Oxidative Stress and Cytokines in the Pathogenesis of Pancreatic Cancer

REVIEW

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Pancreatic cancer is one of the most aggressive, drug-resistant and lethal types of cancer with poor prognosis. Various factors including reactive oxygen species, cytokines, growth factors, and extracellular matrix proteins are reported to be involved in the development of pancreatic cancer. However, the pathogenesis of pancreatic cancer has not been completely elucidated. Oxidative stress has been shown to contribute to the development of pancreatic cancer. Evidences supporting the role of reactive oxygen species and cytokines as a risk for pancreatic cancer and the concept of antioxidant supplementation as a preventive approach for pancreatic cancer have been proposed. Here, we review the literature on oxidative stress, cytokine expression, inflammatory signaling, and natural antioxidant supplementation in relation to pancreatic cancer.
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Key Words: Oxidative stress, Cytokines, Pancreatic cancer

INTRODUCTION

Reactive oxygen species (ROS) and cytokines are considered to be important factors in the pathogenesis of pancreatic cancer.[1,2] As a source of ROS, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) is involved in pancreatic cancer development.[3] ROS activate signaling pathways mediated by p38 mitogen-activated protein kinases (MAPK), NF-κB, and janus kinase/signal transducer and activator of transcription (JAK/STAT),[4-8] which inhibits cancer cell apoptosis[9] and induces cytokine expression[8] and epithelial-mesenchymal transition (EMT).[10,11] High levels of fibronectin and laminin,[10,11] cytokines (interleukin-1β [IL-1β], IL-6, IL-8, and tumor necrosis factor-β [TNF-β],[12,13] and growth factors (insulin-like growth factor-1 [IGF-1] and transforming growth factor-β [TGF-β])[14] are observed in pancreatic cancer. Growth factors,[14] extracellular matrix (ECM) proteins,[10] and cytokines (interferon-γ [IFN-γ] and TNF-α)[14-17] have been shown to activate NOX in the pathogenesis of

pancreatic cancer development. Bioactive compounds such as curcumin, genistein, and resveratrol have antioxidant[18-20] and antitumor activities[21-29] against pancreatic cancer. We will briefly review the role of ROS and cytokines in the pathogenesis of pancreatic cancer. In addition, bioactive compounds that may prevent the development of pancreatic cancer will also be discussed.

