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COMMENTARY

Different roles of interleukin 6 and interleukin 11 in the liver: implications for therapy

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ABSTRACT

The interleukin 6 (IL6) family of proteins regulate important cellular processes and act through a variety of signaling pathways via a shared gp130 receptor. In the liver, there is a large body of evidence showing a protective and pro-regenerative role for IL6 *cis* and *trans* signaling. While a few studies suggest a pathological role for IL6 *trans*-signaling in the liver. IL11 is often thought of as similar to IL6 and redundancy has been inferred. However, recent studies reveal that IL6R and IL11RA are expressed on dissimilar cell types and these cytokines actually have very different roles in biology and pathology. In the liver, IL6R is mostly expressed on immune cells, whereas IL11RA is highly expressed on hepatocytes and hepatic stellate cells, both of which exhibit autocrine IL11 activity. In contrast to the beneficial effects of IL6 in the liver, IL11 causes liver disease and its expression in stromal and parenchymal cells leads to fibrosis, inflammation, steatosis and hepatic failure. In this review, we address IL6 and IL11 in the context of liver function. We end by discussing the possibility of IL6 gain-of-function versus IL11 inhibition as therapeutic approaches to treat liver disease.

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Introduction

The interleukin 6 (IL6) family of cytokines are characterized by their common use of the widely expressed signal-transducing receptor, glycoprotein 130 (gp130). To date, the IL6 family has 10 members: IL6, IL11, IL27, oncostatin M (OSM), leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), cardiotrophin 1 (CT1), cardiotrophin-like cytokine factor 1 (CLCF1), and two recently added cytokines, IL35 and IL39.[1–4] Specificity for IL6 family member signaling is established by binding of the individual cytokines to their cognate, high-affinity 'alpha' receptors (i.e. IL6 to IL6R, IL11 to IL11RA, CNTF to CNTFR), which show cell-specific expression patterns.[5] These cytokine:receptor complexes then bind to gp130 to differentially initiate downstream signaling pathways, including JAK/STAT or MEK/ERK.

IL6 has been reported to play a pathological role across a range of conditions including heart failure, inflammatory diseases (e.g. asthma, rheumatoid arthritis, systemic lupus erythematosus), and cancers.[3,6] In contrast to IL6, IL11 is little studied and the roles of IL11 in disease, aside from its effect in cancer, are only now being appreciated (Figure 1). The IL11 field is also confounded by assumptions that IL11 has cytoprotective, anti-fibrotic, and anti-inflammatory activity based on previous studies of effects of recombinant human IL11 (rhIL11) in mouse models of disease.[7] Only very recently, have experiments shown a central role for endogenous and species-matched IL11 in the pathology of fibro-inflammatory diseases such as inflammatory bowel disease (IBD), cardiorenal and lung fibrosis, and acute and chronic liver disease.[5,8-11]

In this review, we examine the roles IL6 and IL11 in the liver and discuss the therapeutic opportunities these cytokines may provide for liver disease. While the older literature proposed these two cytokines have overlapping and redundant roles in the liver, we discuss recent data that challenges long-held assumptions.

IL6 and IL11 – different children from the same family

Since the discovery and cloning of IL6 in 1986,[12] more than 30 y of extensive research has been carried out on this key cytokine. Analysis of the published literature shows that IL6 is the 6th most studied gene of all time.[13] The same cannot be said for IL11, which was first cloned not long after IL6 in 1990[14] (Figure 1). IL11 remains poorly studied and based on some recent data, it appears that some of the assumed IL11 functions may have been misinterpreted.[7]

IL6 consists of 183 amino acids and IL11 is a 178 amino acid protein but these cytokines share limited (~20%) sequence homology. Crystal structures show that IL11 is dissimilar to IL6 and the key gp130 residues required for their respective hexameric signaling complex formation also differ.[15,16] While these structural and binding properties suggest differences in IL6 and IL11 signaling, perhaps the starkest example of their dissimilarity is apparent in their receptor distribution, which verges on mutual exclusivity (Figure 2).

