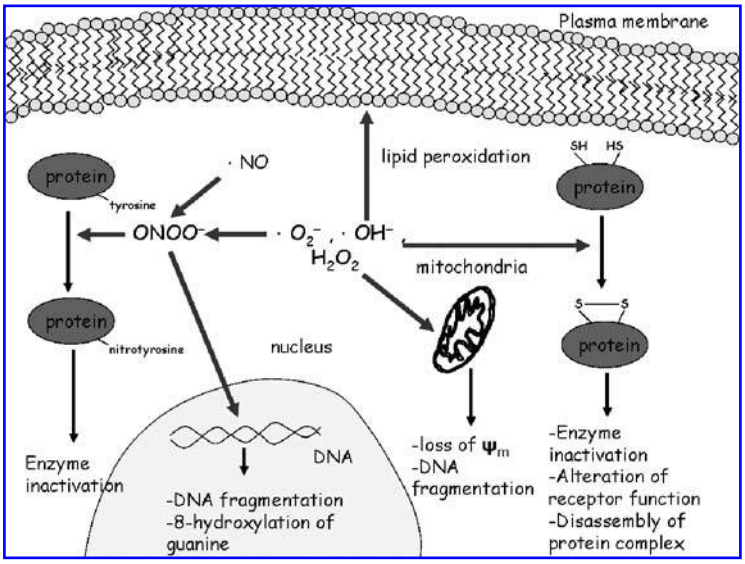

FIG. 1. Direct oxidative damage in pancreatic cells. Reactive oxygen species/reactive nitrogen species (ROS/RNS) can oxidize lipids in the cell membrane, oxidatively modified proteins (*via* nitrosylation and disulfide linkage formation), depolarize the mitochondrial membrane, and induce DNA fragmentation.

Fig. 1 summarizes the direct actions of ROS/RNS on selected biomolecules.

B. Activation of proinflammatory signaling pathways

Apart from their direct detrimental oxidative effects, ROS/RNS can also serve as second messengers in intracellular signaling. Redox-regulated signaling cascades involving mitogen-activated protein kinases (MAPKs), nuclear factor kappa B (NF-κB), and apoptotic pathways are discussed in more detail in a later section. Switching on proinflammatory cascades not only exerts direct effects on the pancreatic cells, but also initiates the migration, adhesion, and infiltration of inflammatory cells into the exocrine pancreas. Genes known to be involved in migration and adhesion processes, such as chemotactic cytokines (chemokines) and intercellular adhesion molecules (ICAMs), are under the regulation of the redox-sensitive kinases or transcription factors such as MAPKs, NF-κB, and activator protein-1 (AP-1) (47, 77, 349). The release of chemokines establishes a chemotactic gradient that facilitates the migration of inflammatory cells toward the exocrine pancreas. The inflammatory cells attach to the vascular wall by the traditional "rolling-and-adhesion" process and subsequently become sequestered in the pancreas. The expression of ICAMs brings infiltrated inflammatory cells in close contact with pancreatic exocrine cells, making them more vulnerable to the cytotoxic ROS generated by inflammatory cell respiratory bursts. The ROS that originate from nonpancreatic cells can eventually trigger an extraneous "oxidative burden" on the pancreas. More important, this vicious cycle is apparently self-sustained. That is, the nonpancreatic cell–derived ROS continuously activate redox proinflammatory transcription factors, leading to more inflammatory cell sequestration, and ultimately producing extensive damage. In short, ROS/RNS are capable of exerting damage in two phases: (a) acute injury by direct attacks on cellular components and activation of signaling cascades, and (b) long-term inflammatory cell recruitment and secondary oxidative injury.

It should be stressed that oxidative stress is only one of the mediators in inflammatory cascade regulation. A substantial body of evidence reveals that important processes of the immune system not related to redox regulation would contribute to some of the factors in controlling inflammatory cascade. Recent *in vivo* studies illustrated that an array of inflammatory factors, such as IL-1, IL-6, IL-10, TNF-α, Fas, chemoattractant cytokine receptor, and neurokinin receptor, play a crucial role in mediating inflammatory cascade during pancreatitis (237, 289). Of great interest in this context, these signaling pathways could directly lead to trypsin cascade, acute-phase response, and apoptotic cell death, resulting in pancreatic injury in a redox-independent manner (237). Conversely, it is worth noting that oxidative stress seems to be mediator of tissue damage during the pathogenesis of AP and CP rather than acting as an initiating factor of pancreatitis. Extracellular oxygen free radical generation alone did not induce typical enzymatic and morphologic changes of AP (251). Infusion of diethylmaleate, a potent oxidative-stress inducer, could deplete murine pancreatic GSH levels, but did not cause characteristic morphologic alteration and hyperamylasemia (105), indicating that ROS/RNS alone would not serve as the initiating factor of pancreatitis.

III. Antioxidants Against ROS/RNS-Generating Enzymes in Pancreatic Inflammation

A. Antioxidant enzymes and related proteins

Establishment of redox balance is highly complicated, requiring sophisticated regulation of scavenger bioavailability and of ROS/RNS generation. The major cellular ROS scavenger in the pancreas is GSH (a tripeptide consisting of glutamate, cysteine, and glycine). The thiol group in the cysteine moiety of GSH accounts for its reducing power. GSH concentration in the pancreas is ~2 μmol/g tissue, the fourth highest concentration among the visceral organs (114, 216). Pancreatic GSH turnover is less only than that in the kidney and liver, which have twofold and fourfold the turnover rates of the pancreas (114). Hence, it appears that the pancreas is "evolutionally prepared" for defense against oxidative stress.

The removal of ROS, in particular of ROS in the peroxide

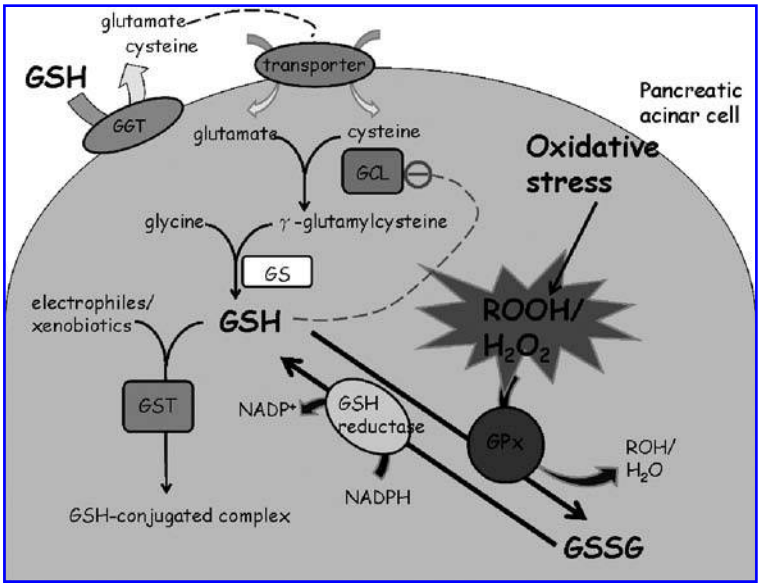

FIG. 2. Glutathione (GSH) metabolism in pancreatic acinar cells. GSH is hydrolyzed by γ-glutamyl transpeptidase (GGT) extracellularly. The amino acids are transported into the cytoplasm by amino acid transporter and condensed to form γ-glutamylcysteine by glutamate cysteine ligase (GCL). The dipeptide then reacts with glycine to form active GSH in a GSH synthase (GS)-dependent fashion. GSH scavenges ROS by two mechanisms: (a) oxidation of thiol groups to form GSSG *via* GSH peroxidase (GPx); and (b) direct conjugation to electrophilic substances by the action of GSH S-transferase (GST).

family (ROOH), depends on the action of the selenium-containing enzyme GSH peroxidase (GPx). GPx facilitates the reduction of peroxides into water or related alcohols through oxidation of GSH. GSH reductase then catalyzes the transfer of an electron from nicotinamide adenine dinucleotide phosphate (NADPH) to the oxidized glutathione molecule, GSSG, to recycle back to its reduced form. Independent of its GPx-dependent activities, GSH has the ability to scavenge electrophilic chemicals, such as xenobiotics, through direct conjugation and subsequent excretion from the cells.

Adequate bioavailability of GSH requires a highly regulated biosynthesis procedure in addition to continuous recycling. In brief, GSH is hydrolyzed or undergoes transpeptidation by γ-glutamyl transpeptidase (GGT) extracellularly, yielding amino acids glutamate, cysteine, or γ-glutamylamino acid. These amino acids are transported into the cytoplasm by amino acid transporter and condensed into γ-glutamylcysteine by the rate-limiting enzyme glutamate cysteine ligase (GCL), also known as γ-glutamyl cysteinyl synthase. The dipeptide γ-glutamylcysteine reacts with glycine to form the bioactive antioxidant GSH in a GSH synthase (GS)-dependent fashion. As delineated in Fig. 2, GSH exerts a negative-feedback influence on GCL, maintaining the intracellular GSH concentration in the range of 0.5 to 10 m*M*. The sophisticated cooperation of GSH reductase and GCL preserves a cytoplasmic GSH/GSSG ratio between 30:1 and 100:1, so that cells are prepared to fight against oxidative insults. It should be noted that the ratio is subject to change in different cellular compartments. For example, the GSH:GSSG ratio is only 1:1-3:1 in the endoplasmic reticulum of pancreatic exocrine cells, presumably because disulfide linkages play a role in proper protein folding during the secretory actions (135). Although the pancreas has a relatively low level of GCL transcripts and enzymatic activity (67), the exocrine pancreas itself can synthesize bioactive GSH. Dispersed rat pancreatic acini can actively synthesize GSH from precursor amino acids, and the trans-sulfuration pathway is functionally intact in the pancreas (216). Actually, the abundance of amino acids favors the formation of γ-glutamylcysteine, despite the low GCL activity.

Although GSH is the major cellular antioxidant in the pancreas, other cellular antioxidants also are present in the pancreas. In particular, vitamin C (353), vitamin E (186), and vitamin A (10) are present in the pancreas in considerable amounts. These antioxidants may also be responsible for cellular defense against oxidative stress.

The association between antioxidant enzymes and pancreatic inflammation has been studied extensively over the last decade. Low activity or expression or both of antioxidant enzymes can exacerbate the oxidative burden during pancreatitis. The pancreatic GPx level was shown to be significantly altered in different experimental AP and CP models and AP patients (294). Induction of AP by taurocholate (59), ischemia/reperfusion (213), caerulein (90, 91), and arginine (61) depleted GPx activity in the pancreas. Pancreatic GPx levels were also decreased in animals with TNBS-induced CP (195), and in hyperstimulation-induced CP (72), as well as in human CP patients (57). The decrease in GPx activity extended systemically. Patients with AP had low red blood cell GPx activity (212). It was reported that patients with severe AP had lower serum GPx levels than did patients with mild, indicating that GPx activity may correlate with the severity of pancreatic inflammation (330). Another GSH-metabolizing enzyme, GCL, is closely associated with the pathogenesis of AP. A different expression profile of GCL was observed in different experimental pancreatitis models of AP. Mild edematous, but not severe necrotizing AP, enhanced the protein expression of the catalytic subunit of GCL (240). The reason is that necrotizing AP exhibited elevated RNase activity in the cytosol, degrading the transcribed GCL mRNA, thus abrogating the translational process (240). Failure in GCL expression in the severe form of AP might provide a clue that this pathophysiologic mechanism is crucial in differentiating necrotizing from edematous pancreatitis, probably *via* the control of the redox state of the pancreas during AP.

The activity of other antioxidant-scavenging enzymes, such as superoxide dismutase (SOD) and catalase (CAT), also was decreased in the course of pancreatitis (57, 59, 61, 64, 90, 195, 213). Depletion of multiple antioxidant enzymes impairs

the scavenging power against ROS, ultimately producing a redox imbalance. Although the expression profiles of antioxidant enzymes differed among studies (185, 222, 288, 293, 303, 329, 338), it is generally believed that antioxidant enzymes are protective against pancreatitis, given that elevated expression of antioxidant enzymes should inhibit the development of pancreatitis (154).

Recent advances in pancreatitis research have drawn attention to ROS-scavenging antioxidant proteins. Thioredoxin (Trx), a dithiol-containing redox-sensitive protein, is one of the candidates that is closely associated with the pathogenesis of pancreatic inflammation. Patients with severe AP show higher Trx-1 serum levels than do patients experiencing only a mild attack (229). Trx-1 serum level correlated well with AP severity, as demonstrated by Ranson score, C-reactive protein, interleukin (IL)-6, leukocyte count, and serum amylase (229), implying that this antioxidant protein is upregulated in response to oxidative stress. Overexpression of Trx-1 was shown to attenuate pancreatic injury in caerulein-induced AP and experimental CP in rodents (228, 230). This finding is bolstered by the finding that therapeutic intraperitoneal administration of recombinant human Trx-1 after AP induction can abolish caerulein-induced pancreatic injury (228). The protective effect of Trx can be attributed to its ROS-scavenging capacity and the subsequent inhibition of proinflammatory cascades and profibrogenic pathways (228, 230). Trx can also exert antioxidant-independent anti-inflammatory actions (see IV *(A)* on the MAPK-activating pathway by Trx-1 oxidation). Further investigation is required to explore the possible involvement of the non–ROS-scavenging ability of Trx in treating pancreatic inflammations.

