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Editorial: Cytokines in liver diseases

A B S T R A C T

This special issue on 'Cytokines in Liver Diseases' was inspired by many talks and presentations on liver cancer during the 2nd Aegean Conference on Cytokine Signaling in Cancer (ACCSC) held at Heraklion, Crete, Greece on May 30–June 04, 2017 (Cytokine 2018, 108: 225–231). The liver is the biggest blood filtration and detoxification unit, and is a vital metabolic organ. Being constantly exposed to potentially harmful dietary chemicals, drugs, alcohol abuse and pathogens, the liver displays an extraordinary capacity to repair tissue damage and to regenerate. Moreover, only a healthy liver can provide the vast majority of plasma proteins, plus serving as a key organ for body homeostasis and metabolic fitness. Occasionally, the liver may have to deal with chronic damage inflicted by hepatotropic infections such as hepatitis viruses and metabolic derangements caused by obesity and the consequent metabolic syndrome. Overwhelming the natural defenses of the liver can compromise its vital functions and this can lead to more severe liver disease such as fibrosis that may progress towards cirrhosis and eventually to hepatocellular carcinoma (HCC). However, in obesity, a worldwide crisis that has been developing during the last few decades, HCC can develop in the fatty liver bypassing the fibrosis and cirrhosis stages. With the availability of effective therapies and vaccination strategies for hepatitis viruses, over nutrition has become the biggest new threat for a healthy liver. Cytokines and chemokines play a key role in the initiation and perpetuation of acute and chronic injury to the liver, and thus they contribute to most liver pathologies. The topic of cytokines in liver diseases is so vast that it cannot be adequately covered in this special issue. However, we have attempted to provide a glimpse of hot topics through comprehensive reviews and a few accompanying original articles on key research areas.

Hepatocyte injury elicits an inflammatory response to contain tissue damage and to help in the healing process. Many cytokines and chemokines regulate the inflammatory response as well as the tissue repair process that begins with the hepatic fibrogenic response [1,2]. Deregulation of this protective physiological wound healing process mainly occurs in three ways. First, when the rate of injury exceeds the repair and regeneration processes due to too frequent exposure to the harmful agent as in the case of alcohol abuse, or due to the failure to eliminate the causative agent as in chronic hepatitis infections. Second, through deregulated production and/or increased bioavailability of the inflammatory mediators, which usually occurs as a sequel to the first but may also result from greater production or the loss of endogenous modifiers. Third, amplified biological response to the mediators, which may result from defective signal attenuation or from signal amplification. The inflammatory mediators are produced not only by immune cells, but also by parenchymal cells and non-parenchymal cells such as hepatic stellate cells (HSC), the primary mediator of the repair process itself.

In addition to being the central organ of energy metabolism, the liver is an important immunological organ [3–5]. The human liver is estimated to harbor up to 10×10^9 immune cells that are largely comprised of classical T cell subsets, natural killer (NK), NK-T (NKT) cells, and macrophages. Besides, the liver receives 30% of the circulating blood every minute that brings in more leukocytes during hepatic inflammation. The immune environment of the liver at homeostasis is generally tolerogenic, conceivably due to its position as the primary destination of gut-derived signals that activate the innate immune system. However, cytokines and chemokines elaborated by activated macrophages, lymphocytes, and other leukocytes are key contributors to hepatic inflammation and its resolution, or its progression towards liver pathologies.

