LETTER

The multi-hit process and the antagonistic roles of tumor necrosis factor-alpha and adiponectin in non alcoholic fatty liver disease

Dear Editor

We have read with interest the review by Paschos and Paletas[1], focused on the pathogenesis and diagnosis of non-alcoholic fatty liver disease (NAFLD). We hereby would like to highlight two additional important points: 1) the "multi-hit hypothesis" and 2) the contribution of the endocrinologically active adipose tissue to the pathogenesis of insulin resistance (IR) and NAFLD.

Traditionally, non-alcoholic steatohepatitis (NASH) is considered to be induced by the so-called "two-hit hypothesis"[2] mentioned by the authors[1]. However, it is unlikely that only one of the recognized mechanisms explains the pathogenesis of NAFLD in all affected patients. Currently, NAFLD develops as a consequence of a "multi-hit process" which provides a model that summarizes the complex factors and interactions leading from adipocytokines, free fatty acids (FFAs) metabolism and IR to NAFLD[3]. The initial hit, which leads to the development of simple steatosis, renders hepatocytes susceptible to a variety of hits that follow, which finally lead from simple steatosis to NASH. The following hits appear to be genetic or environmental perturbations leading to liver cell inflammation and necrosis with fibrogenic cascade activation, resulting in fibrosis and even in cirrhosis in a minority of NAFLD patients. Specifically, after NAFLD development, the liver becomes extremely vulnerable to multiple insults; endotoxinemia, Kupffer cell activation, adipocytokine alterations, hepatic stellate cells (HSCs) activation and mitochondrial dysfunction, oxidative stress and lipid peroxidation may stimulate inflammation, cell death and fibrosis in some patients with environmental and genetic susceptibilities that, in turn, induce progressive liver disease (NASH, cirrhosis)[3]. IR and subsequent hyperinsulinemia are key pathogenetic factors in both simple steatosis and in progression from simple steatosis to NASH.

The adipocytes secrete adipocytokines, whereas inflammatory cells infiltrating adipose tissue secret cytokines. The balance between various adipocytokines/cytokines plays an important role in hepatic and systemic insulin action. The roles of tumor necrosis factor (TNF)-α and adiponectin in IR syndrome and NAFLD have been investigated more than other adipocytokines. High TNF-α and low adiponectin is a condition capable of leading to IR[4]. TNF-α is a key factor in IR and NAFLD and multiple TNF-α-induced mechanisms may be involved in IR, liver fibrosis, cell death and apoptosis[3]. Indeed TNF-α: aggravates peripheral uptake of glucose by suppressing GLUT4 expression; induces lipolysis resulting in increased serum and intrahepatic FFAs by suppressing adipocyte genes expression; activates c-jun-N-terminal kinase (JNK) and Ikappa kinase (IKK)-β, thereby inducing IR by serin phosphorylation of insulin receptor substrate (IRS)-1 and IRS-2 and hepatic fibrosis (through c-Jun); triggers the production of suppressor of cytokine signaling (SOCS)-3 in the liver, resulting in early degradation of IRS1 and IRS-2; activates caspase-8, which triggers the mitochondrial death, DNA degradation and Fas-mediated apoptosis; and activates cytocolic sphingomyelinase, thereby increasing ceramide, an inhibitor of the activity of the mitochondrial electron-transport chain, resulting in increased mitochondrial production of reactive oxygen metabolites (ROMs), which promote cellular necrosis. A vicious cycle involves the ROMs-mediated TNF-α release by hepatocytes, Kupffer cells and adipocytes. TNF-α, in turn, enhances mitochondrial permeability, thereby depleting mitochondrial cytochrome c and blocking the transfer of electrons along the respiratory chain, which may further increase mitochondrial ROMs formation and lipid peroxidation. Noticeably, TNF-α administration can induce IR, whereas neutralization of TNF-α (treatment with infliximab) improves insulin sensitivity[3]. Adiponectin is a polypeptide secreted exclusively by adipocytes and has important metabolic and immune functions. It acts as an insulin sensitizer, inhibiting intrahepatic lipid accumulation. Adiponectin also protects the liver from steatosis and progression to NASH via downregulation of aldehyde oxidase 1 expression, which promotes the production of ROMs, cell damage and fibrogenesis[3]. Besides, adiponectin has antiinflammatory properties by inhibiting monocyte adhesion to endothelial cells, and endothelial cell activation and transformation of macrophage to foam cells, thereby modulating endothelial inflammatory response. In this respect, delivery of recombinant adiponectin to mice fed with a high-fat and alcohol-containing high-fat diet and to genetically obese (ob/ob) mice noticeably alleviated abnormal liver function tests, steatosis, inflammation, and hepatomegaly in both murine populations[5].

These two key mediators inhibit the synthesis and activity of each other thereby allowing a metabolic balance. This could be of paramount importance in diseases associated with IR syndrome, when the critical balance is impaired, leading to chronic inflammation and IR[4]. Adiponectin inhibits the expression, secretion and action of TNF-α, thereby ameliorating insulin sensitivity. TNF-α suppresses adiponectin transcription, secretion and action, enhancing IR. This represents a simple example of the continuous and complicated relationship among the different beneficial and detrimental adipocytokines/cytokines reflected in IR and NAFLD[3].

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