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Review

Progress on the role of reactive oxygen species-mediated tumor microenvironment in pancreatic cancer

Xufeng Tao[1], Vay Liang W(Bill) Go[2], Gary Guishan Xiao[1, 2, 3, *]

[1]*School of Chemical Engineering, Dalian University of Technology, Dalian 116024, China;* [2]*The UCLA Agi Hirshberg Center for Pancreatic Diseases, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States;* [3]*Functional Genomics and Proteomics Laboratory, Osteoporosis Research Center, Creighton University Medical Center, Omaha, NE, United States*

Abstract: Pancreatic cancer (PC) is a devastating malignant tumor with high incidence and mortality rate worldwide. Meanwhile, the surgical approaches and drugs of this disease remain challenging. In recent years, reactive oxygen species (ROSs) study has become a hotspot in the field of PC research. ROSs may regulate tumor microenvironment (TME), cancer stem cells (CSCs) renewal and epithelial-mesenchymal transition (EMT), which result in drug-resistance and recurrence of the PC. Currently, TME that includes immune infiltrates, fibroblasts, vascular vessels and extracellular matrix has become a hotspot in the cancer research. Meanwhile, numerous researches have shown that ROSs-mediated TME plays a central role in the occurrence and development of PC. Targeting ROSs may be promising therapeutic treatments for the PC patients. Therefore, the purposes of the review were manifold: (1) to summarize the regulations of ROSs in tumorigenesis and drug-resistance of PC; (2) to investigate the modulation of ROSs in signaling cascades in PC; (3) to study the effects of ROSs in stromal cells in PC; (4) to generalize the potent therapies targeting ROSs in PC. Overall, this review summarized the current status of ROSs in PC research and suggested some potential anti-PC drugs that may target ROSs.

Key words: pancreatic cancer; tumor microenvironment; reactive oxygen species; cancer stem cells; drug-resistance

活性氧介导的肿瘤微环境在胰腺癌发生与发展中作用的研究进展

陶旭锋[1]，Vay Liang W(Bill) Go[2]，肖桂山[1, 2, 3, *]

[1]大连理工大学化工学院，大连 116024；[2]美国加州大学洛杉矶分校大卫格芬医学院胰腺疾病中心，加利福尼亚州，洛杉矶；[3]美国克里顿大学医学中心骨质疏松研究中心功能基因组学和蛋白质组学实验室，内布拉斯加州，奥马哈

摘 要：胰腺癌是一种在全世界范围内发病率和死亡率都很高的恶性肿瘤，当前缺少有效的手术方法和治疗药物。近年来，活性氧(reactive oxygen species, ROSs)已成为胰腺癌研究领域的热点。ROSs可调节肿瘤微环境(tumor microenvironment, TME)、肿瘤干细胞(cancer stem cells, CSCs)更新和上皮-间质转化(epithelial-mesenchymal transition, EMT)等过程，从而导致胰腺癌的耐药和复发。当前，包括免疫浸润、成纤维细胞、血管和细胞外基质在内的TME已成为肿瘤研究的热点。同时，已有大量文献报道ROSs介导的TME在胰腺癌的发生与发展中具有重要的作用，靶向调节ROSs可能是治疗胰腺癌的一种方法。因此，本文综述了ROSs在胰腺癌肿瘤发生和耐药中的调控作用、ROSs在胰腺癌信号转导中的作用以及ROSs在胰腺癌基质细胞中的作用，并总结了靶向调节ROSs的抗胰腺癌的潜在药物。

关键词：胰腺癌；肿瘤微环境；活性氧；肿瘤干细胞；耐药
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1 Introduction

Pancreatic cancer (PC), as the fourth leading cause of cancer mortality in the western countries, is a devastating malignant disease with a low 5-year survival rate (< 10%) and a median survival of 8–12 months [1, 2]. Despite China has a lower incidence of PC than western world,

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*Corresponding author. E-mail: gxiao@dlut.edu.cn

the incidence of this cancer is getting higher and higher in China [3]. Only in 2016, 71 721 people died from PC, with the number of deaths outweighing that in the USA (http://www.healthdata.org/gbd/about/protocol). Currently, extensive researches about PC have been investigated, but few surgical methods or drugs are proven to be effective for treating this disease. It's urgent to explore the underlying pathology of PC.