Another antioxidant enzyme that is closely related to the pathogenesis of pancreatitis is metallothionein (MT)-1. It is a small cysteine-rich heavy metal–binding protein, exhibiting potent scavenging property. In patients with CP with or without diabetes, the pancreatic expression of MT-1, localized mainly in acinar cells, was enhanced (205). Hyperstimulation-induced AP revealed an elevated pancreatic mRNA and protein-expression levels of MT-1 (105). Pancreata from CP induced by repeated administration of caerulein exhibited augmented MT-1 expression in a time-dependent manner (344). Induction of MT-1, by either injection of zinc (325) or genetic overexpression (106), was shown to be protective against caerulein-induced and taurocholate-induced AP, as evidenced by decreased serum amylase, suppression of acinar cell injury, and attenuation in pancreatic edema. Mice with genetic deletion of MT-1 were more susceptible to caerulein-induced pancreatitis (237). This convergence of evidence indicates that MT-1 is induced during episodes of pancreatitis, which could protect the animal from oxidative damage. It is noteworthy that MT-1 induction might rely on the redox imbalance during the episode of pancreatitis. Diethylmaleate administration, exerting pancreatic oxidative stress, is strong enough to induce MT-1 expression, to an extent similar to hyperstimulation (105). This is in line with the results from other studies showing that MT expression could be strongly stimulated with oxidative stress in different tissues, including heart, lung, liver, and kidney (101). In this regard, possible cross-talk between antioxidant proteins or enzymes might exist in such as way that the activity of antioxidant proteins or enzymes would control the expression levels of ROS-scavenging proteins, orchestrating the resultant redox status.

The GSH-metabolizing enzyme GSH S-transferase (GST) may be involved in redox balance regulation during pancreatic inflammation. It is responsible for catalyzing the reaction of glutathione conjugation with xenobiotic and electrophilic substances. GST exists in alpha (A), mu (M), pi (P), and theta (T) subtypes. GST-A and GSTM are located primarily in the ductal system and lumen (193, 256), whereas GSTT is situated in the pancreatic acinar cells (191, 203). Numerous studies have revealed a strong correlation between GST mutation and the incidence as well as the severity of pancreatitis. Patients with biliary AP and idiopathic CP have been found to have a functional genotype of GSTT-1 gene (denoted GSTT-1* A) (245, 246). Similarly, GSTM1-null genotypes were found to be significantly less common in alcoholic CP patients (315). Hence, individuals carrying a functional genotype of GST, which is expected to be more resistant against oxidative stress, appear to be more susceptible to developing pancreatic inflammation in response to environmental stresses and toxins. The paradox could be explained by detrimental effects of GST on the bioactivation of xenobiotics, because the toxicity of many chemicals may be enhanced by GSH conjugation (18). Alternatively, such mutations may disrupt the GSH balance. The conjugation of GSH with xenobiotic molecules, followed by subsequent cellular excretion, can lead to GSH depletion from cells. This "suicidal conjugation" leads to permanent loss of GSH, interrupting normal GSH recycling by the GPx/GHS reductase system (245). As a result, the cellular GSH:GSSG ratio is upset, eventually leading to establishment of oxidative stress.

It is of interest to note that the GST mutation is *less* prevalent in patients in North America than in patients from other regions (22), implying that lifestyle and other environmental factors may be involved in normalizing the effects of GST mutation in pancreatitis development.

B. ROS/RNS-generating enzymes

The details of ROS/RNS generation are discussed subsequently. In particular, the changes in enzymatic activities or their expression levels during the course of both AP and CP are also extensively reviewed here. Table 1 summarizes the details of the expression profiles and activities of the ROS/RNS enzymes, as well as their antioxidant counterparts, in the pathogenesis of pancreatitis.

C. Xanthine oxidase

Xanthine oxidase (XOD) is the molybdenum-containing enzyme involved in purine metabolism. It catalyzes the conversion of hypoxanthine to xanthine and of xanthine to uric acid. The reaction couples to the reduction of molecular oxygen with the cooperation of the cofactor flavin adenine dinucleotide (FAD), thus giving rise to superoxide and hydrogen peroxide. XOD is expressed in numerous tissues including liver, kidney, lung, intestine, and pancreas (208, 350). XOD is generally expressed in cytoplasm, but its particular subcellular localization varies among cell types (103). XOD can be produced from its reduced form, xanthine dehydrogenase (XDH).

Freshly isolated xanthine oxidoreductase (XOR) exists pre-

TABLE 1. COMPARISON OF EXPRESSION/ACTIVITY OF ANTIOXIDANT PROTEINS AND ROS/RNS-GENERATING ENZYMES IN PATIENTS AND BETWEEN DIFFERENT EXPERIMENTAL AP AND CP MODELS

	Antioxidant enzymes/proteins				*ROS/RNS-generating enzymes*			
	GPx	*SOD*	*CAT*	*Antiox proteins*	*XOD*	*NOS*	*CYP 2E1*	*NADPH oxidase*
Caerulein	AP ↓pan (90, 91) ↑pan (222) CP ↓pan (72)	AP ↓pan (64, 91, 222)	AP ↓pan (91, 222)	AP ↑GCL pan (240) ↑MT-1 pan (105) CP ↑MT-1 pan (344)	AP ↑isolated acini (291) No change pan (52, 78, 224)	AP ↓cNOS ↑iNOS pan (6)	N/A	AP ↑pan (125, 309) ↑acinar cells (345)
Intraductal bile acid infusion, TNBS, and related	AP ↓pan (59) ↑pan (329) No change pan (338) CP ↓pan (195)	AP ↓pan (59) ↑pan (329) No change pan (338) CP ↓pan (195)	N/A	AP No change GCL pan (240)	AP ↑ser (99, 241) ↑pan (52)	AP ↑iNOS pan (250,314)	N/A	N/A
Arginine	AP ↓pan (60, 61)	AP ↓pan (60, 61) ↑pan (293) ↑acinar cell (288)	AP ↓pan (60, 61) ↑pan (293)	N/A	N/A	AP ↓CNOS ↑iNOS PAN (295) ↑iNOS acinar cells (210)	N/A	N/A
Surgical manipulation-induced AP [ischemia/reperfusion, (OB) and related]	AP ↓pan (213)	AP ↓pan (213)	AP ↓pan (202)	N/A	AP ↑pan (224) both IR and OB	AP ↑NOS pan (14, 317)		AP ↑pan (39) OB
WBN/Kob rats	N/A	CP ↑pan (288)	N/A	N/A	CP ↑pan (350)	N/A	N/A	CP ↑pan (198)
Other pancreatitis model (hyperlipidemia,alcohol, DBTC)	CP ↓pan (328) DBTC	AP ↓pan (223) CDE-diet CP ↓pan (341) High lipid diet ↓pan (328) DBTC	N/A	N/A	AP ↑pan (223) CDE-diet CP No change pan (328) DBTC	N/A	CP ↑pan (153, 225) EtOH	CP ↑pan (198) DBTC

(*continued*)

TABLE 1. COMPARISON OF EXPRESSION/ACTIVITY OF ANTIOXIDANT PROTEINS AND ROS/RNS-GENERATING ENZYMES IN PATIENTS AND BETWEEN DIFFERENT EXPERIMENTAL AP AND CP MODELS (*CONTINUED*)

	Antioxidant enzymes/proteins				*ROS/RNS-generating enzymes*			
	GPx	*SOD*	*CAT*	*Antiox proteins*	*XOD*	*NOS*	*CYP 2E1*	*NADPH oxidase*
Other pancreatitis model (hyperlipidemia,alcohol, DBTC)		↓PSCs (13) pressure ↓pan (185) DBTC						
Patients	AP ↓ser (212, 330)	AP ↓ser (294) No change ser (212)	AP ↑ser (294)	AP ↑Trx ser (229)	AP ↑pan (303)	AP ↑iNOS ser, monocyte (300)	CP ↑pan (319)	N/A
	CP ↓pan (57) ↓ser (294)	CP ↓pan (57) ↑ser (294)	CP ↓pan (57) ↑ser (294)	CP ↑MT-1 pan (205)	CP ↑pan (303)			

↑/↓ pan: increase/decrease expression or activity in the pancreas.
↑/↓ ser: increase/decrease expression or activity in the serum.
Antiox proteins, antioxidant proteins.
EtOH, ethanol-induced pancreatitis.
IR, ischemia-reperfusion.
N/A, the related studies are not available.
OB, obstruction.

dominantly in the form of XDH, exhibiting negligible xanthine oxidase activity but high affinity toward xanthine/NAD^+. On oxidation of its cystein residues, XHD converts to XOD reversibly, attaining high enzymatic activity toward the substrate O_2, but not NAD^+. Irreversible conversion to XOD can be achieved by restricted proteolytic cleavage (219).

It has been reported that XOD conversion takes place during an ischemia/reperfusion state (239), which is a common pathologic phenomenon during outbreaks of AP or CP (75, 307). Results from another study revealed that conversion of XDH to XOD could also be attained by the proteolytic enzyme trypsin *in vitro* (286), implying that intracellular active trypsin may participate in XOD activation during AP episodes. The details of XOD activation in pancreatitis are summarized in Fig. 3.

A substantial body of evidence indicates that XOD-derived ROS play an important role in the pathogenesis of both AP and CP. The xanthine-XOD system alone has been demonstrated to trigger AP-like lesions in isolated pancreatic acini, as evidenced by intrapancreatic trypsinogen activation, swollen mitochondria, and zymogen granule damage (217). These observations are in good agreement with more recent findings indicating that perfusion of the pancreatic glands with hypoxanthine-XOD results in an elevated amylase level, edema, and necrosis (192).

Caerulein, a cholecystokinin (CCK) receptor agonist, can trigger generation of XOD-derived oxygen radicals in isolated pancreatic acini (291). Moreover, an association be-

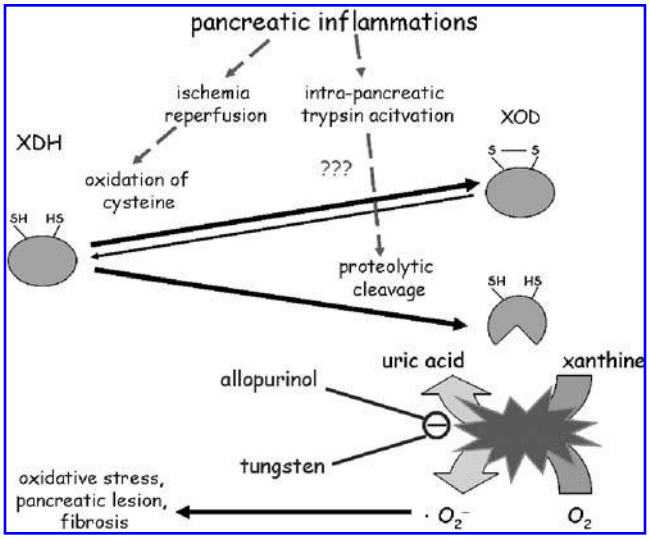

FIG. 3. Involvement of xanthine oxidase (XOD) in pancreatic inflammations. Xanthine dehydrogenase (XDH) converts to active XOD *via* oxidation of cysteine residues to disulfide linkage or proteolytic cleavage. Ischemia/reperfusion and intrapancreatic trypsinogen activation may be involved in the process. Active XOD can generate superoxide free radicals and thus may produce oxidative damage and pancreatic lesions. Allopurinol, a specific XOD inhibitor, or tungsten, an inactivator of XOD, could abolish XOD activity, thus limiting pancreatic lesions and oxidative stress.

tween XOD and the pathophysiology of pancreatic inflammation has also been demonstrated in *in vivo* systems. Serum XOD levels were elevated in the early phase of AP after intraductal taurocholate administration (99, 241). Mice fed with a CDE diet exhibited elevated pancreatic XOD activity over controls (223). Augmentation of pancreatic XOD activity was observed in 8-week-old WBN/Kob rats (before development of CP), and this augmentation correlated well with histologic damage (350). Marked XOD-derived oxidative stress, colocalized with local expression of a proinflammatory marker, was observed in a resected pancreas specimen from a pancreatitis patient (303). These observations imply that XOD-derived superoxide and peroxide are upregulated during pancreatic inflammation, leading to pancreatic lesions and activation of proinflammatory pathways. It should be emphasized that the occurrence of XOD-derived ROS generation depends on the etiology or experimental methods that induce the pancreatitis. In general, it is usually observed in severe forms of AP (such as with the intraductal infusion–induced or ischemia/reperfusion model), but not in milder forms (such as after hyperstimulation).

Hyperstimulation-induced AP by caerulein injection did not elevate pancreatic XOD activity (78, 224). Invasive treatments, such as intraarterial infusion of oleic acid, partial obstruction of the pancreatic duct with secretin stimulation, or ischemia/reperfusion (but not caerulein stimulation alone) can elevate pancreatic XOR activity in isolated canine pancreas (224). XOD-derived oxygen free radicals were observed in necrohemorrhagic pancreatitis (after intraductal taurocholate infusion), but not in mild pancreatitis (after caerulein stimulation) (52). Enzyme inhibition/inactivation studies suggest that XOD targeting may represent a therapeutic strategy for treatment of pancreatic inflammations.

