Inflammation and Cancer: IL-6 and STAT3 Complete the Link

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There is growing evidence that tumors are sustained and promoted by inflammatory signals from the surrounding microenvironment. Two papers by Grivennikov et al. and Bollrath et al. in this issue of *Cancer Cell* demonstrate the importance of the interleukin-6 family of proinflammatory cytokines and their downstream effector STAT3 in colitis-associated colon cancer.

Inflammation is now recognized to be important in the pathogenesis of many types of malignancies. For example, even with close surveillance and appropriate treatment of inflammatory bowel disease (IBD), the risk of colorectal cancer in the setting of ulcerative colitis remains substantial. Given its important role in mediating inflammatory signals, attention has been focused on the role of NF-κB and its upstream activator, IKKβ, in mediating the link between inflammation and cancer. NF-κB plays a central role in the activation of numerous proinflammatory cytokines in multiple cell types, including macrophages, T cells, and epithelial cells. Through conditional deletions of *IKK*β, NF-κB has been shown to play a procarcinogenic role principally in immune (myeloid) cells but also in epithelial cells (Greten et al., 2004; Maeda et al., 2005). Given its tight link to NF-κB, IL-6 was an early candidate for the myeloid-derived factor that could promote tumorigenesis. Human patients with colon cancer were known to have elevated levels of IL-6. Michael Karin's group drew attention to the elevated levels of IL-6 in murine models (azoxymethane plus dextran sodium sulfate [AOM + DSS]) of colitis-associated cancer (CAC) (Greten et al., 2004) and later reported that the gender bias in liver cancer susceptibility could be largely explained by the higher serum levels of IL-6 exhibited by males (Naugler et al., 2007).

IL-6 belongs to a larger family of cytokines that signal through a common signaling receptor, gp130, expressed on many cell types. IL-6 binds to the sIL-6R receptor (gp80, present either on the cell surface or in solution), which then induces dimerization of gp130 chains resulting in activation of the associated Janus kinases (JAKs) (Figure 1A). JAKs phosphorylate gp130, leading to the recruitment and activation of the STAT3 and STAT1 transcription factors as well as other molecules (SHP2, Ras-MAPK, and PI3K) (Heinrich et al., 2003). The importance of IL-6 signaling in mediating tumorigenesis has been examined in some studies, and the results are equivocal, whereby IL-6 inhibits the in vitro growth of some cell types but appears to promote the in vivo growth of tumors in models of prostate, breast, and lung cancers (Knupfer and Preiss, 2007). However, none of these earlier studies examined the role of IL-6 in an inflammatory model of de novo tumorigenesis.

In this issue of *Cancer Cell*, two elegant papers demonstrate that STAT3, a nuclear transcription factor downstream of gp130, is necessary for the growth of colitis-associated colorectal cancer in mice (Grivennikov et al., 2009; Bollrath et al., 2009). Both groups generated mice deficient for STAT3 in intestinal epithelial cells (IECs) by crossing *Stat3* floxed mice to *villin*-Cre transgenic mice and demonstrated that both CAC tumor size and incidence in the AOM + DSS model of CAC were markedly reduced in mice lacking STAT3 in IECs. Grivennikov et al. demonstrate that the phenotype is remarkably similar to that seen in IL-6 knockout mice, and they show that IL-6 is produced by primarily by bone marrow-derived myeloid cells. Conversely, exogenous administration of IL-6 to mice during tumor initiation resulted in an increase in tumor burden and multiplicity, while IL-6 administration during the late stages of CAC growth increased tumor burden. In the study by Bollrath

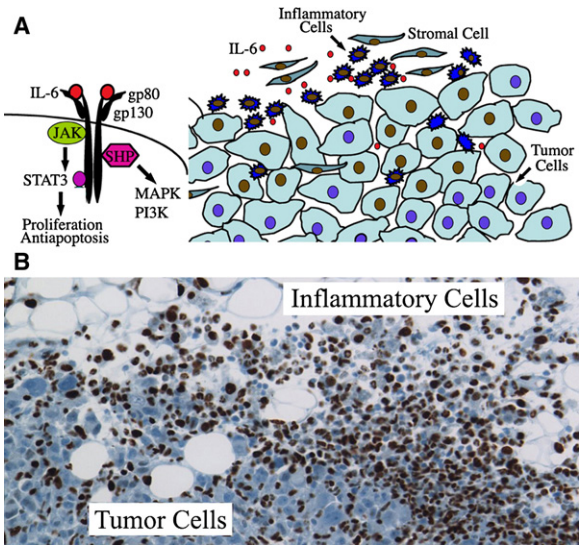

Figure 1. Autocrine IL-6 Mediates gp130/JAK/STAT3 Signaling and Promotes Tumorigenesis
(A) IL-6 produced by inflammatory and stromal cells within the tumor microenvironment binds to gp80/gp130, leading to Janus kinase (JAK) activation and phosphorylation of STAT3, which regulates expression of genes mediating proliferation and preventing apoptosis. (B) Activated STAT3 (indicated by brown immunostaining) is found in tumor cells and inflammatory cells particularly on the invasive edge of tumors. (A breast carcinoma example is shown.)