A large number of researches have shown that reactive oxygen species (ROSs) induced-oxidative stress can deregulate the body's cellular defense system, and cause the release of oxygen-free radicals [4, 5]. Multiple phase II detoxification enzymes including NADP(H) quinone oxidoreductase 1 (NQO1), heme oxygenase-1 (HO-1), catalase (CAT) and superoxide dismutase (SOD) constitute this defense system. Up-regulation of these proteins eases oxidative injury and can prevent mutagenesis and cancer [6–8]. Recently, tumor microenvironment (TME) that consists of immune infiltrates, fibroblasts, vascular vessels and extracellular matrix has become a hotspot in the cancer research [9, 10]. It is also well known that ROSs contribute to the occurrence and development of PC, and the levels of ROSs are notably increased in patients with PC accompanied with abnormal release of multiple inflammatory cytokines [11]. These factors can regulate TME and thereby cause tumor development, drug-resistance, recurrence, invasion and metastasis of PC [10, 12, 13]. Understanding the crosstalk between ROSs and PC cells is pivotal to develop new efficient therapies for PC.

There are some reviews showed the important actions of ROSs-mediated TME in PC, but most of them are concentrated on one or several aspects. Meanwhile, there are a lot of new viewpoints and perspectives in this field in recent years. Therefore, a timely comprehensive update about the regulatory role of ROSs in PC was made available in this review. We summarize recent research progresses about the regulatory effects of ROSs on tumorigenesis, drug-resistance, stromal components and signaling cascades of PC (Fig. 1). Moreover, we also highlight some encouraging preliminary data of anti-PC drugs that targeting ROSs.

2 Effects of ROSs on tumorigenesis and drug-resistance in PC

Previous studies have observed higher ROSs level in the nutrient-limited medium-cultured PC cells compared to normal cells [14]. DNA injury mediated by ROSs facilitates the initiation of carcinogenesis and the malignant transformation of cells, and ROSs thereby promote cancer cell survival and tumor progression as