Allopurinol, a specific XOD inhibitor, was shown to attenuate injurious effects in the pancreas after ischemia/reperfusion (132) or *ex vivo* perfusion (264). Allopurinol treatments have also been reported to attenuate AP in various animal models including caerulein-induced (333), biliopancreatic duct obstruction/ischemia–induced (131), arginine-induced (60), and taurocholate-induced AP models (138). Furthermore, allopurinol has been shown to suppress SOD inhibitor–induced fibrogenic gene expression in rat PSCs, indicating that XOD-derived hydrogen peroxide plays a critical role in the progression to fibrosis (299). Inhibition of XOD has also been shown to attenuate TNBS-induced oxidative stress, collagen deposition, lobular atrophy, and α-smooth muscle actin expression in PSC (302). Administration of tungsten, a competitive antagonist of molybdenum, which thereby inactivates XOD, has also been shown to suppress the onset of CP in WBN/Kob rats (350). All of these findings point to XOD as a source of ROS that exert deleterious effects on the pancreas in both AP and CP.

Clinically, controversy remains with respect to whether XOD inhibition has therapeutic benefits on pancreatic inflammation. Budzyñska *et al*. (30) and Romagnuolo *et al*. (255) reported that prophylactic administration of allopurinol (200–300 mg/kg) did not protect against endoscopic retrograde cholangiopancreatography (ERCP)-induced AP. However, another group of investigators found that a high dose (600 mg/kg) of allopurinol prevented the onset of ERCP-induced AP (149). The discrepancy of these two studies may be due to the differing dosages of allopurinol administrated to the patients. It is possible that the lower doses were not sufficient to inhibit endogenous XOD activity, and thus failed to prevent ERCP-induced AP.

Another clinical trial concerning this enzyme inhibitor also yielded negative results. Given at dose 300 mg/d, allopurinol did not affect pain or activities levels in CP patients (16). However, the study of Banks *et al*. (16) was small in scale ($N = 13$) and did not report serum marker levels or biopsy analysis, so it is difficult to know whether the treatment had any internal effects on CP severity that did not translate into effects on pain and activity. Thus, a larger-scale study of allopurinol in CP patients with more-precise measures should be carried out. Likewise, more randomized, double-blinded clinical trials should be conducted to validate the beneficial effects of XOD inhibition in these disorders. Until such results are produced, the efficacy of XOD inhibition in the treatment of CP remains unresolved.

D. Nitric oxide synthase

Nitric oxide synthase (NOS) is the NADPH-dependent enzyme responsible for catalyzing the conversion of L-arginine and oxygen to citrulline and the free radical nitric oxide (NO). NOS exists in three subtypes: neuronal NOS (nNOS, type I), inducible NOS (iNOS, type II), and endothelial NOS (eNOS, type III), which differ from one another in terms of tissue distribution, physiologic role, and regulatory mechanism (50, 226). Both nNOS and eNOS are Ca^{2+} dependent and constitutively expressed in neurons and endothelial cells, respectively (known as constitutive NOS, cNOS), maintaining tonic regulation and neuron transmission (50). Meanwhile, iNOS is Ca^{2+} independent and induced during inflammatory processes (50). It is generally believed that NOS localizes in the plasma membrane, facilitating diffusion between neighboring cells for signal transduction (226). Localization of NOS to the plasma membrane is necessary for maximal NO production (108, 139, 226). NOS can also be targeted to other subcellular regions, such as the nucleus, mitochondria, and Golgi, where the cellular functions they serve have yet to be delineated (108, 139, 226).

The constitutive bioavailability of NO resides primarily with nNOS and eNOS, which are expressed in pancreatic nerves and vasculature, respectively. Emerging evidence indicates that acinar cells may also be a source of NO in the pancreas; such locally produced NO could play a role during pathologic status of pancreatitis. Both nNOS and eNOS can be detected by immunoblotting and immunohistochemistry in rodent pancreatic acinar cells (215, 337). Findings from functional *in vitro* studies support the hypothesis that biologically active NO could be generated within acinar cells. Pancreatic acinar cells can actively convert arginine to citrulline and elevate cellular nitrite content on stimulation (3, 124, 334). Nonselective NOS inhibition was shown to abolish secretagogue-induced amylase secretion in isolated pancreatic acini and in acinar cells (3, 334). Intravenous administration of the nonspecific NOS inhibitors *N*-nitro-L-arginine or *N*-nitro-L-arginine methyl ester suppressed secretagogue-induced pancreatic secretion in rats and mice (82, 144). It should be emphasized that inhibition of pancreatic enzyme secretion plays an active role in the development of AP. Secretion of proteases, particularly of trypsin, is inhibited during the course of pancreatitis, thus leading to autodigestion

of the gland. Hence, these data might imply that NOS activity could influence the severity of pancreatic inflammation by controlling pancreatic secretion.

Different isoforms of NOS have differing expression profiles and impacts on the pathogenesis of pancreatic inflammation. AP induction by caerulein- or arginine-induced AP *depleted* constitutive NOS activity in the pancreas (6, 295). Nonspecific inhibition of NOS enhanced the severity of caerulein-induced AP (9, 331) and closed-duodenal loop–induced AP (220). Conversely, AP could be attenuated by the NOS substrate L-arginine or the NO donor sodium nitroprusside (9, 331). eNOS-knockout mice subjected to caerulein-induced AP exhibited augmented intrapancreatic trypsin activity and serum lipase levels (83). Taken together, these findings indicate that constitutive RNS regulate normal exocrine secretion and may protect against pancreatitis. These paradoxic observations may be explained by the fact that constitutive NO is generated in a relatively small amount, whereas its inducible counterpart is generated in surges. The miniscule levels of RNS normally present are not sufficient to trigger nitrosative damage. Constitutive NO is known to exert beneficial effects in the pancreas because of enhancement of pancreatic microcirculatory blood flow (83), inhibition of leukocyte adhesion (331), and suppression of cathepsin B, which is crucial in pancreatic trypsinogen activation (50). Unlike constitutive eNOS, iNOS has been shown to have an altered expression profile during AP pathogenesis, which is associated with deleterious effects on the pancreas. *Elevated* expression of pancreatic iNOS was observed in caerulein-induced AP (6, 312), arginine-induced AP (295), taurocholate-induced AP (250, 314), experimental post-ERCP–induced AP (100), and ischemia/reperfusion-induced AP (14, 317). The expression of the iNOS was localized mainly in the vascular smooth muscle cells and endothelial cells (6, 14). It has been shown that patients with severe AP have elevated expression of iNOS in monocyte (300). Furthermore, selective inhibition of iNOS has been shown to ameliorate experimental AP in Australian possums (263) and in rats (14, 42). Meanwhile, genetic deletion of iNOS has been shown to inhibit hyperstimulation, elevated intrapancreatic trypsin, and neutrophil infiltration (58). The deleterious effects of iNOS may be attributed to its high NO-production activity. iNOS produces a large amount of electrophilic NO during AP pathogenesis, subsequently activating a proinflammatory cascade, leading to inhibition of cellular respiration and formation of irreversible nitrosylation and nitration of cellular proteins, which eventually results in pancreatic cell death (both necrotic and apoptotic) (50). Although contradictory findings have been reported (96, 243), it is generally believed that iNOS exerts its detrimental effects *via* NO overproduction, which subsequently leads to oxidative nitrosative damage. NOS involvement in pancreatitis pathogenesis is summarized in Fig. 4.

It is worth noting that the effects of administering NOS inhibitor, substrate, or direct NO donor on pancreatic inflammation depend on the administrative route and dosage applied. L-Arginine is usually protective against AP, as mentioned earlier, but can induce pancreatic lesions when injected intraperitoneally at very high doses (250–500 mg/100 g) in rats (161, 207, 298), rabbits (33), and mice (56, 352). Arginine-induced AP is considered as one of the noninvasive methods for triggering acute necrotizing pancreatitis, with morphologic alternations and complications similar to those seen in the clinical setting (38, 68, 129, 161). Arginine alone could enhance *in vitro* iNOS expression in pancreatic acinar cells (210), indicating that excessive arginine alone could lead to inflammatory response in the cells. Thus, care must be taken to choose an optimal dose and administration route to achieve therapeutic goals with minimal side effects in the clinical setting. Clinical trials targeting NOS alone have yet to be carried out. Further studies should be conducted to verify whether novel selective iNOS inhibitors provide an alternative therapy against pancreatic inflammation (42, 263)

E. Cytochrome P450

Cytochrome P450 (CYP) is the family of monooxygenases responsible for metabolism of a wide variety of exogenous substrates (xenobiotics) in addition to endogenous substrates (177). Its name is derived from its characteristic absorbance at 450 nm when it is in its reduced state after binding to carbon monoxide. CYP catalyzes the oxidation of xenobiotics or

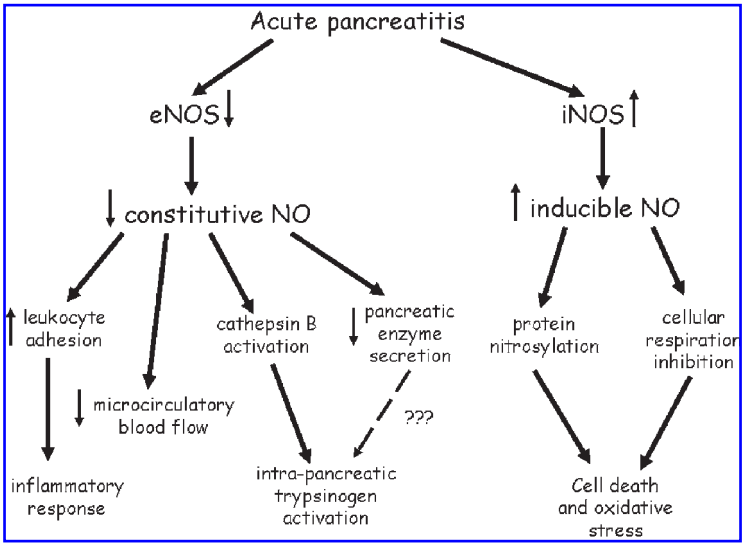

FIG. 4. Differential-expression profile of different nitric oxide synthases (NOSs) during AP. Endothelial NOS (eNOS) is depleted during pancreatic inflammation, leading to impairment of pancreatic microcirculatory blood flow and suppression of pancreatic secretion. This circumstance promotes leukocyte adhesion, facilitating cathepsin B activation. Conversely, inducible NOS (iNOS) is upregulated during AP, resulting in cell death and oxidative stress.

endogenous substrates by using molecular oxygen as an oxidizing agent in an NADPH-dependent manner. The enzyme is located in the smooth endoplasmic reticulum and shares some similarities with mitochondrial cytochrome oxidase, as evidenced by their high binding affinity with oxygen and carbon monoxide (177). Functionally, the CYP family enzymes are primarily involved in the biosynthesis of steroids, fatty acids, and bile acids; a small number of CYP enzymes participate in xenobiotic metabolism, namely CYP1-4 (118). This class of xenobiotic-metabolizing CYPs is known as a detoxification enzyme group because of the enzymes' ability to attach an activated oxygen or hydroxyl group to lipophilic xenobiotics, which can then be solubilized by phase II enzyme *via* conjugation with a glucuronic acid, sulfate, or acetyl group (118).

However, in some cases, oxidation of xenobiotics is disastrous, making them more toxic and reactive than their parent compounds. More important, CYPs tend to facilitate the reduction of oxygen to superoxide free radicals in the absence of a substrate for hydroxylation (177). Even in the presence of substrate, the "leaky property" of CYPs enables free radical molecules to escape easily, producing oxidative stress (118, 177). In addition, CYP2E1, one of CYP subclasses, converts ethanol to a carbon-centered radical, known as 1-hydroxyethyl radical, which can exert oxidative damage on cells directly (165).

Among the xenobiotic-metabolizing CYPs, CYP2E1 has been shown to correlate particularly well with the development of pancreatitis because it metabolizes low-molecular-weight xenobiotics including ethanol (118, 177). Actually, it is well documented that chronic alcohol consumption can induce pancreatic inflammation in humans and in an experimental model, and CYP2E1 seems to serve as a pivotal factor in ethanol-derived toxicity toward pancreatic cells (11, 321). Alcohol metabolism not only takes place in the liver, but also occurs in the pancreas, albeit to a lesser extent. Pancreata from rat and human normally expresses low levels of CYP2E1 (225, 285). Prolonged ethanol administration induced CYP2E1 expression in the rat pancreas (225), together with CYP enzymatic activity (153). Likewise, pancreatic biopsies from alcoholic CP patients had elevated levels of CYP2E1 (319). These findings imply that ethanol can upregulate pancreatic CYP2E1 expression in CP, and thus can exert toxic effects on the gland, probably through ROS generation.

