# IL6 Signaling in Cancer: Not Always Bad News

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Understanding the molecular mechanisms that underpin the pleiotropic effects of IL6 in disease are critical to better inform when this cytokine should be therapeutically targeted to provide the most benefit to patients. This is particularly important for cancer and other pathologic conditions strongly linked to chronic inflammation. Shriki and colleagues provide mechanistic evidence that IL6 protects against chronic liver injury and its ensuing tumor development, thereby challenging the prevailing paradigm that IL6 always acts as a tumor-promoting cytokine. These observations contribute to an emerging view of dichotomous and complex activities of IL6 in solid malignancies and will help understand which patients under which circumstances receive the most benefit from therapies that interfere with IL6 signaling.

*See related article by Shriki et al., p. 4766*

In his classic 1986 paper, Harold Dvorak described cancers as caricatures of "Wounds that do not heal." This still provides a useful conceptual framework to help understand how signaling pathways optimized for wound healing become hijacked for tumor progression. The IL6 family of cytokines and its associated latent transcription factor STAT3 provide a "poster child" to illustrate the Dvorak paradigm. Indeed, this signaling axis provides an important molecular link by which cancer-associated inflammation fuels tumor promotion across a wide range of solid malignancies both as a cancer cell–intrinsic mechanism as well as dampening the antitumor response by immune cells (1). However, examples emerge where genetic ablation of *Stat3* in the transformed epithelium of mice facilitates tumor progression. The latter has been attributed to STAT3's functional overlap with STAT1 and associated compensation by STAT1 in *Stat3*$^{KO}$ intestinal epithelium (2), or to the capacity of STAT3 to interfere with NF-κB signaling, thereby suppressing myeloid tumor infiltration and vascularization in lung adenocarcinoma (3).

The article by Shriki and colleagues in this issue of *Cancer Research* (4) reexamines the role of IL6/STAT3 signaling in the context of liver inflammation and specifically in the physiologically important setting of chronic inflammation as a predisposing etiology for nonalcoholic steatohepatitis (NASH), which has an estimated prevalence of 10% across the U.S. population. The authors resort to a genetic model based on deficiency of the multidrug resistance gene 2 (*Mdr2*), which results in regurgitation of bile from leaky ducts into the portal where it triggers and sustains periductal inflammation, cholestatic hepatitis, and fibrosis, which collectively mimics NASH in humans. Not only have humans with mutations in the *Mdr2* ortholog *MDR3/ABCB4* an increased risk for dysplasia and subsequent development of hepatocellular carcinoma (HCC), but the preneoplastic lesions in *Mdr2*$^{KO}$ mice also spontaneously develop over time into metastatic liver cancer when mice are 4 to 6 months of age. Intriguingly, while both genders of *Mdr2*$^{KO}$ mice develop these pathologies, they occur earlier in females than in males.

It would have been reasonable to assume that the development of disease in *Mdr2*$^{KO}$mice would have been fueled by IL6, but Shriki and colleagues found the exact opposite: IL6-deficient *Mdr2*$^{KO}$ compound–mutant mice showed exacerbated chronic liver injury and hepatic fibrosis, along with increased tumor burden when aged. Similar effects were also observed in adult mice upon IL6 neutralization with an anti-IL6 mAb similar to those used clinically for the treatment of the lymphoproliferative Castleman disease. Finally, the authors investigated the contribution of IL6 trans-signaling, a mechanism whereby ligands bind to a membrane-cleaved, soluble isoform of the cognate IL6 receptor (IL6R) subunit to extend responsiveness to cells in which expression of the membrane-bound counterpart is limiting. Inhibition of IL6 trans-signaling also enhanced inflammation and HCC burden in *Mdr2*$^{KO}$;sgp130Fc compound mutant mice, which express a soluble version of the shared GP130 receptor subunit that acts as a trap for the IL6/soluble IL6R complex.

Consequently, the authors established that the anti-inflammatory and tumor-suppressing activity of IL6 in the context of Mdr2-deficiency is specific to hepatocytes rather than cholangiocytes, because hepatocyte-specific *Stat3* ablation also aggravated bile acid–induced liver injury, inflammation, and HCC burden. This finding is consistent with studies that GP130-specific manipulation of STAT3 signaling affects hepatocyte recovery from concanavalin A–induced and T-cell–mediated injury (5). Indeed, STAT3-dependent induction of anti-apoptotic and proliferation-supporting transcriptional programs in hepatocytes, as observed in many other (pre)neoplastic epithelial cell types (1), is likely to also play a role in Mdr2-deficient tumors, as the size of individual tumors in IL6 signaling–deficient animals remains smaller than their proficient counterparts. An interesting confirmatory twist to the involvement of IL6 signaling arises from a previous observation that estrogen can transcriptionally suppress IL6 gene expression (6). This observation allows the authors to reconcile the increased HCC susceptibility of female *Mdr2*$^{KO}$ mice, where ovariectomy, and presumably the associated rise in IL6, reduced liver injury and inflammation, and also suppressed the subsequent formation of dysplastic nodules and frank HCCs.