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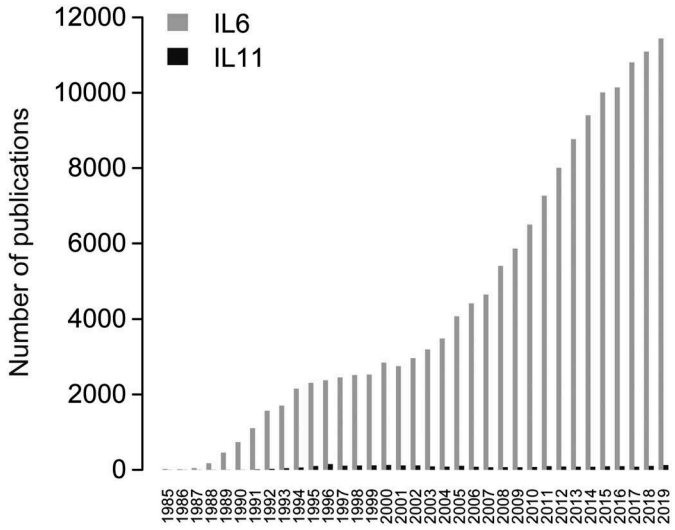

Figure 1. Number of publications for IL6 (gray) or IL11 (black) by year (1985–-2019). The R package Pubmedwordcloud was used to generate these plots using case insensitive keywords 'il6', 'il-6', 'interleukin-6', 'interleukin 6' for IL6 and 'il-11', 'interleukin-11' and 'interleukin 11' for IL11.

While IL6R is expressed most highly on immune cells, IL11RA is expressed in stromal cells, such as fibroblasts and hepatic stellate cells, and also on parenchymal cells, including hepatocytes[5,10,18,19]. Hence, it may be expected that IL6 biology relates mostly to immune functions whereas IL11 activity is more closely linked to the stromal and parenchymal biology. Another intriguing dissimilarity is that in healthy humans IL6 is highly expressed across tissues whereas IL11 is barely detectable (https://gtexportal.org/home/index.html).

These biological pointers suggest distinct roles for IL6 and IL11 and this is apparent when we look at the phenotypes of individuals with naturally occurring genetic loss-of-function (LOF) mutations in the general population. IL6R LOF in humans leads to recurrent infections, inflammatory derangement, eczema and eosinophilia.[20] In contrast, IL11RA LOF is associated with craniosynostosis, delayed tooth eruption and joint laxity.[21] LOF mutations in gp130, the shared partner of IL6R and IL11RA, cause a combined phenotype of craniosynostosis and immune dysfunction, consistent with loss of both IL6 and IL11 signaling.[22]

In summary, IL6 is an established pro-inflammatory factor that plays an important role in human inflammatory and immune diseases (e.g. rheumatoid arthritis and cytokine storm), where its therapeutic inhibition is established as -beneficial.[23] While we know much less about IL11, it has emerged as an important pro-fibrotic factor across organs and, more recently, as a hepatotoxin.[5,8-11]

IL6R and IL11RA expression in hepatocytes and hepatic stellate cells

IL6, originally termed B cell growth/stimulatory factor II (BSF2),[24] was initially shown to stimulate acute phase response from HepG2 cells and rat hepatocytes.[25] Subsequent studies showed that IL6 can be produced from and act on the liver and IL6 is a well-established and important determinant of the acute phase response, which involves secretion of CRP, serum amyloid A, hepcidin, among other factors from hepatocytes. Thus, it is abundantly clear that IL6 stimulates hepatocytes, directly or indirectly.

The published literature states that hepatocytes express the IL6R[26,27] and this would fit with a direct effect of IL6 on hepatocytes. However, recent studies of primary human and mouse hepatocytes have struggled to detect IL6R expression at the transcriptional, translational or protein levels whereas gp130 and IL11RA are abundantly detected.[28] This suggests that IL6 could possibly act indirectly on hepatocytes, perhaps via Kupffer cells, infiltrating immune cells, in *trans*, via very low levels of receptor expression or through other yet-to-be-determined mechanisms. These conflicting data present a conundrum that requires further study but differences may reflect, at least in part, the variable characteristics of primary hepatocytes used in the recent studies as compared to HepG2 or AML12 cell lines, often used in the previous literature.

