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Interleukin-6: a therapeutic Jekyll and Hyde in gastrointestinal and hepatic diseases

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Introduction

Interleukin-6 (IL-6) was discovered and cloned in 1986. Its receptor IL-6R (CD126) has an unusual organisation, consisting of two proteins: an 80kDa IL-6 receptor and a 130kDa signal transducer (gp130). IL-6 and its receptor interact to form a complex consisting of two IL-6 molecules plus two IL-6 receptor proteins and two gp130 proteins. The dimerised gp130 then transduces the signals, a process known as trans-signalling. In addition, a soluble IL-6 receptor also exists and exerts an agonistic effect in complex with IL-6 and can couple with the gp130 to effect transduction. Activation of gp130 leads to activation of JAK kinases and phosphorylation of STAT3, which is translocated to the nucleus and leads to gene expression.[1] However, STAT3 also negatively regulates IL-6 signalling by inducing suppressor of cytokine signalling 3 (SOCS3) that in turns inhibits JAK kinase.[1]

IL-6 is critically involved in both acute and chronic inflammation. At the beginning of acute inflammation, it plays a key role being the main inducer of acute phase reactants such as C-reactive protein, fibrinogen and serum amyloid A protein. When its activity as a proinflammatory cytokine persists, acute inflammation turns into chronic inflammation that includes immune responses. In particular, IL-6 has a detrimental role that favours mononuclear cell accumulation at sites of injury through MCP-1 production, angioproliferation, anti-apoptotic function on T cells and in promoting Th-17 cell differentiation.[2] A large number of studies have demonstrated that IL-6 is over-produced in several diseases, and it plays a fundamental role in the pathogenesis of rheumatoid arthritis, asthma, systemic lupus erythematosus, multiple sclerosis, psoriasis, alcoholic hepatitis, viral hepatitis, and in Crohn's disease and ulcerative colitis, the two major forms of inflammatory bowel disease (IBD).

IL-6 and IBD

Several lines of evidence suggest that IL-6 is involved in IBD pathogenesis.[3] Human studies have reported that IL-6 and IL-6R plasma concentrations are increased in both Crohn's disease and ulcerative colitis, but no correlation with disease activity exists. Interestingly, increased levels of plasmatic IL-6 might predict clinical relapse in both forms of IBD. In addition, in the inflamed mucosa IL-6 is also up-regulated, as lamina propria mononuclear cells isolated from IBD specimens produce a higher amount of IL-6 compared to controls. In

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particular, mucosal T cells and macrophages have been shown to be the major source of IL-6 and to activate gp130 positive T cells. IL-6 trans-signalling in turns induces STAT3 activation, which mediates anti-apoptotic signals and increased resistance to death of lamina propria T cells. In experimental colitis IL-6 is mainly involved in the chronic phases of the disease. Recently, the transcription factor NFATc2 has also been demonstrated to be critically involved in IL-6 dependent T cell resistance to apoptosis and activation in experimental colitis, while IFN regulatory factor-4 (IRF4) controls IL-6 production as IRF4 deficient mice are protected from experimental IBD and produce low mucosal IL-6.[45] In addition, specific blockade of IL-6 either by soluble gp130 or anti-IL-6 receptor administration has been proven to be beneficial in several colitis models.[6] A pilot clinical study showed that treatment with IL-6 receptor antibody also improved the remission but did not improve the endoscopic and histological score in patients with active Crohn's disease.[7] Further clinical trials with a larger population of patients with IBD are required to clarify the safety and efficacy of IL-6 receptor antibody in treating these patients.

Beside leukocytes, epithelial cells also express IL6-R and gp130, but the effect of IL-6 trans-signalling on intestinal epithelium is still not well understood. In the paper by Jin *et al*[8] *(see page 186)*, the authors elegantly show that administration of recombinant IL-6 leads to epithelial STAT3 activation, resulting in increased enterocyte survival and intestinal hyperplasia, and epithelial protection after intestinal injury and ischaemia–reperfusion. These results show for the first time that in disease conditions characterised by increased epithelial cell damage, IL-6 administration might be beneficial for barrier function.

