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Review Article

Free radical biology for medicine: learning from nonalcoholic fatty liver disease ☆

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ABSTRACT

Reactive oxygen species, when released under controlled conditions and limited amounts, contribute to cellular proliferation, senescence, and survival by acting as signaling intermediates. In past decades there has been an epidemic diffusion of nonalcoholic fatty liver disease (NAFLD) that represents the result of the impairment of lipid metabolism, redox imbalance, and insulin resistance in the liver. To date, most studies and reviews have been focused on the molecular mechanisms by which fatty liver progresses to steatohepatitis, but the processes leading toward the development of hepatic steatosis in NAFLD are not fully understood yet. Several nuclear receptors, such as peroxisome proliferator-activated receptors (PPARs) α/γ/δ, PPARγ coactivators 1α and 1β, sterol-regulatory element-binding proteins, AMP-activated protein kinase, liver-X-receptors, and farnesoid-X-receptor, play key roles in the regulation of lipid homeostasis during the pathogenesis of NAFLD. These nuclear receptors may act as redox sensors and may modulate various metabolic pathways in response to specific molecules that act as ligands. It is conceivable that a redox-dependent modulation of lipid metabolism, nuclear receptor-mediated, could cause the development of hepatic steatosis and insulin resistance. Thus, this network may represent a potential therapeutic target for the treatment and prevention of hepatic steatosis and its progression to steatohepatitis. This review summarizes the redox-dependent factors that contribute to metabolism alterations in fatty liver with a focus on the redox control of nuclear receptors in normal liver as well as in NAFLD.

Contents

Abbreviations: ROS, reactive oxygen species; NR, nuclear receptor; FA, fatty acid; TAG, triacylglycerol; MCD, malonyl-CoA decarboxylase; ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase; SCD1, stearoyl-CoA desaturase-1; G-3-P, glycerol 3-phosphate; CPT-1, carnitine palmitoyl transferase 1; TCA, tricarboxylic acid; HMG-CoAR, 3-hydroxy-3-methylglutaryl-CoA reductase; ER, endoplasmic reticulum; 4-HNE, 4-hydroxynonenal; NASH, nonalcoholic steatohepatitis; UCP-2, uncoupling protein 2; PPARα/γ/δ, peroxisome proliferator-activated receptors α/γ/δ; PGC-1α/β, PPARγ coactivators 1α and 1β; SREBP, sterol-regulatory element-binding protein; AMPK, AMP-activated protein kinase; LXR, liver-X-receptor; FXR, farnesoid-X-receptor; ACOX, acyl-CoA oxidase; SOD, superoxide dismutase; CAT, catalase; GSH, glutathione; FAT/CD36, FA translocase; NRF, nuclear respiratory factor; mtTFA, mitochondrial transcription factor A; NAFLD, nonalcoholic fatty liver disease; FOX, forkhead box class; MAPK, mitogen-activated protein kinase; CREB, cAMP-responsive element-binding protein; IRS, insulin receptor substrate; HC, hydroxycholesterol; NFE2L2, nuclear factor (erythroid-derived 2)-like 2; UPR, unfolded protein response; GPX, glutathione peroxidase; GST, glutathione *S*-transferase; GRx, glutathione reductase; ALA, α-lipoic acid

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Introduction

Oxidative stress, which accounts for the dysfunction or death of hepatocytes and other liver cells, contributes to the pathogenesis of acute and chronic liver diseases [1,2]. Even though reactive oxygen (ROS)[1] and nitrogen species are normally produced by the metabolism of normal cells, in hepatic diseases an overproduction of free radicals that overcomes the antioxidant defenses occurs, inducing liver injury [3]. At high concentrations, free radicals are dangerous for several cellular constituents. However, at low or moderate concentrations, they may act as regulatory mediators in signaling processes. Various sources of free radicals are implicated and can be classified as mitochondrial, principally from Complexes I and III, and extramitochondrial, such as cytochrome P450, xanthine oxidase, nitric oxide synthase, and NADPH oxidase [2]. Neutrophils and Kupffer cells are the primary producers of free radicals in the liver, whereas the major sites of ROS release in hepatocytes are the cytochrome P450 system and mitochondria [4]. In addition, iron may act synergistically with other free radical sources to promote liver lipid peroxidation through the Fenton reaction [5].

