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REVIEW

Nicotinamide adenine dinucleotide phosphate oxidase in pancreatic diseases: Mechanisms and future perspectives

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Abstract

Pancreatitis and pancreatic cancer (PC) stand as the most worrisome ailments affecting the pancreas. Researchers have dedicated efforts to unraveling the mechanisms underlying these diseases, yet their true nature continues to elude their grasp. Within this realm, oxidative stress is often believed to play a causal and contributory role in the development of pancreatitis and PC. Excessive accumulation of reactive oxygen species (ROS) can cause oxidative stress, and the key enzyme responsible for inducing ROS production in cells is nicotinamide adenine dinucleotide phosphate hydrogen oxides (NOX). NOX contribute to pancreatic fibrosis and inflammation by generating ROS that injure acinar cells, activate pancreatic stellate cells, and mediate macrophage polarization. Excessive ROS production occurs during malignant transformation and pancreatic carcinogenesis, creating an oxidative microenvironment that can cause abnormal apoptosis, epithelial to mesenchymal transition and genomic instability. Therefore, understanding the role of NOX in pancreatic diseases contributes to a more in-depth exploration of the exact pathogenesis of these diseases. In this review, we aim to summarize the potential roles of NOX and its mechanism in pancreatic disorders, aiming to provide novel insights into understanding the mechanisms underlying these diseases.

Key Words: Nicotinamide adenine dinucleotide phosphate hydrogen oxides; Pancreatitis; Pancreatic cancer; Reactive oxygen species; Mechanism

Core Tip: Nicotinamide adenine dinucleotide phosphate hydrogen oxides (NOX) plays a significant role in the development of pancreatitis and pancreatic cancer (PC) by contributing to pancreatic fibrosis and inflammation. It achieves this by generating reactive oxygen species, which damage acinar cells, activate pancreatic stellate cells, and induce macrophage polarization. Moreover, NOX promotes PC progression by interfering with abnormal cell apoptosis, initiating the epithelial to mesenchymal transition processes, and leading to cell genomic instability. A thorough understanding of NOX's involvement in pancreatic diseases is crucial for comprehending the underlying mechanisms of pancreatitis and PC. This review provides a summary of NOX's potential roles and mechanisms in pancreatic disorders, emphasizing areas that require further investigation.

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INTRODUCTION

Incidence of diseases of the pancreas, including acute and chronic pancreatitis (CP) and pancreatic cancer (PC) are rising globally[1-3]. Acute pancreatitis (AP) is the leading cause for gastrointestinal-disease related hospital admissions and is associated with significant morbidity, mortality and socioeconomic burden[4]. CP causes persistent pain, as well as exocrine and endocrine pancreatic insufficiency. It also poses a risk factor for the development of PC[5]. PC is the malignancies with an incidence/mortality ratio of as high as 94% and a 5-year survival rate of about 9%[6]. Although researchers have been dedicated to exploring these diseases, the precise pathogenesis remains unclear. Research indicates that aberrant redox homeostasis occurs in both pancreatitis and PC. Reactive oxygen species (ROS) exert oxidative stress on the pancreatic cells, deregulating the redox homeostasis and promoting inflammation and tumorigenesis by initiating an aberrant induction of signaling networks[7,8].

Nicotinamide adenine dinucleotide phosphate hydrogen oxidases (NOX) is indeed a primary source of cellular ROS. During the development of PC and pancreatitis, the levels of ROS in pancreatic tissue are significantly increased, the source of these ROS is related to dysregulation of NOX in pancreatic cells[9,10]. The dysregulation of NOX plays an important role in pancreatitis and PC. Therefore, to clarify the regulatory mechanism of NOX in pancreatic cells will be more conducive to understanding the pathological process of pancreatitis and PC. In a word, we will present the existing evidence regarding the role and the mechanism of NOX in both pancreatitis and PC.

NOX IN AP

AP occurs as a result of the abnormal activation of pancreatic enzymes, which leads to the digestion of the pancreas itself and surrounding organs[11]. It is primarily characterized by localized inflammation of the pancreas and can even cause systemic organ dysfunction. Acinar cell injury leading to premature activation of pancreatic enzymes is considered the primary factor in the initiation of AP[12]. The subsequent inflammation triggered by the necrosis of acinar cells plays a crucial role in the progression of the disease[13]. Among the immune cells responding to the released chemotactic factors from injured acinar cells during pancreatitis, macrophages are among the earliest[14]. Therefore, both acinar cells and macrophages play significant roles in the development of AP. As the disease worsens, AP can even cause multiple organ dysfunction, known as severe AP, which has a high mortality rate and attracts significant clinical attention[15]. Therefore, this section focuses on exploring the regulatory role of NOX in acinar cells, macrophages, and other organ failures associated with AP.

