**Title: Type 3 cytokines IL-17A and IL-22: new players in liver fibrosis**

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Advanced liver disease (cirrhosis) is the 14th cause of death worldwide (*1*). It starts as an abnormal wound-healing response known as fibrosis or scarring of the liver induced by inflammation during persistent (chronic) liver injury caused by viruses (such as hepatitis B and C), environmental toxins, alcohol consumption and/or fat-rich diet leading to fatty liver disease or non-alcoholic hepatic steatosis (NASH) (*2*). Liver fibrosis can progress gradually over many years to cirrhosis and liver cancer with expensive and limited treatments and the need for liver transplantation. Despite a lot of research efforts, there is no approved effective treatment to limit liver fibrosis progression and prevent development of cirrhosis and cancer.

Inflammation is one of the major modulators of fibrosis progression. Inflammation is composed of a spectrum of responses from different immune cells characterized by the secretion of small soluble factors called cytokines. Inflammation is like peppers that can either be hot, mild or sweet. Inflammation can be divided into three types. Type 1 (characterized by secretion of interferon gamma) is highly inflammatory (hot) but is surprisingly anti-fibrotic. In contrast, type 2 (characterized by secretion of interleukin (IL-) 4 and 13) is the most modest type of inflammation (sweet) but is profibrogenic. Finally, type 3 (characterized by secretion of IL-17 and IL-22) is quite inflammatory but its function during liver fibrosis remains poorly understood.

We used liver biopsies from patients with different causes and degrees of fibrosis to characterize the type of inflammation in these different conditions. We had previously reported that type 1 inflammation was unchanged during fibrosis progression while type 2 inflammation was associated with fibrosis progression only in fatty liver disease (*3*). In the present study, we observed that type 3 inflammation was strongly associated with fibrosis in all types of chronic liver injury (*4*). We have discovered that IL-22, one of the major type 3 cytokines, accelerates fibrosis as it amplifies the signal of transforming growth factor beta (TGF-β), the main cytokine with fibrogenic properties that is produced during liver inflammation. The fibrogenic nature of IL-22 had been unknown and debated up to now. This new finding allowed us to understand its interaction with TGF-β. Indeed, IL-22 was elevated in the livers of individuals with advanced fibrosis confirming its pathogenic effect. Using cultured cells, we demonstrated that IL-22 in combination with TGF-β sensitize hepatic stellate cells, responsible for formation of scar tissue in the liver.

Similarly, another type 3 cytokine, IL-17A, has been known as an agent amplifying inflammation, through recruitment of pro-inflammatory cells, and enhancing fibrosis (*5*). These findings demonstrate that type 3 cytokines have the capacity to potentiate TGF-β dependent fibrosis through distinct mechanisms. We then identified neutrophils and mast cells as the main sources of IL-17A in humans.

The balance between the two cytokines IL-17A and IL-22 during different stages of liver disease and their combined roles remain unknown and further studies are needed. Nevertheless, we demonstrated in mice that using small molecules called antagonist to inhibit the production of the type 3 cytokines IL-17A and IL-22, delays the development of hepatic fibrosis. These findings allow us to better understand the pathogenic role of type 3 cytokines and elucidate how to intervene with their production to prevent the progression of fibrosis and consequently the development of cirrhosis and liver cancer.

Further studies will be required to understand the dynamic process of recruitment to the liver and activation of cells producing IL-17A and IL-22 that trigger a tissue-repair response. The objective will be to examine how the balance between the pro-inflammatory and anti-inflammatory signals is disrupted and to identify the mechanisms involved and how best to interfere with them to return to a normal state. Given that the replacement of healthy tissue by scar tissue favors the development of more serious pathologies like cirrhosis and cancer, it is vital to learn how to block inflammatory cells from entering the liver, or to change their inflammatory profiles to protect against such pathologies. Various treatment regimens, as well as frequency and doses that would be effective in blocking the effects of type 3 responses, must be pursued in preclinical mouse models prior to being ultimately tested in humans. Medications that successfully target type 3 cytokines such as IL-17A and IL-22 have already been approved for the treatment of psoriasis in humans. This avenue appears promising for liver fibrosis as well. (723 words)

**References**

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