Editorial

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IL-1 cytokine family members and NAFLD: Neglected in metabolic liver inflammation

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Nonalcoholic fatty liver disease (NAFLD) is a major cause of liver disease throughout the world [1]. It is currently considered as the hepatic manifestation of metabolic syndrome and reflects a large spectrum of liver diseases ranging from rather benign steatosis to steatohepatitis, cirrhosis, and hepatocellular carcinoma [2,3]. The pathogenesis of NAFLD involves various hits including lipotoxicity, gut-derived signals such as endotoxin, signals from the innate immune system such as toll like receptors (TLRs) or pro-inflammatory cytokines, oxidative stress, and others. There is increasing evidence that mediators released from the adipose tissue of obese subjects, such as adipocytokines and classical cytokines, are key players in NAFLD [4].

NAFLD is frequently associated with morbid obesity which is often accompanied by chronic inflammation. Obesity and associated insulin resistance are characterized by increased adipose tissue expression of various pro-inflammatory mediators such as tumour necrosis factor-alpha (TNFα), interleukin-1 alpha/beta (IL-1αβ), IL-6, and others [5]. Several IL-1 family (IL-1F) cytokine members are produced by human adipose tissue in case of obesity. Whereas certain IL-1F members such as IL-1α, IL-1β, or IL-18 are potently pro-inflammatory, others such as IL-1 receptor antagonist (IL-1Ra) or IL-37 (previously named IL-1F7) are anti-inflammatory [6,7]. Processing of IL-1β or IL-18 requires cleavage by caspase-1, a protease under the control of the inflammasome [8]. Caspase-1 and IL-1β activity in adipose tissue is increased in both diet-induced and genetically induced animal models of obesity and mice deficient in caspase-1 or obese animals treated with a caspase-1 inhibitor are more insulin sensitive [9]. We recently observed that IL-1β and IL-37 expression was much higher in subcutaneous/visceral adipose tissue compared to the liver suggesting that the adipose tissue might reflect a major source of inflammatory mediators in morbid obesity [10]. Systemic levels of IL-1Ra are increased in subjects with severe obesity although may not be able to sufficiently neutralize the activity of pro-inflammatory IL-1F members [11].

IL-1F members have been demonstrated to affect insulin/glucose metabolism and regulate metabolic dysfunction. IL-1β is upregulated in the adipose tissue of obese insulin-resistant mice and adipocyte-derived IL-1β has been shown to control liver cell insulin sensitivity [12,13]. *IL-1α*$^{-/-}$ mice have lower fasting glucose and insulin levels and improved insulin sensitivity [5]. IL-1β is able to reduce insulin receptor substrate-1 expression at a transcriptional level through ERK dependent and independent mechanisms [14]. Treatment of type 2 diabetes patients with recombinant human IL-1Ra improves glycemic control, clearly highlighting the role of inflammation in type 2 diabetes and insulin resistance [15]. In a diet-induced obesity model, treatment with XOMA 052, a neutralizing anti-IL-1β antibody, improved insulin sensitivity and led to beta-cell sparing [16]. Elevated IL-1β, IL-6, or IL-1Ra concentrations predict risk for type 2 diabetes in humans [17,18]. Type I IL-1 receptor (IL-1RI) may mediate various aspects of metabolic inflammation as free fatty acids, which are abundantly available in obesity, together with TLR stimulation up-regulate and induce pro-inflammatory cytokines, and IL-1RI engagement results in amplification of inflammation [19]. This is of interest, as disruption of this receptor exerted significant protection from diet-induced insulin resistance independent of obesity [20]. Overall, all these data suggest that IL-1F members might critically control insulin resistance and metabolic inflammation in various obesity-associated disorders.