NOX causes acinar cell damage

Pancreatic acinar cells are secretory cells that primarily synthesize, store and ultimately release digestive enzymes into the duodenum[16]. However, when exposed to harmful stimuli, acinar cells exhibit inflammatory characteristics by activating signaling transduction pathways associated with the expression of inflammatory mediators[17]. The injury or death of acinar cells can initiate inflammatory cascades, which is the main pathogenesis of AP.

Pancreatic acinar cells constitutively express NOX subunits p67phox and p47phox in the cytosol, as well as NOX1 and p22phox in the membrane, which could be activated by cerulein[18]. Upon activation, a complex of the cytosolic subunits translocates to the membrane and facilitates NOX-dependent formation of superoxide and other secondary ROS. In the early stage of AP, the NOX activity of acinar cells is significantly upregulated, leading to the activation of downstream nuclear factor kappa-B (NF-κB) pathway and stimulation of interleukin (IL)-6 expression[18]. In addition to inducing AP, NOX can also participate in a series of inflammatory cascade reactions to promote the progression of AP.

NOX hyperactivity disrupts mitochondrial membrane potential, leading to ATP depletion and subsequent injury in pancreatic acinar cells[19]. The excessive production of ROS by NOX induced zymogen activation, mitochondrial dysfunction and cytokine expression, which further injury to pancreatic acinar cells[20,21]. And the use of the NOX1

inhibitor could suppress these responses and alleviate inflammation in alcoholic AP model. To further investigate the mechanism of NOX action on acinar cells in AP, Ju *et al*[22] discovered that NOX mediated the activation of Janus kinase (JAK)2/signal transducer and activator of transcription and mitogen-activated protein kinases (MAPKs) (ERK, JNK, p38) to induce the expression of transforming growth factor (TGF)-β1 in cerulein-stimulated pancreatic acinar cells, thereby facilitating the progress of AP. Furthermore, NOX is believed to be involved in acinar cell death. NOX upregulates IL-6 and mediates ROS-induced apoptosis in pancreatic acinar cells stimulated with the cholecystokinin analogue cerulein [23]. It is known that cerulein induced the expression of apoptosis-inducing factor (AIF) in pancreatic acinar cell. During the process of cell apoptosis, AIF relocates from the mitochondria to the cytoplasm, and subsequently enters the cell nucleus, resulting in the aggregation and fragmentation of nuclear DNA, ultimately inducing apoptosis in pancreatic acinar cells[24,25]. Previous studies have indicated that NOX activation might be the upstream events of AIF expression, leading to cerulein-induced apoptosis in pancreatic acinar cells[26].

NOX is involved in the M1 polarization of macrophage in AP

Accumulating evidences shows that both the number and activation of macrophages play a crucial role in determining the severity of AP[27-29]. Damaged pancreatic acinar cells release cell contents including trypsin, zymogen granules, cytokines, cell-free DNA and other damage-related molecular patterns, which recruit and activate inflammatory macrophages[30]. Macrophages can be categorized into two main subtypes, M1 and M2, based on their stimuli and function *in vitro*[31]. M1 macrophages are responsible for producing cytokines and inflammatory mediators, which contribute to the amplification of local and systemic inflammation. As a result, they dominate the pro-inflammatory phase of AP. On the other hand, M2-like macrophages are prevalent during the process of pancreas repair/regeneration [32]. Therefore, M1 macrophages are dominated during the development of AP.