REACTIVE OXYGEN SPECIES AND NICOTINAMIDE ADENINE DINUCLEOTIDE PHOSPHATE OXIDASE IN PANCREATIC CANCER

Since ROS and pro-inflammatory cytokines induce genetic instability, these factors may contribute to cancer development.[1,30] Activation of NOX releases high amounts of ROS, which may contribute to development of cancers. Pro-inflammatory cytokine IFN-γ induces the activation of a family of NOX, dual
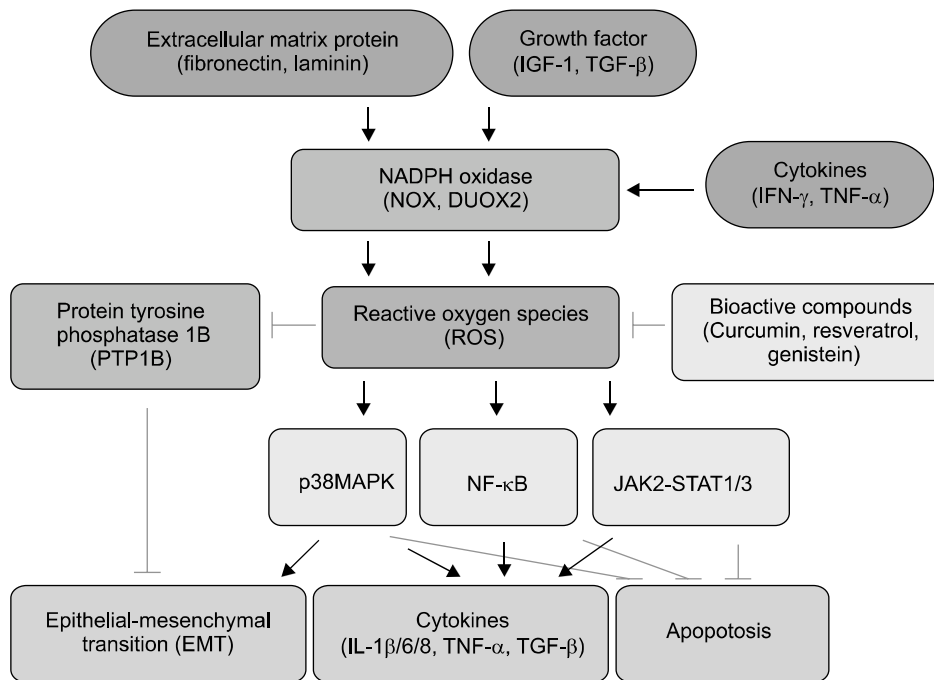
Figure. Crosstalk of reactive oxygen species (ROS) and cytokines for cancer-related signaling in pancreatic cancer. High levels of growth factors (insulin-like growth factor-1 [IGF-1], transforming growth factor-1 [TGF-β]), cytokines (interleukin-1β [IL-1β], IL-6, IL-8, and tumor necrosis factor-α [TNF-α]), and extracellular matrix (ECM) proteins (fibronectin and laminin) are observed in pancreatic cancer. Growth factors, cytokines (interferon-γ [IFN-γ], TNF-α) and ECM proteins activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) and dual oxidase 2 (DUOX2) and produce ROS in pancreatic cancer cells. ROS activate signaling pathways mediated by p38 mitogen-activated protein kinase (MAPK), NF-κB, and janus kinase/signal transducer and activator of transcription (JAK/STAT), which inhibits cancer cell apoptosis and induces cytokine expression and epithelial-mesenchymal transition (EMT). ROS inhibit protein tyrosine phoshatase 1B (PTP 1B) which suppress EMT. Therefore, ROS induce phosphorylation of p38 MAPK and EMT in the course of pancreatic cancer development. Bioactive compounds, having antioxidant activities, such as curcumin, resveratrol, and genistein, reduce ROS levels and thus, may inhibit ROS-mediated signaling of p38 MAPK, NF-κB, and JAK/STAT. The compounds inhibit EMT and cytokine expression and induce cancer cell apoptosis.

oxidase 2 (DUOX2), to produce ROS in human pancreatic cancer cells.[16]

K-ras mutation is identified in 95% of pancreatic cancer, implying its critical role in the pathogenesis of pancreatic cancer. Recent study showed that NOX2 protein is present in pancreatic tumor cells and tumorigenic cells expressing K-ras while NOX2 was absent in the non-tumorigenic pancreatic ductal epithelial cells.[31] In pancreatic cancer cells with K-ras, genetically silencing rac decreases ROS production and inhibits cell growth.[31] The study demonstrates that NOX is important for ROS production and growth inhibition in K-ras-expressing cells since rac is a component of the active form of NOX.

Growth factors and ECM proteins mediate growth of pancreatic cancer cells. Growth factors such as IGF-1 and IGF-2 stimulate NOX4 and produce ROS, which protect pancreatic cancer cells (MIA PaCa-2 and PANC-1) from apoptosis.[9,14] In addition, ROS induce activation of JAK2-STAT1/3 pathway, leading to suppression of apoptosis.[5] ECM proteins fibronectin and laminin also activate NOX in pancreatic cancer cells.[10] ROS

have shown to mediate epithelial-mesenchymal transition (EMT) in pathophysiological condition.[11] NOX4-generated ROS are involved in TGF-β-induced EMT in pancreatic cancer cells by activating p38 MAPK and inhibiting protein tyrosine phosphatase 1B (PTP1B).[11] Since PTP1B inhibits EMT, inhibition of PTP1B by ROS contribute EMT in pancreatic cancer development.