But what is the underlying mechanism that results in this apparent paradoxical finding? The authors note that the level of IL6 is moderately elevated in livers and hepatocytes of *Mdr2*$^{KO}$ mice, which is in stark contrast to the massive induction of IL6 expression in models of acute liver injury, inflammation, and carcinogen-induced HCC formation (6). Moderate, but persistent elevation of IL6 is a classic hallmark associated with, and possibly a driver of, cellular senescence and the senescence-associated secretory phenotype (SASP). Indeed, SASP-associated genes are reduced in *Mdr2*$^{KO}$ mice with IL6-signaling deficiency, leading the authors to speculate that IL6-dependent senescence confers a tumor-suppressing role at the stage of preneoplastic lesions. In contrast, interference with IL6 trans-signaling, which provides an inflammation-associated "boost" to classical signaling

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through membrane-bound IL6R (7), results in a "collapse" of the SASP response, thus allowing preneoplastic hepatocytes to escape and to become fully transformed.

The last piece to the puzzle is to understand why deficiency of IL6 signaling results in increased liver inflammation and the formation of preneoplastic lesions, which was not fully explored by Shriki and colleagues. The chronic injury triggers a wound-healing response associated with an initial influx of neutrophils and macrophages to provide a first line immune defense as well as to trigger epithelial proliferation and matrix remodeling. IL6 is an important orchestrator of the (hepatic) acute phase response and can promote proliferation, which is locally augmented by additional trans-signaling via myeloid cell–derived proteases that cleave membrane-bound IL6R. Thus in the absence of IL6 signaling, the wound healing response remains impaired and likely results in excessive exposure of hepatocytes to neutrophil-derived reactive oxygen metabolites. In turn, this increases the chance for mutagenic insults and consequently the development of preneoplastic lesions as observed in the *Mdr2*$^{KO}$;*Il6*$^{KO}$ mice.

Parallels can also be drawn between IL6 and the related cytokine IL11. Both cytokines signal through GP130/STAT3, albeit engaging via their ligand-specific IL6R or IL11R receptor subunits, and regulate overlapping genes. This functional overlap points towards some degree of redundancy whereby IL11 can play compensatory roles in its absence of IL6 as documented during acetaminophen (APAP)-induced liver injury, where IL11R-deficient mice display increased systemic levels of IL6 in the serum (8). While this has not been explored in the study by Shiriki (4), the unexpected observation of IL6 as a tumor suppressor could be a consequence of a compensatory spike in IL11. The authors indicate a marked increase in hepatic fibrosis in the absence of IL6. Indeed, IL11 is considered as a critical driver of fibrosis (9) and therefore one could speculate that the hepatic fibrosis observed in *Mdr2*$^{KO}$;*Il6*$^{KO}$ mice could result from compensatory induction of IL11. Similarly, IL11 has been reported to have confounding roles during liver injury (9). Akin to its regenerative properties, Nishina and colleagues uncovered a protective role for IL11 during APAP-induced liver injury in response to oxidative stress (8).

A comprehensive understanding of the kinetics, dynamics, temporal, and spatial aspects of IL6 signaling is critical to inform when therapies that target IL6-signaling should be employed for the management of chronic inflammatory diseases and cancer. Indeed, studies indicate that blockade of IL6/IL6R binding leads to an increase in systemic IL6 (7). This can have ramifications for patients undergoing long-term IL6-targeting therapies, especially given the well-appreciated pleiotropic effects of IL6. Indeed, liver injury and toxicity have been observed following repeated administration of therapeutic antibodies directed against IL6 or IL6R (10); these observations align with the findings in Shriki and colleagues.

Accumulating evidence clearly suggests that IL6 signaling can be protective against pathologic conditions such as liver injury and HCC, which goes against the prevailing dogma that IL6/STAT3 is tumor-promoting. The emerging narrative of IL6 as a mediator of wound healing and antitumor responses coincides with the concept that tumors arise from unresolved inflammation. Importantly, IL6 signaling has proven to be more nuanced than previously thought. Thus, it is imperative we elucidate the full spectrum of IL6 biochemistry and its consequential biological responses in disease, as this has implications in the appropriate and effective use of IL6-targeting therapies.

## Authors' Disclosures

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