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Role of Transcription Factors in Gastrointestinal Malignancies

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Targeting Arachidonic Acid Pathway-Associated NF-κB in Pancreatic Cancer

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30.1 Introduction

Pancreatic cancer is the fourth-leading cause of cancer-related morbidity, with 39,590 deaths and 46,420 estimated new cases in 2014 in the United States [1]. Mutations are considered to be the genetic event occurring at the beginning of the development process of pancreatic cancer, leading to cellular proliferation due to constitutive activation of intracellular pathways [2]. The latter is related to numerous alterations in growth factors and their receptors, involved in the control of growth and differentiation during transduction pathways [2]. There are several molecular signaling pathways that play a vital role in cell survival, proliferation,

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angiogenesis, metastasis, and promotion of pancreatic cancer, as well as in chemoresistance, including epidermal growth factor receptor (EGFR), nuclear factor-kappa B (NF-κB), signal transducer and activator of transcription factor 3 (STAT3), and arachidonic acid (AA) pathway [3].

30.2 Arachidonic Acid Pathway-Associated NF-κB Signaling in Pancreatic Cancer

The transcription factor NF-κB plays a critical role in pancreatic cancer as involving at the downstream stage of many signaling cascades including AA pathway. AA is an upstream mediator and regulator of NF-κB pathway. NF-κB and activation protein 1 (AP-1) can bind to the cis-acting elements in the promoter of phospholipase A2 (PLA2), cyclooxygenase (COX-2), and lipoxygenases (LOXs), and these pathways are upregulated in several cancers. The active form of PLA_2 stimulates the proliferation of MIAPaCa-2 pancreatic cancer cells by the activation of mitogen-activated protein kinases (MAPKs)/NF-κB [4]. PLA_2s gene knockout and transgenic studies demonstrated the pro-tumorigenic role of PLA_2 in pancreatic cancer [5].

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A chemical compound bromoenol lactone (BEL) caused decrease in agonist-induced activation of EGFR in pancreatic cancer cells [6]. The NF-κB inhibition has become a major target in natural drug discovery, and it is necessary for survival and immunity of cell because it regulates the immune, inflammatory, and carcinogenic responses [7]. Compared to normal pancreatic tissues, NF-κB, which is linked with COX-2, is constitutively expressed in 67% of human pancreatic cancers. Zhang et al. [5] reported the acute pancreatitis induced by PLA2 by the activation of transcription factor NF-κB. Gong et al. [8] reported combinatorial target of COX-2/NF-κB/STAT3/prostaglandin receptor E-prostanoid 4 pathway for effective treatment of pancreatic cancer [8, 9] reported the TLR4-/NF-κB-/COX-2-mediated inflammatory pathway involved in tumorigenesis of pancreatic cancer.

Although COX-2 expression along with NF-κB is incremented in several types of malignancies including pancreatic, esophagus, colon, and breast cancers [10–12], the molecular mechanism is still unclear. It has been reported that COX-2 has inherent role in pancreatic ductal adenocarcinomas initiation and progression by the activation of the PI3K/AKT pathway [13]. In cancer, prostaglandin E2 (PGE2) the metabolite of COX-2 is overexpressed in the majority of epithelial malignancies [14, 15]. Approximately 80% of human pancreatic ductal adenocarcinomas (PDA) overexpress the tumor form of mucin 1 (tMUC1), a heavily glycosylated membrane-tethered glycoprotein generally expressed on glandular epithelial cells [16]. tMUC1 is overexpressed and aberrantly hypoglycosylated in malignant cells [16].

In a study, it has been shown that, in addition to the overexpression of tMUC1, the tumors have high levels of COX-2 and PGE2 [17]. Mucin 1 (PDA.MUC1) mice are highly resistant to celecoxib (a COX-2 inhibitor) and gemcitabine when each drug is administered independently; however, a clinical relevant antitumor response was observed after treatment with a blend of MUC1 vaccine, celecoxib, and gemcitabine [18]. Previous reports suggested that the transmembrane mucin glycoprotein mucin 1 (MUC1) is overexpressed in pancreatic ductal adenocarcinomas along with COX-2. Molecular studies by Nath et al. [17] demonstrated the MUC1 associated with the same gene locus where NF-κB/p65 binds with the COX-2 promoter. The study suggests that MUC1 regulates pancreatic ductal adenocarcinomas through COX-2/NF-κB pathway [17]. Animal LOXs were classified into five different types—5-LOX, 8-LOX, 11-LOX, 12-LOX, and 15-LOX [19]. LOXs also involved in various human cancers including colon, pancreatic, lung, breast, and prostate [10]; however, comparatively diminutive efforts have been made to explicate its role in cancer development.