DUOX is one of the 7 members of the NOX family. The pro-inflammatory stimuli such as IFN-γ enhance the expression of DUOX2, leading to the production of substantial amounts of extracellular H_2O_2 in human pancreatic cancer BxPC-3 and AsPC-1 cells.[16] H_2O_2 induces the activation of STAT1 and NF-κB signaling pathways in pancreatic cancer cells.[16] Crosstalk of ROS and cytokines in cancer-related signaling is summarized in Figure. ROS are produced by NOX with stimulation of extracellular matrix (ECM) proteins,[10,11] growth factors,[14] and cytokines.[15-17] ROS activates p38 MAPK,[8] NF-κB,[4] and JAK2-STAT1/3,[5] which is believed to contribute to the carcinogenesis of pancreas since these signaling mediators induce ECM and expression of cytokines (IL-1β, IL-6, IL-8, TNF-α, and TGF-β)[12-15,32-34] as well as inhibit apoptosis of

cancer cells. Antioxidant compounds such as curcumin,[18] resveratrol,[19] and genistein[20] may inhibit ROS-mediated signaling and thus prevent the development of pancreatic cancer.

INFLAMMATORY CYTOKINES IN PANCREATIC CANCER

Cytokines promote pancreatic tumor cell progression by modulating tumor microenvironment as well as directly acting on cancer cells for growth, invasion and metastasis. Cytokines are produced from the leukocytes and stellate cells which are infiltrated into the damaged tissues. In the serum of pancreatic cancer patients, pro-inflammatory cytokines IL-6, IL-8, TGF-β, TNF-α, and IL-1β were increased compared to healthy controls.[2,12-15,32-34]

IL-6 induces the expression of vascular endothelial growth factor (VEGF) in pancreatic cancer cells and stimulates angiogenesis and tumor vascularization.[35] IL-6 induced phosphorylation of STAT3, which in turn, mitochondrial localization of pSTAT3 promotes pancreatic tumorigenesis by activating cell proliferation and inhibiting autophagy.[36]

IL-1β promotes pancreatic cancer cell invasiveness.[37] IL-1β induces constitutive activation of NF-κB and expression of cyclooxygenase-2 of pancreatic cancer cells and these cancer cells become chemoresistant.[38,39] Patients with both a high IL-6 level and a high IL-1β level exhibited shortened overall and progression-free survival, a reduction in the tumor control rate, and a high dose intensity of gemcitabine monotherapy compared with pancreatic cancer patients with low levels of both IL-6 and IL-1β.[40] Therefore, the serum levels of IL-6 and IL-1β predict the efficacy of gemcitabine monotherapy in patients with advanced pancreatic cancer.

IL-8 stimulates the expression of VEGF, neuropilin-2, and VEGF receptor, which are key molecules in angiogenesis. In addition, IL-8 increases the activation of MAPK pathway for cell growth, survival, and tumorigenesis.[12] It has been reported that IL-8 promotes tumor aggressiveness and invasiveness in pancreatic cancer.[32] In addition, IL-8 enhances the invasiveness by regulating matrix metalloproteinase-2 activity in human pancreatic cancer cells.[41] Both IL-8 and chemokine CXCL12 promote migration and invasion of pancreatic cancer cells.[32]

TNF-α promotes pancreatic cancer cell proliferation.[14] TNF-α induces the invasiveness of human pancreatic cancer cells and promotes tumor growth and metastasis in mice.[42] Treatment of anti-TNF-α suppresses tumor growth and metastasis.[42]

BIOACTIVE COMPOUNDS IN PANCREATIC CANCER

Treatments for pancreatic cancer patients are surgery, chemotherapy, radiation, and targeted therapy. However, low survival rate of patients with pancreatic cancer needs improved therapeutic and chemopreventive strategies. Since ROS mediate cancer-associated signaling in pancreatic cancer development as described above, supplementation of antioxidant compounds may prevent pancreatic cancer development. Curcumin, resveratrol, and genistein have antioxidant activities[18-20] and showed anti-cancer effects against pancreatic cancer in vitro and in vivo experiments.[21-29]