NOX-induced ROS production has a role in maintaining the polarization of M1 macrophage[33,34]. The involvement of NOX in mediating macrophage M1 polarization has been studied in various organs. For instance, NOX4 has been shown to induce macrophage M1 polarization following spinal cord injury[35]. In breast cancer, M1 macrophages exhibited significantly increased levels of ROS and mRNA expression of NOX2, NOX5, and CYBA (p22phox) compared to M2 macrophages[36]. Moreover, it is reported that NOX2 could mediate macrophage M1 polarization in traumatic brain injury through NF-κB pathway[37]. Regarding the pancreas, Han *et al*[38] discovered that NOX-mediated oxidative stress the polarization of M1 macrophages in the pancreas, thereby promoting the progression of AP *via* the activation of NF-κB and inflammasome pathways. Accordingly, NOX is capable of mediating the polarization of M1 polarization and contributing to the progression of AP. Further research is warranted to elucidate the underlying mechanisms by which NOX maintains M1 macrophages in the context of AP.

NOX is involved in AP-associated organ dysfunction

Despite the mild nature of AP in most patients, about 20%-30% experience a severe form that frequently results in dysfunction of one or multiple organs, requiring intensive care[39]. Moreover, recent studies have uncovered a link between NOX and organ dysfunction in AP, in addition to its role in inducing local inflammation in the pancreas.

Carrascal *et al*[40] showed that circulating exosomes involved in the progression of inflammation from the pancreas to distant organs leading to organ dysfunction in AP. Interestingly, these exosomes' impact is dependent on NOX. Specifically, NOX is activated by proteins carried by exosomes, resulting in the production of free radicals and the promotion of an inflammatory response. Furthermore, NOX inhibitor pretreatment blocked the expression of IL-1β and tumour necrosis factor alpha mRNAs induced by exosomes obtained from patients with severe AP.

NOX is widely distributed and is participated in various pathological processes of different organs. Yang *et al*[41] showed that NOX regulate the activity of downstream p-AKT and glycogen synthase kinase (GSK)-3β by regulating ROS levels, thereby affecting the release of inflammatory mediators and regulating AP-related kidney injury. Jin *et al*[42] found NOX2 and NOX4 were upregulated in lung tissue of severe AP and NOX-mediated ROS could activate NACHT, LRR, and PYD domains-containing protein 3 inflammasome and NF-κB signaling and facilitate AP-associated lung injury. Wen *et al*[43] showed that hyperactivity of NOX underlies myocardial injury in severe AP by promoting ROS generation with increased oxidative stress and cardiomyocyte apoptosis *via* activating the MAPK pathway. Moreover, NOX is involved in the process of intestinal barrier damage in sever AP, which was associated with an increase in the systemic concentration of cytokines, oxidative stress and activated NF-κB and p38 MAPK expression[44].

In summary, NOX promotes the development of AP by causing acinar cell damage and inducing macrophage polarization into M1 type (Figure 1). Moreover, NOX also be involved in distant organ dysfunction in AP. While the specific mechanism of NOX act on acinar cell and macrophages needs further study, which help us to further elucidate the pathogenesis of AP.

NOX IN CP

CP manifests from a long-term inflammation, which results in a significant replacement of the parenchyma by extracellular matrix (ECM)-rich connective tissue (*i.e.*, fibrosis) and permanent organ damage[45]. Notably, fibrosis is the hallmark histological feature of CP[46]. Fibrosis is a post-injury repair response in which tissue homeostasis is disrupted and fibrotic changes occur under the action of specific cytokines and a pro-oxidative environment, eventually leading to organ dysfunction[47]. The current clinical treatment of CP is limited to symptomatic treatment and management of complications. Thus, a better understanding of the mechanism underlying the pathogenesis of CP is necessary in order to develop more effective therapeutic options to attenuate the progression of the disease. Clarifying the mechanism of