Nonalcoholic fatty liver disease (NAFLD), the most frequent hepatic pathology [6], is characterized by the development of oxidative stress and changes in redox balance [7]. The pathogenesis of NAFLD is multifactorial and includes lipid metabolism alterations, mitochondrial dysfunction, inflammation, and oxidative stress [8–12]; moreover, hepatic iron deposits in some cases may contribute to NAFLD, even though their role is still controversial [13]. Excessive accumulation of lipids is strongly associated with insulin resistance [14], and it is widely accepted that NAFLD represents the hepatic manifestation of a systemic impairment of the insulin network [15]. However, it is still unclear whether insulin resistance causes lipid storage in liver or whether the increase in lipids itself or their metabolite intermediates may play a causal role in the development of hepatic or systemic insulin resistance [16]. The homeostasis of metabolic pathways is finely modulated through a network of programs, which involves transcription factors, kinases, and phosphatases, as well as nuclear receptors (NRs). The result is a fine balancing of the intermediary metabolism to meet metabolic demands.

Free radicals play a role in the activation or inhibition of signaling pathways that can modulate cellular lipid metabolism. An example of how oxidative stress may dysregulate redox signaling leading to hepatic steatosis is provided by alcoholic liver disease (ALD) [17]. In fact, the oxidation of ethanol determines a more reduced cellular state and activates the microsomal induction with consequent impaired utilization of oxygen and free radical-induced toxicity [18], which in turn inhibit fatty acid oxidation and promote lipogenesis through the modulation of several NRs [19,20]. Even though NAFLD is histologically identical to ALD, it is not associated with alcohol consumption and presents a different natural history [21]. The dysregulation of redox biology in NAFLD has already been extensively reviewed, particularly pointing out its role in the progression of steatohepatitis and in the involvement of adipokines and immune system [22–26]. The definition of redox-dependent molecular alterations responsible for the development of steatosis provides new insights into the role of ROS as controllers of liver lipid metabolism under physiological and pathological conditions. Moreover, as several findings suggest that increased ROS levels induce various signaling pathways that may trigger insulin resistance in numerous settings [27], a redox control may be implicated in the early development of fatty liver.

Taking into account the pivotal role played by several NRs and transcription factors in the development of NAFLD [28], this review outlines the recent knowledge of the role played by free radicals in the regulation of the transcriptional network that modulates lipid metabolism in NAFLD, suggesting a redox-centered pathogenic theory. Finally, updated evidence of the impact of NAFLD on hepatic antioxidant defense and on the role of antioxidant targeting therapy is also discussed.

Redox regulation of key enzyme activity in lipid metabolism in NAFLD

The liver plays a central role in all the steps of lipid metabolism (schematized in Fig. 1):

- lipogenesis by conversion of excess carbohydrates;
- fatty acid (FA) oxidation to produce energy;
- cholesterol and phospholipid metabolism.

Lipid metabolism is controlled by:

(1) the activity of key enzymes triggered by the binding of an activator or inhibitor;
(2) post-translational modifications, which may shift the equilibrium between an inactive and an active enzyme; and
(3) transcriptional regulation, which affects the level of expression of key enzymes and is effective over a longer time scale.

Cellular redox state may affect the activity of several enzymes involved in lipid metabolism, cause post-translational modifications directly (glutathionylation, carbonylation), or by the modulation of phosphatases/kinases, act as second messengers or induce conformational changes to NRs and/or act as NR ligands [29]. The intracellular redox status is established by several redox pairs, such as NADH/NAD^+, NADPH/$NADP^+$, and reduced glutathione/oxidized glutathione [30,31]. Thus, these ratios serve as an index of the availability of reducing equivalents required for lipogenesis. When an excess of reducing equivalents occurs in rat liver mitochondria, β-oxidation may be partially suppressed [32,33]. Some of the enzymes involved in lipid metabolism whose activity is modulated by redox status are shown in Table 1.

NAFLD is a condition in which hepatocytes, which normally hold only small amounts of storage lipid, contain supraphysiological amounts of fat, caused by an imbalance between lipid uptake and synthesis that exceeds oxidation and removal. Patients affected by NAFLD show an increase in both uptake and synthesis