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NF-κB Fans the Flames of Lung Carcinogenesis

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Abstract

This perspective on Deng et al. (beginning on p. ***XXX*** in this issue of the journal) examines the link between nuclear factor kappa B (NF-κB) and lung tumorigenesis. Experiments in genetically engineered mouse models of lung cancers are elucidating pro-tumorigenic roles of NF-κB activation in lung cancer pathogenesis. Our growing understanding of the tumor-promoting NF-κB downstream effector pathways could lead to the development of novel approaches for lung-cancer therapy and chemoprevention.

It is becoming increasingly recognized that the pathogenesis of cancer reflects the dynamic interplay between transformed cells and normal host elements within the tumor microenvironment (1–3). Although myriad genetic and epigenetic alterations in tumor suppressors and oncogenes underlie autonomous defects of cancer cells, host cells play additional key roles in modulating oncogenic pathways. Secreted and membrane-bound factors produced in the stroma may stimulate tumor-cell growth and survival during early stages of transformation; in more advanced disease, these factors may evoke changes in tumor-cell differentiation and modify the extra-cellular matrix so as to foster invasion and metastasis. An intricate cross-talk between vascular components and bone-marrow-derived cells is also critical to generating a robust blood supply that satisfies the escalating metabolic demands of progressing tumors (4,5).

Histopathologic studies have established that immune cells are frequently an important component of the tumor microenvironment throughout disease development, but the precise dynamics between immune responses and cancer progression remain to be clarified fully (6–12). First, experiments in murine models suggest that some host reactions may eliminate nascent tumors or restrain the growth of established disease through a process called “immunoediting” that produces a state of immune equilibrium (13). Consistent with immunoediting, clinical investigations have demonstrated that dense, intra-tumoral cytotoxic and memory-type cluster of differentiation 8 $(CD8)^+$ T cell infiltrates are associated with a decreased incidence of metastasis and a prolonged survival of patients with multiple cancer types (6,8–10). Second, and in contrast to these findings, a strong link between chronic inflammation and cancer has been known at least since the pioneering nineteenth-century observations of Virchow on this phenomenon (14). The analysis of genetically engineered murine tumors has begun to provide a mechanistic basis for this association, uncovering the

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potent tumor-promoting activities of macrophages, granulocytes, mast cells, and some T lymphocytes (15–17). In a third scenario of host reactivity, immune infiltrates may not be present within tumors, perhaps indicating a lack of immune recognition or the successful evasion of immune control (18).

One variable that might influence the evolution of the anti-tumor immune response is the mixture of cytokines generated in the tumor microenvironment (2,19). Oncogenic stress or tissue damage induced by transformation may provoke cytokine production by both cancer cells and normal stromal elements; this production in turn drives the recruitment of other immune cells that may amplify or modify the cytokine balance. A predominance of interferon-α (IFN-α) and IFN-γ release by cancer cells and stromal elements may elicit a protective reaction through the combined effects of enhancing tumor-cell immunogenicity and stimulating lymphocyte-mediated cytotoxicity (11,12,20). In this way, a particular cytokine profile may effectively control cellular stress and attenuate tissue damage.

The failure to resolve tissue injury, however, can lead to persistent cytokine production with an intensification of tissue destruction, creating a feed-forward, tumor-promoting circuit that resembles, in Hal Dvorak’s metaphor, a wound that fails to heal (21). Unresolved inflammation is a major etiologic factor in a wide range of malignancies, and inflammation induced by persistent microbial infection is a primary cause of stomach and liver carcinomas (15,22). Furthermore, cigarette smoke and asbestos, the most important environmental factors that predispose to lung cancer, induce robust inflammatory reactions as well (23,24). In accordance with a pathogenic role for tumor-promoting inflammation, the long-term use of anti-inflammatory compounds correlates with a reduced incidence of gastrointestinal malignancies and lung cancers in humans (22,25).

Recent work has significantly expanded our understanding of the molecular basis by which persistent cytokine production fosters tumorigenesis. One major pathway involves the signal transducer and activator of transcription (STAT) proteins (26). These products translate information obtained from cytokine receptors into gene-expression programs that include many factors involved in tumor progression, such as cell-cycle proteins, anti-apoptotic molecules, angiogenic factors, and matrix metalloproteinases. STAT-3 plays an especially prominent role in tumor-promoting inflammation, whereupon it may become activated in response to a variety of cytokines produced in the tumor microenvironment, such as interleukin 6 (IL-6), IL-10, and IL-23 (26).

A second pathway that cooperates with STAT-3 in tumor formation is the nuclear factor kappa B (NF-κB) pathway. NF-κB refers to a family of transcription factors that regulate multiple inflammatory cytokines and mediators, adhesion molecules, anti-apoptotic proteins, and angiogenic factors (15,22,27). NF-κB proteins are normally restricted to the cytoplasm by a set of inhibitory proteins, but following receptor-mediated activation of IκB kinases (IKKs), the inhibitors are degraded, thereby allowing nuclear import of the transcription factors. Studies of inflammation-induced colon carcinogenesis have revealed key roles for NF-κB in both tumor cells and myeloid cells (15,22,27).