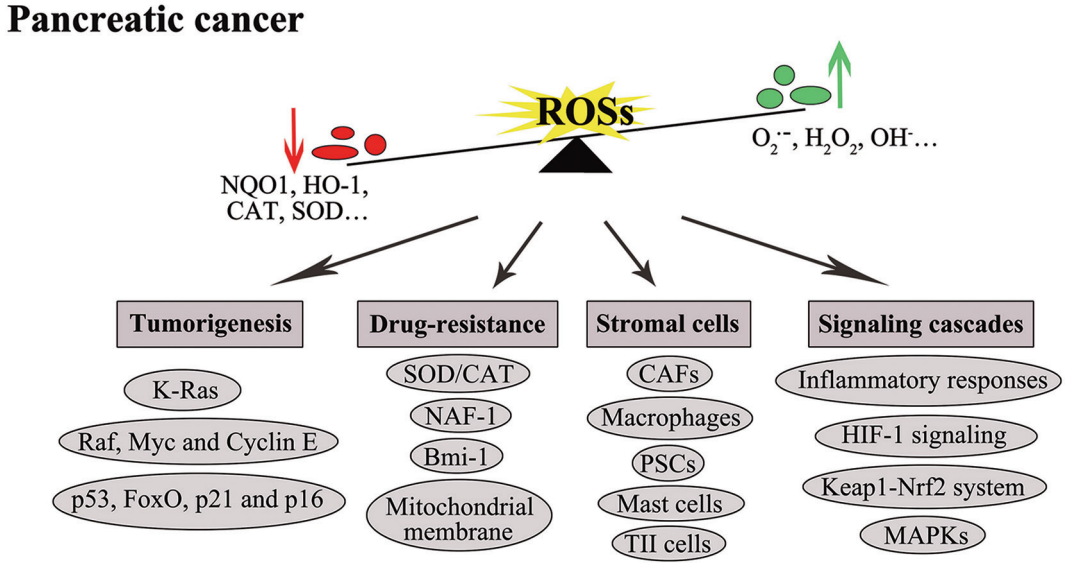

Fig. 1. Reactive oxygen species (ROSs) regulation in pancreatic cancer (PC). ROSs regulate tumorigenesis, drug-resistance, stromal components and signaling cascades in PC through various molecules, cells and signaling pathways, such as K-Ras, SOD/CAT, PSCs and MAPKs. NQO1, NADP(H) quinone oxidoreductase 1; HO-1, heme oxygenase 1, CAT, catalase; SOD, superoxide dismutase; NAF-1, nuclear assembly factor 1; CAFs, cancer-associated fibroblasts; PSCs, pancreatic stellate cells; TII cells, tumor-infiltrating immune cells; HIF-1, hypoxia-inducible transcription factor 1; Keap1, Kelch-like ECH-associated protein 1; Nrf2, nuclear factor E2-related factor; MAPKs, mitogen activated protein kinases.

signaling molecules [15]. Meanwhile, excessive ROSs cause programmed cell death by promoting the release of cytochrome c from mitochondrion to cytoplasm [16]. Thus, ROSs regulation in cancer is a double-edged sword with therapeutic potential, and the dual roles of ROSs in tumor cells may depend on its concentration [13].

Mitochondrial electron-transport chain and oxidants are the primary pathways to produce excess ROSs *in vivo*, and thereby cause various DNA injuries, such as single and double-stranded DNA breaks, DNA modifications and DNA-protein crosslinks [17]. Permanent modification of genetic material induced by ROSs is a vital step that involves mutagenesis and carcinogenesis. Moreover, the stimulation of DNA injury can either induce or arrest transcription, replication errors, genomic instability and signal transduction pathways, which are all associated with the carcinogenesis [18, 19]. Oncogene exerts a key role in the upregulated ROSs production through affecting multiple pathways. Mutant *Ras* gene causes the increase of ROSs level, and further induces DNA injury and malignant transformation [20]. Previous study had proved that *Ras* proto-oncogenes were manifested in adenocarcinoma of pancreas with the highest mutation rates for *K-Ras* (90%) [21, 22]. Activating *K-Ras* mutations is highly associated with tumor progression because of the activation of multiple effector pathways that promote cell proliferation, invasion and metabolic alterations [23, 24]. The increases in ROSs levels may also induce cell proliferation and tumor development as a key downstream effector of *K-Ras* in cancer cells [25]. *K-Ras* transformation triggers the phosphatidylinositol 3'-kinase (PI3K) signal that provides the lipid necessary for the activation of NADPH oxidase (NOX), which ultimately causes ROSs production [26]. Furthermore, the paper of Zhang *et al.* indicated that interleukin-6 (IL-6) synergizes with *K-Ras* to activate the ROSs detoxification program in PC [27]. The study of Saati *et al.* has shown that in the presence of activated *K-Ras*, loss of tumor protein p53-induced nuclear protein 1 (TP53INP1) expression accelerated the formation of pancreatic intraepithelial neoplasia (PanIN) through promoting oxidative status and ROSs release [28]. The paper of Liou *et al.* indicated that mutant *K-Ras* could initiate the transcription of the epidermal growth factor receptor (EGFR) by upregulating mitochondrial generation of ROSs and activation of nuclear factor kappa-B (NF-κB) signaling, which finally induce the formation of PC [29]. Other oncogenes including *Raf*, *Myc* and *Cyclin E* can also inhibit tumor suppressor gene expression, and thus increase the release of ROSs [30]. In addition, restored activity of pathway for ROSs confrontation or elimination plays a pivotal role in PC cells. Meanwhile, some genes, such as *p53*, *FoxO*, *p21* and *p16*, *etc*, can adjust cells to adapt to the remodeled redox balance by regulating oxidative stress in the normal cells; and they can also prevent oxidative injury and lipid peroxidation to DNA and protein via the enhances of antioxidative gene expressions and proapoptotic gene transcriptions [31]. However, cancer cells close the emergency action of multiple antioxidative pathways under this circumstance of ROSs accumulation because of suppressor gene absences [32]. Numerous other factors including serum, fibroblast growth factor (FGF), and insulin like growth factor (IGF) can also stimulate more ROSs production in cancer cells [33]. In addition, it is well known that ROSs exerts a key role in the maintenance and differentiation of stem cell self-renewal [34]. Recent studies have also shown that cancer stem cells are highly drug resistance possibly because these cells use redox regulatory mechanisms to avoid the cell death induced by the antineoplastic drugs, especially the chemotherapy with redox-cycling agent [35].