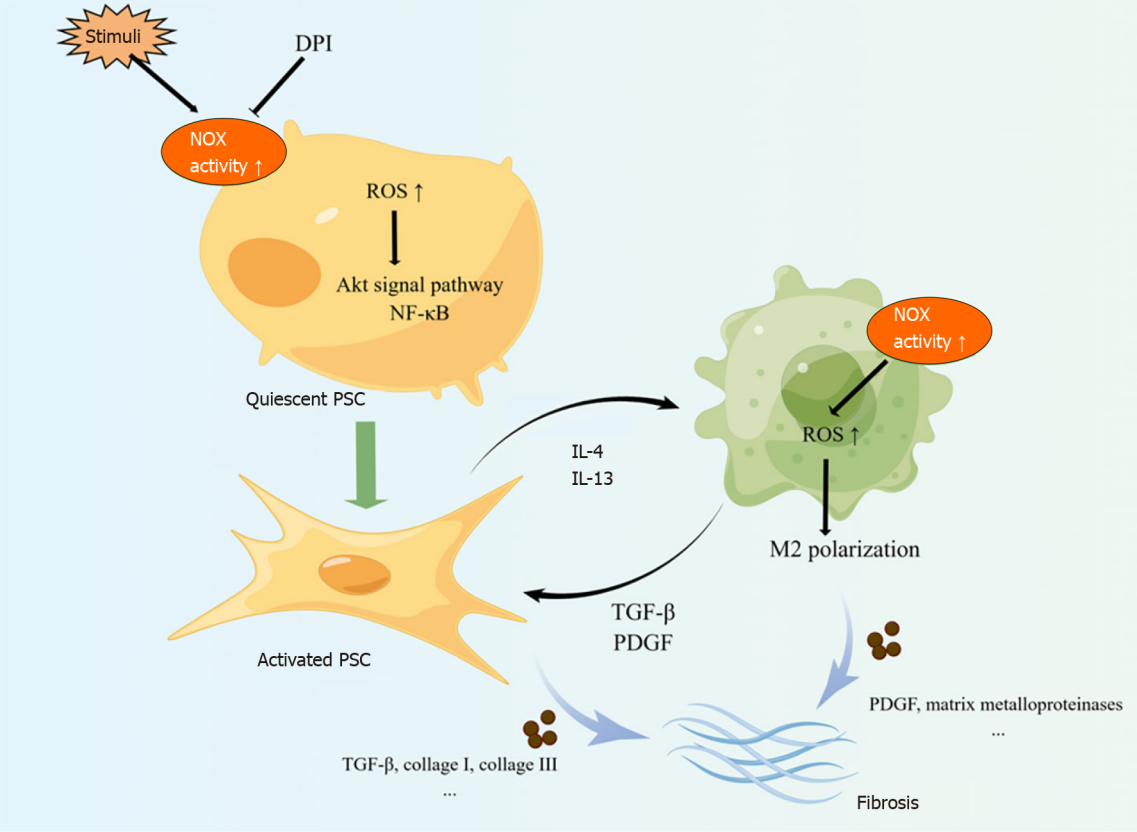

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Figure 1 The scheme of the potential roles of nicotinamide adenine dinucleotide phosphate hydrogen oxides in pancreatic acinar cells and macrophages, which leading the development of acute pancreatitis. NOX: Nicotinamide adenine dinucleotide phosphate hydrogen oxides; AIF: Apoptosis inducing factor; ROS: Reactive oxygen species; NF-κB: Nuclear factor kappa-B; IL: Interleukin; TGF: Transforming growth factor; PDGF: Platelet-derived growth factor; PSC: Pancreatic stellate cell; DPI: Diphenylene iodium.

pancreatic fibrosis in CP and exploring therapeutic methods to delay or reverse pancreatic fibrosis are the basis to finding effective treatment for CP.

NOX induce pancreatic stellate cell activation

The activation of pancreatic stellate cells (PSCs) is the core to CP pathological processes. PSCs exist in two forms, the quiescent state and the activated state. Under physiological conditions, PSCs are in a quiescent state and secrete some growth-promoting cytokines to maintain the basic structure and function of the pancreas. When pancreas tissue damaged or in response to stimulation, PSCs are activated and transformed from their quiescent into myofibroblast-like phenotype, characterized by the disappearance of intracellular lipid droplets and the expression of α-smooth muscle actin (α-SMA) and ECM components such as type I collagen, type III collagen, and fibronectin[48]. PSCs express key components of NOX, p22phox, p47phox, NOX1, gp91phox/NOX2 and NOX4[49]; and NOX is recognized to be involved in PSCs activation.

Masamune *et al*[49] found that upregulating NOX activity in PSCs could induce PSCs activation and proliferation. Furthermore, diphenylene iodium (DPI) abolished ROS production in isolated PSCs and inhibited transformation of freshly isolated PSCs to a myofibroblast-like phenotype. NOX-mediated ROS in PSCs could accelerate fibrosis progression in CP. Xia *et al*[50] found Nox1-derived ROS in PSCs mediate the fibrotic process of CP by activating the downstream redox-sensitive signaling pathways AKT and NF-κB, up-regulating metalloproteases (MMP)-9 and Twist, and producing α-SMA and collagen I and III. However, limited research has been focused on exploring the mechanism of NOX promoting PSCs activation. More studies are needed in this topic.