Curcumin (diferuloylmethane) inhibits the proliferation of pancreatic cancer cells and suppresses the activation of NF-κB.[43,44] Soluble curcumin analogue inhibits NF-κB-DNA binding activity and induces apoptotic cell death in pancreatic cancer cells.[45] Moreover, curcumin inhibits cell growth and induces apoptosis through down-regulating the Notch signaling pathway in pancreatic cancer BxPC-3 and PANC-1 cells.[24,25] Using orthotopic xenograft model of human pancreatic cancer Mia PaCa-2 cells, curcumin enhanced the antitumor activity of gemcitabine by inhibiting cell proliferation and NF-κB-regulated cyclin D1, Bcl-xL and survivin genes.[46] In addition, curcumin inhibits constitutive STAT3 phosphorylation and down-regulation of survivin expression in human pancreatic cancer cells.[47] Regarding EMT in carcinogenesis, curcumin reverses EMT of TGF-β-stimulated pancreatic PANC-1 cancer cells by inhibiting the Hedgehog signaling.[48]

Resveratrol plays dual roles in pancreatic cancer: as a tumor suppressor via the up-regulation of Bax; as a tumor activator via the up-regulation of VEGF-B; and the anticancer effect of resveratrol is much stronger than its cancer promotion effect. Since resveratrol shows chemosensitization effect on tumor cells, the combination of resveratrol with pharmacological inhibitor of VEGF-B has been suggested as a promising modality for clinical pancreatic cancer therapy.[29] The chemosensitization of tumor cells by resveratrol appears to be mediated through its ability to modulate multiple cell-signaling molecules, including drug transporters, cell survival proteins, cell proliferative proteins, and members of the NF-κB and STAT3 signaling pathways.[28] Besides, resveratrol inhibits EMT of pancreatic BxPC-3 and PANC-1 cancer cells through the PI-3K/AKT/NF-kB signaling.[49]

Genistein stimulates apoptotic effects of the chemotherapeutic drugs cisplatin[21] and gemcitabine[22] by inhibiting NF-κB activity. Treatment of genistein inhibits pancreatic cancer cell

growth and induces apoptosis through the down-regulation of NF-κB and Notch-1 signaling.[23] Genistein reverses the epithelial to mesenchymal transition (EMT) of FoxM1-overexpressing pancreatic AsPC-1 cancer cells.[50]

CONCLUSIONS

ROS are produced by the activated NOX in pancreatic cancer. Growth factors, ECM proteins, and cytokines protect pancreatic cancer cells from apoptosis. ROS induce activation of p38 MAPK, NF-κB, and JAK2-STAT1/3 pathway, leading to suppression of apoptosis as well as induction of EMT and cytokine expression which amplify ROS-mediated signaling in pancreatic cancer cells. Cytokines promote pancreatic tumor cell progression, angiogenesis, and the activation of MAPK pathway, which is important for cell growth, survival, and tumorigenesis. STAT3 contributes to tumor initiation by promoting the dedifferentiation of the acinar cells to cancer cells. Since ROS activate STAT3 and MAPK as well as induction of cytokines, targeting ROS may contribute to the prevention of cancer progression in pancreatic tissues. Curcumin inhibits the proliferation of pancreatic cancer cells and suppresses the activation of NF-κB and expression of cyclooxygenase-2 in pancreatic cancer cells. Resveratrol inhibit proliferation of pancreatic cancer. Genistein stimulates apoptotic effects of the chemotherapeutic drugs, and reverses EMT of pancreatic cancer cells. Taken together, supplement of antioxidant compounds may be beneficial for preventing the development and/or initiation of pancreatic cancer.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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