Currently, chemotherapy is the most important method for treating the unresectable PC patients. Specially, gemcitabine has become the standard first-line option with a good performance status for 20 years [36, 37]. Production of ROSs by this chemotherapy is suggested to be one significant mechanism for its cytotoxic action [38, 39]. However, the resistance to this drug has attracted an increasing scientific interest; and it causes the lack of efficacy of current treatments for PC. A large number of studies have proved that the level of ROSs may be directly related to the drug resistance. The excessive ROSs will result in intracellular structures injuries, and further regulate the initiation and execution of apoptosis [40]. The study of Patel *et al.* indicated that exosomes enhanced the chemoresistance of PC cells against gemcitabine partly through the SOD/CAT upregulation and ROSs production [41]. In addition, the paper of Cheng *et al.* showed that resveratrol could inhibit nuclear assembly factor 1 (NAF-1) expression, and thereby caused cellular ROSs accumulation, which further improved the gemcitabine sensitivity of PC cells [42]. Yin *et al.* found that gemcitabine at a certain dose could increase the expression level of Bmi-1 in PC cells. Down-regulation of Bmi-1 notably promoted the ROSs level and thereby enhanced the cytotoxic effect of gemcitabine. The potent mechanism might be that

accumulative ROSs upon gemcitabine therapy disrupted mitochondrial membrane, and finally resulted in cancer cells apoptosis [43].

3 Effects of ROSs on stromal components in PC

Stromal cells are a key component of the tumor progression via regulating carcinogenesis, invasion, metastasis and resistance to therapy [44, 45]. Crosstalk between stromal biology and pancreatic cancer cells builds a specific TME that further contributes to pancreatic tumorigenesis [46]. Indeed, the effects of ROSs in PC have been intensively studied but was principally examined within cancer cells, while research on the role of ROSs in stromal cells in PC is largely insufficient [47]. Stromal components consist of cancer-associated fibroblasts (CAFs), macrophages, pancreatic stellate cells (PSCs), mast cells, tumor-infiltrating immune (TII) cells (e.g., lymphocytes and neutrophils), adipocytes, endothelial cells, and extracellular matrix (ECM), in PC [46, 48].

CAFs and tumor-associated macrophages (TAM) are the most prominent cells in shaping the TME by interacting with other type of cells [49]. In response to ROSs stimuli, the resident quiescent fibroblasts are reversibly transformed into activated fibroblasts, also known as CAFs that expressing alpha-smooth muscle actin (α-SMA) and vimentin [50]. Pancreatic CAFs are major contributors to regulate macrophage phenotype. CAFs induce M2 phenotype transformation partly through enhanced ROSs production in monocytes caused by paracrine secretion of macrophage colony stimulating factor (M-CSF) from pancreatic CAFs, in turn, blockade of M-CSF signaling significantly decreases M2 polarization [49]. Therefore, ROSs can affect pancreatic tumorigenesis by targeting macrophages. PSCs not only participate in secreting factors to promote invasion but regulate metabolism during PC evolution [51]. Under pathological conditions including cancer, quiescent-PSCs activated by ROSs are also the main progenitors of myofibroblast-like phenotype [52, 53]. Increased ROSs generation in Caveolin-1 (Cav-1, the main structural component of caveolae)-knockdown PSCs, which in turn further inhibits the expression of Cav-1, can promote PSC activation, tumor cells growth and induce the metabolic community between stromal cells and cancer cells in PC. Mechanically, positive feedback in Cav-1-ROSs signal pathway induces a shift in energy metabolism to glycolysis, with high levels of glycolysis products such as lactate secreted into the intercellular space and absorbed by adjacent tumor cells [54]. Thus, interruption of the stromal-cancer cells metabolic coupling through regulating Cav-1-ROSs signaling is considered to be an effective method for tumor therapy. It has been reported that stromal Cav-1 mediates different mechanisms in the complex interaction between stromal cells and cancer cells. Knockdown of Cav-1 in PSCs accumulated ROSs to enhance paracrine cytokine signaling and angiogenesis in PC cells. Nrf2, as a key mediator in Cav-1 ablation-induced ROSs production and Shh pathway, may reverse the effects of Cav-1 knockdown on PSCs [55]. In addition, Cav-1 is overexpressed in fibroblasts and endothelial cells, and normally implicated in stromal remodeling during PC progression [56]. PSC-derived soluble factors, stromal-derived factor-1alpha (SDF-1α) and IL-6, are favorable for PC cell proliferation via ROSs detoxification and purine nucleotide synthesis activated by Nrf2 [57]. Osteopontin (OPN), a phosphorylated glycoprotein, is highly expressed in activated PSCs in a ROSs-dependent manner to promote the epithelial-mesenchymal transition (EMT) and cancer stem cell (CSC)-like properties of PC cells [58].

