The Impact of Cytokines and Chemokines on Non-Alcoholic Fatty Liver Disease (NAFLD)

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Abstract—There is a slight or no production of cytokines in the liver, under physiological conditions. However, pathological stimuli, such as lipid gathering, trigger the production of inflammatory molecules by hepatic cells. The active role that cytokines might play lies in the evolution of NAFLD by stimulating hepatic inflammation, cell necrosis and apoptosis, as well as by inducing fibrosis. In this review proof of the pathophysiological impact of cytokines in NAFLD is noted and examined.

Keywords—fatty liver, cytokines, chemokines

There is a slight or no production of cytokines in the liver, under physiological conditions. However, pathological stimuli, such as lipid gathering, trigger the production of inflammatory molecules by hepatic cells. The active role that cytokines might play lies in the evolution of NAFLD by stimulating hepatic inflammation, cell necrosis and apoptosis, as well as by inducing fibrosis. Their fundamental role is also represented by liver regeneration after injury [1]. Proof of the pathophysiological impact of cytokines in NAFLD is further noted and examined. Tumor necrosis factor alpha (TNF-α) is an adipokine produced by multiple types of inflammatory cells, such as monocyte/macrophages, neutrophils and T-cells, as well as by several types of tissue, like the endothelium, adipose tissue or neuronal tissue. TNF-α is produced either directly, by hepatocytes and Kupffer cells, or indirectly, by abdominal fat, in the liver [2]. There have been reports that TNF-α is highly implicated in the evolution of NAFLD and NASH in both humans and animals. The connection between TNF-α expression and insulin resistance in NASH was first reported in a study conducted by Hotamisligil et al [3]. In this study, the adipose tissue was presented as a significant cause of obesity-induced inflammation, mainly by TNF-α expression, inducing inflammation and insulin resistance. There have been reports of upregulated TNF-α expression in adipose tissue in comparison to controls in some rodent models of obesity. In agreement with this study, obese mice without TNF-α indicated enhanced insulin sensitivity [4]. More recent studies have shown that thalidomide-treated mice (anti-TNF-α drug) indicated several improvements in hepatic damage determined by a high-fat diet [5]. Additionally, the employment of anti-TNF-α antibodies in an experimental model of NASH has led to reduced inflammation, necrosis and fibrosis in rats [6]. TGF-β Transforming growth factor beta (TGF-β) is a cytokine/growth factor having various functions, including immunosuppressive, anti-inflammatory and pro-fibrotic characteristics [7] TGF-β1 is the most abundant isoform in the liver, being secreted by multiple types of cells, such as immune, stellate and epithelial cells [7] The role that TGF-β1 plays in hepatic fibrosis is represented by the mediation of stellate cell activation as well as of their production of extracellular matrix proteins [8]. Kupffer cells and stellate cells produce TGF-β1, which triggers the conversion of the remaining stellate cells into myofibroblasts [9.] Laboratory models of hepatic fibrosis triggered by CCl4 or schistosomiasis are characterized by an upregulated expression of TGF-β1 [10]. Additionally, the expression of TGF-β1 mRNA is enhanced in patients with liver fibrosis [11]. In a study conducted by [12], the upregulation of TGF-β1 was described as an early molecular action in progressive fibrotic steatohepatitis. Hasegawa et al. indicated higher levels of TGF-β1 in patients with NASH than in those with fatty liver. Therefore, TGF-β1 serum concentration measurements might help distinguish NASH patients within NAFLD [13]. Polymorphisms inducing elevated angiotensinogen and TGF-β1 are also related to advanced hepatic fibrosis in obese patients with NAFLD Interleukin-6 (IL-6) plays a major role in liver pathology, but has an unclear share in the occurrence of NAFLD. IL-6 activates various cells, namely immune cells, hepatocytes, hematopoietic stem cells and osteoclasts. However, IL-6 is basic in acute phase responses, intervening in the synthesis of some acute phase proteins (C-reactive protein and serum amyloid A) [14]. Therefore, it is possible that IL-6 plays an indirect damaging role in NAFLD pathogenesis. In diet-induced obese mice, insulin sensitivity was improved by IL-6 antibody therapy [15]. IL-6 is also thought to be a predictor marker of insulin resistance and cardiovascular diseases. After bariatric surgery, patients showed reduced IL-6 concentrations based on weight loss and improved insulin resistance. There are elevated have recently showed that the extent of diet-induced NASH was lower in IL-6 knockout mice than in controls [16]. There is a positive correlation noted between IL-6 expression in hepatocytes and the seriousness of NAFLD in humans with NASH. Therefore, IL-6 has a dual influence, on one hand it can improve hepatic regeneration and on the other hand it can stimulate the liver to injury, hepatocyte apoptosis, inducing
insulin resistance and participating in NASH progression. This perplexing impact of IL-6 in NAFLD has been described in a recent study conducted by Yamaguchi. IL-6 pathway neutralization with anti-interleukin-6 receptor antibody (tocilizumab), both increased hepatic steatosis and higher liver damage in mice with methionine choline deficient (MCD) diet-induced NASH [17]. Moreover, in their second study, Yamaguchi et al. [18], demonstrated that both the upregulation of IL-6 and the serious suppression of hepatic IL-6/signal transducer and activator of transcription-3 could promote NASH progression. The anti-inflammatory cytokine, interleukin-10 (IL-10), also known as human cytokine synthesis inhibitory factor (CSIF), manages inflammation in various organs and tissues under physiological or pathological conditions. IL-10 also restricts some of the functions owned by T cells, monocytes and macrophages. It has been identified in several cells in the liver, including hepatocytes, stellate cells and Knupffer cells, but there are few studies investigating the impact of endogenous IL-10 in the evolution of NAFLD. A study employing high fat diet-induced IL-10-deficient mice, indicated that endogenous IL-10 protected hepatic steatosis, but did not protect simultaneous insulin resistance. In the study conducted by Cintra et al. [19] IL-10 inhibition (either by means of an anti-IL-10 antibody or an IL-10 antisense oligonucleotide) proved to lead to elevated expression of pro-inflammatory markers (TNF-α, IL-6, IL-1β, F4/80) and defective insulin signal transduction and steatosis. Esposito et al. observed an opposite relationship between IL-10 levels and metabolic syndrome in obese women, indicating the possible benefit of IL-10 in metabolic syndrome patients also suffering from NAFLD [20]. Nevertheless, the study conducted by Calcaterra et al. [21] did not validate this kind of correlation in obese children and teenagers.

References