Kamari and colleagues addressed in this issue of the *Journal* an important and long overdue topic, namely the role of IL-1α/β in steatosis and steatohepatitis [21]. In their study, they used a diet-induced model of steatosis and steatohepatitis and observed a considerable increase in the hepatic expression of both IL-1 cytokines. Interestingly, despite demonstrating less inflammation, *IL-1α*$^{-/-}$ mice demonstrated increased hepatic cholesterol deposition and higher plasma cholesterol levels suggesting that hepatic fat storage and inflammation are not necessarily parallel events and certain intra-hepatic lipids might exert even protective, anti-inflammatory functions [4]. It also fits with the observation that in certain instances inflammation may precede steatosis and with the fact that liver steatosis in many instances is a rather benign condition without subsequent inflammation [4]. Both IL-1α and IL-1β-deficient mice were almost entirely protected from

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Abbreviations: ASC, apoptosis-associated speck-like protein containing a CARD; IL-1, interleukin-1; IL-1Ra, IL-1 receptor antagonist; IL-1RAcP, IL-1 receptor accessory protein; IRAK, IL-1 receptor associated kinase; Myd88, myeloid differentiation primary response gene 88; NFκB, nuclear factor kappa B; NLRP3, NLR family, pyrin domain containing 3; TRAF6, TNF receptor associated factor 6.

