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Mini-review

Peroxisome proliferator-activated receptor-α activation and excess energy burning in hepatocarcinogenesis

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ABSTRACT

Peroxisome proliferator-activated receptor-α (PPARα) modulates the activities of all three interlinked hepatic fatty acid oxidation systems, namely mitochondrial and peroxisomal β-oxidation and microsomal ω-oxidation pathways. Hyperactivation of PPARα, by both exogenous and endogenous activators up-regulates hepatic fatty acid oxidation resulting in excess energy burning in liver contributing to the development of liver cancer in rodents. Sustained PPARα signaling disproportionately increases H_2O_2-generating fatty acid metabolizing enzymes as compared to H_2O_2-degrading enzymes in liver leading to enhanced generation of DNA damaging reactive oxygen species, progressive endoplasmic reticulum stress and inflammation. These alterations also contribute to increased liver cell proliferation with changes in apoptosis. Thus, reactive oxygen species, oxidative stress and hepatocellular proliferation are likely the main contributing factors in the pathogenesis of hepatocarcinogenesis, mediated by sustained PPARα activation-related energy burning in liver. Furthermore, the transcriptional co-activator Med1, a key subunit of the Mediator complex, is essential for PPARα signaling in that both PPARα-null and Med1-null hepatocytes are unresponsive to PPARα activators and fail to give rise to liver tumors when chronically exposed to PPARα activators.

1. Introduction

Energy balance is a reflection of energy consumption and energy expenditure. The burgeoning pandemic of obesity (body-mass index [BMI] >30 kg/m^2), attributable, in general, to excess energy intake and reduced energy expenditure affects over 500 million adults globally [1,2]. In the United States, obesity rates are among the highest in the world with ~70% of Americans, age 20 years and over, being overweight or obese [2]. Obesity is an established risk factor for metabolic syndrome, type 2 diabetes, cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), and many cancers, including hepatocellular carcinoma (HCC) [3]. NAFLD, which is characterized initially by hepatic fat accumulation (simple steatosis), can progress to nonalcoholic steatohepatitis (NASH), advanced fibrosis, and liver cancer [4,5]. NASH manifests as hepatic steatosis with hepatocellular injury, inflammation, endoplasmic reticulum (ER) stress, and liver cell regeneration [5]. The factors influencing the progression of simple steatosis to NASH and end-stage liver disease, including liver cancer remain complex. Given the precipitous rise in obesity prevalence, liver cancer risk due to NASH is poised to become a major health problem worldwide [3,4]. According to current projections, 25 million Americans will have NASH by year 2025, with 20% progressing to cirrhosis with an added risk of HCC development [3].

Excess energy consumption, with resultant storage of unexpended and de novo synthesized fatty acids as triglyceride in adipocytes, with liver serving as a surrogate reservoir for fat, is an important consideration in the development of hepatic steatosis [1,6]. However, excess storage of lipid in liver by itself may be insufficient to increase liver cancer risk in obesity. In this regard, leptin-deficient ob/ob mice with fatty livers, considered paradigmatic of obesity resulting from excess energy intake, are not normally prone to develop liver tumors at a high incidence [7]. Of interest, however, is that the enhancement of fatty acid oxidation in ob/ob fatty livers that have excess stored fuel with constant influx of excess calories may be important in mediating the processes

Abbreviations: PPAR, peroxisome proliferator-activated receptor; PPRE, peroxisome proliferator-response element; Med1, Mediator complex subunit 1; ACOX1, acyl-CoA oxidase-1; L-PBE/EHHADH, enoyl-CoA hydratase/L-3-hydroxyacyl-CoA dehydrogenase bi-functional enzyme; ER, endoplasmic reticulum.

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important in hepatocarcinogenesis [8]. In fully developed fatty livers, some type of balance between excessive storage of fat and fatty acid oxidation likely operates to maintain the steady-state bland hepatic steatosis [9]. A tilt toward excessive catabolism of energy can occur in these markedly steatotic livers with a second hit, for example with bursting of some hypersteatotic ballooning hepatocytes, that could result in the release of fatty acids responsible for the onset of inflammation [9]. Loss of some liver cells and the onset of inflammation could serve as stimuli for hepatocellular proliferation [4,10]. Regenerated hepatocytes are without accumulated fat and have more mitochondria, and a full complement of cytoplasmic organelles [11]. In general, such cells are better equipped to burn more energy to cause excessive oxidative damage when compared to simple steatotic hepatocytes with reduced fatty acid oxidation capacity. In livers with alcoholic- or nonalcoholic steatohepatitis, all steatotic hepatocytes are progressively replaced by regenerating hepatocytes that in general are resistant to fat accumulation as they are more efficient in energy burning. These livers then have the inherent propensity to progress to cirrhosis and liver cancer.

