A new role for NFκB in immunosurveillance and its implications for cancer immunotherapy

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The activation of NFκB in the tumor microenvironment is associated with inflammatory responses that promote disease progression. We have recently found that the activation of NFκB in the tumor also regulates T cell-mediated immune responses, hence actively participating in cancer immunosurveillance. These findings call for reassessment of the function of NFκB within neoplastic lesions and open new perspectives for anticancer immunotherapy.

NFκB is often activated in a constitutive manner by malignant cells of multiple types, hence promoting tumor growth and metastasis.1,2 Recent studies have identified a critical role for NFκB in murine models of KRAS-elicited lung carcinogenesis.3,4 Tumor infiltration by T lymphocytes is generally associated with active immunosurveillance and hence with improved patient survival. The role of intratumoral NFκB in the regulation of T cell-mediated anticancer immune responses, however, is not clear. Of note, the genes first shown to be under the transcriptional control of NFκB include those coding for MHC class I molecules, β2-microglobulin and interferon (IFN)β, all of which are involved in cellular (antitumor) immune responses. Consistent with an overall pro-tumor activity, NFκB might also dampen antitumor T-cell responses, for example by recruiting and/or boosting the function of immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs). To get further insights into these functionally distinct aspects of the NFκB biology, we investigated how the activity of NFκB in the tumor impacts anticancer T cell-mediated immune responses.5

We observed that the expression of a model antigen by Lewis lung carcinoma (LLC) elicited a spontaneous antitumor T-cell response in mice. Of note, such a response was unable to eradicate subcutaneous tumors or lung metastases. Nonetheless, enhancing the activity of NFκB in the neoplastic lesions enabled the T-cell response elicited by LLC to reject both subcutaneous and metastatic lesions. We found that an increased recruitment of T cells to neoplastic lesions and metastases was critical for the NFκB-dependent rejection of LLC. Microarray studies revealed that multiple chemokines that influence T lymphocytes and myeloid cells are regulated by NFκB in LLC. Among these mediators, chemokine (C-C motif) ligand 2 (CCL2) turned out to mediate an especially important role in the NFκB-dependent rejection of LLC lesions. Of note, stimuli that promote NFκB activation (in particular, the administration of IFNα and a Toll-like receptor agonist) have recently been shown to promote the recruitment of T cells to colorectal cancer lesions.6 Collectively, these findings suggest that NFκB not only mediates pro-tumor functions, but also regulates T cell-dependent anticancer immune responses.

The role of Type I (IFNα/β) and Type II (IFNγ) IFNs in anticancer immunosurveillance is well documented.7,8 In particular, previous studies suggest that IFNα/β may be play a prominent role in the priming of antitumor T cells, while IFNγ may provide a major contribution to the effector stage of the response.7,8 Our findings suggest that NFκB is important for the effector stage of anticancer immune responses, but do not rule out an involvement of NFκB in T-cell priming. NFκB might also modulate and complement the antitumor activity of Type I and Type II IFNs. As discussed below, the cross-talk between the NFκB and IFN signaling pathways may turn out to be pivotal in determining whether neoplastic lesions progress or regress, especially in early stages of carcinogenesis.

To investigate the potential pro- and anti-tumor activity of NFκB in human lung cancer, we delineated an NFκB gene expression signature specific for lung cancer cells.9 Interestingly, we found that high expression levels of NFκB-regulated pro-inflammatory factors such as the myeloid cell-receiving factors chemokine (C-X-C motif) ligand (CXCL)1/3 and interleukin-8 (IL-8) was associated with poor patient survival. Conversely, high expression of NFκB-regulated genes that may be involved in T-cell responses, including CCL2, intercellular adhesion molecule 1 (ICAM1) and

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lymphotixin β (LTB), was associated with improved disease outcome. Of note, the expression levels of multiple pro-inflammatory genes positively correlated with each other but not with those of genes involved in immunosurveillance or with T-cell infiltration. These results suggest that NFκB-regulated inflammatory and immune responses may predominate in different tumors, resulting in a differential impact on disease outcome. Our findings raise several key questions on the activity of NFκB in tumors and potentially open novel avenues for anticancer immunotherapy.

It will be important to determine how the pro- vs. anti-tumor functions of NFκB are mutually regulated. One possibility is that regulators of the alternative NFκB activation pathway such as Lymphotixin α/β (LT α/β) and tumor necrosis factor (ligand) superfamily, member 14 (TNFSF14, also known as LIGHT) specifically control the ability of NFκB to transactivate genes involved in immunosurveillance (Fig. 1). In human lung cancer, the expression of LTB, which encodes for LTβ, was associated more robustly with T cell- than with myeloid cell-recruiting chemokines. Previous studies have defined key functions for IFNα/β and IFNγ in antitumor T-cell priming and effector responses. In particular, IFNγ has been shown to stimulate the expression of T cell-recruiting chemokines such as CXCL9–11. Besides promoting tumor infiltration by antitumor cytotoxic T cells, these factors may also exert direct anti-angiogenic effects.

Figure 1. Potential mechanisms involved in the pro- and anti-tumor functions of NFκB. The activation of NFκB by oncogenes or pro-inflammatory cytokines drives the expression of pro-inflammatory mediators including factors that recruit myeloid cells such as chemokine (C-X-C motif) ligand (CXCL)1/3 and interleukin-8 (IL-8). Upon recruitment, myeloid-derived suppressor cells (MDSC) may dampen antitumor immune responses. In addition, multiple chemokines may directly stimulate angiogenesis and metastatic dissemination. Conversely, in the presence of cytokines such as interferon (IFN)γ, which may be produced by natural killer (NK) or T cells, NF-κB may cooperate with IFNγ-induced transcription factors to stimulate the secretion of high levels of T cell-recruiting chemokines, such as CXCL9–11. Besides promoting tumor infiltration by antitumor cytotoxic T cells, these factors may also exert direct anti-angiogenic effects.
identify patient subsets that are most likely to benefit from this immunotherapeutic regimen. At present, virtually no reliable biomarkers are available to predict clinical responses to immunotherapy, but it is generally believed that an immunologically active tumor microenvironment may be beneficial. Based on our findings, it will be interesting to determine whether increased NFκB activity indicates the presence of a tumor microenvironment that is favorable to immunotherapy.

The ability of specific oncogenes to activate NFκB is well documented. For instance, KRAS, which is one of the oncogenes most commonly mutated in human tumors, is a key driver of NFκB activation (Fig. 1). Since no KRAS-targeting therapies are currently available, it will be worth exploring whether tumors bearing KRAS mutations and exhibiting high NFκB activity are sensitive to immunotherapy.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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