It has been known that ROSs generation is essential to the crosstalk between cancer cells and non-cancer stromal cells in order to drive tumorigenesis. Understanding how to exploit ROSs to modulate stromal biology will not only help with the understanding of tumor initiation and progression, but also allow for the possible development of new anticancer treatments.

4 Effects of ROSs on signaling cascades in PC

4.1 Effects of ROSs on inflammatory responses in PC

Emerging lines of evidence have suggested that inflammation may be a biological response to oxidative stress and ROSs, and it initiates the restoration of homeostasis [59]. In cancers, the cells would achieve a symbiotic relationship with the inflammatory microenvironment, which enhances the adaptation for survival, invasion, metastasis and evasion of host immune systems [60]. Moreover, ROSs production has been associated with the development and progression of pancreatic ductal adenocarcinoma along with the repeated episodes of pancreatitis [61, 62]. The paper of Wu *et al.* indicated that the activation of the signal transducer and activator of

transcription 1 (STAT1) pathway caused by interferon-γ (IFN-γ) induced the up-regulation of Duox2, and thereby generated the high local concentration of extracellular ROSs, which finally resulted in a pro-inflammatory milieu in the pancreas; and these proinflammatory proteins were examined in PC cells [11, 63].

In the classic pathway, pro-inflammatory factors and genotoxic stresses result in the IκB kinase (IKK)-β- and IKK-γ-dependent phosphorylation of IκB, which further induce proteasomal degradation and NF-κB release [64]. Recently, the paper of Kang *et al.* showed that ROSs (such as H_2O_2) up-regulated NF-κB level and subsequently led to the overexpression of receptor for advanced glycation end-products (RAGE), which could decrease oxidative injury of pancreatic tumor cells through decreasing apoptosis and increasing autophagy. Their study also suggested RAGE sustained NF-κB activation via the positive regulation in response to oxidative stress [65].

4.2 Effects of ROSs on hypoxia-inducible transcription factor (HIF)-1 signaling pathway in PC

HIFs, critical regulators of hypoxic adaptation in cancer cells, are able to trigger glycolysis and the remodeling of the extracellular TME [66, 67]. Under hypoxia, the cytoplasmic HIF-1α subunit accumulates, and is translocated to the nucleus to dimerize with the HIF-1β subunit. This heterodimer complex then binds to DNA hypoxia response elements (HREs), and thereby induce expression of numerous genes required for hypoxia adaptation [68, 69]. However, tumors would generate a locally aberrant hypoxic environment because of increased oxidative phosphorylation and outgrowth of vasculature. Specially, HIF-1α isoform is well established to correlate with the metastasis and prognosis of PC, and its high expression caused the advanced tumor stage at diagnosis, poor overall survival, and increased micro-vessel density and lymphnode metastasis [70, 71].

Cancer cells usually take up glucose avidly and convert it to lactate even under experimental environments with adequate oxygen [72]. This phenomenon has been called the aerobic glycolysis or Warburg effect, which also involves the activation of oncogenes and the inhibition of tumor suppressor genes [73, 74]. The pervasive presence of hypoxia in tumors induces the expression of HIF-1, which is a key transcription factor for hypoxic adaptation with its activation of lactate dehydrogenase A (LDHA) [75]. Moreover, in addition to hypoxia, ROSs are potential HIF-1 inducers, and up-regulated generation of hypoxic ROSs is responsible for HIF-1α stabilization, which can promote PC cell invasion [76, 77]. The paper of Wang *et al.* also proved that ROSs regulate glucose metabolism in PC via EGFR/mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK)/HIF-1α signaling pathway [78].