IL-6 and colon cancer

IL-6 has been proposed to also play a role in colon cancer pathogenesis. Increased serum levels of IL-6 have been reported in colorectal cancer patients and they correlate with disease status. In addition, it has been suggested that IL-6 links chronic inflammation and colon cancer. In a murine model of inflammation-associated colon cancer, IL-6 trans-signalling has been involved in tumour formation and administration of antibodies against IL-6R or soluble gp130 inhibited tumour growth.[9] Furthermore, sIL-6R supports the formation of metastases through the control of the adherence of colon tumour cells to the vascular endothelium. Consistently, the signalling molecules related to IL-6 have also been involved in colon cancer pathogenesis. STAT3 has been found to be up-regulated in colon cancer and correlates with tumour grade of invasion and survival. It has been shown that aberrant phosphorylation of STAT3 is present in the epithelium of colonic cancer but not in normal epithelium. Finally, in vitro STAT3 activation leads to increased proliferation of colonic cancer cell lines, and its inhibition is beneficial in xenograft experiments.

IL-6 and liver disease

In the liver, IL-6 was initially identified as a hepatocyte stimulating factor that enhanced production of hepatic acute phase proteins, but was later found to also play an important role in liver regeneration and hepatoprotection.[10] The protective effect of IL-6 on liver injury was further suggested by rodent studies with conditionally targeted disruption of hepatocyte-specific gp130 or STAT3 signalling molecules downstream of IL-6 activation.[10–12] These studies revealed that IL-6 triggered a STAT3 signalling cascade in hepatocytes that induced expression of anti-apoptotic and antioxidant genes, thereby promoting hepatocyte survival.[10–12] However, it has been documented that alcohol-induced liver injury (elevated serum ALT) was enhanced in IL-6 knock-out mice but not in hepatocyte-specific STAT3 knockout mice,[1013] which suggested that in addition to activation of STAT3 in hepatocytes, other mechanisms may also mediate IL-6 hepatoprotection against alcoholic liver injury. In this issue, Jin *et al*[8] report that IL-6 inhibited intestinal epithelial cell death and subsequently maintained intestinal barrier function. This could be an important mechanism contributing to

the hepatoprotective effect of IL-6 in alcoholic liver injury as increased intestinal epithelial cell death and subsequent leakage of endotoxins into the liver are key mechanisms underlying alcoholic liver disease. In addition, another beneficial effect of IL-6 in the liver is to ameliorate fatty liver disease. IL-6-deficient mice are more susceptible to alcoholic and non-alcoholic fatty liver disease, while treatment with IL-6 can reverse such disease.[1014] In vitro treatment of donor livers reduces markedly the mortality associated with fatty liver transplants.[15] In contrast, IL-6 may also play a detrimental role in promoting chronic liver inflammation and hepatocellular carcinoma development.[16]

General therapeutics and conclusions

From the above-reported evidence it seems clear that IL-6 is a double-edged sword in chronic inflammation versus epithelial cell survival. IL-6 is strongly implicated in the pathogenesis of several immunomediated disorders that link chronic inflammation and cancer, such as IBD, colorectal cancer and liver cancer, but IL-6 also displays hepatoprotection and intestinal epithelial protection. Therefore, inhibition of IL-6 seems an attractive target for therapeutic intervention in the treatment of IBD, colon cancer and liver cancer, but short-term activation of IL-6 may have beneficial effects in preventing acute liver injury and ameliorating fatty liver disease. Another plausible clinical application of IL-6 is simple in vitro treatment of donor livers with IL-6 to render marginal fatty livers usable for clinical liver transplantation.[15] In conclusion, a therapeutic strategy using IL-6 for manipulation should be carefully planned in order to specifically inhibit pro-inflammatory and pro-tumourigenic activities, ideally leaving the beneficial part functional.

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