NOX is involved in the M2 polarization of macrophage in CP

In the pancreatic tissue of CP, M2 macrophages are the dominant type of macrophages[51]. These M2 macrophages secret cytokines including TGF-β, platelet-derived growth factor, IL-10 and various matrix metalloproteinases, which play a role in the progression of fibrosis and chronic inflammation in CP[52]. Furthermore, M2 macrophages can activate PSCs, and the cross-talk between activated PSCs and M2 macrophages initiates and sustains the fibrotic process in CP[53]. NOX-mediated ROS can act as second messengers playing an extremely important role in the regulation of macrophage polarization[54-56]. Previous studies showed NOX was involved in M2 polarization of macrophages. Reduced NOX2 expression improves the wound healing functions of M2 macrophages in degrading disulphide protein[57]. Furthermore, the interaction between M2 macrophages with apoptotic bodies triggers instability of NOX2 mRNAs through binding

blockade of RNA-binding protein SYNCRIP to NOX2 3′ untranslated region. And this further defect the ROS production and leads to M2 macrophage polarization[58]. Mongue *et al*[59] found cardiomyocyte NOX4 modulated macrophage polarization toward M2 phenotype in myocardial injury mice model. Intervention of antioxidant butylated hydroxy anisole by inhibiting NOX-mediated O^{2-} production blocked monocyte differentiation to M2 type[60]. These results suggest that NOX may play a role in regulating M2 polarization of macrophages in the pancreas of CP. Further studies are needed to investigate this relationship.

In summary, NOX is involved in the progression of CP (Figure 2). NOX promotes the activation of PSC in the fibrotic process of CP. Moreover, the application of NOX inhibitors *in vitro* effectively inhibits the activation of PSC. Additionally, several studies have shown that NOX induces M2 polarization of macrophages in other organs. It has been established that M2 macrophages promote the occurrence and development of CP. Therefore, further research is needed to investigate whether NOX also plays a regulatory role in the M2 polarization of macrophages in CP.

NOX IN PC

The global burden of PC has increased dramatically over the past few decades and is expected to continue to represent a leading cause of cancer-related mortality[61]. Although efforts are being made to explore the pathological process of PC, its specific etiology remains unclear. Furthermore, PC shows resistance to chemotherapy, and there is currently no effective clinical treatment available[62]. Therefore, elucidating the underlying mechanisms of PC and identifying potential therapeutic targets have been topics of great interest.

KRAS promotes NOX activity

The oncogenic KRAS mutation is the major event in PC; it confers permanent activation of the KRAS protein, which acts as a molecular drive common phenotypes that expose specific vulnerabilities[63]. KRAS transformed PC cells have increased NOX activity and superoxide levels, as compared to parental cells[64,65]. Moreover, several reports have indicated that in human PC, expression of NOX family members is increased when compared to non-transformed pancreatic tissue[66-68]. KRAS gene mutations can lead cells to depart from common phenotypes and expose specific vulnerabilities. One example of such a phenotype is abnormal redox homeostasis, with excessive accumulation of ROS playing a crucial role in causing this aberrant redox homeostasis[69]. The ROS generated by KRAS, primarily relies on NOX production. ROS exerts oxidative stress on cells, which disrupts redox homeostasis and promotes tumor formation. This occurs due to an abnormal activation of signaling networks that initiate tumorigenesis[70]. NOX is a multi-subunit enzyme which is activated through the small GTPase Rac1[71,72]. Consequently, in PC cell lines, presence of oncogenic KRAS links to increased Rac1 activity and superoxide production; and KRAS-induced ROS production can be inhibited by downregulation of p47phox, the cytosolic regulatory subunit of NOX[73,74]. Therefore, there is a close correlation between NOX and the development of PC caused by the oncogenic KRAS gene mutation.

NOX regulates PC cells from apoptosis

One reason why PC is highly aggressive and unresponsive to treatments is its resistance to apoptosis. ROS induce apoptosis indirectly through damage to DNA, proteins and lipids, or more directly through the activation of pro-apoptotic signaling cascades such as SAPK/JNK, ERK1/2, and p38 upon the induction of the MAPK pathways[75]. However, at high concentrations, ROS, especially as H_2O_2, can inhibit caspases, resulting in irreversible damage to cell components and leading to necrosis[76]. Conversely, in certain cases, NOX-produced ROS can trigger an anti-apoptotic effect by activating NF-κB or Akt/ASK1 transduction pathways[77].