The physiopathological roles of various cytokines in the liver have been extensively studied [6]. Under homeostatic conditions, a low-level endotoxin-initiated stimulation of Kupffer cells establishes immune tolerance through secretion of IL-10. Other immune and non-parenchymal cells and their cell surface and secreted molecules also contribute to liver homeostasis. However, the impact of various cytokines on hepatic pathologies is influenced by the balance between their protective verses detrimental effects [5]. The same cytokine may have either a protective or a pathologic effect depending on the context or the stage of disease. For instance, IL-6 protects against fibrosis by promoting hepatocyte proliferation during acute injury/inflammation but it contributes to the development and progression of HCC that often arises in fibrotic livers. The Th1 cytokines IL-12 and IFN-γ are anti-fibrotic, but IL-12 can compromise Th2 responses that are required to control *Schistosoma mansoni* infection. The paradigm of classical Th1, Th2, Th17 and T_{reg} cells has been useful in most instances of immune responses to pathogens, allergens and autoantigens, and to a certain extent in the modulation of immune responses during chronic inflammatory conditions such as obesity and cancer. However, the growing diversity of immune cells and the complex functionality of their cytokine products in immune responses and tissue pathologies have prompted the re-classification of immune responses as type1, type 2 and type 3 based on common transcription factors implicated in cytokine productions and effector functions of immune cells. Whereas the type-1 responses are generally mediated by T-bet$^+$ group-1 innate lymphoid cells (ILC1), Th1 and Tc1 cells, the type-2 responses are mediated by GATA3$^+$ Th2 and Tc2 cells, and the type-3 responses by RORγt$^+$ ILCs, Th17 and Tc17 cells [7]. In this special issue, Shoukry and colleagues, brings this concept to liver homeostasis and discuss the role of the type-3 cytokines IL-17 and IL-22 in liver diseases. Whereas IL-17 is implicated in chronic liver pathologies such as non-alcoholic

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fatty liver disease (NAFLD), fibrosis and biliary cirrhosis, IL-22 is hepatoprotective against alcoholic and non-alcoholic steatohepatitis (NASH) and fibrosis. However, both IL-17 and IL-22 are implicated in the pathogenesis of HCC. Shoukry and colleagues discuss how these cytokines are induced in the liver in response to acute and chronic liver injuries and how their roles change during the development of HCC, identify the gaps in current knowledge and explore therapeutic targeting of these cytokines in liver diseases [8].

Fibrosis is the common consequence of chronic inflammation in liver diseases and a key intermediate stage in the development of HCC. Deregulated cytokine and growth factor signaling, arising from elevated ligand production, enhanced signaling or the loss of control mechanisms in diverse cellular compartments of the hepatic immune system could amplify liver fibrosis and its progression toward HCC. The suppressor of cytokine signaling (SOCS) family proteins is one of the key players implicated in the regulation of cytokine and growth factor signaling [9]. Data from human patients and mouse models have implicated a pivotal role for SOCS1 and SOCS3 in liver fibrosis and HCC development. Whether the SOCS proteins differentially regulate immune cells in the pathogenesis of liver fibrosis is not yet known. Using mice deleted for *Socs1* in the myeloid compartment, Mafanda and colleagues show that SOCS1 expression in macrophages is critical for attenuating hepatic fibrogenesis [10]. Chronic hepatitis virus infections are important cause of liver fibrosis in humans. Cachem et al., show that in patients infected with hepatitis C virus (HCV) the severity of liver fibrosis correlates with altered patterns of HCV core antigen-specific T cells [11]. Specifically, peripheral T cells from chronic HCV patients with advanced liver fibrosis showed a higher propensity to produce IL-6 and IL-17, and to give rise to Trges, senescent and exhausted cells upon antigen stimulation.

Growing knowledge on the pathogenesis of fibrosis and its resolution have identified hepatic stellate cells (HSC) as a potential target for therapeutic modulation of hepatic fibrosis and to prevent its progression toward cirrhosis [12]. Uzonna and colleagues describe the important features of quiescent and activated HSCs, their contribution to hepatic immune tolerance and how they become activated by the inflammatory cytokine milieu following liver injury [13]. A particular emphasis is given to the bidirectional interaction of HSCs with hepatic immune cells namely T lymphocytes, macrophages, dendritic cells and NK/NKT cells. The role of HSCs in animal models of hepatitis induced by ConA or LPS plus D-galactosamine, and the hepatic fibrogenic response during hepatotropic bacterial pathogen challenge is discussed. The authors also present a comprehensive discussion on HSC activation following infections with hepatitis viruses, the protozoan parasite *Leishmania* and the trematode *Schistosoma*. The paper concludes with the current status of therapies targeting HSCs.