Evidence shows that CYP plays a critical role in the pathogenesis of pancreatic inflammation. The pharmacokinetics of a CYP activity probe has been shown to be significantly altered in AP and CP patients (2). Shortened half-lives and increased clearance rates of CYP-sensitive drugs were observed, implying that CYP is induced during episodes of pancreatic inflammations (2). DBTC, an organotin that leads to pancreatic lesions and experimental CP, induced cellular toxicity *via* CYP (311) and subsequent generation of ROS in the pancreas (175). Furthermore, co-administration of DBTC and ethanol aggravated oxidative stress to the pancreas, compared with ethanol alone (328), indicating that these two CYP-sensitive xenobiotics exert additive effects on the pancreas, leading to pancreatic lesions and subsequent pancreatic inflammation.

Numerous clinical investigations concerning the relation between CYP2E1 and alcoholic pancreatitis have been carried out. These studies focused primarily on whether alcoholic CP patients possess genetic alterations in the *CYP2E1* gene. Genetic analysis revealed that *CYP2E1* polymorphisms do not correlate with the incidence of alcoholic CP (32, 36, 41, 104, 316, 342). Rather, carriers of mutations in other genes related to alcohol metabolism, such as alcohol dehydrogenase 2, were at higher risk of pancreatitis (32, 194). Hence, the *CYP2E1* gene is unlikely to be involved in the susceptibility to and pathogenesis of alcoholic pancreatitis. Mutation of a single or multiple nucleotides in *CYP2E1* is not sufficient to trigger CP. However, other genetic alterations related to *CYP2E1* processing and stability might be involved in CP pathogenesis, as prolonged ethanol consumption was reported to increase the protein, but not the transcript, of *CYP2E1* in the pancreas (225). Thus, it is tempting to speculate that genes involved in controlling *CYP2E1* stability and posttranslational modification could be candidates for CYP2E1 protein upregulation during CP development. Further investigations should be carried out to identify the culprit of *CYP2E1*-related gene effects in pancreatitis development.

F. Nicotinamide adenine dinucleotide phosphate oxidase

Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is the transmembrane flavoprotein enzyme that catalyzes the univalent reduction of oxygen by using NADPH as an electron donor to create the superoxide free radical. It is a multimeric enzyme consisting of five different subunits, including Nox (*e.g.*, $gp91^{phox}$), Nox organizer (NOXO; *e.g.*, p47), and Nox activator (NOXA; *e.g.*, p67), p22 and p40. The participation of Rac would elicit full oxidase activity (163). It was found primarily in leukocytes and has been shown to play an active role in host-defense mechanisms and inflammatory processes (28). NADPH oxidase is not confined to phagocytes, but also exists in many different tissues including colon, kidney, spleen, testis, blood vessels, and even pancreas (39, 121, 133, 198, 296, 346). NADPH oxidase is regulated *via* two distinct mechanisms. The first pathway depends on the spontaneous translocation of its subunits. In the resting state, NOXO, NOXA, and p40 reside in the cytosol, whereas Nox and p22 are located in the plasma membrane. On stimulation, NOXO translocates to the membrane, recruiting NOXA and interacting with the p22 subunit. The interaction between NOXA and p22 is crucial for the oxidase activity of Nox (121, 296).

The second regulatory mechanism relies on *de novo* synthesis of the NADPH oxidase subunits. Obviously, augmentation of the expression of this enzyme would undoubtedly enhance ROS generation. Tumor necrosis factor alpha (TNF-α) and proinflammatory cytokine can upregulate transcription of p22 in vascular smooth muscle cells (70). Vasoactive peptide, angiotensin II, has been shown to increase the expression of p22 and p67 in rat aorta and adventitial fibroblasts, respectively (107, 234). Elevated renal expression of p22 and Nox-1 has also been detected on subcutaneous infusion of angiotensin II (37).

NADPH oxidase expression is particularly high in inflammatory cells like neutrophils and macrophages, which are sequestered in the pancreas during the course of pancreatic inflammations. The sequestered enzyme generates large amounts of superoxide (a so-called respiratory burst),

exerting direct oxidative stress on surrounding pancreatic cells. Thus, it is generally believed that infiltrated inflammatory cells are the cellular source of NADPH oxidase. However, emerging evidence suggests that nonneutrophil NADPH oxidase is also involved in pancreatitis development. Actually, different NADPH oxidase subunits were expressed in pancreatic acinar cells (39, 346) and PSCs (133, 198). The expression and enzymatic activity of NADPH oxidase was elevated in obstruction-induced pancreatitis and caerulein-stimulated AP, respectively (39, 309). These findings are in keeping with an *in vitro* study demonstrating that caerulein provoked oxidase activity, which was abolished by anti-sense oligonucleotide against p22 and p47 (347). Conversely, p47 expression was shown to colocalize within fibrotic regions in WBN/Kob rats (198). Platelet-derived growth factor (PDGF), a potent profibrogenic factor, could stimulate NADPH oxidase activity and diphenylene iodium (DPI)-abolishable ROS production in isolated PSCs (198). These findings imply that NADPH oxidase serves as an important mediator in inflammatory and fibrogenic processes in pancreatic inflammation.

Inhibitor or gene-targeting studies have further revealed that NADPH oxidase is closely associated with the pathophysiology of pancreatitis. NADPH oxidase inhibition suppressed caerulein-induced expression of IL-6 *in vitro* (346). Secretagogue-induced activation of proinflammatory transcription factor NF-κB could also be reversed by the NADPH oxidase inhibitor DPI and antisense oligonucleotides against p22 and p47 (346). Moreover, mice with genetic deletion of the p47 subunit exhibited an attenuated intrapancreatic trypsinogen activation and hyperamylasemia in caerulein-induced AP (125). These findings suggest that NADPH oxidase produces detrimental effects during AP *via* three different mechanisms: direct oxidative stress, activation of proinflammatory cascades, and facilitation of autodigestion of the pancreas. Conversely, p47-deficient PSCs were shown to be unresponsive to PDGF-induced proliferation (133). Meanwhile, apocynin, an NADPH oxidase inhibitor, dose-dependently antagonized PDGF-induced DNA synthesis in wild-type PSCs (198). *In vivo* findings also supported the supposition that NADPH oxidase is involved in CP pathogenesis. Prolonged DPI treatment was shown to inhibit morphologic damage and fibrosis in the WBN/Kob rat and DBTC-induced experimental CP animals (198). Taken together, these findings implicate NADPH oxidase as a major culprit in the development of pancreatic inflammation. Treatment targeting NADPH oxidase may be beneficial in pancreatitis, possibly *via* inhibition of superoxide generation, thus ceasing proinflammatory and profibrogenic gene expression. The likely mode of activation of NADPH oxidase in both AP and CP is depicted Fig. 5.

IV. Redox-Sensitive Signaling Cascades in Pancreatic Inflammation

Regardless of the cellular or enzymatic source of ROS/RNS, the redox-imbalance status established would commonly converge on activation of proinflammatory cascades and related signaling pathways. These pathways involve cross-talk between phosphorylation and dephosphorylation processes, ubiquitination-mediated proteolysis, and alterations in membrane permeability. In this section, the detailed cellular mechanisms involving redox regulation are discussed. In particular, the redox-sensitive pathways involved in pancreatic inflammations are reviewed extensively.

A. Mitogen-activated protein kinase

The mitogen-activated protein kinase (MAPK) family of enzymes includes well-known redox-sensitive mediators during the pathogenesis of pancreatic inflammations. MAPKs are responsive to cytokines, growth factors, hormones, and cellular stress and control numerous cellular pro-

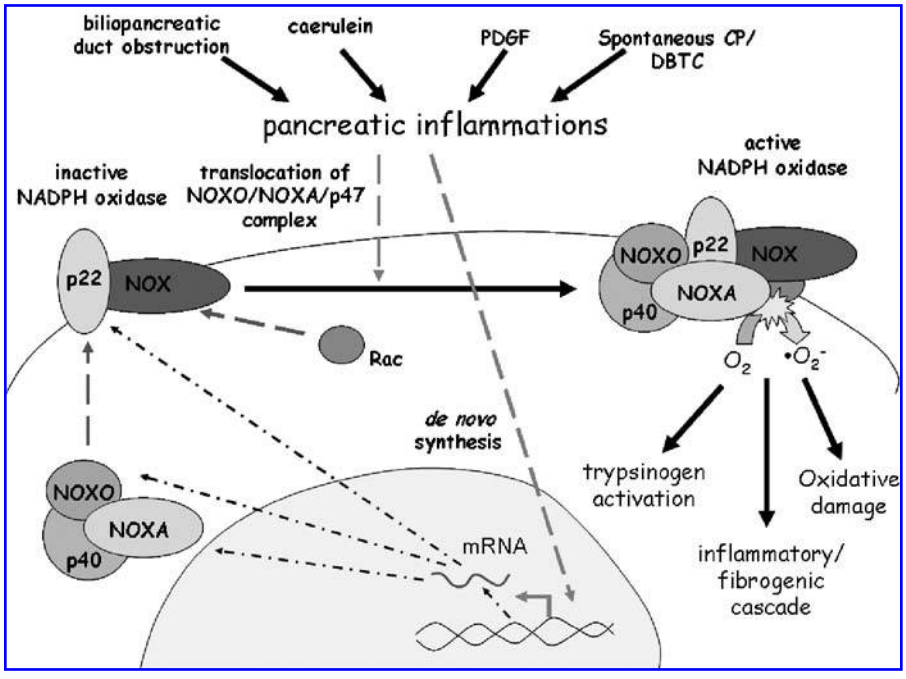

FIG. 5. Different stimuli or risk factors are involved in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation during pancreatic inflammations. The modes of activation include (a) translocation of different subunits and (b) *de novo* synthesis of NADPH oxidase subunits. The resultant activation of NADPH oxidase leads to oxidative damage, proinflammatory and profibrogenic pathways, and intrapancreatic trypsinogen.

cesses, including cytoskeleton arrangement, transcription factor activation, apoptosis, proliferation, and differentiation (201). The five major classes of MAPKs include p38MAPK, extracellular-regulated kinase (ERK) 1/2, Jun N-terminal kinase (JNK), ERK $^3/_4$, and ERK 5 (201, 269). MAPK regulation depends on dual-phosphorylation at the T-X-Y motif by upstream kinases known as MAPK kinases [MAPKKs, mitogen ERK kinases (MEKs)], which in turn are activated by MAPKK kinases (MAPKKKs, MEKKs). Activation of MAPKs can be counteracted by dephosphorylation by phosphatases such as MAPK phosphatase-1 and phosphatase 2A (85, 269). MAPK serves as a signal-cascade check point, directly controlling gene transcription by interacting with transcription factors and nuclear proteins, such as c-jun and cAMP-responsive element binding protein. The detailed hierarchic regulation has been extensively reviewed elsewhere (123, 127, 287) and is not detailed in the present article.

ROS/RNS induce MAPK activation in numerous cell types, including cardiomyocytes, vascular smooth muscle cells, endothelial cells, hepatocytes, T lymphocytes, and pancreatic exocrine cells (26, 53, 62, 122, 156, 313, 336). ROS may not interact directly with MAPKs. Oxidative stress–induced ERK activation could be abolished by inhibiting the upstream mediators MEK1 and MEK2 (172, 174), implying that ROS targets upstream effectors of MAPKs. In addition, oxidative stress may trigger activation of epidermal growth factor receptor (110, 116, 134, 354) and PDGF receptor (164), even in the absence of their ligands, directly activating the small G protein–binding protein Ras and subsequently leading to ERK activation. Oxygen radicals, generated by ultraviolet (UV) light, could directly activate TNF-α receptor (TNFR) (278), leading to activation of p38MAPK (201) and JNK (167, 181) in a TNF-α–independent fashion. Beyond cell-surface receptors, oxidative stress could activate intracellular proteins to trigger MAPK. Src kinase, a protein tyrosine kinase, was activated directly by ROS (173), switching on the Ras pathway and triggering ERK activation (152, 275). Src kinase activation also led to phosphorylation and activation of phospholipase C (PLC) gamma, resulting in the release of inositol triphosphate (IP_3) and diacylglycerol (DAG) (15, 324). Enhanced release of calcium from intracellular stores after IP_3 activated ERK in a calmodulin-dependent manner (89, 102, 113, 272). Elevated intracellular calcium also triggered protein kinase C (PKC) activation, turning on the Raf pathway (31), further activating ERK (356). Furthermore, oxidative stress diminished counteracting phosphatase activity by protein phosphatase (249, 332) and specific dual phosphatase (147), thus resulting in activation of ERK (173) and JNK (147), respectively.

Nitric oxide would activate Ras *via* nitrosylation of a cystein residue, leading to ERK activation (169). RNS-induced Ras activation not only turned on ERK signaling, but also activated p38MAPK and JNK (168, 201). The underlying mechanism by which RNS induces p38MAPK activation may involve the ability of RNS to nitrosylate Trx (343). Nitrosylated Trx dissociated from apoptosis signal–regulating kinase 1 (ASK-1), leading to its activation and resulting in activation of p38MAPK and JNK. Trx is not only subject to nitrosylation but is also easily oxidized. ROS-induced oxidation of Trx led to dissociation of Trx from ASK-1, leading to ASK oligomerization (followed by autophosphorylation of ASK-1) and, subsequently, selective activation of p38MAPK and JNK (199).