Recently, it has been shown that treatment with omega-6 fatty acids increases leukotrienes B4 (a LOX metabolite) levels in human pancreatic ductal epithelial (HPDE and HPDE-Kras) and cancer (AsPC1 and Panc1) cells, in vitro [20]. Compared to EL-Kras/5LO+/+ mice, EL-Kras mice lacking 5LO (EL-Kras/5LO−/−) had decreased mast cell infiltration and developed fewer pancreatic lesions [20]. These results suggest the LOXs involvement in pancreatic cancer. Previously, the progression of human pancreatic cancer cells by leukotrienes B4 (LTB4) via MAPK and PI-3 kinase pathways was reported, although it did not affect the activity of JNK/SAPK [21]. In fact, different LOXs exhibit tumor response in a tissue-specific

manner either pro-tumorigenic or antitumorigenic activities [22]. Inhibitors of lipoxygenases have been found to be very effective in the suppression of pancreatic cancer cell lines as well as pancreatic adenocarcinoma. In a study, the inhibition of 5-lipoxygenase by zileuton (5-LOX inhibitor) in pancreatic cancer cells by inducing apoptosis, SW1990, has been demonstrated [23].

30.3 Targeting Arachidonic Acid Pathway-Associated NF-κB by Phytochemical Compounds for Prevention and Therapy of Pancreatic Cancer

Phytochemical agents and their derivatives act as anticancer drugs by inhibiting the migration, invasion, growth, survival, and metastasis of cancer cell during the carcinogenesis process by multiple pathways [24]. Cannabinoid (1), lupeol (2), plumbagin (3), quercetin (4), sulforaphane (5), triptolide (6), γ-tocotrienol (7), boswellic acid (8), curcumin (9), and garcinol (10) are different phytochemicals exhibiting anticancer activities against various cancers, including pancreatic, by targeting AA pathway and NF-κB-mediated signaling pathways (Table 30.1).

Moreover, paclitaxel, etoposide and teniposide, vinblastine and vincristine, and camptothecin derivatives are reported anticancer agents [25, 26]. These compounds act by inhibiting the expression of NF-κB and associated genes by modulating various signal transduction pathways [25, 26]. Researchers reported that individual phytochemicals and in combination with chemotherapeutics can prevent pancreatic cancer by inhibiting several signaling pathways [27]. Phenolics can inhibit the promotion and progression of cancerous cell by modulating the activities of NF-κB and AP-1 [28]. Curcumin downregulates the expression of NF-κB, COX2, and phosphorylated STAT3 in peripheral blood mononuclear cells in some pancreatic cancer patients [29] (Fig. 30.1). Lev-Ari et al. [30] reported that combination of curcumin and gemcitabine enhanced cytotoxic effect against pancreatic adenocarcinoma in vitro, decreasing the COX-2 and p-ERK1/2 levels.

Cascinu et al. [31] conducted a clinical trial in pancreatic cancer, by using celecoxib (COX-2 inhibitor) associated to oxaliplatin and gemcitabine. The expression of COX-2 was found in 30 tumors as well as NF-κB expression was found in 16 tumors. Authors reveal that COX-2 inhibitor does not enhance the efficacy of gemcitabine/oxaliplatin. Nafamostat mesilate inhibits induced apoptosis in pancreatic cancer cells, but its maximum concentration (1.8×10^{-7} M) is not effective to inhibit NF-κB [33]. The recommended dose of regional arterial infusion of nafamostat mesilate (1.8×10^{-6} M), used to target gemcitabine-induced NF-κB activation, in combination with gemcitabine is found to be safe in pancreatic cancer patients [32]. The inhibition of gemcitabine-induced NF-κB activation enhances the antitumor activity of gemcitabine against pancreatic cancer [34].

Pristimerin, a quinonemethide triterpenoid, exhibited antiproliferative and proapoptotic activities in pancreatic cancer cells by inhibiting multiple signaling pathways NF-κB/COX-2 [35]. Nordihydroguaiaretic acid (NDGA), a 5-LOX inhibitor,

Table 30.1 Phytochemicals targeting AA pathway associated transcriptional factros for cancer prevention and therapy

Phytochemical	Mechanism	References
Cannabinoid (1)	Upregulation of CB2 receptor	[37]
	Upregulation of p8, ATF-4, and TRB3 genes	
Lupeol (2)	Reduced activation of NF-κB	[38]
	Reduced protein expression of PKCa/ODC, PI3K/Akt, and MAPK pathways	
Plumbagin (3)	Decrease in NF-κB/p65 phosphorylation	[39]
	Inhibition of STAT3 phosphorylation	
	Upregulates the expression of IL-6	
	Inhibited expression of Cdc25A, cyclin D1, and MMP9	
	Decreased expression of proliferative markers such as PCNA and ki67	
Quercetin (4)	Diminished ALDH1	[40]
	Inhibition of NF-κB	
	Reduced proliferation, angiogenesis, cancer stem cell-marker expression	
	Induction of apoptosis	
Sulforaphane (5)	Diminished NF-κB binding, induction of apoptosis	[41]
	Blockage of tumor growth and angiogenesis	
Triptolide (6)	Downregulates NF-κB	[42]
	Inhibition of HSF1 and HSP70	
	Inhibition of glycosylation of Sp1	
	Inhibition of hexosamine biosynthesis	
	Inhibition of *O*-GlcNAc transferase	
ɣ-Tocotrienol (7)	Inhibition of NF-κB activity	[43]
	Inhibition of cell growth and cell survival	
	Decreased p65 (ReIA) binding	
	Inhibition of proliferation, angiogenesis, invasion	
Boswellic acid (8)	Downregulate the expression of COX-2, MMP-9, CXCR4, and VEGF and inhibit the expression level of c-Myc	[44]
Curcumin (9)	Downregulation of iNOS, COX-2, and 5-LOX expression	[45]
	Upregulation of p21 expression	
Garcinol (10)	Reduction in PGE2 expression	[46]
	Downregulation of NF-κB and COX-2	
	O2, nitric oxide (NO), iNOS, and COX2	