4.3 Effects of ROSs on Kelch-like ECH-associated protein 1 (Keap1)-nuclear factor E2-related factor (Nrf2) system in PC

The Keap1-Nrf2 system plays a pivotal role in oxidative stress and ROSs responses [79, 80]. Under normal circumstances, Keap1 is bound to Nrf2; and thereby Nrf2 activity can be inhibited through the degradation in ubiquitin proteasome pathway [81]. However, Keap1 is unable to bind to Nrf2 when the cells are exposed to oxidative injury. Subsequently, Nrf2 translocates to nucleus and binds to antioxidant response element (ARE) in DNA [82]. The activation of Nrf2 results in the transcription of several cytoprotective genes, such as antioxidant enzymes, drug-metabolizing enzymes and drug transporters, which contribute to the restoration of redox system [83]. As a result, Nrf2 activator is used in clinical trials as a chemopreventive compound [84]. However, PC is featured by persistent Nrf2 activation conferring therapy resistance which indicates a pro-tumorigenic role of Nrf2 [85]. Recent studies have determined that Nrf2 could also reduce cancer cells injury induced chemotherapeutic agents just as protecting normal cells [84]. The poor survival in PC patients correlates with the up-regulation of Nrf2 expression, which is also induced during the course of drug resistance [86]. Therefore, this disruption of Nrf2-Keap1 system protects oxidative and/or ROSs injury but thereby may facilitate cancer progression.

4.4 Effects of ROSs on mitogen activated protein kinases (MAPKs) in PC

It is well known that ROSs also trigger MAPKs pathway, which can regulate the cell migration and metastasis [87]. In mammalian systems, there are three subgroups of MAPKs: ERK, c-jun N terminal kinase (JNK) and p38 MAPK; and they further regulate the activities of transcription factors including NF-κB and activator protein-1 (AP-1) [88]. Finally, this ROSs mediated-MAPKs activation leads to the local tumor invasion and distant metastasis [89]. The paper of Li *et al.* has indicated that the inhibitors of ERK, p38 and ROSs could effectively inhibit the invasion of PC cells under high glucose conditions [90].

ROSs are well known to participate in several signaling cascades of cancer. The active signaling makes PC cells more vulnerable to intracellular ROSs induced cell death. To control elevated ROSs release for PC prevention, some potent antioxidant agents (such as vitamin A and E, *etc*.) are under investigation. However, many basic and clinical studies have indicated that these antioxidants are associated with unfavorable outcomes to treat PC [91]. Maybe it's because that ROSs tend to promote the tumorigenesis when its concentration is reduced by antioxidants to below a specific threshold. This phenomenon is associated with multiple complicated mechanisms by targeting redox system of PC.

5 Therapies against oxidative stress in PC

Currently, a great number of compounds have been proven to have potent therapeutic effects on PC by affecting ROSs release (Table 1). Capsaicin, *N*-vanillyl-8-methyl-nonenamide, is the pungent component of chilli fruits. The paper of Zhang *et al.* demonstrated that capsaicin promoted mitochondrial death pathway and apoptosis in PC cells though ROSs accumulation *in vitro* and *in vivo* [92]. Lai *et al.* indicated that Brucein D, the active quassinoid of Bruceae Fructus, effectively inhibited PI3K/Akt signaling via ROSs induction, and thereby restrained the tumor growth of PC [93]. *N*-acetylcysteine (NAC) is a classic antioxidant; and the paper of Shimojo *et al.* has proven that alleviation of ROSs by NAC inhibits hypoxia-induced EMT and hepatic metastasis of PC [94]. Sanguinarine, mainly derived from the root of *Sanguinaria canadensis*, is an isoquinoline alkaloid that inhibits CSC's proliferation and colony formation through oxidative damage. However, the antiproliferative effects of sanguinarine can be diminished by pretreatment with the thiol antioxidants NAC and glutathione (GSH) [95]. Curcumin, a natural polyphenol isolated from turmeric, could prevent SOD-driven H_2O_2-induced PC metastasis by inhibiting PI3K/Akt/NF-κB signaling pathway [96]. Nimbolide is an active ingredient of neem tree flowers and leaves; and the paper of Subramani *et al.* showed that nimbolide significantly decreased the proliferation and metastasis of PC cells via promotion of mitochondria-mediated apoptotic cell death which caused by the up-regulation of ROSs [97]. Melatonin (*N*-acetyl-5-methoxytryptamine), an indoleamine secreted by the pineal gland, commonly acts as a powerful endogenous antioxidant. Melatonin in association with chemotherapy promotes ROSs generation and mitochondrial membrane depolarization to enhance chemotherapeutic agent-induced cytotoxicity and apoptosis *in vitro* [98, 99]. *N*-nitrosobis (2-oxopropyl) amine (BOP) induced-PC is associated with a rise in lipid peroxidation products (LPO) and the depletion of SOD, CAT, GSH and glutathione peroxidase (GSH-Px) in pancreas. The administration of melatonin increases antioxidant processes and decreases cancer nodules via recovering enzymatic antioxidants [100].