Activation of JNK could also be achieved by dissociation of ASK-1 from the ASK-GST complex in response to oxidative stress. Actually, ASK-1 is an important upstream kinase regulating the activation of p38MA PK and JNK in response to redox imbalance. Deletion of ASK-1 protected against H_2O_2-induced activation of p38MAPK and JNK activation, indicating that ASK-1 serves as an important mediator in ROS-induced MAPK activation (306). Figures 6 and 7 summarize how oxidative stress activates MAPKs.

Emerging evidence has implicated MAPKs in the pathophysiology of AP. Treatment of rat pancreatic acini with CCK can immediately induce MAPK activation in a calcium-independent manner, as evidenced by myelin basic protein kinase activity (85). Likewise, *in vitro* studies have demonstrated that p38MAPK, JNK, and ERK1/2 were activated on hyperstimulation with secretagogues (65, 268, 320). These *in vitro* studies are supported by a number of *in vivo* studies indicating that experimental pancreatitis led to MAPK activation. Infusion of supramaximal caerulein induced activation of p38MAPK, JNK, and ERK1/2 in the pancreas during early pancreatitis (65, 120, 268, 277). Moreover, it has been demonstrated that JNK activity correlates with serum marker levels and intrapancreatic cathepsin B activity in caerulein-induced AP (120). Activation of MAPKs stimulates proinflammatory gene expression in pancreatic acinar cells. MAPK inhibition or transfection with dominant mutant MAPK genes abolished stress-induced cytokine expression (27, 143), indicating that MAPK would control inflammatory processes in pancreatic acinar cells by directing cytokine expression.

As mentioned earlier, *in vitro* and *in vivo* stimulation of caerulein could also result in ROS generation (137, 346, 347), thus implying a possible correlation between secretagogue-induced ROS and MAPK activation. However, caerulein-provoked MAPK activation, particularly of ERK1/2 and p38MAPK, usually took place *earlier* than that of ROS generation (1–5 *vs*. 15 min, respectively) (65, 268, 346). Moreover, CCK-induced activation of p38MAPK, JNK, and ERK1/2 in isolated pancreatic acini was not blocked by pretreatment with *N*-acetylcysteine (NAC), which is a potent antioxidant (63). Hence, it appears unlikely that secretagogue-induced MAPK activation could be mediated by ROS. The paradoxic phenomenon could be explained by the propensity of PKC to activate MAPK. Actually, the PKC inhibitors GF-109203X or staurosporine abolished CCK-provoked ERK1/2 and JNK activation *in vitro* (63, 66, 85).

Furthermore, PKC activation could activate MAPK in pancreatic acini, to an extent similar to CCK (65). However, it should be emphasized that ROS from infiltrating neutrophils, which would not be a factor *in vitro*, might also be involved in MAPK activation during the course of AP. Superoxide and H_2O_2 generated by inflammatory cells might activate MAPK in pancreatic acinar cells secondary to the primary activation. Actually, treatment of isolated pancreatic acini with H_2O_2 and menadione, a strong superoxide generator, induced activation of p38MAPK, ERK1/2, and JNK that is comparable to CCK-induced MAPK activation (63). NAC treatment inhibited pancreatic p38MAPK activation in biliopancreatic duct ligation models, with the concomitance of suppression of leukocyte TNF-α (248, 262). This

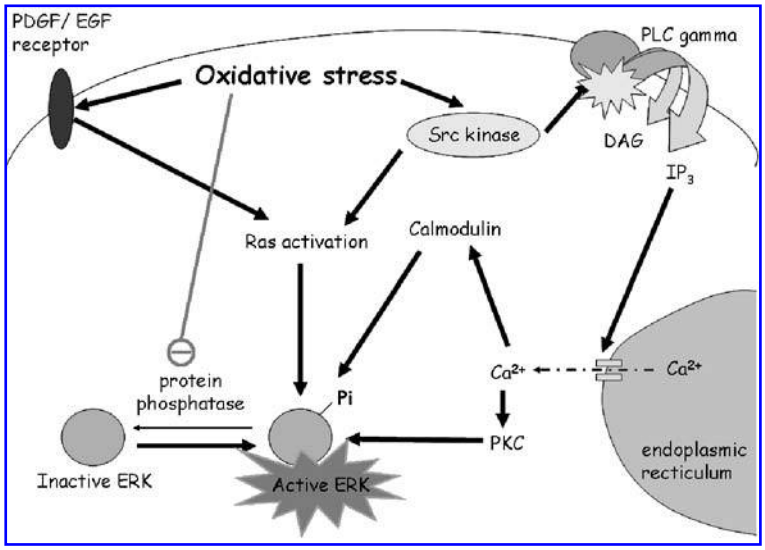

FIG. 6. Mechanism of redox-regulated extracellular regulated kinase (ERK) activation. Oxidative stress may trigger activation of epidermal growth factor receptor (EGFR) and platelet-derived growth factor (PDGF) receptor, directly activating the small G protein–binding protein Ras and subsequently leading to ERK activation. Reactive oxygen species (ROS) could also activate Src kinase to switch on the Ras pathway and trigger ERK activation. Oxidative stress–dependent Src activation could also directly activate phospholipase C (PLC) gamma to yield inositol triphosphate (IP_3) and diacylglycerol (DAG). IP_3 would bind to the IP_3 receptor in the endoplasmic reticulum, elevating intracellular calcium and resulting in activation of protein kinase C (PKC) and calmodulin. These two protein kinases would eventually activate ERK *via* phosphorylation in its activated sites. ROS could also inhibit protein phosphatase, resulting in substantiation of ERK activation.

suggests a possible linkage between leukocyte-induced ROS and pancreatic p38MAPK activation. Further investigation should be carried out to illustrate the role of leukocyte-derived ROS in MAPK activation in AP pathogenesis.

MAPK activation also is involved in the pathogenesis of CP. Ethanol, a well-known inducer of CP, and its metabolite acetaldehyde, were shown to activate p38MAPK, ERK1/2, and JNK, together with the proinflammatory transcription factor AP-1, in rat PSCs (12, 196). The activation of MAPK could be abolished by pretreatment with the antioxidant NAC. More important, the acetaldehyde-induced α1(I)-procollagen could be retarded by cotreatment with the p38MAPK inhibitor SB203580, implying that p38MAPK serves as a major regulator in relaying the signal from acetaldehyde-provoked ROS to profibrogenic gene expression (196).

Similar findings were obtained in other studies by using external-pressure application rather than chemically induced models of CP. Intrapancreatic pressure is elevated in CP pancreata (80, 93); thus, external-pressure treatment mimics the augmented pancreatic pressure that develops during the course of CP. Application of external pressure induced activation of p38 MAPK and ERK1/2 in rat PSCs (326). A gradual decline in SOD activity and increased intracellular ROS generation were also observed in pressure-exposed PSCs (13). The pressure-induced activation of p38MAPK could be reversed by pretreatment with antioxidants, indicating that oxidative stress serves as an upstream activator of MAPKs (13). Pretreatment of PSCs with a p38MAPK blocker inhibited pressure-provoked fibrogenic gene expression and collagen secretion (13). Moreover, treatment of PSCs with either H_2O_2 or 4-hydroxy-2,3-nonenal, a lipid peroxidation product, activated all three classes of MAPKs and subsequently led to procollagen gene expression (155, 156). This convergence of findings indicates that ROS generation activates MAPKs in PSCs, leading to transcription of certain profibrogenic genes and thus leading to development of pancreatic fibrosis. However, relevant clinical studies remain scattered. More investigations should be conducted to determine the role of ROS-activated MAPK in CP pathogenesis.

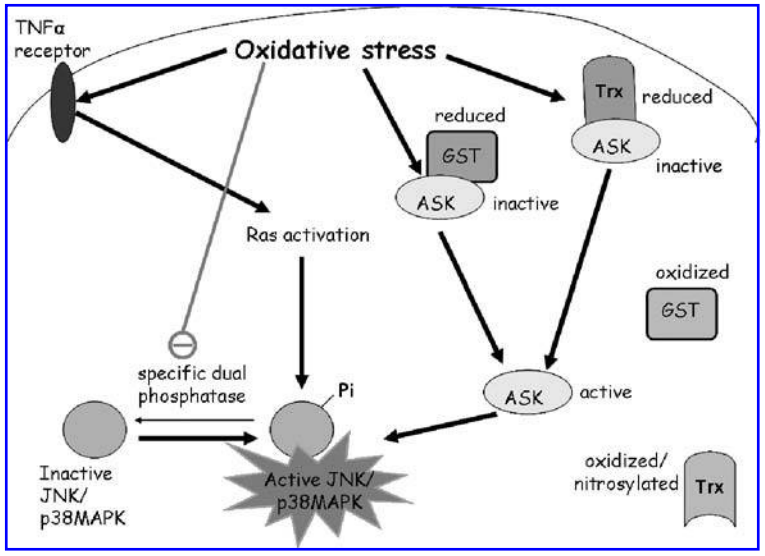

FIG. 7. Mechanism of redox-regulated p38 mitogen-activated protein kinase (p38MAPK) and Jun N-terminal kinase (JNK) activation. Oxygen radicals, generated by ultraviolet light, could directly activate TNF-α receptor (TNFR), leading to activation of p38MAPK and JNK in a Ras-dependent manner. Reactive oxygen species/reactive nitrogen species (ROS/RNS) could lead to oxidation/nitrosylation of thioredoxin (Trx), thus resulting in dissociation from apoptosis signal–regulating kinase (ASK). Oxidative stress could also lead to dissociation of the complex of ASK and glutathione S-transferase (GST). Dissociated ASK could activate itself by autophosphorylation and subsequent phosphorylation of p38MAPK and JNK. ROS could also inhibit specific dual phosphatase, resulting in substantiation of JNK activation.

B. Nuclear factor kappa B (NF-κB)

ROS not only initiate MAPK activation, but also regulate the potent proinflammatory transcription factor NF-κB. NF-κB was first characterized in B cells bound to the immunoglobulin κ-enhancer, thus giving rise its name, and was later found to be ubiquitously expressed in numerous tissues and cell types, including pancreatic exocrine cells. This transcription factor is basically a heterodimer/ homodimer consisting of either p65/ Rel A, Rel B, c-Rel, p105/p50, or p100/p52. When in its resting state, it couples to its inhibitory counterpart, inhibitor of NF-κB (IκB). This interaction prevents NF-κB from nuclear translocation by masking its nuclear-localization sequence (NLS).

NF-κB can be activated *via* a "canonic" or "noncanonic" mechanism. The classic pathway involves activation of upstream IκB kinase (IKK) complex, the degradation of IκB, and translocation of free NF-κB into the nucleus. In brief, activated IKK complex phosphorylates IκB at serines 32 and 36. The serine-phosphorylated IκB is subjected to degradation by ubiquitin-mediated 26S proteasome, which exposes the NLS of NF-κB, thus enabling nuclear translocation. The noncanonic pathway involves IKKα-dependent proteolytic processing of p100 to its activated form, p52. Many substances can trigger the noncanonic pathway, including TNF-α, lipopolysaccharide (270), lymphotoxin-β (74), and B cell–activating factor (51). After binding to their corresponding receptors, these ligands trigger the phosphorylation of a specific IKKα dimer. On phosphorylation, p100 undergoes partial proteolysis to yield the p52:RelB dimer, which directly activates NF-κB.

Activated NF-κB dimers, from both canonic and noncanonic pathways, bind to a specific DNA motif (κB sequence, 5′GGG PuNNPyPyCC-3′) (Pu, purine; N, nucleotide; Py, pyrimidine) (97) and initiate the transcription of downstream proinflammatory genes by recruiting a coactivator (or removal of corepressors). The transcriptional activity of NF-κB can be modulated by phosphorylation of the subunits in the dimer. It has been reported that serine phosphorylation of p65 enhanced transcriptional activity toward the κB sequence. Mutation of Ser 536 to Ala impairs transactivation induced by protein kinase B activation, indicating that additional phosphorylation and dephosphorylation processes may fine-tune the resultant transcriptional activity of NF-κB (188, 281, 282).

It has been long thought that oxidative stress triggers NF-κB activation. Such activation could be because NF-κB–activating agents such as TNF-α and phorbol myristate acetate (PMA) tend to form ROS (97, 145, 290). NF-κB could be activated by H_2O_2 and other peroxides in many cell types, including pancreatic acinar cells (97). NF-κB activation can be blocked by antioxidants or ROS-scavenging enzymes like SOD (97). Over the decades, however, this well-established theory has been challenged by several studies showing inconsistencies and contradictory results. Some cell types, such as lymphoblastoid T cells, monocyte cell lines, and mouse alveolar epithelial cells, did not exhibit NF-κB activation in response to H_2O_2 (166, 235). Overexpression of CAT failed to protect COS-1 cells from TNF-α–provoked NF-κB activation (292). Moreover, ROS/RNS seem to antagonize the effect of cytokines on NF-κB activation. TNF-α–induced IκBα degradation, nuclear translocation, and κB sequence binding were markedly retarded in the presence of H_2O_2 (166). It has been suggested that oxidation of cysteine residues in the IKK complex accounts for the inactivation of NF-κB activation by ROS (166, 235). The p50 protein was also subjected to oxidative modification of cysteine residues (235). The cysteine 62 of p50 is highly reduced in the nucleus, and oxidation of this cysteine residue impaired DNA binding with the κB sequence (200, 218). Many NF-κB–activating protein kinases, including protein kinase A (PKA) and MEKK-1, can also be oxidatively modified, possibly making them incapable of initiating NF-κB activation (235). It should be emphasized that these phenomena have been demonstrated *in vitro*, in a cell system or in purified recombinant protein. Furthermore, the tendency of oxidative stress to activate or inhibit NF-κB depends on the cell type, ROS-generating system, and protocol used.