prevented the progression of acute pancreatitis by inhibiting multiple pathways, including NF-κB [36]. Nexrutine®, an anti-inflammatory nutraceutical, inhibited growth of pancreatic cancer cells and reduced levels and activity of NF-κB, expression of COX-2, and subsequent decreased levels of PGE2 and PGF2 [8]. 6-Shogaol (a phenol extracted from ginger) alone and in combination with gemcitabine suppressed the growth of pancreatic tumors, by suppressing the TLR4-/NF-κB-/COX-2-mediated pathway [9].

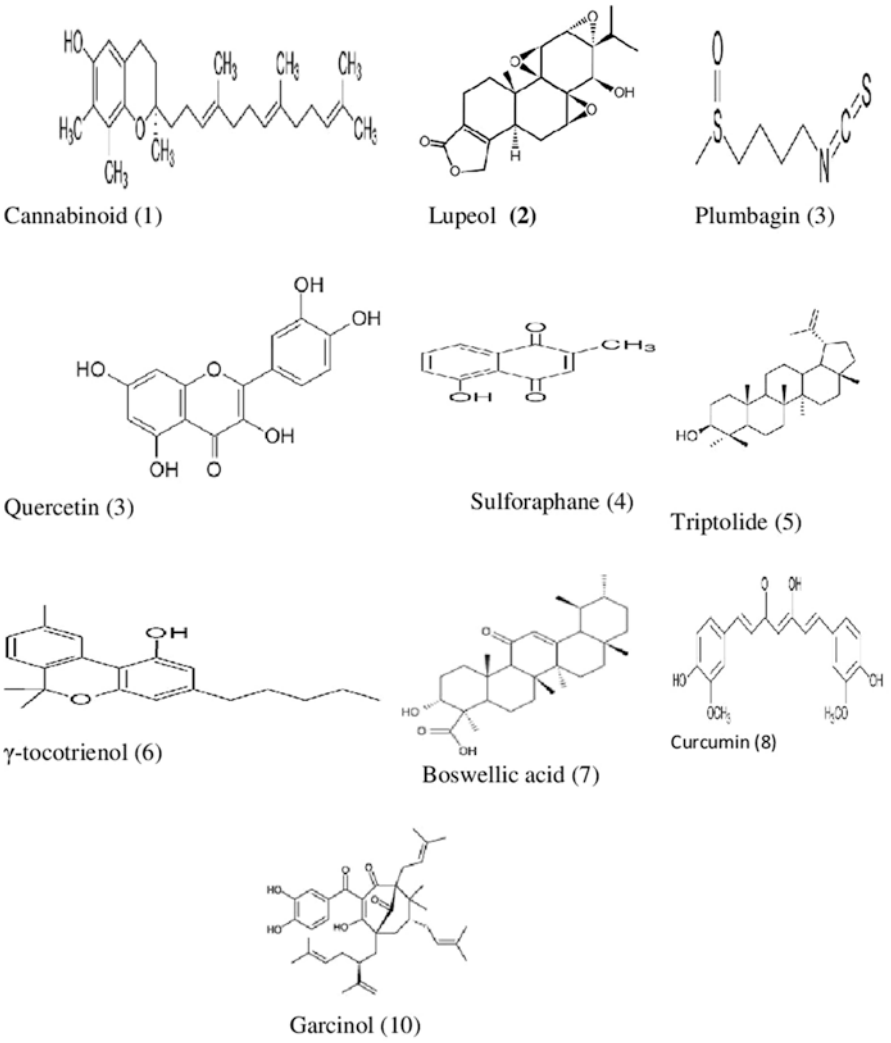

Fig. 30.1 Chemical structures of some of the important anticancer phytochemicals by targeting AA cascade-associated NF-κB pathway

30.4 Conclusions and Future Directions

NF-κB is an important transcription factor and has a crucial role in pancreatic cancer as it is involved at the downstream stage of many signaling cascades including AA pathway. Metabolic enzymes and products of AA pathway are also involved in activation of NF-κB. Cross talk between eicosanoids and NF-κB plays a key role in pathophysiology of pancreatic cancer. Therefore, researchers have considered AA cascade-associated NF-κB pathway as novel therapeutic target in pancreatic cancer.

Moreover, several AA cascade-associated NF-κB pathways are targeted by natural products. Therefore, these compounds have been suggested as novel preventive and therapeutic agents against pancreatic cancer.

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