Another important cell type in the liver is the hepatic stellate cell (HSC). Activated HSCs are the main drivers of liver fibrosis and a therapeutic target cell in nonalcoholic steatohepatitis (NASH)[29–31] . In disease, HSCs undergo a cellular transition to become invasive, collagen secreting and pro-inflammatory myofibroblasts.[32] This phenomenon is similar to fibroblast-to-myofibroblast transformations in other organs, which is dependent on IL11 signaling.[7]

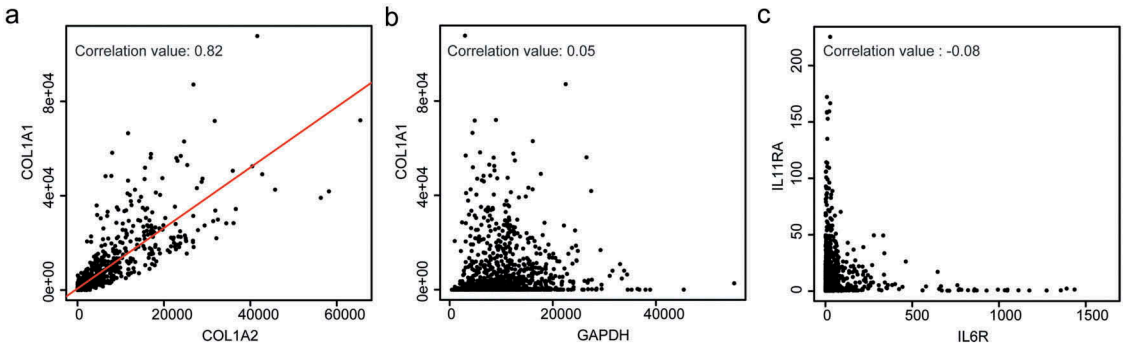

Figure 2. IL11RA is expressed on different cell types as compared to IL6R. Graphs showing example data for (a) correlated gene expression (*COL1A1* vs *COL1A2*), (b) unrelated gene expression (*COL1A1* vs *GAPDH*), and (c) *IL11RA* vs *IL6R* gene expression, which appears largely exclusive and in disparate cell types. The expression values are normalized counts obtained from the FANTOM consortium.[17]

Profiling of primary human HSCs at the protein level shows high expression of IL11RA and gp130 but no (or very low) detectable IL6R.[10] As with hepatocytes, HSCs are known to be IL6-responsive and are a source of IL6 themselves.[33,34] However, based on the receptor expression data,[10] HSCs do not appear to be a direct target for IL6, unless direct binding of IL6 to gp130 in the absence of the alpha receptor was possible, which has been reported.[35,36] In contrast, IL11 can act directly on HSCs through binding to its cognate IL11RA receptor and this effect can be either paracrine or autocrine, as HSCs themselves secrete large amounts of IL11 when stimulated by disease factors.[10]

IL6 gain-of-function could be a therapeutic approach for treating liver disease

There is a large body of data showing that, overall, the effects on IL6 on liver health – separate to its role in the acute phase response – are beneficial and that IL6 activity in the liver promotes cytoprotection, regeneration and is metabolically advantageous.[26,37,38] In addition to *cis*-signaling, IL6 can also bind to soluble IL6R (sIL6R), which is generated from membrane-bound IL6R expressing cells by ADAM-mediated proteolysis. In this way, IL6:sIL6R complexes can signal in *trans* to activate cells that express gp130 but do not have their own IL6R. An artificial fusion protein construct of IL6 coupled to sIL6R, called Hyper-IL6, has been shown to potently activate cells, including hepatocytes, independent of IL6R.[26,39]

