NF-κB in Pancreatic Cancer

Guido M. Sclabas, Shuichi Fujioka, Christian Schmidt, Douglas B. Evans, and Paul J. Chiao*

Departments of Surgical Oncology and Molecular Oncology, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030

Abstract

Although the genetic profile of pancreatic cancer is emerging as a result of much research, the role of specific genetic alterations that initiate tumorigenesis and produce its cardinal clinical features of locally aggressive growth, metastasis, and chemotherapy resistance remains unresolved. Recently, a number of studies have shown that the inhibition of constitutive NF-κB activation, one of the frequent molecular alterations in pancreatic cancer, inhibits tumorigenesis and metastasis. It also sensitizes pancreatic cancer cell lines to anticancer agent-induced apoptosis. Therefore because of the crucial role of NF-κB in pancreatic cancer, it is a potential target for developing novel therapeutic strategies for the disease. In vivo and in vitro models that mimic the tumorigenic phenotypes in the appropriate histological and molecular concert would be very useful for confirming the suspected role of the pancreatic cancer signature genetic lesions and better understanding the molecular basis of this disease.

Key Words: NF-κB; IκBα; pancreatic cancer; tumorigenesis; metastasis; apoptosis; angiogenesis.

Introduction

A key point that has emerged from the analysis of mutations present in human pancreatic adenocarcinoma is that the cancer a unique profile of genetic and molecular alterations that distinguishes it from all other cancers (1,2). Genetically, pancreatic cancer is one of the better-characterized neoplasms (1,3). For example, it is known that HER-2/neu is overexpressed in about 90% of duct lesions and in 70% of invasive pancreatic adenocarcinoma; that point mutations in the K-ras gene exist in 45% of duct lesions and about 80–95% of pancreatic adenocarcinomas; inactivation of the p16 (Ink4a/Arf) is at an intermediate stage in 71% of ductal lesions; inactivation of p53 is identified in 50 to 75% of pancreatic cancers; inactivation of Smad4/DPC4 is found in 50% of the cancers, and BRCA2 mutation occurs relatively late and in much lower frequency (4–9). NF-κB activity is found constitutively activated in about 70% of pancreatic cancers (10). These studies show that pancreatic cancer presents a quite consistent set of genetic alterations in contrast to most other adult cancers (11). The combination of cDNA microarray and cDNA-based CGH analyses can expand the list of signature mutations for pancreatic cancer. However, the role this genetic lesion profile plays in pancreatic cancer induction and metastasis is still unclear. This review focuses on the possible role of NF-κB, one of the recently identified molecular alterations in
pancreatic cancer, in the initiation or progression of pancreatic adenocarcinoma.

**Oncogenic Activity of NF-κB**

NF-κB is a family of pleiotropic transcription factors that orchestrate the expression of a plethora of genes that play key roles in growth, oncogenesis, differentiation, apoptosis, tumorigenesis, and immune and inflammatory responses (12–14). Five members of mammalian NF-κB are described: NF-κB₁ (p50 and its precursor p105), NF-κB₂ (p52 and its precursor p100), c-Rel, RelA (p65), and RelB (15–18), each of which has a 300 residue-long Rel homology domain (RHD) (13,19–23). The C-terminal domains are responsible for dimerization with other Rel proteins, but sequence-specific interactions come primarily from loops in the N-terminal domain (24). Interaction of c-Rel, RelA (p65) and RelB with its inhibitors, referred to as IκB, results in inactive complexes in the cytoplasm by masking the nuclear localization signal, which is located at the C terminal end of the Rel homology domain (13,19–23). Currently, the inhibitor proteins IκBa, IκBβ, IκBγ, IκBe, Bcl-3, and the Drosophila protein Cactus are described and characterized (13,19–23).

In most cell types, NF-κB proteins are sequestered in the cytoplasm in an inactive form through their noncovalent association with the inhibitor IκB (16). This association masks the nuclear localization signal of NF-κB, thereby preventing NF-κB nuclear translocation and DNA binding activity (25). NF-κB is activated through complex signaling cascades that are integrated by activation of IκB kinase complex (IKK) (26–30), which phosphorylates IκB bound to NF-κB complexes as its substrates (31). Consequently, NF-κB proteins are translocated into the nucleus, where they activate transcription of their target genes (13,20). One of the key target genes regulated by NF-κB is its inhibitor IκBa. A feedback inhibition pathway for control of IκBa gene transcription and downregulation of transient activation of NF-κB activity is described (32–34).

The c-rel member of the Rel/NF-κB family of pleiotropic transcription factors was first identified as a cellular homolog of the v-rel oncogene from a highly oncogenic retrovirus (35). The v-Rel oncoprotein induces aggressive leukemias and lymphomas in chickens and transgenic mice and is able to transform avian lymphoid cells and fibroblasts, indicating the possibility that other members of Rel/NF-κB are oncogenes (36–38).

Many reports demonstrated that members of the NF-κB and IκB families are involved in the development of cancer. Chromosomal amplification, overexpression and recurrent genomic rearrangement in the genes encoding c-Rel, Bcl-3, p105 (p50), and p100 (p52) are identified in many human hematopoietic cancers and several types of solid tumor, such as human non-small cell lung carcinomas (NSCLC) (39), squamous carcinomas of head and neck, and in adenocarcinomas of breast and stomach (40,41), thyroid carcinoma cell lines (42), colon, prostate, breast, bone, and brain cancer cells (43).

Constitutive NF-κB activation has been found in many human hematopoietic malignancies and several types of solid tumors such as pancreas and breast cancers, as a result of mutations activating continuously upstream signaling kinases or inactivating inhibitory IκB proteins. For example, NF-κB constitutive activation was initially reported in Hodgkin’s disease as a direct consequence of mutations in the IκBα gene, which generate non-functional inhibitory proteins (44–46). Constitutive NF-κB activity is also detected in 93% of childhood acute lymphoblastic leukemia (C-ALL) (47). These results suggest a crucial role for NF-κB in leukemia cell survival.

Constitutive activation of NF-κB is also emerging as a characteristic of various types of solid tumors, including breast (48–51), ovarian (43,48), colon (48), pancreatic (10), bladder (50), and prostate carcinomas (52–54), as well as in melanomas (55).

In light of constitutive NF-κB activation found in approx 70% of pancreatic adenocarcinomas and the recent progress in elucidating its role in this disease, constitutive NF-κB activation in pancreatic cancer is reviewed in greater detail below.

**Constitutive Activation of NF-κB in Pancreatic Cancer**

Our initial study demonstrated that NF-κB is constitutively activated in 67% (16 of 24) of human pancreatic adenocarcinoma, but not in normal pancreatic tissue, and in 69% (11 of 16) of pancreatic adenocarcinomas in chickens and transgenic mice and is able to transform avian lymphoid cells and fibroblasts, indicating the possibility that other members of Rel/NF-κB are oncogenes (36–38).