Table 1. Therapies targeting ROS in PC

Drugs	Targeted strategy	Mechanism	Reference
Capsaicin	ROS ↑	Promoting mitochondrial death pathway and apoptosis in PC cells	[92]
Brucein D	ROS ↑	Inhibiting PI3K/Akt signaling	[93]
NAC	ROS ↓	Inhibiting hypoxia-induced EMT and hepatic metastasis	[94, 95]
Curcumin	ROS ↓	Preventing PC metastasis by inhibiting PI3K/Akt/NF-κB signaling pathway	[96]
Nimbolide	ROS ↑	Decreasing the proliferation and metastasis of PC cells via promotion of mitochondria-mediated apoptotic cell death	[97]
Melatonin	ROS ↑	Enhancing chemotherapy-induced cytotoxicity and apoptosis	[98, 99]
	LPO ↓, SOD ↑, CAT ↑, GSH ↑, GSH-Px ↑	Increasing antioxidant processes and decreasing cancer nodules	[100]
TPEN	ROS ↑	Inducing PC cell death via stimulating mitochondrial metabolism and restraining autophagy	[101]
Dicumarol	NQO1 ↓	Inducing cell killing and oxidative stress in PC cells by competing with NADH for the binding site of the oxidized NQO1 form	[102]
AgNPs	ROS ↑	Increasing NO and NO_2 and disturbing iNOS, eNOS, and nNOS as well as	[103]
	RNS ↑	SOD1, SOD2, SOD3, GPX-4 and CAT to induce cell death	

NAC, *N*-acetylcysteine; TPEN: N,N,N,N-Tetrakis (2-pyridylmethyl)-ethylenediamine; AgNPs: silver nanoparticles; EMT: epithelial-mesenchymal transition; PC: pancreatic cancer; LPO, lipid peroxidation products; NQO1, NADP(H) quinone oxidoreductase 1.

Zinc chelator TPEN [N,N,N,N-Tetrakis (2-pyridylmethyl)-ethylenediamine, a lipid-soluble metal chelator] has been shown to induce PC cell death in a dose-dependent manner via triggering ROSs outbreak and restraining autophagy [101]. Dicumarol (3,3'-Methylenebis[4-hydroxycoumarin]) derived from coumarin can inhibit NAD(P)H: NQO1 through competing the binding site of the oxidized NQO1 form with NADH in order to induce cell killing and oxidative stress in PC cells [102]. Oxidative and nitro-oxidative stress causes programmed cell death in PC. Silver nanoparticles (AgNPs) is a key contributor for the accumulation of ROSs and reactive nitrogen species (RNS) in human pancreatic ductal adenocarcinoma cells [103]. These candidate drugs may be promising therapeutic treatments for the PC patients. However, further investigations in preclinical and clinical settings should be implemented in the further.

6 Conclusion

In conclusion, redox-modulating treatments to target ROSs level in PC cells will be promising therapies. Among them, up-regulation of ROSs metabolizing capacity performed by antioxidants can inhibit PC growth. However, some studies showed that clinical application of antioxidants are associated with the rising incidence rate of cancer, probably because of the suppression of cancer cells apoptosis mediated by ROSs. Therefore, further researches on the actions and mechanisms of ROSs in PC are still expectant. We believe that ROSs should benefit the targeted therapy of PC, given their extensive range of effects in the future.

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