Given the limited evidence for IL6R expression on primary human hepatocytes or HSCs, IL6 *trans*-signaling may be of specific importance for liver health. Indeed, while *IL6* knockout mice have impaired liver regeneration following partial hepatectomy or chronic injury,[40,41] only Hyper-IL6 (not IL6) reverses D-galactosamine-mediated liver toxicity and promotes hepatocyte proliferation and survival.[42] A similar phenotype was observed in mice subjected to hepatectomy in that only Hyper-IL6 (but not IL6) accelerated liver regeneration.[43] Exacerbation of acute liver damage in mice following blockade of *trans*-signaling using soluble gp130 (sgp130) further supports a role for IL6 *trans* signaling in promoting liver health.[44,45] Hence, Hyper-IL6 treatment could potentially be beneficial for patients following liver damage by boosting hepatocyte regeneration. Recently, an approach of transplanting Hyper-IL6-pretreated hepatic progenitor cells into the injured livers of mice was shown to promote liver regeneration.[46] While the weight of experimental data points to a beneficial effect of IL6 *cis* and *trans* signaling in the liver, hepatic IL6 *trans* signaling has also been suggested as maladaptive.[26,37,47-49] However, specific therapeutic inhibition of IL6 *trans*-signaling using gp130 decoy constructs was found to have no beneficial effect in two independent studies of murine NASH.[28,50]

Overall, the manipulation of IL6 signaling for patient benefit in liver disease is hard to envision in the near future. While the majority of the data point to IL6 gain-of-function (in *cis* or *trans*) as beneficial, the literature is discordant and administration of Hyper-IL6-like therapies may have untoward effects. In the clinic, therapies targeting IL6 (sarilumab) or IL6R (tocilizumab) are approved for inflammatory conditions (e.g. rheumatoid arthritis, cytokine storm) but may possibly be associated with hepatocellular injury.[51] Outside the liver, clinical trials investigating the therapeutic potential of IL6 inhibition with therapeutic antibodies or decoy molecules and of JAK/STAT inhibition with small molecules are underway for cancer as well as for additional inflammatory and autoimmune diseases.[51]

Inhibiting IL11 signaling to treat liver disease

Most of the published literature on IL11 in the liver suggests that IL11 gain-of-function is beneficial for liver health. For instance, rhIL11 was shown to be protective in mouse models of ischemia/reperfusion injury, acetaminophen (APAP)-induced liver injury (AILI), acute endotoxemia, and Concanavalin A-induced T cell-mediated hepatotoxicity.[52–57] Based on the premise that the beneficial effects of rhIL11 in mice infer the true biology of IL11, a single clinical trial using rhIL11 was performed in patients with chronic Hepatitis C.[58]

However, Widjaja et.al recently showed that species-matched IL11 is in fact hepatotoxic and induces reactive oxygen species (ROS)-dependent hepatocyte cell death via c-Jun N-terminal kinase (JNK) while also inhibiting liver regeneration.[8] The discrepancy of these newer findings with the published literature, where a high dose of rhIL11 was injected to rodents, may be explained by the fact that while rhIL11 binds to mouse IL11RA, it does not activate the same signaling pathways as endogenous IL11. As such, rhIL11 injection to the mouse inhibits physiologically relevant IL11 signaling (i.e. rhIL11 is an antagonist of murine IL11 signaling in the mouse). This has a large implication for our understanding of IL11 biology in the liver and other organs.

Using a mouse model, Widjaja et al. showed that therapeutically targeting IL11 signaling using neutralizing IL11RA antibodies 10 hours following acetaminophen-induced liver damage, reverses hepatic failure, promotes liver regeneration and improves survival. This study also suggested the translational potential of anti-IL11 therapies as an adjunctive approach to the current standard of care (N-Acetyl Cysteine (NAC)) for patients suffering from liver damage due to acetaminophen poisoning.

