Journal of Medical Toxicology Research

Editorial

A SCITECHNOL JOURNAL

Non-alcoholic Fatty Liver Disease and Hepatic Lipotoxicity

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Introduction

Obesity has reached pandemic proportions around the world. Its secondary sequelae-nonalcoholic fatty liver disease (NAFLD) has become one of the most prevalent chronic liver disorders for people of all ages. There is evidence that up to one third of the population developed NAFLD was due to obesity and its associated metabolic disorders [1]. On the other hand, approximately one third of hepatocellular carcinoma (HCC) patients do not have a medical history with etiology of infection with hepatitis B or hepatitis C, thus frequently diagnosing the malady from idiopathic or NAFLD [2].

NAFLD is featured with ectopic lipid accumulation in the liver and encompasses a spectrum of fat-associated liver conditions [3]. Generally, simple steatosis (fatty liver) occurs at the preliminary stage of NAFLD which may progress to nonalcoholic steatohepatitis (NASH), fibrosis and cirrhosis, in which a subpopulation transforming to HCC. Despite the high prevalence of NAFLD, only a small proportion of patients with fatty liver develop to NASH, characterized by lobular and portal inflammatory infiltrates of monocytes and tissue fibrosis, with high risk of advancing to cirrhosis and HCC. Notably, subjects with simple steatosis have almost similar life expectancy to the general population without survival defects.

A "multiple-hit process" model has been put forth to understand the molecular events about NAFLD induced liver injury [4]. It's believed that the initial "hit" is an ectopic accumulation in liver fat, resulting in hepatic lipotoxicity, which eventually triggers the inflammatory response in the microenvironment of liver and causes other "hits'. At the onset, hepatic fat accumulation and liver insulin resistance was bonded with the morbidity of NAFLD. It's generally thought that accumulation of Triacylglyceride is safe but harmful effect was brought about by accumulation of high levels of saturated free fatty acids (SFA), free cholesterol, ceramide, sphingolipids and other lipid metabolites in hepatocytes, which activate different molecular pathways to cause reactive oxygen species (ROS) production, altered mitochondrial energy coupling, increased membrane permeabilization by BAX, cell stress, inflammation, etc., and eventually resulting in cell death through apoptosis, necrosis and inflammatory pathways.

Stressed or damaged cells release a variety of dangerous signals that drive the progression of liver injury. In the recent years, cell-derived extracellular vesicles (EVs) had been uncovered to be a novel damage-associated molecular signals involved in the "hits" of hepatic lipotoxicity [5]. EVs are a kind of heterogeneous population of extracellular vesicles surrounded by lipid membrane, including exosomes, ectosomes, or microparticles, and apoptotic bodies, which was released by cells during both physiological or cell stress conditions. EVs contain a variety of bioactive molecules, including non-coding RNAs and various proteins, which could enter into the circulation to take part in systemic regulation for both normal physiological and pathological processes. For instance, it was found hepatocytes exposed to the palmitic acid, one saturated lipotoxic lipid abundantly present in circulation of patients with NASH, will produce and release plentiful EVs in the liver microenvironment. These released EVs will act on various hepatic cells to induce different biological responses involved in NAFLD pathogenesis, such as immune modulation, pathological angiogenesis and fibrosis.

Due to the primary role of obesity-related adipocyte insulin resistance on hepatic lipotoxicity, restoration of insulin action is a major treatment targeting to lipotoxicity. Reversal of lipotoxicity with insulin sensitizers, such as pioglitazone, metformin, and thiazolidinediones, had been widely tested [6]. Administration of metformin is associated with a certain extent of histological benefit. Pioglitazone was proved to enhance insulin sensitivity in adipose tissue to store more fat and prevents excessive rates of lipolysis, and reduces SFA accumulation in liver and ameliorates live fibrosis. Recently, a three year trial of pioglitazone in 101 patients with NASH confirmed its long-term safety and efficacy, suggesting that pioglitazone may become the standard of care for population with NASH. Glucagon-like peptide 1 receptor agonists have also been shown to be highly effective to treat NASH, thus opening a promising treatment avenue for reverse of hepatic lipotoxicity. Furthermore, there are many other agents, such as Sodium–glucose Cotransporter 2 (SGLT2) inhibitors, CCR2 and CCR5 inhibitors, pan caspase inhibitor, FXR agonist etc., under development in Phase 2-3 trial, targeting to different pathways to restore metabolic homeostasis, ameliorate inflammatory response for improvement of life quality of patients with NASH.

Most important of all, it should be emphasized that hepatic lipotoxicity is secondary to fat insulin resistance, a characteristic of adipose tissue dysfunction due to obesity. Adipose tissue lies in the center of metabolism of whole body to maintain energy balance of whole body. There's evolutionarily acquired mechanism in preventing lipid accumulation in the liver by promoting Adipogenesis in mammalian [7]. In the future, we need deepen understanding of the central role of adipose tissue in modulation of systemic energy balance and the crosstalk between liver and adipose tissues. It should be kept in mind that improvement of energy balance is prerequisite for clearing away of hepatic lipotoxicity.

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Received: September 20, 2017 **Accepted:** January 02, 2018 **Published:** January 09, 2018

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