NAFLD, which affects 20–30% of the general population and is a leading cause of chronic liver disease, is an emerging pandemic that often requires liver transplantation in the Western populations [14]. NAFLD begins with increased accumulation of lipids in hepatocytes. It can progress towards the inflammatory form of the disease NASH and then to liver fibrosis and cirrhosis in up to 20% of NASH patients. Notably, NAFLD can promote HCC without necessarily going through chronic hepatitis and cirrhosis. The progression of NAFLD to NASH is accompanied by increased fatty acid (FA) oxidation and formation of reactive oxygen species (ROS) leading to oxidative stress, hepatocyte death and initiation of the inflammatory cascade. Among the many factors that modulate energy metabolism in hepatocytes, growth hormone (GH) plays an important role in hepatoprotection. GH signaling occurs in a pulsatile manner and distinct pulse levels in females and males contributing to pharmacologic differences to drug action. Kaltenecker and colleagues discuss the current knowledge implicating the GH-JAK2-STAT5 signaling axis in hepatic lipid metabolism in rodents and humans [15]. In parallel, they describe how targeted disruption of JAK2 or STAT5 in mouse hepatocytes upregulates key molecules involved in lipid metabolism (e.g., PPARγ, CD36, SREBP-1c), alters metabolic pathways in the liver and contributes to the development of steatosis, NAFLD, fibrosis and HCC. Even though liver fibrosis promotes HCC, the protective mechanisms of JAK2-STAT5 signaling against neoplastic transformation in the setting of deregulated FA metabolism are far more complex. This complexity arises from the ability of STAT5 to control the stability of fibrogenic TGF-β, oncogenic STAT3 activation and the expression of cell cycle inhibitors Cdkn1a and Cdkn2b. In contrast to its anti-tumor role in fatty liver-associated HCC, STAT5 promotes oncogenesis in the setting of diethylnitrosamine (DEN)-induced HCC. In an accompanying original research article, Kaltenecker et al., show that hepatocyte-specific STAT5 deficiency does not impair hepatic inflammation but reduces tumor burden that is accompanied by decreased activation of c-Jun N-terminal Kinase (JNK) [16].

Even though the impact of innate immune signaling on the development of chronic inflammation in NAFLD and its progression towards NASH is well established, the critical players involved in this transition are only beginning to be identified. Hartman and colleagues focus on the emerging role of type-III interferons (IFN-III), specifically IFN-λ, in the pathogenesis of NAFLD and NASH [17]. Epidemiological studies implicate genetic variants of *IFNL4*, which was characterized based on its genetic polymorphism and susceptibility to HCV infection, and possibly that of the neighboring *IFNL3* to NAFLD and fibrosis, but the underlying molecular mechanisms remain unclear. Despite using different receptor chains, the molecular signaling pathways of IFN-III and IFN-I overlap to a large extent, both leading to activation of STAT2, formation of STAT1/2 heterodimer, its interaction with IFN regulatory factor 9 (IRF9), formation of the IFN-stimulated gene factor 3 (ISGF3) complex, its binding to IFN-stimulated response elements (ISRE) in IFN-stimulated genes (ISG). Studies on animal models of high-fat diet (HFD)-induced obesity have delineated differential roles of IFN-I signaling in immune cells and hepatocytes. Whereas IFN-I signaling in specific immune cell types protects from HFD-induced NAFLD, its loss in hepatocytes promotes disease. Although similar mechanistic studies on the role of IFN-III are hampered by the lack of *IFNL4* gene in rodents as well as by the lack of IFNλR1 in murine hepatocytes, the implications of IFNL3 in animal models of NAFLD and NASH are awaited. Hartman and colleagues also summarize the human data and mouse studies on the role of various upstream activators and downstream mediators of IFN-I and IFN-III pathways in NAFLD and NASH, and the prospect of using porcine models, as pigs harbor an *IFNL4* gene and porcine hepatocytes express IFNλR1.