Study have found that growth factors can induce the production of ROS by mediating NOX in PC cells, thus protecting the cells from apoptosis[72]. The oncosuppressor p53 gene plays a crucial role in the process of apoptosis in cancer cells. Research has found that NOX1 inhibits tumor cell apoptosis by regulating p53 deacetylation, suppressing its transcriptional activity, and activating the SIRT1 pathway[78]. Mochizuki *et al*[77] noted that ROS, generated by NOX4, transmits signals for cell survival through the AKT-ASK1 pathway. Furthermore, Lee *et al*[66] demonstrated that NOX4-generated ROS promote PC cell survival by inhibiting JAK2 dephosphorylation. Study has discovered that the application of a NOX inhibitor, Tyrosine, effectively inhibits cell proliferation of human and hamster PC cells by inhibiting the G1 phase of the cell cycle with cyclin D1 downregulation and inactivation of AKT-GSK3β and ERK1/2 signaling pathways[79]. Therefore, NOX could regulate PC cells from death.

NOX facilitates epithelial to mesenchymal transition in PC

The epithelial to mesenchymal transition (EMT) is a crucial mechanism by which tumor cells acquire motility and invasiveness[80]. More and more evidence indicates that EMT plays a vital role in the pathogenesis, invasion, metastasis, and drug resistance of PC[81,82]. It is worth noting that recently, it has been discovered that many important EMT regulators are sensitive to redox reactions, thereby being able to elucidate the molecular basis of EMT from a redox perspective[83].

NOX4, a subunit of NOX, has been implicated in the EMT process in PC[84]. NOX4 mRNA correlation with EMT gene expression such as collagen (COL1A2, COL3A1, COL5A2), MMP2, MMP9 and fibronectin (FN1)[85]. Additionally, studies have discovered that NOX4-derived ROS transmit TGF-β-triggered EMT signals through PTP1B in PC[86]. Furthermore, Witte *et al*[87] proposed that TGF-β1-induced EMT in PC cells is mediated through RAC1/NOX4/ROS/p38 MAPK cascade. More recent research has demonstrated that NOX4 caused inactivation of lysine demethylase 5A, leading to increased methylation modification of histone H3 and regulation of transcription of EMT-associated gene SNAIL1.