Although contradiction exists, ROS have been shown to switch on, rather than inhibit, NF-κB activation during AP episodes. Actually, NF-κB has been implicated in the pathogenesis of AP in both experimental and clinical settings (39, 126, 247, 248, 265, 314). The NF-κB activation took place, not only in peripheral cells, but also within pancreatic acinar cells (265, 314). Mice with conditional overexpression of IKK exhibited an AP-like inflammatory response (4). Meanwhile, knocking out NF-κB could attenuate histologic damage and TNF-α expression in caerulein-induced AP (7). Ample *in vitro and in vivo* findings support the hypothesis that ROS *promote* NF-κB activation in early pancreatitis. For example, AP induction by caerulein, taurocholate, and biliopancreatic duct ligation triggered NF-κB activation, which could be abolished by pretreatment with NAC (126, 248, 314). These findings are consistent with the *in vitro* investigations showing inhibitory effects of NAC on nuclear κB binding after hyperstimulation of pancreatic acinar cells and isolated pancreatic acini (24, 346). Similarly, PMA-primed neutrophils were shown to promote NF-κB activation in pancreatic acinar cells, and this activation could be antagonized by NAC or SOD (157). Exogenous H_2O_2 also induced NF-κB activation in acinar cells, isolated acini, and pancreatic lobules (5, 88, 274), demonstrating a crucial role for ROS in NF-κB activation. Moreover, prolonged H_2O_2 treatment enhanced transcription of p105 (also known as NF-κB1) in acinar cells, implying that chronic oxidative stress increases NF-κB activity *via de novo* synthesis of the transcription factor (327).

Tyrosine phosphorylation on IκB may represent another mechanism of ROS-induced NF-κB activation (5). H_2O_2 treatment induced phosphorylation of IκB at Tyr42 residue, possibly through the actions of the tyrosine protein kinase $p56^{lck}$ and ZAP-70 (182). The tyrosine phosphorylation of IκB may trigger dissociation from the NF-κB homo/heterodimer and subsequent NF-κB activation (145). Oxidative stress may also promote phosphorylation of ataxia/telangiectasia–mutated (ATM) protein and NF-κB essential modulator (NEMO) modification, which in turn activate NF-κB *via* IKK (335). However, it remains to be determined whether ATM/ NEMO plays a role in ROS-induced NF-κB activation in AP pathogenesis. Figure 8 is a summary illustrating the redox regulation of NF-κB activation.

NF-κB does not appear to play a role in CP pathogenesis. Ethanol-sensitized PSCs exhibited oxidative stress but no evidence of activated NF-κB (196, 197). Cytokine-induced matrix metalloproteinase-1 secretion in periacinar myofi-

broblasts (*i.e.*, activated PSCs) was not altered by NF-κB inhibition, indicating that the fibrogenic process is not associated with NF-κB activation (301). Electrophoretic mobility-shift assay and luciferase assay experiments have demonstrated that exogenous addition of H_2O_2 or 4-hydroxy-2,3-nonenal did not cause NF-κB activation (155, 156). However, PSCs were able to respond to acute-phase cytokines and activate NF-κB, implying that PSCs participate in the development of acute inflammatory responses (279).

C. Apoptotic pathways

Apoptosis is characterized by distinct cellular morphology, membrane integrity, and selective activation of protease. Unlike necrosis, it is energy dissipating and involves highly coordinated cellular processes triggered by intrinsic or extrinsic factors. Intrinsic factors include mitochondria-targeting substances activated by environmental stress, ultraviolet radiation, and oxidative stress. Meanwhile, extrinsic factors initiate apoptosis *via* activation of cell-surface receptors such as TNFR and Fas (257). These two pathways both initiate programmed cell death through mechanisms involving alterations of mitochondria. The central executers of the apoptotic pathways are Bcl-2 family proteins and caspases (cysteinyl aspartic acid–specific proteases). The Bcl-2 family includes proapoptotic (*e.g.*, Bax, Bak, Bcl-X_s) and antiapoptotic (*e.g.*, Bcl-2, Bcl-X_L) members that coexist harmoniously at rest (257). In the presence of a death signal, the carboxyl terminal of Bax inserts into the mitochondrial membrane and triggers oligomerization with Bak (119). This interaction alters mitochondrial membrane permeability (MMP), releasing cytochrome *c* to cytoplasm (160, 258). Antiapoptotic Bcl-2 and Bcl-X_L inhibit Bax activation by restricting its mitochondrial translocation and hindering its accessibility to proapoptotic signals, respectively (46, 94). On exposure to cytosol, cytochrome *c* interacts with apoptotic protease-activating factor-1 to form an apoptosome, which in turn activates procaspases that execute cell-death processes (355). Caspases induce cell death by inhibiting DNA replication, inactivating DNA-repairing enzymes including poly(ADP-ribose) polymerases and topoisomerase (34, 261), activating caspase-dependent DNase (180), and destroying nuclear and DNA structures (187). The cells responsive to the death signal in mitochondria-mediated apoptosis are known as type II cells (267). It should be emphasized that cytochrome *c* release is *not* the major upstream activator of the caspase pathway. Actually, type I cells elicit the death signal *via* mitochondria-independent pathway. Extrinsic death signals interact with their corresponding receptors to activate caspases in type I cells, which is independent of cytochrome *c* release. Caspase 8, for instance, can be activated directly by Fas or TNFR *via* recruitment of adaptor proteins such as TNFR-associated death domain (TRADD) and Fas-associated death-domain protein (FADD) (211).

As mentioned earlier, oxidative stress is an intrinsic factor that can initiate apoptosis *via* direct interactions with mitochondria. It has been reported that H_2O_2 depolarized the mitochondrial membrane (loss of ψ_m), leading to cytochrome *c* release, caspase-3 activation, and DNA fragmentation (54, 266). H_2O_2 -induced apoptosis appears to rely on promotion of mitochondrial translocation of the Bax oligomer (257). Note that cytochrome *c* release disrupts the electron-transport chain, resulting in leakage of ROS into the cytoplasm (44, 348). This ROS leakage produces an additional "oxidative burden" on the cells, resulting in further disruption of the mitochondrial membrane. Persistence of this vicious cycle triggers apoptosis.

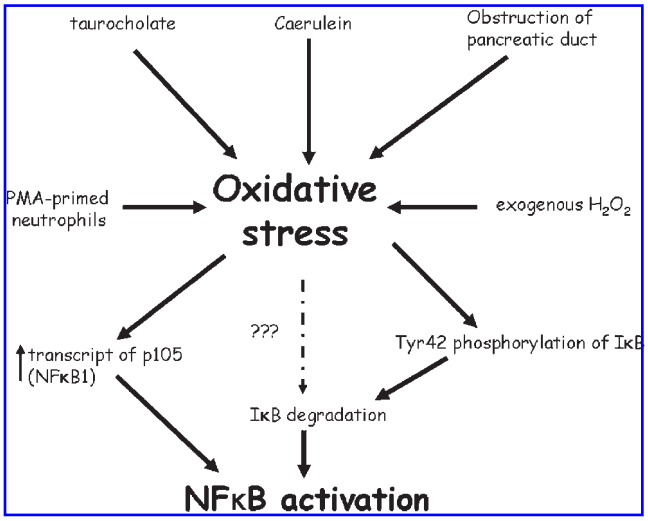

FIG. 8. Nuclear factor kappa B (NF-κB) activation by ROS in acute pancreatic inflammation. Acute oxidative stress triggers tyrosine phosphorylation of IκB. Prolonged exposure of oxidants leads to elevated transcription of NF-κB1. Oxidative stress could also promote NF-κB activation by a yet-to-be defined mechanism.

On top of the ROS proapoptotic influence, RNS can also promote apoptosis. Exogenous treatment with NO or peroxynitrite leads to apoptotic cell death in many different cells. Prolonged NO exposure could elevate Bax, with concomitant suppression of Bcl-X_L and subsequent cytochrome *c* release (48, 49). However, some findings suggest that RNS can inhibit apoptosis. NO can block caspase activity by *S*-nitrosylation at cysteine in its catalytic site (202). NO can also enhance expression of the antiapoptotic gene *Bcl-2* and thus preserve the integrity of the mitochondrial membrane (112). Furthermore, NO can induce the expression of heat-shock protein 70, which inhibit apoptosome formation and cytochrome *c* release (158, 209, 260). Ultimately, the effects of RNS may vary by cell type and be concentration dependent. For example, a high NO concentration tends to induce apoptosis, whereas a physiologic dose inhibits it (48, 49).

It is noteworthy that overwhelming ROS/RNS generation would trigger not only apoptosis but also necrotic cell death. In case of uncontrolled oxidative stress, lipid peroxidation takes place extensively, resulting in cellular burst and rupture. The swelling of cell and organelle triggers spillage of intracellular contents into the extracellular milieu, thus leading to necrosis (130). A polyunsaturated fatty acid such as arachidonic acid would promote the giant DNA fragmentation and eventually induction of membrane-integrity loss. Extensive ROS/RNS generation could also induce a direct damage in the mitochondrial membrane, leading to depletion of ATP and eventually switching apoptosis to necrosis (130).

Although necrosis and apoptosis are very distinct cellular processes, they are not mutually exclusive and coexist un-

der certain conditions, such as acute pancreatic inflammation. Pancreatic acinar cells underwent both apoptosis and necrotic cell death in different experimental AP models, including caerulein, obstruction, and CDE diet-induced AP (91, 146). The mechanism of AP-provoked apoptosis has yet to be resolved, but emerging evidence has demonstrated the involvement of oxidative stress. Supramaximal stimulation of pancreatic acinar cells with caerulein upregulated the expression of apoptosis-inducing factor, caspase 3 activation, and DNA fragmentation, resulting in a decrease in cell number. These effects were abolished by the NADPH oxidase inhibitor DPI (345, 347). Investigations using direct ROS-generating agents provide further insight into the involvement of oxidative stress–induced apoptosis in AP pathogenesis. Exogenous addition of H_2O_2 disrupted mitochondrial membrane potential and induced apoptosis in pancreatic acinar cells (88, 233). Glucose oxidase–induced oxidative stress enhanced the Bax/Bcl-2 ratio (proapoptotic to antiapoptotic ratio) in acinar cells, leading to nuclear loss and DNA fragmentation (283). Menadione induced apoptosis in freshly isolated acinar cells, as evidenced by annexin expression and caspase activation (55). Figure 9 summarizes the regulatory pathways of glucose oxidase and menadione-mediated ROS-induced apoptosis. Moreover, melatonin, a potent antioxidant, prevented apoptotic cell death induced by ischemia/reperfusion-associated pancreatitis (213). Taken together, these findings indicate that ROS play an active role in AP-associated apoptosis. Recent studies have shown prominent acinar cell apoptosis in mild pancreatitis, but more necrosis in severe pancreatitis (23, 146). Apoptosis in acinar cells may protect against pancreatitis, possibly by inhibiting the inflammation associated with massive necrosis (25). Thus, it is possible that the apoptotic pathway may serve as a "negative-feedback" protection mechanism in ROS-mediated cellular injury. In other words, ROS are not necessarily detrimental, but rather may initiate apoptosis to restrict extensive necrotic damage during acute inflammation.

The exact mechanism by which oxidative stress regulates the apoptotic process is uncertain. However, recent studies reveal that pancreatitis-associated protein (PAP)-1 is a key factor in redox-regulated apoptosis during the pathogenesis of pancreatitis. Actually, PAP-1 is strongly upregulated in different experimental models of pancreatitis, including caerulein-induced AP (29), taurocholate-induced AP (151), and obstruction-induced AP (109). It is in line with the results from a clinical study indicating that the mRNA expression level of PAP-1 was enhanced in a patient with severe necrohemorrhagic pancreatitis (232). Patients with AP showed a significant elevation of serum PAP-1 levels, of which its expression levels correlate well with the severity of AP (151). Exogenous addition of H_2O_2 or menadione could strongly induce *PAP-1* gene expression in the pancreatic acinar cell line (233). Induction of oxidative stress triggers the binding of *PAP-1* promoter, illustrating that ROS could mediate its *de novo* synthesis (86). Overexpression of *PAP-1* could inhibit ROS-induced apoptosis, directly, indicating that *PAP-1* is involved in the ROS-induced apoptotic process during pancreatitis (233), and thus further confirming the role of *PAP* in redox regulation of apoptosis during an episode of pancreatitis.