et al., the investigators also employed *gp130*$^{Y757F/Y757F}$ mice, which contain a mutant gp130 receptor molecule that shows enhanced STAT3 activity, to demonstrate a role for increased STAT3 activation in the acceleration of colorectal cancer. Bollrath et al. also point to a possible role for IL-11, an IL-6 family member, as suggested from an earlier study of gp130 in gastric cancer (Ernst et al., 2008).

The studies by Grivennikov et al. and Bollrath et al. suggest that STAT3 appears to function through increased epithelial proliferation and protection against AOM- and DSS-induced epithelial cell apoptosis. A similar requirement for STAT3 in de novo skin tumorigenesis was established by John DiGiovanni's group (Chan et al., 2004). In this two-stage chemical carcinogenesis model, the mutagen 7, 12-dimethylbenz[a]anthracene (DMBA) led to a marked increase in the number of keratinocyte stem cells undergoing apoptosis in STAT3-deficient mice compared with nontransgenic littermates and a corresponding decrease in the proliferative response to 12-O-tetradecanoylphorbol-13-acetate (TPA). Thus, STAT3 can mediate tumorigenesis by protecting cells from apoptotic stimuli and by promoting cell-cycle progression.

The studies by Grivennikov et al. and Bollrath et al. add to the growing literature regarding the oncogenic importance of persistently activated STAT3 in many types of cancer, including colorectal cancer (Yu and Jove, 2004). The mechanisms of constitutive STAT3 activation include (among others) both autocrine and paracrine production of IL-6 leading to STAT3 phosphorylation. The current studies suggest a model whereby STAT3-dependent tumorigenesis is mediated by IL-6 signals from the tumor microenvironment, and indeed, STAT3 activation in human tumors is often observed at the invasive front of tumors adjacent to inflammatory cells (Figure 1A).

As a transcription factor, STAT3 principally mediates its effects by regulating gene expression. A number of STAT3 target genes including those encoding Bcl-X_L, survivin, Hsp70, cyclin D1, c-Myc, and others were identified to be upregulated during tumor formation in these current studies that may indeed be responsible for mediating CAC. However, not all putative STAT3 target genes were consistently upregulated. It is suggested by Bollrath et al. that STAT3 may enhance nuclear localization of β-catenin (a known player in colorectal carcinogenesis), and it is of interest whether there is crosstalk between the Wnt/β-catenin pathway and the IL-6/gp130/STAT3 pathway.

Perhaps the most interesting aspect of these studies is the observation that DSS-induced mucosal inflammation or colitis was markedly increased in both IL-6-deficient mice and in mice lacking STAT3 in IECs, which correlated with an increase in the expression of proinflammatory cytokines within the colonic mucosa. It is unclear, however, how injured IECs lacking STAT3 result in enhanced production of inflammatory cytokines and a lower risk of cancer. One highly speculative hypothesis is that the increase in AOM + DSS-induced epithelial apoptosis in the STAT3-deficient mice is sufficient to mediate enhanced recruitment of acute inflammatory cells that produce proinflammatory cytokines. It is even possible that this acute inflammation may be antitumorigenic, and that STAT3 may influence the degree or type of inflammation and as a result modulate tumor formation. Interestingly, in the Grivennikov et al. study, the number of regulatory T cells increased and Th17 cells decreased in an IL-6-dependent manner. Several recent studies have linked IL-6 to Th17 differentiation, and further work is clearly needed to determine whether the qualitative immune cell makeup of the AOM + DSS-induced colitis and tumors differs between wild-type versus STAT3 IEC-deficient or IL-6-deficient animals.

In summary, the studies by Grivennikov et al. and Bollrath et al. demonstrate the significance of IL-6/STAT3 signaling in promoting CAC. Furthermore, their findings clearly suggest that inhibitors of IL-6 signaling such as blocking antibodies or JAK inhibitors, which are presently in clinical trials for other diseases, should be considered for the treatment of patients with colorectal cancer.

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