A central importance of IL11 in NASH has also recently been described.[10] In this study, a specific effect of IL11 on HSC-to-myofibroblast transformation was shown and inhibition of IL11 signaling genetically or with antibodies reduced liver fibrosis, inflammation and hepatocyte damage. Most recently, a role for IL11 in steatohepatitis has also been observed, inferring a role for pathological IL11 signaling in hepatocytes themselves in the early stages of metabolic liver disease.[28]

Based on data from preclinical models, targeting Transforming Growth Factor β1 (TGFβ1) as a therapeutic strategy for treating acute and chronic liver disease has been proposed.[59,60] However, systemic and long-term inhibition of TGFβ1 provokes inflammation and autoimmune diseases, in addition to increasing risk of neoplasia and cardiovascular problems.[61,62] While IL11 acts downstream of TGFβ1 (and many other disease factors) in hepatocytes and HSCs,[10] it is important to recognize that the safety profile for inhibiting

IL11, rather than TGFβ1 upstream, is promising. Humans lacking TGFβ1 have severe childhood onset IBD,[63] whereas loss of IL11RA function in humans has mild effect, as discussed above. Furthermore, long-term treatment of mice with high dose (10 mg/kg) of anti-IL11 therapy is well tolerated both in healthy mice and in models of liver disease over many months.[10] Whether or not anti-IL11 therapy translates to the clinic for treating human liver disease has yet to be tested.

Concluding remarks

Here we reviewed the biology of IL6 as compared to IL11 in the context of liver health, disease and regeneration. There is a substantial body of work relating to IL6 function in the liver and, overall, this shows that IL6 *cis* and *trans* signaling to be beneficial for liver function and regeneration. In contrast, the literature on IL11 in the liver is limited and the earlier studies that suggested IL11 is beneficial for the liver were likely misinterpreted due to a reliance on the use of rhIL11 in mouse models of liver disease. Thus, paradoxically, inhibiting IL11 activity, rather than potentiating it, may be as a therapeutic approach for treating liver disease.

In the case of IL6, while its inhibition is highly effective for treating inflammatory diseases (Table 1), its activity overall is beneficial for liver function. Delivering an IL6 gain-of-function therapeutic (e.g. Hyper-IL6) might be envisaged in liver disease but this approach could be pro-inflammatory and there remains the possibility of IL6 *trans* signaling being hepatotoxic. There are also potential issues with manufacturing, pharmacokinetics and immunogenicity for alien protein constructs like Hyper-IL6. On the other hand, there is strong genetic evidence in humans and mice of an acceptable safety profile for IL11 inhibition. Thus, therapeutic antibodies against IL11 or IL11RA offer an accepted therapeutic approach for targeting liver diseases with an established mechanism of action in both acute and chronic liver diseases (Table 1).

Table 1. Overview of established and hypothetical uses of IL6 or IL11 therapies across organs and diseases.

Approach	Molecule	Disease
IL6 *trans* gain-of-function	Hyper-IL6	Acute liver failure[42,44,45*] Partial hepatectomy[43*]
Inhibition of IL6 *cis* and *trans* signaling	Anti-IL6 or IL6R antibodies	Cancer (Prostate cancer, renal carcinoma, and multiple myeloma)[64,65#] Castelman's disease[66] Cytokine storm syndrome[67] Giant cell arteritis[68] Neuromyelitis optica[69#] Rheumatoid arthritis[51,70,71] Systemic juvenile idiopathic arthritis[72] Takayasu arteritis[73]
Inhibition of IL6 *trans*-signaling only	Gp130 decoy constructs (e.g. soluble gp130)	IBD[51#]
Inhibition of IL11 signaling	Anti-IL11 or IL11RA antibodies	Acute liver failure[8*] Cardiorenal fibrosis[5*] Idiopathic pulmonary fibrosis[9*] Inflammatory bowel disease[11*] Metabolic liver disease[10,28*] NASH[10*]

* pre-clinical study; # ongoing clinical trial.

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Disclosure of potential conflicts of interest

S.A.C. and A.A.W. are co-inventors on a number of patent applications relating to the role of IL11 in human diseases that include the published patents: WO/2017/103108, WO/2017/103108 A2, WO/2018/109174 A2, WO/2018/109170 A2, WO/2019/073057. S.A.C. is co-founder and shareholder of Enleofen Bio PTE LTD, a company that developed anti-IL11 therapeutics.

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