Apoptosis in exocrine tissue has been described in DBTC-induced CP in rats (115), WBN/Kob rats (288, 289), and CP patients (19). It is hypothesized that injury may trigger apoptosis in acinar cells, which are then gradually replaced by a fibrotic matrix secreted from activated PSCs. A clear relation between oxidative stress and apoptosis in CP has yet to be established. However, a recent study implicated the antioxidant enzyme SOD in apoptosis in CP. WBN/Kob rats develop CP at 12 weeks, and SOD expression in pancreatic acinar cells was found to be upregulated during the onset and at a late stage of the disorder (288). Interestingly, the expression profile of SOD coincided with acinar cell apoptosis, implying that SOD may serve as a defensive mechanism against oxidative stress or proapoptotic stimulation (288). Another investigation revealed that tocotrienol, a vitamin E isomer, rich fraction (TRF) from palm oil triggers apoptosis in activated PSCs, as evidenced by DNA fragmentation, caspase activation, enhanced MMP, and cytochrome *c* release (254). The TRF-induced apoptotic pathway is apparently spe-

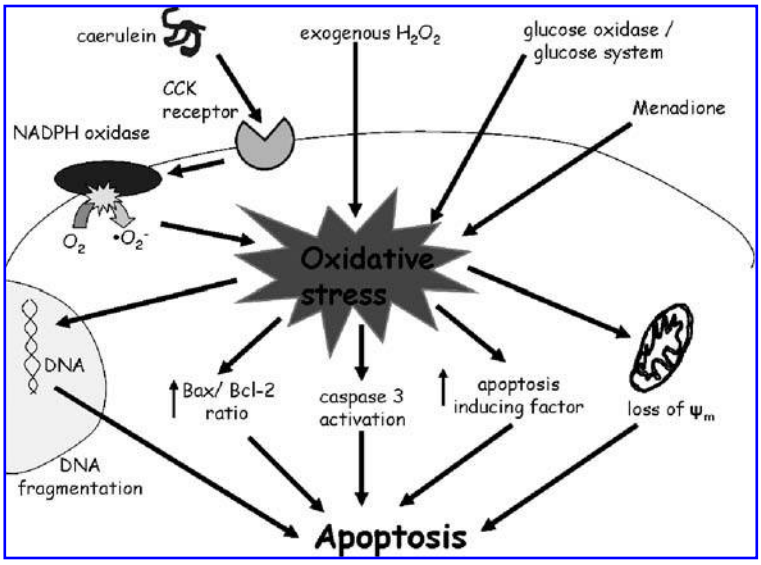

FIG. 9. Propensity of stimuli to induce ROS-dependent apoptotic responses. Caerulein, a ROS-generating system (such as glucose-oxidase and menadione), and ROS itself can provoke apoptosis in pancreatic acinar cells during pancreatitis.

cific to activated PSCs, as quiescent PSCs or acinar cells did not respond to the TRF (254). On the contrary, α-tocopherol did not trigger apoptosis, implying that the proapoptotic response in TRF-treated PSCs cannot be attributed to antioxidant effects (probably because of the structure-specific effect). Moreover, acinar cells in the CP pancreas would undergo apoptotic cell death *via* activation of the death signals Fas and FasL, independent of ROS generation (289). Activation and proliferation of PSCs are critical in CP development. Actually, spontaneous apoptosis took place in PSCs under certain circumstances, which might be important for termination of the wound-healing response after pancreas injury. Prolonged culture of PSCs leads to the elevated expression of TNF-α–related apoptosis-inducing ligand (TRAIL) and caspase 8 activity, implying involvement of the extrinsic apoptotic pathway in PSCs (162). It remains unresolved whether CP-provoked oxidative stress plays a role in PSC apoptosis. If so, ROS might serve as an important signal that fine-tunes the development of CP by striking a balance between apoptosis and PSC activation.

D. Cross-talk between MAPK, NF-κB, and apoptotic pathways may occur in pancreatic inflammation

As discussed earlier, it is well documented that activation of MAPKs, NF-κB, and apoptotic pathways depends on oxidative imbalance during pathogenesis of pancreatic inflammations. However, little is known about which pathway is preferentially switched on in response to increased levels of ROS in the pancreas. The choice of a specific redox-sensitive pathway (or dominant pathway) undertaken determines the fate of pancreatic cells and subsequently the resultant severity of glandular injury. Activation of ERK1/2 and NF-κB favors cell survival and an inflammatory response, whereas the apoptotic pathway leads to cell death and inhibits inflammation. Hence, cumulative evidence indicates that a sequential relation exists between the three redox-sensitive pathways mentioned. That is, they are interrelated, reinforcing or suppressing one another.

The MAPK JNK triggers the proapoptotic response in many cell types (257, 351). Activation of JNK has been shown to result in cleavage of Bid and induce caspase-8–independent apoptosis (76). JNK may also regulate antiapoptotic proteins such as Bcl-X_L and Bcl-2 (257). JNK could phosphorylate the E3 ubiquitin ligase ITCH, which in turn leads to ubiquitination and degradation of the caspase-8 inhibitor FLIP (FADD-like IL-1â–converting enzyme-like inhibitory protein), resulting in activation of the apoptotic pathway (40). Similar to JNK, p38MAPK has been demonstrated to play a crucial role in mediating apoptotic events under oxidative stress. p38MAPK is activated on exposure to proapoptotic agents in different kinds of cells, including lung cancer cells, prostate cancer cells, neuronal cells, vascular smooth muscle cells, and pancreatic acinar cells (62, 231). Interestingly, these apoptotic effects were inhibited on treatment of a specific p38MAPK inhibitor or dominant-negative mutant, indicating that p38MAPK directly regulates apoptosis (45, 236, 305). The underlying mechanism may rely on the ability of p38MAPK to phosphorylate the antiapoptotic protein Bcl-2. Incubation of p38MAPK with Bcl-2 resulted in cytochrome *c* release from isolated mitochondria (67). However, mutation of two crucial phosphorylation sites in Bcl-2 (Ser^{87} and Thr^{56}) blocked this cytochrome release, indicating that phosphorylation of Bcl-2 is crucial in p38MAPK-mediated cytochrome *c* release (69). It is believed that phosphorylation of Bcl-2 induces conformational change, leading to interference with its channel-formation properties and interaction with proteins in the mitochondrial membrane, resulting in change in MMP and apoptosis induction. The phosphorylation of Bcl-2 could also impair its heterodimerization with proapoptotic Bax, thus allowing more Bax to translocate into mitochondria (128). It has also been suggested that p38MAPK may phosphorylate the transcription factor MEF-2 and subsequently cause mitochondrial depolarization and apoptosis *via* the action of orphan nuclear-receptor TR3/Nurr77 (231).

On the contrary, ROS-sensitive NF-κB apparently inhibits the apoptotic pathway and promotes cell survival under environmental stress (351). Inhibition or deficiency of NF-κB enhanced apoptosis in different cell types (322, 323). NF-κB has been shown to negate the apoptotic pathway by regulating the expression of antiapoptotic genes including the caspase-3 inhibitors XIAP and FLIP (257). In addition, numerous studies have indicated that the antiapoptotic effects of NF-κB may be due to direct interaction with JNK (73, 297). Inhibitor of JNKK2 kinase, which suppresses JNK activation, was positively regulated by NF-κB (257). Expression of mutant IKKâ resulted in elevated JNK activation (43). Moreover, inhibition of IκBα degradation prolonged TNF-α–induced JNK activation and its subsequent apoptotic response (140).

Like NF-κB, ERK1/2 sometimes counteracts JNK, promoting cell survival. Recent studies in pancreatic acinar cells demonstrated that ERK1/2 can directly regulate NF-κB activity. ERK1/2 served as an upstream mediator by directly phosphorylating the IKK complex, which subsequently activated NF-κB (178). It has also been demonstrated that ERK is required for persistent activation of NF-κB in cultured rat vascular smooth muscle cells (141). Inhibition of ERK resulted in resistance of IL-1â–induced IκBβ degradation, implying that ERK is a critical player in the temporal regulation of NF-κB activation (141). Conversely, proteolytic cleavage of NF-κB1 can liberate p105-associated MAPKKK, which can in turn activate ERK1/2 (20). Taken together, the three ROS-sensitive pathways can interact with each other and orchestrate the resultant cell fate under pathologic conditions. However, it should be emphasized that most of this complicated cross-talk has not been demonstrated in pancreatic inflammations. Further investigations are required to determine whether the pathways exist in pancreatic exocrine cells and play a role in the pathogenesis of pancreatic inflammations. Figure 10 summarizes the proposed cross-talk between MAPK, NF-κB, and apoptosis in pancreatic inflammation.

V. Therapeutic Approaches: Antioxidants, Enzyme Inhibitors, or Upstream Mediators?

A. Antioxidant therapy in pancreatic inflammations: translation from basic research to the clinic

Although pancreatic inflammations have been studied for decades, no specific treatments exist for these catastrophic disorders. Enteral as well as parenteral nutrition, antibiotic treatment, surgical removal of necrotic tissue, and other related surgical interventions such as cholecystectomy are

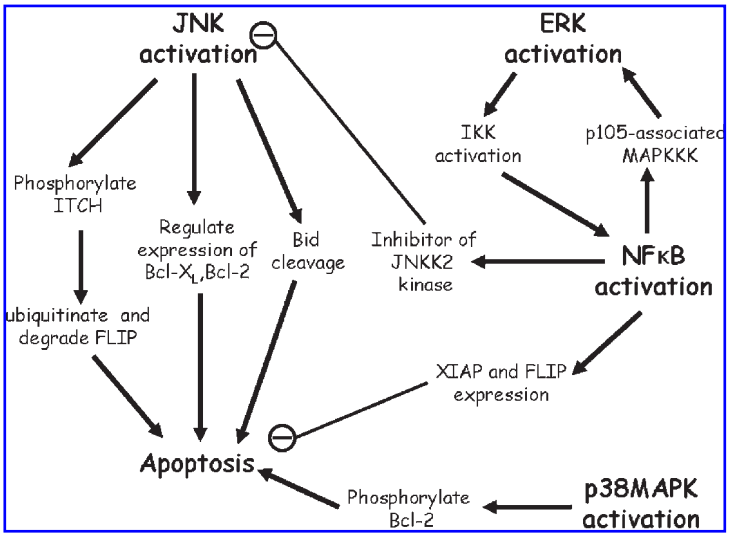

FIG. 10. Cross-talk between redox-sensitive signals. Jun N-terminal kinase (JNK) activation could lead to Bid cleavage and regulate the expression of Bcl-X_L and Bcl-2. JNK could phosphorylate the E3 ubiquitin ligase ITCH, leading to degradation of the caspase-8 inhibitor FLIP (FADD-like IL-1β converting enzyme–like inhibitory protein), resulting in activation of the apoptotic pathway. p38 Mitogen-activated protein kinase (p38MAPK) could phosphorylate Bcl-2, thus preventing its antiapoptotic ability, and lead to apoptosis. Conversely, nuclear factor kappa B (NF-κB) inhibits the apoptotic pathway by enhancement of transcription of caspase inhibitors XIAP and FLIP. NF-κB could also inhibit apoptosis *via* elevation of expression of inhibitor of JNKK2 kinase, resulting in JNK inactivation and ceasing apoptosis. Cleavage of NF-κB positively regulates extracellular regulated kinase (ERK), whereas ERK itself could directly activate NF-κB in an IKK-dependent manner. Note that most of the complicated cross-talk has not been demonstrated in pancreatic exocrine cells or during pancreatitis.

prevalent treatments for AP (189, 206). CP patients are usually treated with pain management, pancreatic supplementation, and surgical removal of pseudocysts (206). However, these treatments are mostly passive in nature (enteral/parenteral nutrition), although some are invasive (surgical management). Most of the treatments target the symptoms and complications of the diseases (*e.g.*, sepsis, exocrine/endocrine insufficiency, pain) rather than the primary insults. Thus, clinicians seek new effective medications against pancreatitis and hope they will work synergistically with the prevalent therapy.

Antioxidant therapy is a promising potential candidate because its therapeutic efficacy has been demonstrated in experimental AP and CP. In a British study, patients with idiopathic chronic, alcoholic chronic, or idiopathic acute pancreatitis were treated with combined antioxidants, including organic selenium, â-carotene, vitamin C, vitamin E, and methionine. Recurrent attacks and pancreatic pain were significantly attenuated in the active-treatment group (310). Another study using similar combined antioxidant therapy reported a reduction in pancreatic pain in CP patients and fewer hospital admissions during the year with antioxidant treatment than they had had during the previous year (71). A similar investigation showed that combined antioxidant treatment was associated with significant improvements in quality of life in terms of pain, physical and social functioning, and general health perception in CP patients (159). Bolus intravenous administration of vitamin C (10 g/day) alleviated pancreatitis symptoms, enhanced the cure rate, reduced the complications, and decreased hospital stays in AP patients (84). A concomitant decrease in leukocyte counts and amylase in urine and blood was found in the high-dose vitamin C treatment group (10 g/day) compared with the low-dose treatment group (1 g/ day), implying that an adequate dose of vitamin C may attenuate the severity of clinical pancreatitis.