Mani and Andrisani discuss the impaired IFN signaling in HBV infections and HBV-associated HCC [18]. Even though most of the infected individuals clear the virus, 5–10% of them develop chronic HBV infection. Among these HBV carriers, who number more than 250 million in endemic areas, nearly 1 million die from HBV-associated liver pathologies such as fibrosis, cirrhosis and HCC. Even though antivirals and IFN-I are the mainstay of anti-HBV treatment, a significant proportion of HBV carriers are refractory to IFN-I. Mechanisms of this unresponsiveness are incompletely understood. IFN-I inhibits HBV replication by repressing STAT1/2-mediated transcription of the viral genome, and HBV targets the STAT1 transcription factor via mechanisms that are not yet clear. The authors discuss how HBV subverts the various modulators of STAT1 activation such as the methyltransferases PRMT1 and SETD2, nuclear E3 ligase RNF2, RIG-I and RIG-G. They also elaborate on how IFN-I impairs HBV replication by inhibiting DNA repair mechanisms via modulating Apolipoprotein B Editing Complex 3 (APOBEC3), which is essential for cell intrinsic responses to viral infections. Finally, the authors elaborate on how HBV hijacks the chromatin modifying polycomb repressor complex 2 (PRC2) complex, RNA helicase DDX5, and lncRNA HOTAIR, which inhibits the expression of genes that confer pluripotency in cancer stem cells. How this pathway could contribute to HBV-associated HCC development, and the association between the loss of IFN-I signaling in cancer stem cells and tumor aggressiveness in other cancers are also discussed. Ashkar and colleague show that IL-15, in addition to stimulating NK cells to

produce IFNγ that inhibits hepatitis C virus (HCV) replication in hepatoma cells, exerts a direct antiviral effect independently of IFN-I [19]. Their findings implicate the ERK signaling pathway in the inhibition of HCV replication by both IFNγ and IL-15 in hepatocytes.

Another consequence of deregulated lipid metabolism in the liver is the upregulation of endoplasmic reticulum (ER) stress in hepatocytes. As the major source of plasma proteins, producing up to 30 g proteins per day, the liver is especially vulnerable to ER stress that is increased during the acute phase response elicited by systemic inflammation. The ER stress itself induces inflammation through mechanisms involving the pro-inflammatory transcription factor NF-κB and cytokines IL-1β and IL-6. This establishes a feed forward loop and amplifies liver injury. Kozlov and colleagues describe how the ER stress is regulated by the unfolded protein response (UPR), which reduces the burden on the ER through inhibition of protein synthesis and by degrading ER targeted mRNA via multiple pathways [20]. They elaborate on how the unresolved ER stress amplifies the inflammatory response and contributes to hepatic dysfunction during various liver pathologies. The potential for pharmacological intervention of ER stress in various liver pathologies such as steatohepatitis, liver fibrosis and HCC is also discussed.

In summary, we anticipate an increase in the number of articles addressing the roles of cytokines, chemokines and growth factors in obesity, type-2 diabetes, metabolic syndrome, hepatic inflammation, liver fibrosis and the development and progression of HCC in the near future. Research in these areas could lead to the development of better diagnostic and prognostic markers (which are clearly in need for specific liver disease conditions), and to the identification of new therapeutic targets to control liver diseases. These advances will prolong lives of individuals suffering from fibrosis, steatohepatitis or HCC and improve their quality of life. Insights into liver physiology and pathology may also improve our understanding of the associated pathologies in other organ systems, in particular the gastrointestinal tract and the impact on the gut microbiome. As the liver supplies the fuel and building blocks to cells in other organs, altered liver functions will impact on rapid cell proliferation associated with tissue regeneration (e.g., bone marrow, gut) and immune cell expansion during infections. The liver being the major site of cholesterol synthesis, liver dysfunction could also influence sex hormone levels and related disorders. Overall, the increasing global incidence of NAFLD is expected to augment not only the burden of metabolic and cardiovascular diseases but also many other disease conditions. The *Cytokine* looks forward to contributions from authors at large with future work directed at understanding the complex extracellular mediators and intracellular molecules that drive vicious cycles of liver destruction, which is crucial to cope with the looming surge in liver-related pathologies.

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