Abstract

This perspective on Liby et al. (beginning on page 1427 in this issue of the journal) discusses the importance of the finding that two synthetic triterpenoids prolonged survival in a pancreatic cancer mouse model. This finding is significant because pancreatic cancer is one of the deadliest human cancers. These compounds inhibited the interaction between NF-κB and signal transducer and activator of transcription 3, and determining the mechanisms underlying this inhibition will help to rapidly move these compounds into phase 1 clinical trials. Cancer Prev Res; 3(11); 1379–81. ©2010 AACR.

Despite many recent advances in treatment and surgery, pancreatic cancer has one of the worst prognoses of all cancers. Only 20% of patients have localized, potentially curable tumors at the initial diagnosis (1), and diagnosis at an advanced stage, as often occurs, makes pancreatic cancer difficult to treat. This disease has a complex etiology that involves both environmental and genetic factors. Although cigarette smoking has been linked to at least 25% of cases, recent studies reveal that obesity and type II diabetes are two major modifiable risk factors for this highly lethal disease (2). A better understanding of the mechanistic effects of obesity and diabetes on the pancreas would pave the way for new strategies for prevention or therapy of pancreatic cancer (2).

Over the past decade, at least a dozen molecular pathways implicated in pancreatic carcinogenesis have been unraveled. Moreover, global gene expression profiling and the use of microarray databases have facilitated the identification of hundreds of genes that are differentially expressed in pancreatic cancer (3). Validation of these genes as biomarkers for early diagnosis, prognosis, or treatment efficacy, however, is still incomplete. Although several studies indicated the plausible contribution of some genetic factors to the development and progression of pancreatic cancer, common genetic variants associated with this disease remain poorly understood. A Japanese genome-wide association study in 991 cases of invasive pancreatic ductal adenocarcinoma and 5,209 controls identified single-nucleotide polymorphisms present in the three chromosomal loci 6p25.3, 12p11.21, and 7q36.2 that were significantly associated with increased risk of pancreatic cancer (4).

The relatively low survival rate of patients with pancreatic cancer is primarily due to a late diagnosis and the absence of effective treatments. Standard current pancreatic cancer therapies, such as gemcitabine or erlotinib, are not very effective, emphasizing the need for novel chemopreventive and better therapeutic strategies for this disease. Synthetic and naturally occurring substances have been evaluated in cell culture and in vivo animal models for their pancreatic cancer chemopreventive potential (5). Some chemopreventive agents, such as curcumin or resveratrol, were reported to sensitize pancreatic cancer cells to standard chemotherapeutic drugs (e.g., gemcitabine or erlotinib). However, only a few clinical trials of these agents have been completed or initiated in this setting, and more are needed. Pancreatic cancer risk increases with age, but genetic and environmental factors also can increase the risk. Premalignant epithelial lesions of the pancreas have been used for screening. Development of chemopreventive agents is particularly needed for individuals with the aforementioned risk factors and for patients with premalignant pancreatic lesions (5).

Inflammation is implicated in the majority of human malignancies, including pancreatic cancer (6–9), and chronic inflammation is estimated to contribute to about 15% to 20% of all human cancers. Prolinflammatory enzymes, such as cyclooxygenase-2 and inducible nitric oxide synthase, and cytokines, including tumor necrosis factor-α (TNF-α), are overexpressed and/or overproduced in inflammation-associated carcinogenesis. The expression of these proinflammatory proteins is regulated primarily by the transcription factor NF-κB. Because NF-κB is highly active both in inflammatory cells, such as macrophages,
and in cells found in inflamed tissues, it is recognized as a key mediator of inflammation (10). Moreover, constitutive activation of this redox-sensitive transcription factor is frequently observed in many human tumor specimens and is associated with a poor prognosis. Cells having abnormally elevated NF-κB activity are more resistant to drug and radiation therapies. A high level of NF-κB contributes to the impaired ability of a cell to undergo apoptosis, which would eliminate defective or damaged cells. NF-κB normally is sequestered in the cytoplasm in an inactive complex with the inhibitor of NF-κB α (IκBα). Phosphorylation and subsequent ubiquitination of IκBα render this inhibitory protein inactive through proteasome-mediated degradation and thereby release NF-κB for translocation into the nucleus. The key enzyme that is involved in IκBα phosphorylation is IκB kinase (IKK), especially IKKβ (11, 12).

In addition to NF-κB, signal transducer and activator of transcription 3 (STAT3) is recognized as an important mediator of inflammation associated with tumor promotion. Persistently activated STAT3 stimulates proliferation, survival, and invasion of tumor cells and suppresses antitumor immune responses (13, 14). Recent attention has focused on the interplay or cross talk between NF-κB and STAT3 in controlling the cross talk or physiologic interactions of malignant cells with the tumor microenvironment, especially with inflammation and immune cells that infiltrate tumors (15). Thus, the IKK/NF-κB and STAT3 pathways seem to be central signaling hubs in inflammation-mediated tumor promotion and progression (16). Furthermore, maintenance of constitutively elevated NF-κB activity requires STAT3, which is also frequently activated in cancer. STAT3 prolongs retention of NF-κB in the nucleus, which occurs through p300-mediated acetylation of RelA/p65 (17). The interplay between NF-κB and STAT3, however, does not seem to be unidirectional. Therefore, NF-κB might also control the activation of STAT3, specifically in intestinal epithelial cells. This control can be achieved by recruiting bystander cells (i.e., myeloid cells) that secrete STAT3-activating cytokines such as interleukin-6 (IL-6) and TNF-α by inducing the transcription of genes that encode these proinflammatory cytokines (16).

The suggestion has been made that IL-6 released by either myeloid cells or T lymphocytes would promote epithelial cell proliferation through STAT3 activation. In support of this speculation, deletion of the gene encoding IL-6 and the intestinal epithelial cell–restricted deletion of STAT3 both suppressed the development of colitis-associated cancer (ref. 16 and references therein). In this context, the inflammation microenvironment is as important as the tumor cell population, even in the formation of tumors that are not caused by chronic inflammation (18). This idea led to the suggestion that the tumor microenvironment is frequently activated in cancer. STAT3 prolongs retention of NF-κB in the nucleus.

3 Besides STAT3, there are many factors that can cause a retention of NF-κB in the nucleus.


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References

Breaking the NF-κB and STAT3 Alliance Inhibits Inflammation and Pancreatic Tumorigenesis

Young-Joon Surh, Ann M. Bode and Zigang Dong