Review Article

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The Role of Inflammatory Mediators in the Pathogenesis of Nonalcoholic Fatty Liver Disease

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With a markedly increased prevalence of obesity, non-alcoholic fatty liver disease (NAFLD) now becomes the most common cause of chronic liver disease in both adults and children. The etiology and pathogenesis of NAFLD are multifactorial and remain incompletely understood. According to the "two-hit" theory, inflammatory cytokines and adipokines are activated by oxidative stress and they are involved in insulin resistance, necroinflammatory steatohepatitis and fibrosis. This review discusses the latest updates on the role of some of important inflammatory adipokines and cytokines in the pathogenesis of NAFLD with an emphasis on their potential therapeutic implications. **(Pediatr Gastroenterol Hepatol Nutr 2012; 15: 74~78)**

Key Words: Nonalcoholic fatty liver disease, Obesity, Inflammation, Adipokine, Cytokine, Pathogenesis, Insulin resistance

INTRODUCTION

Obesity has become one of serious health problems worldwide, and its prevalence is increased both steadily and remarkably. With a markedly increased prevalence of obesity, non-alcoholic fatty liver disease (NAFLD) now becomes the most common cause of chronic liver disease in both adults and children, and its prevalence is estimated at 20-35% in a general population worldwide [1-4]. NAFLD is a chronic inflammatory disease that is characterized by the pathological accumulation of fat in the liver in the absence of alcohol intake. NAFLD encompasses a clinical spectrum of liver diseases ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), and it eventually leads to fibrosis and cirrhosis or hepatocellular carcinoma [3,5]. The development of NAFLD has been strongly associated with many factors including obesity, type 2 diabetes, insulin resistance, dyslipidemia and other components of metabolic syndrome [6].

Recent animal experimental and clinical studies have shown the growing evidences that suggest an important role of adipokines and cytokines in the pathogenesis of NAFLD. This review focuses on the role of several adipokines and cytokines as important in-

flammatory mediators in NAFLD.

PATHOGENESIS

The etiology and pathogenesis of NAFLD are multifactorial and remain incompletely understood. It is generally accepted, however, that multiple genetic and environmental factors may be involved in the sequential insults of "two-hit" process proposed by Day and James [7]. The first hit involves the accumulation of triglycerides within the hepatocytes. It has been recognized that hepatic steatosis leads to hepatic insulin resistance with the activation of such enzymes as protein kinase-theta and Jun N-terminal kinase (JNK) [7]. These initial lesions make the liver more susceptible to the second hit, which is caused by the oxidative stress and proinflammatory cytokines including TNF-α, TGF-β, IL-6 and IL-8. This leads to the development of hepatic injury, inflammation and fibrosis, eventually leading to the evolution of hepatic steatosis to NASH [7-9].

Obesity and insulin resistance are closely associated with the pathogenesis of NAFLD. It is now recognized, however, that genetic factors may also be involved in the first hit process. Romeo et al. identified a single neucleotide polymorphism (rs738409 or G allele) in the palatin-like phospholipase 3 (*PNPLA-3*) gene that is strongly associated with increased liver fat content. These authors also reported that this allele was most common in Hispanics who are known as ethnic group with the highest prevalence of NAFLD [10]. According to another study in a multiethnic group of obese children and adolescents, the presence of this G allele variant increased an susceptibility to the hepatic steatosis and it also caused morphologic changes in the size of adipocytes without increasing hepatic or peripheral insulin resistance [11].

In the second hit process, oxidative stress is thought to play a crucial role. Oxidative stress results from an imbalance of prooxidants (production of reactive oxygen species and reactive nitrogen species) and antioxidants (depletion of glutathione and vitamin E) and leads to lipid peroxidation in mitochondria [12]. Oxidative stress activates nuclear factor

kappa B (NF-kB), which stimulates the synthesis of proinflammatory cytokines [13]. It has been proposed that cytokines secreted by adipose tissue play a role as important mediators in the development of NASH and subsequent progression of liver disease. The final products of lipid peroxidation, including malonaldehyde and 4-hydroxynonenal, have chemotactic properties, and these molecules are involved in the activation of proinflammatory cytokines and the stimulation of hepatic collagen-producing stellate cells. These phenomena eventually lead to a mixed lesion, known as NASH, and it is characterized by the degeneration and necrosis of hepatocytes, the infiltration of inflammatory cells and fibrosis [8,9,13]. Ongoing oxidative stress and lipid peroxidation cause the continued production of collagen, which leads to fibrosis and then hepatic cirrhosis [9].

INFLAMMATORY MEDIATORS

Adipocytokines have a broad-spectrum of biological effects on food intake, energy expenditure and metabolism. Many animal experimental and clinical studies have shown that adipocytokines play a crucial role in the pathogenesis of NAFLD.

Leptin

Leptin is an adipocyte-derived, negative feedback hormone. In hypothalamus, leptin stimulates anorexigenic pathways and thereby reduces food intake in humans [14]. Serum leptin level is increased by overfeeding and obesity, glucocorticoid treatment, glucose and insulin administration, but it is decreased by fasting, sustained exercise, cold exposure and weight loss [15,16]. Leptin acts as an insulin-sensitizing hormone and it reduces lipid content of myocytes, hepatocytes and pancreatic β-cells [17]. If animals are devoid of the activity of leptin, including *ob/ob* mice (leptin gene mutation), *db/db* mice and *fa/fa* rats (leptin receptor gene mutations), they would not only become obese and insulin-resistant but also develop hepatic steatosis. But leptin injections attenuate the onset of fatty liver and metabolic derangement [18]. It has also been shown, however, that serum leptin level is also

increased in obese patients with NAFLD in a proportional manner to the body mass index (BMI) and the severity of hepatic steatosis [19]. This brings up the concept of leptin resistance. The anti-steatotic and insulin-sensitizing actions of leptin are decreased in obesity. This may be due to the defects in leptin signaling pathway or transport across blood brain barrier [20]. Animal experimental models have shown that leptin also acts as an important fibrogenic factor possibly with the mediation of transforming growth factor-beta (TGF-β) or with the direct involvement of the activation of hepatic stellate cells [21].

