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Commentary

IL-11 drives postsurgical hepatocellular carcinoma recurrence

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Hepatocellular carcinoma (HCC) remains a major world-wide health issue and is the third leading cause of cancer-related mortality [1]. Effective therapy for HCC is a major challenge, in part due to inadequate understanding of its molecular characteristics. Although surgery is applied as the first-line of treatment for HCC, the liver has a robust ability to regenerate creating a microenvironment that is fit for regrowth of the tumor. Furthermore, surgery can induce metastasis through mechanisms involving increased circulating tumor cells, neutrophil recruitment, barrier destruction, and extracellular matrix and vasculature remodeling [2].

In this issue, Wang et al. report that IL-11/STAT3 signaling axis drives postsurgical HCC recurrence by promoting cell proliferation [3]. The authors use a variety of experimental techniques involving perforation and hepatectomy to demonstrate that wounding process trigger HCC outgrowth via upregulation of IL-11. They supplement these studies, with IL-11 knockout (KO) mice, which demonstrated a significantly decreased ability for tumor regeneration, a tumor extrinsic role of IL-11. Additionally, the authors then show that inhibiting IL-11 signaling in vitro, via siRNA targeting IL-11/STAT3 signaling, significantly increased apoptosis, a tumor intrinsic role of IL-11 signaling.

STAT3 can be activated by multiple IL-6 family cytokines including IL-6, IL-11, oncostatin M (OSM) and leukemia inhibitory factor (LIF). Although all these cytokines signal through a common Glycoprotein 130 (gp130) subunit, the surface receptor responsible for the recognition of the individual cytokines varies, providing additional regulation of specificity. The role of NF-κB and IL-6 in inflammation and HCC progression has long been studied. However, emerging evidence supports that IL-6 family cytokines can undertake different roles in cancer stem cell (CSC) maintenance, cellular proliferation, inhibition of apoptosis and promotion of angiogenesis. Importantly, it was previously shown that IL-11 plays a more central role in gastric tumorigenesis as opposed to IL-6 signaling. Clinicopathological data from 2011 was the first to demonstrate a correlation in HCC between IL-11 expression within the tumor and bone metastases [4]. A follow-up study then found that intratumor IL-11 was associated with poor survival after curative resection of HCC, providing strong clinical rationale for the current study [5]. The central role of IL-11 is supported with the authors' observation that IL-11*rα* but not IL-6Ra knockout animals are protected against recurrence despite increased IL-6 levels following surgical resection.

Other investigators have investigated the role of IL-11 in HCC. A study from 2014 reported that TGF-β upregulated the long non-coding RNA (lncRNA)-ATB, which led to an increase in STAT3 signaling via stabilization of IL-11 RNA [6]. Another group found that Astragaloside IV, an active component of *Astagalus membranaceus*, significantly downregulated LncRNA-ATB. This was accompanied by HCC cell apoptosis and decreased HCC cell viability in vitro as a result of downregulation in the IL-11/STAT3 signaling [7]. This data suggest upstream disruption may provide an alternative approach to blocking IL-11 signaling. Additionally, transmembrane p24 trafficking protein 3 (TMED3) has been shown to promote HCC progression through IL-11/STAT3 signaling [8]. Combined, this paper adds to the growing body of literature that highlights IL-11/STAT3 as strong drivers of HCC tumor progression.

To evaluate the therapeutic potential of targeting IL-11 downstream signaling, the authors tested the STAT3 inhibitor Napabucasin and demonstrated that this drug interfered with the proliferation of hepatocytes and prevented lesion outgrowth in their innovative experimental models. These striking findings support clinical evaluation of Napabucasin at the time of liver surgery as a preventative measure for recurrence. Previous studies in pancreatic cancer ascribed inhibition of CSCs as the main mechanism of action for Napabucasin [9]. However, the authors of the current manuscript did not investigate IL-11-mediated changes in CSC frequency and limited their focus to alterations in cellular proliferation and apoptosis. Additionally, recent evidence suggests that surgery can contribute to metastatic spread by triggering inflammation and that cyclooxygenase inhibitors can prevent micrometastasis [10]. Although Wang et al. demonstrated that the tumor cells are the source of IL-11 and IL-11*rα* expression by the microenvironment is essential to the regrowth process, the expression of IL-11*rα* on particular cell types remains an open question [3]. However, lack of increased expression of CCR8 and CXCR1 in the tissue indicates that neutrophil accumulation resulting from hepatectomy is most likely not the cause for tumor regrowth. Instead, these observations support

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that the role of IL-11 in wound healing and compensatory proliferation is the main driver of tumorigenesis.

Taken together, the authors highlight the role surgical trauma may be playing in the upregulation of IL-11 and evidence for a therapy that has shown efficacy in other cancers. This study is valuable in terms of understanding the link between liver regeneration and cancer recurrence post-surgical resection. Furthermore, consideration of the context dependent role of IL-6 family cytokines in disease pathogenesis can provide more effective targeting with enhanced specificity.

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Declaration of Competing Interest

The authors have declared that no conflict of interest.

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