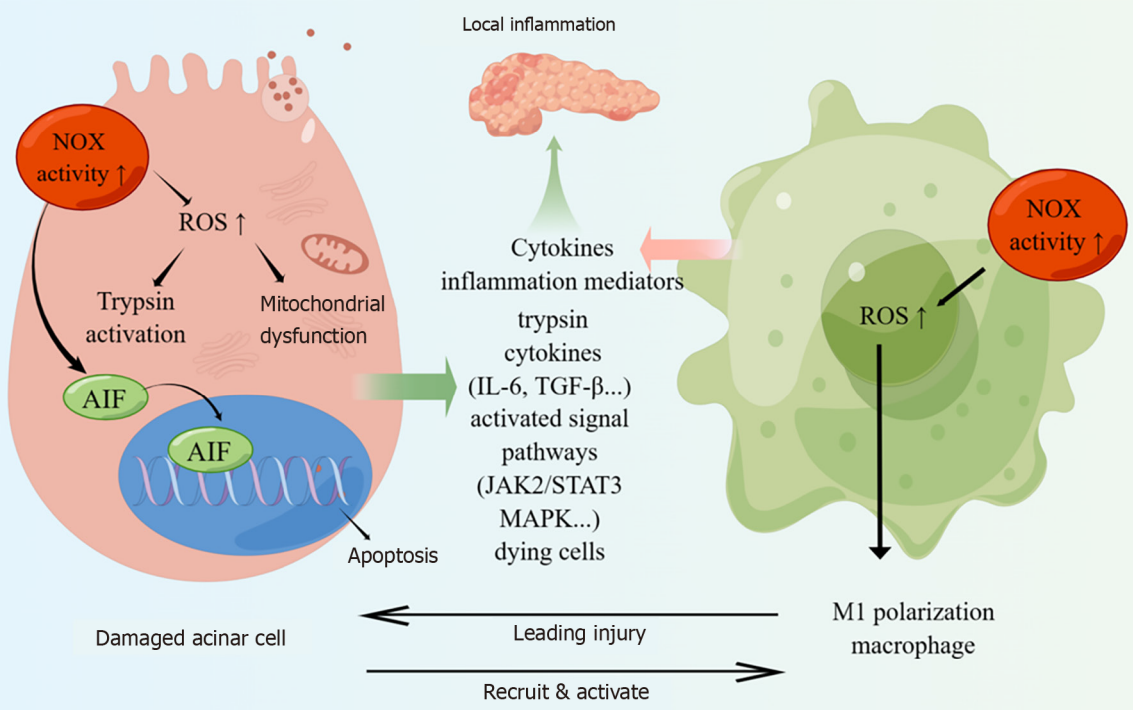

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Figure 2 The scheme of the potential roles of nicotinamide adenine dinucleotide phosphate hydrogen oxides in pancreatic stellate cells and macrophages, which facilitating pancreatic fibrosis of chronic pancreatitis. NOX: Nicotinamide adenine dinucleotide phosphate hydrogen oxides; AIF: Apoptosis inducing factor; ROS: Reactive oxygen species; TGF: Transforming growth; IL: Interleukin; JAK: Janus kinase; STAT: Signal transducer and activator of transcription; MAPK: Mitogen-activated protein kinase.

Moreover, the deficiency of NOX4 has been shown to suppress hypoxia-induced EMT in PC cells[88].

NOX and genomic instability

Extensive reviews have investigated the impact of ROS on DNA damage. Cell exposure to chronic oxidative stress has been reported to elicit genomic instability. Moreover, there is evidence indicating elevated ROS levels in genomically unstable clones[89,90]. Although the precise function of NOX in cellular transformation remains unclear, several studies provide suggestive evidence for its role. NOX4 induces the production of ROS, which damages mitochondrial DNA and leads to mitochondrial dysfunction[91]. In addition to its known involvement in chromosomal instability, NOX1, NOX2, NOX4, and DUOX have been associated with the regulation of p53 transcription factor activity[92-94]. Moreover, p53 mutation can "transform" NOX4 from a protective and good prognostic indicator into a harmful one by promoting programs favorable to cancer progression, including EMT, cell migration, cell adhesion, and angiogenesis[85].

There are studies suggest a relationship between NOX and oncogene in PC. Ogrunc *et al*[95] demonstrated that NOX4 promotes the transformation of PC cells expressing oncogenes by generating mitogenic ROS. This transformation leads to a compromised DNA damage response and oncogene-induced cellular senescence bypass. Ju *et al*[96] identified that NOX4 as a critical factor that facilitates the interaction between KRAS activation and p16 inactivation, promoting the occurrence of PC.

In summary, NOX plays a crucial role in the progression of PC. NOX could regulate PC cells from death, promote the EMT process, and induce genomic instability (Figure 3). Furthermore, NOX is also involved in the key oncogenic process of abnormal redox homeostasis induced by the oncogene KRAS in PC. It is worth noting that that among the subunits of NOX, NOX4 has been extensively studied in relation to PC and has been found to promote PC through various mechanisms. Therefore, NOX4 may represent a potential therapeutic target for PC, but further research is needed to confirm this.

PERSPECTIVE

As we known, NOX is a membrane-bound multi-component enzyme complex. Different isoforms of NOX are distributed in different tissues, cells, and subcellular structures, exerting specific functions under physiological and pathological conditions. Although studies have demonstrated the significant role of NOX in pancreatitis and PC, the exact subunit of NOX responsible for these conditions remains unclear. NOX subunits express differently in acinar cells, PSCs and macrophages. Identifying the specific subunits participate in promoting pancreatic disorders progression help us better understand the pathogenesis of pancreatitis and PC. Further studies are needed to explore this topic.