Nevertheless, controversy concerning the effectiveness of antioxidant treatment in clinical pancreatitis persists. In 2003, 46 consecutive AP patients were administrated a multiple antioxidant therapy (intravenous selenium, NAC, and ascorbic acid plus β-carotene and α-tocopherol, delivered *via* nasogastric tube). The combined antioxidant treatment restored plasma vitamin C and selenium levels, but did not reduce in-hospital mortality (318). One study indicated that treatment with enteral nutrition supplemented with antioxidants (β-carotene, vitamin C, vitamin E) did not exert any protective effects on pancreatic injury, as assessed by levels of plasma carboxypeptidase activation peptide and complications of pancreatitis (238). A double-blind, randomized, placebo-controlled trial revealed a suppression of oxidative stress markers with intravenous injection of combined antioxidants, but failed to demonstrate any protective effects on organ dysfunction, primary and secondary end point of organ dysfunction, and patient outcome (280). Furthermore, antioxidant therapy failed to prevent, prophylactically, the onset of pancreatitis in several studies. ERCP, a well-established approach in the diagnosis and treatment of biliary and pancreatic diseases, has been shown to induce mild AP (98). Prophylactic administration of a high dose of the potent antioxidant NAC (70 mg/kg 2 h before and 35 mg/kg at 4-h intervals for a total of 24 h) failed to attenuate post-ERCP pancreatitis (150). Similarly, another study revealed no protective effects of a high oral or intravenous dose of NAC in ERCP-induced pancreatitis, as measured by serum and urine amylase activity (204). A single dose of â-carotene, 12 h before the ERCP, also failed to protect patients from the onset of post-ERCP pancreatitis in a double-blind study; however, the treatment did prevent progression to severe AP (171).

It remains ambiguous whether an antioxidant alone or in combination with the prevalent treatment exerts therapeutic or prophylactic effects on patients with pancreatitis. In addition, the scale (number of subjects) in each investigation mentioned earlier is relatively small (N = 10–84). Larger-scale double-blind, randomized, placebo-controlled trials examining the efficacy of antioxidant therapy should be conducted in the clinical setting.

B. Potential therapy targeting upstream mediators

Antioxidant therapy aims at removal of generated ROS/RNS. However, a continuum of oxidative stress exists in the pathogenesis of pancreatitis. Scavenging the generated ROS/RNS should inhibit (or delay) oxidative damage and activation of proinflammatory pathways instantaneously, but this effect is not long-lasting. Hence, suppression of ROS/RNS generation by therapeutic strategies targeting inhibition of ROS/RNS-generating enzymes would be more effective against pancreatic inflammations in the long term. However, clinical trials examining ROS-generating enzyme inhibitors thus far have yielded marginal or unsatisfactory results (30, 150, 255).

Recent advances in basic research have revealed that stimulus or upstream signals regulating the ROS/RNS-generating enzymes might also play a role in the pathogenesis of pancreatic inflammations, thus opening a possible new therapeutic avenue against these diseases. Angiotensin II, a vasoactive and proinflammatory peptide, has been shown to be an upstream regulator of a number of ROS-generating enzymes, including xanthine oxidase (170), nitric oxide synthase (242, 304), and NADPH oxidase (37, 107, 234). Interestingly, our group and others have shown that angiotensin II is involved in development of both acute and chronic pancreatic inflammations.

Pancreatic expression of angiotensinogen, the precursor of angiotensin II, was upregulated in caerulein-induced and obstruction-induced AP (39, 308). Saralasin, a nonspecific antagonist for angiotensin II receptor, could inhibit the onset of AP, as indicated by improved pathohistology and plasma α-amylase (137). Furthermore, specific angiotensin II type 1 receptor (AT_1R) blocker, losartan, ameliorated pancreatic injury induced by hyperstimulation with caerulein and obstruction of the biliopancreatic duct (39, 309). Moreover, candesartan, another AT_1R antagonist, alone or in combination with angiotensin-converting enzyme inhibitor, exerted beneficial effects against CP in WBN/Kob rats, as evidenced by attenuation in granulocyte infiltration and fibrosis (339, 340). Knocking out AT_1R resulted in an improved fibrogenic process, blunted PSC activation, and reduction of transforming growth factor-â expression in experimental CP animals (214). The AT_1R-blocker losartan induced cell apoptosis in a dose- and time-dependent manner in human PSCs, but had no proliferative effect in the same condition (179), indicating that AT_1-receptor antagonism can inhibit the onset of CP, at least in part, by inducing apoptosis in PSCs. Taken together, these findings indicate that this vasoactive peptide correlates well with the pathogenesis of pancreatic inflammations and that treatment with angiotensin II receptor blocker (ARB) is beneficial against AP and CP.

An immediate question remains to be addressed: does angiotensin II elicit its deleterious effects *via* generation of ROS? Actually, nonselective ARB inhibited glutathione depletion, oxidative modification of proteins, and lipid peroxidation in caerulein-treated rat pancreas (137). AT_1R blockade attenuated pancreatic NADPH oxidase in caerulein-stimulated animals (309). Prophylactic administration of losartan also suppressed NADPH oxidase p67 and p22 expression in obstruction-induced AP animals, with the concomitance of reversal effects on GSH depletion and oxidative stress (39). These findings are in good agreement with the *in vitro* studies. Exogenous administration of angiotensin II induced ROS generation in isolated PSCs and exocrine pancreatic acinar cells (198 and our unpublished data). These findings strongly support the view that ROS is involved in angiotensin II–induced proinflammatory actions in the pathogenesis of pancreatitis. Inhibition of angiotensin II activity may provide an alternative for therapy targeting oxidative stress during episodes of pancreatic inflammation, but this approach has yet to be proven in a clinical setting. Figure 11 summarizes the proposed mechanism(s) of angiotensin II involved in the ROS generation in pancreatic inflammations.

VI. Concluding Remarks

In summary, oxidative stress plays a critical role in both acute and chronic pancreatic inflammation. Generation of ROS/RNS from numerous enzymatic systems, including xanthine oxidase, nitric oxide synthase, CYP2E1, and NADPH oxidase, not only directly oxidizes a wide range of biomolecules, but also switches on several stress-activated

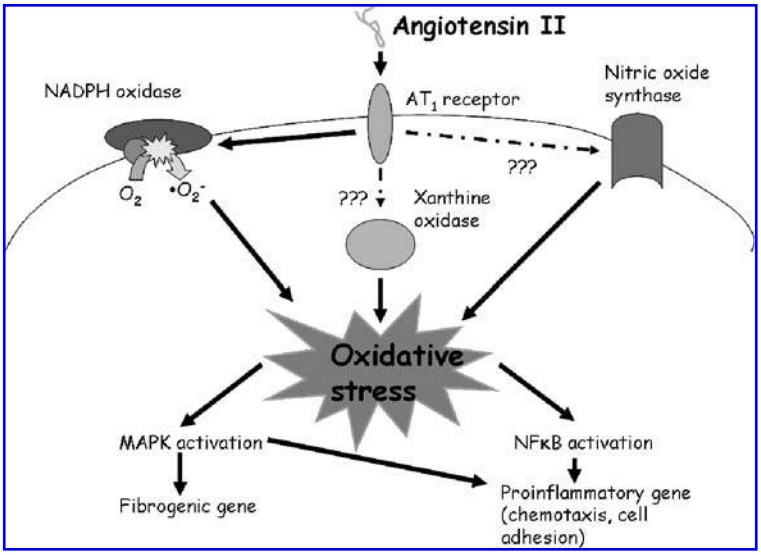

FIG. 11. Potential mechanism of regulation of redox-sensitive signals by angiotensin II during the pathogenesis of pancreatitis. Angiotensin II induces nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, or probably xanthine oxidase (XOD) and nitric oxide synthase (NOS), resulting in activation of MAPKs and NF-κB, thus leading to proinflammatory and profibrogenic responses.

pathways, including MAPKs and NF-κB, triggering proinflammatory actions. More important, oxidative stress is self-amplifying, because of recruitment of ROS-generating inflammatory cells to the pancreas. The recruited inflammatory cells exacerbate the oxidative burden on the glands by means of a respiratory burst, thus leading to further insult. In certain circumstances, ROS can trigger apoptotic responses, limiting extensive necrosis, and thus restricting a disastrous insult in the acute phase of inflammation.

Although oxidative damage and activation of proinflammatory/apoptotic pathways appear to take place simultaneously during AP and CP, the threshold ROS/RNS levels may differ. Activation of proinflammatory/ apoptotic pathways might require only a tiny amount of ROS/RNS, which could be achieved in a restricted cellular compartment (142, 176). Conversely, oxidative damage to biomolecules probably requires extensive production of ROS/RNS that overwhelm the defense mechanisms. The amount of ROS/RNS required to trigger stress-activated pathways is probably far less than that required for oxidative damage. In this context, it is tempting to speculate that a diminutive time lag may exist between the activation of proinflammatory pathways and the occurrence of oxidative damage in the course of pancreatic inflammations (*i.e.*, stress-induced pathways activation occurs slightly earlier than oxidative damage). Advances in ROS-detection techniques, precise molecular biology technology, and compatibility of *in vitro* and *in vivo* systems would definitely help resolve this issue. Understanding this oxidative stress–related pathophysiology would help clinicians to determine the most appropriate therapy for targeting certain mediators precisely during the course of pancreatitis, especially for preventing the onset of surgery-induced pancreatitis and post-ERCP pancreatitis (38, 98).

Therapeutic approaches targeting oxidative stress have been carried out in the clinical setting; however, an effective and promising regimen has yet to be achieved. The efficacy of antioxidant therapy is limited because of its relatively short-term effects on redox balance. Recent advances in basic research indicate that blockade of angiotensin II actions may relieve oxidative stress during AP and CP pathogenesis. However, some investigations reported that certain ARBs can induce mild AP themselves (92, 95). It should be noted that some of the patients mentioned earlier received a diuretic drug (hydrochlorothiazide) simultaneously, which might be the culprit in triggering spontaneous AP. Moreover, other confounding influences such as smoking habits, alcohol consumption, exposure to environmental toxins, and alterations in immunity should not be neglected. Although it is still unclear whether ARBs could alone trigger pancreatic inflammation, care should be taken concerning such potential side effects. A large-population, double-blind, randomized, and placebo-controlled clinical trial examining ARBs and AP/CP is a must to validate the effectiveness of ARBs in oxidative-stress management during pancreatitis.

Acknowledgments

We acknowledge the financial support from the Research Grants Council of Hong Kong awarded to P.S.L. (project no. CUHK 4364/04M and CUHK 4537/05M).

Abbreviations

AP, acute pancreatitis; AP-1, activator protein-1; ARB, angiotensin II–receptor blocker; ASK-1, apoptosis signal-regulating kinase 1; AT_1R, angiotensin II type 1 receptor; ATM, ataxia telangiectasia mutated; caspases, cysteinyl aspartic acid–specific protease; CAT, catalase; CCK, cholecystokinin; CDE, choline deficiency-ethionine; cNOS, constitutive NOS; CP, chronic pancreatitis; CYP, cytochrome P450; DAG, diacylglycerol; DBTC, dibutyltin dichloride; DPI, diphenylene iodium; eNOS, endothelial NOS; ERCP, endoscopic retrograde cholangiopancreatography; ERK, extracellular-regulated kinase; ESR, electron spin resonance; FAD, flavin adenine dinucleotide; FADD, Fas-associated death domain; FLIP, FADD-like IL-1â–converting enzyme-like inhibitory protein; GCL, glutamate cysteine ligase; GGT, γ-glutamyl transpeptidase; GPx, glutathione peroxidase; GS, glutathione synthase; GSH, reduced glutathione; GSSG, oxidized GSH; GST, glutathione *S*-transferase; H_2O_2, hydrogen peroxide; HOCl, hypochlorous acid; ICAM, intercellular adhesion molecules; IKK, IκB kinase; IL, interleukin; iNOS, inducible NOS; IP_3, inositol triphosphate; IκB, inhibitor of NF-κB; JNK, jun N-terminal kinase; MAPKs, mitogen-activated protein kinases; MAPKK, mitogen-activated protein kinase kinase; MAPKKK, mitogen-activated protein kinase kinase; MDA, malondialdehyde; MEK, mitogen ERK kinase; MMP, mitochondrial membrane permeability; MT, metallothionein; NAC, *N*-acetylcysteine; NADPH, nicotinamide adenine dinucleotide phosphate; NEMO, NF-κB–essential modulator; NF-κB, nuclear factor kappa B; NLS, nuclear localization sequence; nNOS, neuronal NOS; NO, nitric oxide; NOS, nitric oxide synthase; NOXA, Nox activator; NOXO, Nox organizer; PDGF, platelet-derived growth factor; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PMA, phorbol myristate acetate; PSCs, pancreatic stellate cells; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; Trx, thioredoxin; TNBS, trinitrobenzene sulfonic acid; TNF-α, tumor necrosis factor alpha; TNFR, tumor necrosis factor alpha receptor; TRADD, TNFR-associated death domain; TRAIL, TNF-α–related apoptosis-inducing ligand; TRF, tocotrienol-rich fraction; WBN/Kob, Wistar Bonn/Kobori; XDH, xanthine dehydrogenase; XOD, xanthine oxidase; XOR, xanthine oxidoreductase; $\cdot NO_2^-$, nitrogen dioxide radical; ·O, singlet oxygen; $\cdot O_2^-$, superoxide; $\cdot OH^-$, hydroxyl free radical.

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Address reprint requests to:
Po Sing Leung
Department of Physiology, Faculty of Medicine
The Chinese University of Hong Kong
Shatin, New Territorries, Hong Kong
China

E-mail: psleung@cuhk.edu.hk

Date of first submission to ARS Central, May 5, 2008; date of final revised submission, July 9, 2008; date of acceptance, July 9, 2008.

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