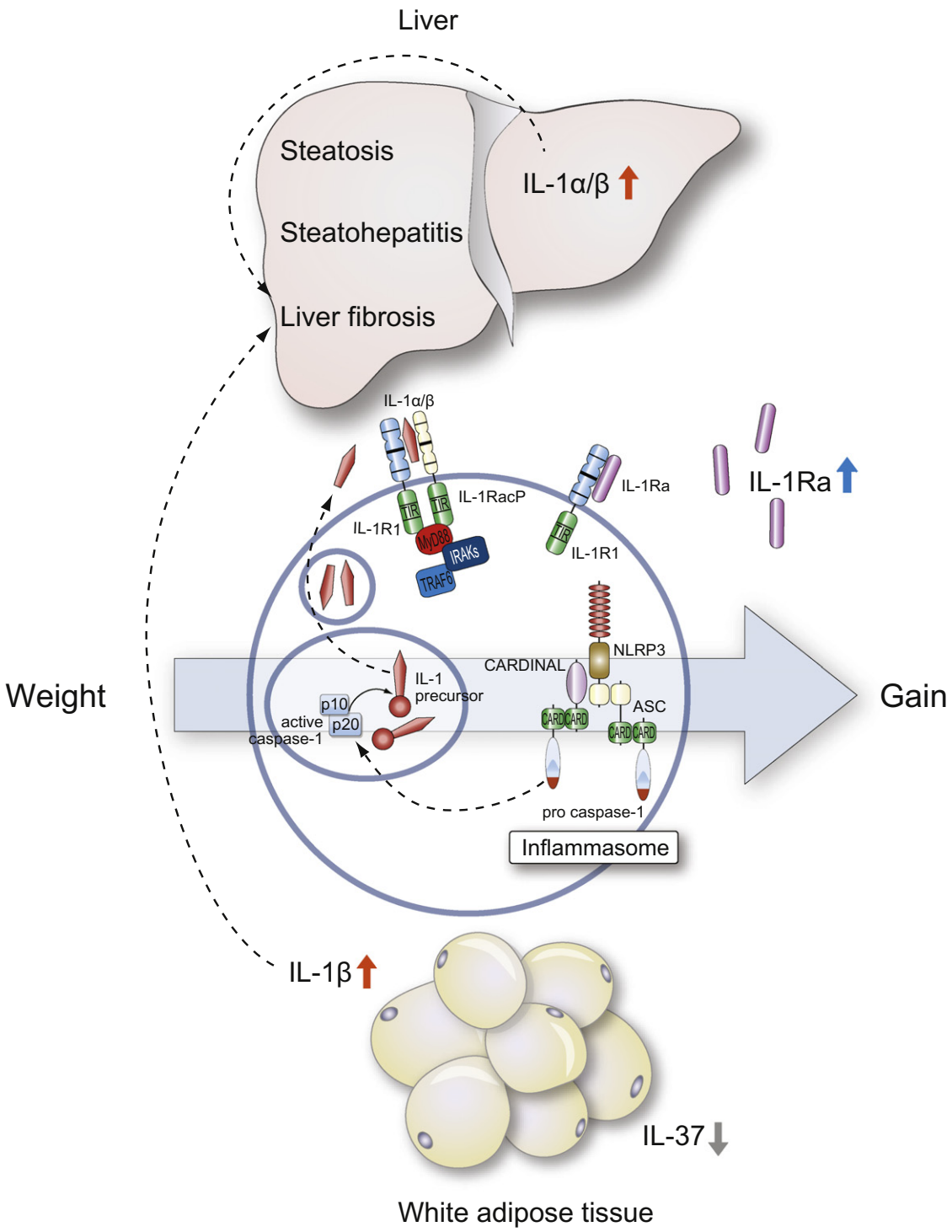

Fig. 1. Intra- and extrahepatic IL-1 cytokine family members may contribute to hepatic steatosis and steatohepatitis. IL-1α and IL-1β are activated and released from specialized lysosomes and cleaved from precursor proteins by active caspase-1. The inflammasome is a highly specialized protein complex that consists of procaspase-1 and members of the NLR family such as ASC and NLRP3. It is activated by intracellular danger-associated molecular patterns (e.g. peptidoglycan) and by endogenous danger signals such as uric acid and ATP. Whereas IL-1α is constitutively expressed by various cell types such as epithelial cells, IL-1β is strongly up-regulated by activated macrophages. IL-1α and IL-1β bind to IL-1RI and then recruit IL-1 receptor accessory protein (IL-1RAcP). Downstream signaling involves recruitment of MyD88 to the Toll-IL-1-receptor (TIR) domains of IL-1RI and IL-1RAcP. IL-1 receptor associated kinase (IRAK) and IκB kinase ß (IKK-β) are activated. These proximal events finally result in activation of transcription factors such as NF-κB. The natural occurring inhibitor IL-1 receptor antagonist (IL-1Ra) binds to and blocks IL-1RI signaling. IL-37, another anti-inflammatory IL-1 family member, suppresses inflammation most likely through intracellular interaction with SMAD3. Hepatic and extra-hepatic IL-1 sources might contribute to metabolic liver inflammation. IL-1-type cytokines, especially their pro-inflammatory protagonists (IL-1αβ), may drive metabolic liver inflammation whereas anti-inflammatory members of the IL-1-cytokine family such as IL-1Ra or IL-37 due to decreased production fail to counteract inflammatory pathways as observed in nonalcoholic steatohepatitis.

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inflammation after diet-induced steatosis, suggesting that these pro-inflammatory IL-1 cytokines might be crucially involved in the development of liver inflammation. Importantly, IL-1α and IL-1β KO mice demonstrated lower mRNA levels of both inflammation and fibrosis-related genes including a significant decrease in TGFβ, highlighting the close pathophysiological relationship between inflammation and fibrosis. A key insight of their studies was also the fact that hepatic and not bone-marrow-derived-IL-1α/β deficiency protected against diet-induced inflammation and fibrosis. The relevance of this data is, however, uncertain as it has been demonstrated that full reconstitution of Kupffer cells may occur beyond 9 weeks after bone marrow transplantation and the authors only allowed a 2 week recovery period after transplantation before starting the atherogenic diet. Experiments with hepatocyte- or Kupffer cell/macrophage-specific *IL-1α/β*$^{-}$ mice are needed to clearly address these issues. This is of importance as other extrahepatic cell types such as adipocytes could be important sources of IL-1α/β in obesity, as suggested by several studies [10]. The results presented in the Kumari study are in accordance with another recent report showing that, in a diet-induced model of obesity, TLR9 controls steatohepatitis via IL-1β [22]. These authors also found that IL-1β increases lipid accumulation in hepatocytes, regulates inflammation, hepatic insulin resistance, and fibrosis. Overall, these studies together convincingly show that IL-1α/β are important mediators in metabolic liver inflammation.

In summary, this work by Kumari and colleagues provides important novel insights on the role of IL-1F cytokine members in hepatic steatosis and steatohepatitis. It still has to be figured out which IL-1 sources are of key relevance in this and other experimental models of NAFLD as extrahepatic sources could critically contribute to hepatic and overall systemic inflammation (Fig. 1).

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Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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