Regulation of metabolic targets in hepatic and tumor cells

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Liver is the most important organ for lipid metabolism. Many factors can result in lipid metabolism disorders in liver, such as metabolic syndrome, high-fat diet, and excessive alcohol drinking. Fatty liver disease is divided into NAFLD (non-alcoholic fatty liver disease) and AFLD (alcoholic fatty liver disease) according to the etiology, which affects millions of Chinese. NAFLD and AFLD each begin with the accumulation of lipids in liver, then lead to steatohepatitis, fibrosis and ultimately cirrhosis [1–2]. Once it reaches the stage of steatohepatitis, curative treatment will be more difficult and progression will be irreversible.

Apart of fatty liver disease, metabolism reprogramming is a major hallmark of cancer. Enhanced aerobic glycolysis, also known as “Warburg Effect” is a typical feature of cancer [3]. Therefore, better understanding of the molecular mechanisms by which steatosis develops is essential for treatment strategies for both fatty liver disease and cancer.

Many researches have demonstrated that the capacity of liver to deal with the metabolic energy substrates, carbohydrates and fatty acids is overwhelmed, resulting in the accumulation of toxic lipid species [4–5]. These metabolites induce hepatocellular stress, injury and death, leading to fibrosis and genomic instability which predispose to cirrhosis and hepatocellular carcinoma. Therefore, understanding the lipid metabolism is important for treatment of fatty liver disease.

SREBPs are transcription factors involved in the regulation of fatty acid, triglyceride, and cholesterol synthesis. Once activated, the mature form of SREBPs is released, escorted to the Golgi, and then transported to the nucleus where it binds to sterol response elements and activates transcription. SREBP1c activates genes involved in fatty acid synthesis, whereas SREBP-2 mediates cholesterol synthesis [6]. SREBP-1c is mostly expressed in the liver and increases the expression of several genes involved in de novo fatty acid synthesis including fatty acid synthase (FAS), acetyl CoA carboxylase (ACC), and stearoyl-CoA desaturase 1 (SCD1) [7]. SREBP-1c has been implicated in the pathogenesis of AFLD [8] and NAFLD [9]. ChREBP is another transcription factor that acts similarly to SREBP on lipid synthesis. ChREBP plays an important role in the conversion of carbohydrates to triglyceride in the setting of increased carbohydrate intake [10]. Upon activation, ChREBP induces transcription of genes involved in glycolysis (liver pyruvate kinase), lipogenesis (ACC and FAS), and gluconeogenesis (glucose-6-phosphatase) [11]. ChREBP is involved in NAFLD [11] and AFLD [12]. LXR complexes with retinoid X receptor (RXR) to activate transcription of its downstream targets [13]. LXR can be activated by glucose, glucose-6-phosphate, and oxysterols, and is involved in cholesterol homeostasis. LXR regulates lipogenic genes such as FAS and ACC, and also regulates the expression of transcription factors such as SREBP-1c and ChREBP [14]. Insulin resistance is an independent predictor and risk factor of fatty liver disease that contributes to its pathogenesis. Insulin resistance is characterized by reduced glucose disposal in liver, adipose tissue and muscle, which results in increased fat mobilization [15]. Moreover, Insulin resistance is often associated with fibrosis in NAFLD patients [16].

The abnormal lipid metabolic signals as mentioned above always lead to obvious fat accumulation and irreversible hepatocellular injury though endoplasmic reticulum (ER) stress and oxidative stress [17]. ER stress is triggered by the accumulation of unfolded and misfolded proteins, so-called unfolded protein response (UPR). This results in increased levels of proapoptotic proteins and induction of transcriptional proteins involved in lipid synthesis such as SREBP-1c and SREBP-2 that are necessary for the repair of cell membranes. The occurrence and action of ROS is of pivotal importance in the pathogenesis of fatty liver disease by induction of oxidative stress [18].

The public health and economic impacts of fatty liver disease
disease have emerged globally and provoked intense interest among patients, regulators and the biotechnology and pharmaceutical industries [19]. In this issue of Chinese Journal of Natural Medicines (CJNM), we are pleased to organize several foundational research papers and one comprehensive review about lipid metabolism.

LIU Hai-Liang et al. reported that the effect of Berbamine (BM) on ethanol-induced hepatic injury in mice and its underlying mechanism [20]. Results were shown that BM significantly inhibited lipopolysaccharide (LPS) or acetate-induced IL-1β and IL-6 mRNA expression in RAW264.7 cells. Hepatic histopathology analysis showed that inflammatory cells infiltration and lipid accumulation were suppressed by 25 and 50 mg kg⁻¹ BM administration in ethanol-induced hepatic injury mouse model. Meanwhile, BM treatment significantly inhibited serum ALT and AST levels, hepatic triglyceride (TG) and total cholesterol (TC) contents and hepatic lipid accumulation in ethanol-fed mice. Remarkably, the mechanism of action of BM was related to the reduction of ethanol-induced NF-κB and STAT3 and ERK pathway in liver. Thus, this study reports a natural compound BM, which can be applied for the treatment of alcoholic liver diseases. As a potential candidate therapeutic drug, it can inhibit inflammation effectively while exist low toxicity.

Intestinal microbiome is also important in maintaining physiological and metabolic homeostasis [20]. Many kinds of probiotics are related to fatty liver and insulin resistance [21-22]. YI Hong-Wei and his colleagues reported the protective effects of Bifidobacterium longum (BL) and Selenium-enriched Bifidobacterium longum (SeBL) on alcohol plus high fat diet (HFD) induced mice hepatic injury [23]. They found that SeBL inhibited lipid accumulation in hepatocytes; reduced serum AST and ALT levels; improved dyslipidemia; decreased serum FFAs, TC, TG and LDL-C levels. In addition, SeBL inhibited alcohol plus HFD-induced hepatocyte oxidative stress through decrease in hepatic MDA levels and increase in SOD activity. SeBL also regulated lipid metabolism related genes such as AMPK, PPAR-α and SREBP1. Although BL showed similar protective effect, SeBL was more effective than BL. In summary, SeBL protected mice from alcohol plus HFD-induced hepatic injury in mice because of its inhibitory effect on hepatocellular oxidative stress, lipogenesis and inflammation. Selenium enhanced the protective effect of BL. This research demonstrates that SeBL represents a promising nutritional supplement for alcohol or HFD-induced hepatic injury.

More and more evidences show that metabolism disorder is also an important factor of tumor development. Enhanced glucose metabolism is one of the hallmarks of pancreatic cancer [24]. FU Xiao et al. reported that MUC1, a transmembrane protein, is a global regulator of glucose metabolism and essential for progression of pancreatic cancer [25]. They found that MUC1 knockout (KO) cells uptook less glucose and secreted less lactate with a much lower proliferating rate compared with wild type. As the elevated glucose metabolism is known to facilitate cancer cells to gain chemotherapy, they treated wild type and MUC1 KO cells with gemcitabine and FOLFIRINOX in vitro and in vivo. Their results showed that MUC1 KO significantly sensitized pancreatic cancer cells to chemotherapy. This article suggests that it is effective to increase the chemosensitivity of tumor cells by changing the metabolic status.

Metabolism plays a pivotal role in many processes of biological process. Therefore, in-depth understanding of the metabolic mechanism can help us to control developments of various disease, and find potential drugs.

References