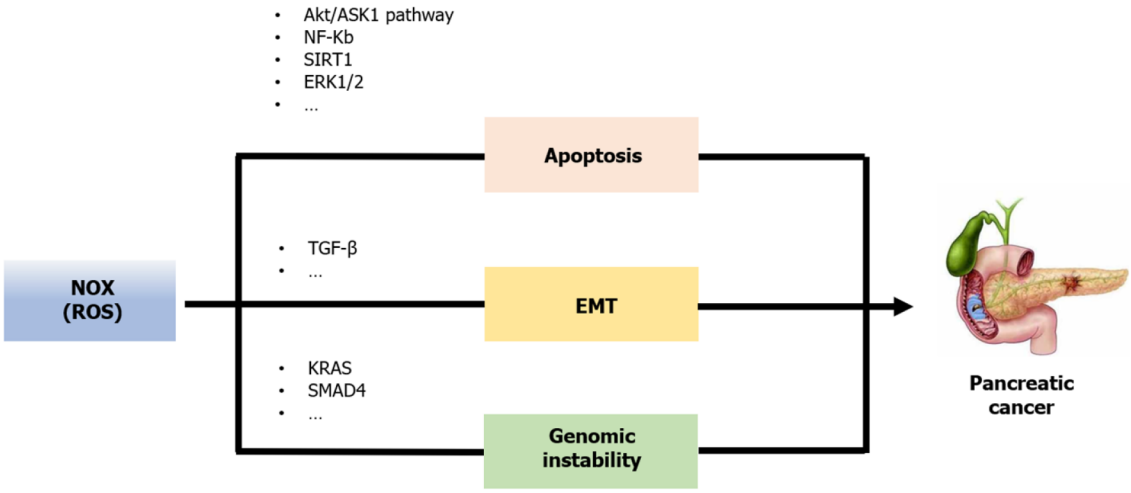

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Figure 3 The scheme of the potential roles of nicotinamide adenine dinucleotide phosphate hydrogen oxides in pancreatic cancer. ASK: Apoptosis signal regulating kinase; TGF: Transforming growth; SIRT: Silent information regulator; NF-κB: Nuclear factor kappa-B; ERK: Extracellular regulated protein kinases; SMAD: Drosophila mothers against decapentaplegic protein; NOX: Nicotinamide adenine dinucleotide phosphate hydrogen oxides; AIF: Apoptosis inducing factor; ROS: Reactive oxygen species; EMT: Epithelial to mesenchymal transition.

Although numerous studies were conducted on the investigation of pancreatitis and PC, no effective methods of prevention and treatment have been developed. Since NOX play an important role in both pancreatitis and PC, it may be considered as a therapeutic target. Study showed inhibition of NOX by DPI suppresses apoptosis of pancreatic acinar cells by reducing the expression of apoptosis-associated genes and caspase-3 activity[97]. NOX2 inhibitor, GSK2795039, caused about 50% reduction in the level of serum amylase activity in AP mice[98]. Apocynin is a specific inhibitor of NOX. Recent studies proved that apocynin could prevent AP and AP-associated organs injury[41-44]. NOX1 knockout alleviate pancreatic fibrosis in CP mice[50]. In terms of PC, drug resistance is the main reason why chemotherapy drugs cannot achieve ideal treatment effects. It is worth noting that NOX is associated with chemotherapy resistance[99-101]. Recent breakthroughs in cancer treatment consisting of new combinations of existing medications. It reminds us that chemotherapy with NOX inhibitor may achieve better therapeutic effects in PC. More studies are needed to verify the therapeutic effect of NOX in pancreatic diseases.

Though they are distinct diseases of pancreas that pancreatitis is benign and PC is malignant, numerous studies indicate that pancreatitis is linked to PC[102,103]. The exact nature of this association is not fully elaborated. Aberrant redox homeostasis is the common features in the pathogenesis of pancreatitis and PC, which could be mediated by NOX. Therefore, further study may focus on the role of NOX in the transformation of pancreatitis and PC which help us clarify the complex relationship between them.

CONCLUSION

In conclusion, NOX plays a role in the occurrence and development of pancreatitis by regulating various types of pancreatic cells, such as acinar cells, PSCs, and macrophages. Additionally, it promotes PC progression by participating in abnormal cell apoptosis, triggering the EMT processes, and causing cell genomic instability. Understanding the role of NOX in pancreatic diseases is crucial for a gaining a deeper understanding of the underlying mechanisms of pancreatitis and PC. Further research is needed to uncover the specific functions of different subtypes within the NOX family in these diseases. Moreover, the development of NOX-specific inhibitors is necessary to validate the feasibility of targeting NOX as a treatment approach for pancreatic diseases.

FOOTNOTES

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