In this issue of the journal, Deng et al. (28) show that loss of the G protein-coupled receptor family C type 5a gene (*Gprc5a*) in mouse lung epithelial cells resulted in NF-κB activation accompanied by aberrant cytokine and chemokine expression *in vivo* and *in vitro*. This altered mixture of cytokines recruited inflammatory macrophages to the mouse lung, engendering a chronic inflammatory state that stimulated lung epithelial-cell proliferation and eventually pulmonary adenocarcinomas.

Along with this work of Deng et al., four other recently published studies (29–32) highlight the complex pathogenic role of NF-κB and inflammation in lung tumorigenesis. Meylan et al.

(31) employed advanced genetic tools in demonstrating that the concomitant activation of *Kras* and loss of *p53* triggers NF-κB and downstream effector pathways in mice. They then inhibited the NF-κB pathway, which suppressed *de novo* Kras/p53-mutant-driven lung cancer initiation and caused a significant regression of established cancers. Independently, Barbie et al. (29) used a systematic functional genomic approach with a short hairpin RNA (shRNA) screen to identify the serine-threonine kinase gene TANK-binding kinase 1 (*TBK1*) as a gene whose expression is essential for the survival of KRAS-driven human non-small-cell-lung-cancer cell lines through its activation of the NF-κB pathway. These intriguing observations not only identify a potentially drug-sensitive target (TBK1) that is essential for the survival of Kras-driven cancers, but also more generally implicate the NF-κB pathway as a target for lung cancers that depend on Kras (29). In complementary work, the Karin laboratory (32) provided compelling evidence that chronic lung inflammation caused by tobacco smoke promotes lung cancer development in both carcinogen-initiated and mutant Kras-driven models. In these systems, inactivation of the NF-κB pathway in myeloid cells attenuated tumor development, implicating a host contribution to lung-cancer formation. Last, Houghton et al. (30) identified a novel mechanism of inflammation-driven lung cancer in the Kras-derived model. Their series of genetic and biochemical studies demonstrated that neutrophil elastase generated by tumor-infiltrating neutrophils can gain access to an endosomal compartment within tumor cells; this action facilitated the degradation of insulin receptor substrate, which in turn enhanced tumor proliferation through the phosphatidylinositol pathway. These five studies (including Deng et al.) underscore the interplay of tumor cells and myeloid elements in lung carcinogenesis and the common theme of NF-κB-pathway activation in this interplay.

As with all innovative studies, however, the results of Deng et al. raise many additional questions for investigation. What is the precise molecular mechanism by which *Gprc5a* regulates the NF-κB pathway? Since loss of *Gprc5a* leads to activation of the pathway and promotes lung inflammation and tumorigenesis, might Gprc5a activation lead to NF-κB suppression? Understanding this interaction more fully might yield new targets for chemotherapy and/or chemoprevention of lung cancer. What other genetic events are required for tumor progression in the lung cancers facilitated by knockout of *Gprc5a*? Comprehensive genomic and proteomic analyses of *Gprc5a*$^{-/-}$ murine lung cancers might uncover novel genes and pathways that are relevant to lung cancer. Although the authors indicate that *Gprc5a*$^{-/-}$-cultured epithelial cells, which manifest NF-κB activation, are wild type for both *Kras* and *p53*, what is the status of these two essential genes upon progression to adenocarcinoma?

In a broader context, is the requirement for NF-κB activation limited to Kras-driven lung cancers, or does this requirement apply to other types of non-small cell lung cancers as well? Previous studies have revealed a correlation between the extent of pulmonary inflammation and Kras mutational status in human lung cancers, but this work did not take into account the status of p53 or examine other genetic subsets (33). Do other known drivers of lung oncogenesis, such as epidermal growth factor receptor (EGFR), epidermal growth factor receptor 2 (HER2), or echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase (EML4-ALK) fusion also engage the NF-κB pathway? If so, then perhaps a chemoprevention trial with an NF-κB inhibitor in a high-risk population should be contemplated. The *Gprc5a*$^{-/-}$ mouse model and other genetically engineered lung cancer systems might prove instrumental in evaluating this approach preclinically. One caveat to the use of broad-spectrum NF-κB inhibitors, however, is that they might also suppress protective cytotoxic responses. Indeed, a more-detailed understanding of the critical tumor-promoting NF-κB downstream effectors might identify more-selective targets for therapy or prevention, thereby preserving effective anti-tumor immunity. Such approaches also might be combined effectively with inhibition of STAT-3 since this pathway not only fuels tumor promotion but also mediates immune escape. In short, the best way to extinguish the flames of lung carcinogenesis just may involve blocking the “oxygen” provided by NF-κB.

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