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Commentary

Interleukin-24 therapy- a potential new strategy against liver fibrosis

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Hepatic disorders including cholestasis-induced liver fibrosis, hepatitis, cirrhosis, alcohol consumption-related liver disease (ALD), nonalcoholic steatohepatitis (NASH), hepatocellular carcinoma (HCC) are associated with hepatic inflammation. The study of cytokines and their roles in progression and treatment of various diseases in specific tissues, has increased since the complete sequencing of human genome and advances in genetic engineering. Newly identified cytokines have been produced as recombinant proteins and tested in animal models, with the aim of developing therapies for liver fibrosis [1].

In recent years, interleukin-24 (IL-24) has attracted a lot of attention in regard to its ability to induce cancer cell-specific death. IL-24 has anti-proliferative and antitumor activities inducing apoptosis specifically in transforming cells [2]. Initially, IL-24 was identified as a negative regulator of human melanoma, and later it was proven to suppress cancer growth in several tissues [3]. On the negative side, IL-24 is associated with autoimmune disorders such as psoriasis and rheumatoid arthritis [1].

IL-24 and its functions in liver fibrosis have been poorly understood, however, a recent study published by Wang et al in *EBioMedicine,* addressed this important issue [4]. The report demonstrates that hepatic fibrosis associated with cirrhosis and NASH, correlates with imbalanced expression of IL-20 and IL-24 in the liver. Thus, patients with liver fibrosis exhibited reduced IL-24 but increased IL-20 hepatic expression, compared to healthy donors, and this differential was higher in more serious liver injuries. Interestingly, IL-24 was colocalized with markers of hepatocytes, while IL-20 was present in hepatic stellate cells (HSC). Both IL-24 and IL-20 are members of IL-20 subfamily of IL-10 family of cytokines.

IL-10 family cytokines are key players in fibrosis-related inflammation associated with fibroproliferative disorders such as liver fibrosis [5]. In injured tissues, chemotactic signals trigger recruitment of macrophages and neutrophils which produce proinflammatory cytokines that induce activation of fibroblasts to start wound healing and tissue remodeling which include synthesis of extracellular matrix (ECM) [6]. The immune response also triggers anti-inflammatory and anti-proliferating cytokines to balance these processes [5]. In inflammatory disorders, the anti-proliferative response is deficient, and excessive ECM replaces normal tissue leading to fibrosis [7]. The most studied members of IL-10 family with critical roles in hepatic fibrosis are IL-10, IL-20 and IL-22[5]. IL-10 is an anti-inflammatory cytokine that counteracts hyperactive immune responses protecting tissues from excessive remodeling ECM [7]. In the liver, IL-20 cytokine has key roles in inflammatory pathological processes, and mediates communication between epithelial hepatic cells and leukocytes to promote tissue regeneration after injury and cell survival while inhibiting apoptosis [8]. IL-22 has hepatoprotective and anti-fibrotic properties, being a candidate for the treatment of ALD [9]. However, IL-22 was also found to promote tumor growth and enhanced liver susceptibility to HCC development [10].

The new publication by Wang et al. brings into focus a role of IL-20 in promoting liver fibrosis by causing IL-24 downregulation [4]. Based on clinical observations, the authors investigated a possible involvement of IL-20 and IL-24 dysregulation in liver injury induced by TAA in mice (TAA-mice), and also in high-fat diet (HFD)-induced metabolic liver injury in mice. In all tested models, markers of liver fibrosis, free radical-stress and inflammation were correlated positively with IL-20 and negatively with IL-24. Furthermore, administration of IL-24 before TAA treatment, decreased IL-20 expression and prevented liver injury in TAA-mice. Using isolated HSC and hepatocytes from IL-20R1 and IL-20R2-deficient mice, the authors showed that IL-24 prevents HSC activation and hepatocyte damage through an IL-20R1-independent manner. Additionally, IL-20R2 knockout mice with liver fibrosis induced by TAA, CCl_4 or HFD had more severe liver fibrosis compared to wild-type mice with identical treatments, suggesting that IL-24 acts through IL-20R2 that might be dimerized with other still unknown variant of IL-receptor. Liver from cirrhotic patients exhibited increased expression of IL-20R1 and especially IL-20R2, and a reduced expression of IL-22R1 as compared to samples from non-fibrotic livers.

The two cytokines have opposite effects not only in fibrogenesis but also in countering each-other's expression levels in hepatocytes and HSC. Hepatocytes in vitro expressed IL-20, IL-24 and IL-20R1/IL-20R2, IL-20R2/IL-22R1 receptors, and TAA treatment caused IL-20

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increase in the absence but not in the presence of IL-24. However, the study did not address the expression of IL-20, IL-24 and their receptors in HSC *in vitro*. The molecular mechanisms underlying the regulation of IL-20 and IL-24 expression and the crosstalk between the two cytokines, are still to be revealed.

In summary, this new study demonstrates a beneficial role of IL-24 in antagonizing IL-20-promoted liver fibrogenesis, suggesting that IL-24 could have translational potential for clinical treatment of liver fibrosis.

Declaration of Competing Interests

The authors declared no conflicts of interest.

Contributors

Sharon DeMorrow initiated writing this commentary, wrote the manuscript.

Anca D. Petrescu performed literature research, wrote the manuscript.

Both authors critically edited and approved the final manuscript.

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