Tumor Necrosis Factor-alpha (TNF-α)

TNF-α is synthesized and secreted by visceral adipocytes, stromovascular cells and macrophages. TNF-α mainly acts in an autocrine/paracrine fashion in adipose tissue and it plays a central role in the generation of insulin resistance in rodents [22]. It does so directly by reducing mRNA expression of glucose transporter 4, reducing lipoprotein lipase activity and increasing the expression of hormone sensitive lipase in the adipose tissue. TNF-α also impairs insulin signaling through JNK-mediated serine phosphorylation of insulin receptor substrate proteins in the surrounding adipocytes [22,23]. Serum TNF-α level is elevated in obese and diabetic patients while weight loss reduces its levels [24]. Little is known about the correlation between serum TNF-α levels and insulin resistance. It has been reported, however, that adipocyte TNF-α mRNA levels are well correlated with the BMI, body fat and hyperinsulinemia. In addition, it has also been proposed that the local production of TNF-α by Kupffer cells plays a key role in the pathogenesis of NASH [4,22].

Adiponectin

Adiponectin is one of the cytokines that are secreted by white adipocytesand it has peculiar anti-inflammatory properties including the modulation of inflammatory cells, the down-regulation of NF-kB activation and the inhibition of release of TNF-α, IL-6 and chemokines [25]. In contrast to other adipokines, adiponectin is also known to have an anti-lipogenic, insulin-sensitizing activity. It is also known that the expression of adipokines and their serum level are reduced in obesity and other various insulin-resistant conditions [26]. In a murine model of obesity and diabetes, the insulin resistance is improved following the treatment with adiponectins [27]. It is recognized that adiponectin prevents triglyceride accumulation in hepatocytes by increasing β-oxidation of free fatty acids while decreasing de novo synthesis within hepatocytes.

Interleukin-6 (IL-6)

IL-6 is an endocrine cytokine with pleiotropic action ranging from inflammation to host defense (regulation of B and T cell functions) and tissue injury [28]. IL-6 is associated with hyperinsulinemia and insulin resistance, and it may also play an important role in the pathogenesis of NASH [29,30]. Serum IL-6 level is markedly elevated in obese patients, which is the predictor of the development of type 2 diabetes, metabolic syndrome and cardiovascular diseases [24]. Paradoxically, the body weight and insulin resistance are decreased with the addition of IL-6 to the cerebrospinal fluid (CSF) of rats. This might be because IL-6 acts on the hypothalamus and thereby stimulates the energy expenditure. Due to the pleiotropic effects of IL-6, it cannot be effective in treating obesity or metabolic complications in humans although it can be expected that it may causes a weight loss [29].

Resistin

Resistin is one of the adipokines that have recently been identified, and it is secreted by adipocytes and peripheral blood macrophages. Several rodent models have shown that resistin may be an important link between insulin resistance and obesity [31]. Serum resistin levels are correlated with IL-6 and BMI [32,33]. In resistin-deficient mice placed on a high-fat diet, fatty infiltration and secretion of LDL-cholesterol are decreased. This implies that resistin may be involved in the pathogenesis of hepatic steatosis [34]. But no biological actions of resistin are established in humans yet.

THERAPEUTIC IMPLICATIONS

Of various inducers of pro-inflammatory cytokines, adiponectin may be first considered as a candidate treatment agent for NAFLD. Its serum levels are decreased in patients with obesity, type 2 diabetes or coronary artery diseases [27,35]. Another therapeutic target of interest is the constitutive androstane receptor (CAR) [36]. The CAR ameliorates the sensitivity to glucose and steatosis by inhibiting hepatic lipogenesis and inducing β-oxidation. In addition, peroxisome proliferator-activated receptor (PPARα) is responsible for the increase in the oxidation of fatty acids and the decrease in serum levels of triglycerides. In patients with NAFLD, PPARα levels are decreased considerably but those of the prolipogenic transcription factor Sterol Regulatory Element Binding Proteins (SERBP-1c) are significantly increased [37,38]. For these reasons, PPARα is also considered to be an interesting target to study in relation to lipid metabolism and obesity.

Further studies are warranted to clarify the molecular mechanisms by which abnormal fat accumulation and oxidative imbalance occur in patients with steatotic livers, which would be essential for improving the diagnostic and therapeutic approaches. From this context, future therapeutic targets would focus on new convincing molecules which can prevent fat accumulation in hepatocytes as well as improve the insulin sensitivity.

CONCLUSION

This review discusses the latest updates on the role of some of important inflammatory adipokines and cytokines in the pathogenesis of NAFLD. It also highlights their crucial role as a key regulator of insulin sensitivity, hepatic fat accumulation, hepatic injury and inflammation and fibrosis. Future therapeutic targets would focus on new convincing molecules which can prevent fat accumulation in hepatocytes as well as improve the insulin sensitivity.

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