The evidence that excess energy burning plays a role in hepatocarcinogenesis goes back to the reports of the induction of liver tumors by chemicals that are capable of inducing proliferation of peroxisomes in liver cells and enzymes responsible for fatty acid catabolism [12]. These chemicals include fibrate class of lipid lowering drugs and other structurally diverse chemicals, which we called *peroxisome proliferators* as these compounds induce proliferation of peroxisomes in hepatocytes [12]. Peroxisome proliferators induce fatty acid oxidation systems in liver by a receptor-mediated mechanism [13–17]. This receptor, designated peroxisome proliferator-activated receptor-α (PPARα), is responsible for the peroxisome proliferator-induced phenotypic responses that include peroxisome proliferation, enhanced fatty acid oxidation resulting in excess energy burning in liver, and hepatocarcinogenesis [17–19]. Sustained activation of this receptor by either exogenous or endogenous activators, results in increased energy combustion and excess generation of reactive oxygen species (ROS) contributing to oxidative stress leading to the development of liver tumors in rodents with possible implications to human liver carcinogenesis [19–22]. This brief review focuses on the PPARα-related increases in fatty acid oxidation, energy burning and liver tumor risk.

2. Peroxisomes, peroxisome proliferation and peroxisome proliferators

2.1. Peroxisomes

Peroxisomes are single membrane-limited cytoplasmic organelles, devoid of DNA with a finely granular matrix that are present in a wide variety of cells in human, animals, fungi and plants [23–25]. In liver parenchymal cells, peroxisomes measure ~0.2–1.0 μM in diameter and are few in number, accounting, under physiological conditions, for less than 2% of cytoplasmic volume. Peroxisomes contain an array of H_2O_2-generating oxidases together with the H_2O_2-degrading catalase [22,23,26,27]. The concept of, – and the designation “peroxisome” were introduced In 1965 by De Duve to bring attention to the organelle that has the enzymatic composition for the H_2O_2 generation and degradation [23]. Of the variety of H_2O_2 producing oxidases present in peroxisomes, fatty acyl-CoA oxidase 1 (ACOX1) of the peroxisomal fatty acid β-oxidation system (described below) is critical in regulating energy metabolism and in the exclusive metabolism of very-long chain fatty acids [24]. Because of the presence of ACOX1 and other oxidases, including ACOX2, ACOX3, urate oxidase (UOX), D-amino acid oxidase, and L-α-hydroxy acid oxidase, peroxisomes are responsible for ~20% oxygen consumption in liver [22–27]. More than 60 proteins are present in peroxisomes that participate in a variety of complex metabolic functions such as lipid metabolism, synthesis of bile acids, membrane phospholipids, and cholesterol, and degradation of uric acid, purines, polyamines and amino acids [24]. Thus, peroxisomes orchestrate a number of key physiological functions. The dual role of peroxisomes in generating and countering ROS and their function in fatty acid β-oxidation may be critical in maintaining cellular integrity. New findings suggest that human peroxisomes are also involved in antiviral innate immunity, peptide hormone metabolism, brain aging, Alzheimer’s disease and other age-related diseases [28,29].

2.2. Peroxisome proliferation and peroxisome proliferators

In eukaryotic cells peroxisomes are few in number and smaller in size compared to mitochondria. Liver parenchymal cells contain approximately 350–400 peroxisomes that occupy less than 2% of the cytoplasmic volume. On the other hand, each liver cell contains 1000–2000 mitochondria that occupy nearly 20% of the cytoplasmic volume. Of interest is that the number of peroxisomes per liver cell increases over 7-fold, resulting in a nearly 20-fold increase in peroxisome volume density, when rats and mice are fed a diet containing clofibrate or its analogs that are lipid lowering drugs [26]. Several of the structural analogs of clofibrate are potent inducers of hepatomegaly with striking induction of hepatic peroxisome proliferation, along with modest increase in smooth endoplasmic reticulum [30]. Fibrate class of drugs such as methyl clofenapate, nafenopin, bezafibrate, gemfibrozil and others are several orders of magnitude more potent than clofibrate in inducing hepatic peroxisome proliferation. Based on studies with two other novel lipid lowering compounds, [4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio] acetic acid (Wy-14,643) and 2-chloro-5-(3, 5-dimethylpiperidinosulfonyl) benzoic acid (tibric acid) it was suggested that the peroxisome proliferative property and hypolipidemic responses are interrelated [12]. Because of the structural diversity of these agents, we called these agents peroxisome proliferators, to highlight their common predictable biological property of inducing peroxisome proliferation in liver [12]. Certain phthalate-ester plasticizers, such as di-(2-ethylhexyl)-phthalate (DEHP), and di-(2-ethylhexyl) adipate (DEHA), used in the manufacture of polyvinyl chloride plastics, also induce peroxisome proliferation and lower serum lipids [31,32]. Moreover, the frequent association of hepatic peroxisome proliferation with drug-induced hypolipidemia suggested that yet unidentified peroxisomal enzymes might be responsible for the hypocholesterolemic and hypotriglyceridemic effects [12]. These observations served as a solid foundation for the concept that peroxisomes participate in lipid metabolism and for the subsequent discovery of fatty acid β-oxidation within the peroxisome [12,33].

2.3. Peroxisome proliferators are hepatocarcinogenic

In view of the therapeutic importance of drugs in controlling hyperlipidemic states in man and since such individuals receive these for several years, it became important to ascertain the adverse effects, including cancer, if any, of the long-term exposure to these peroxisome proliferators [20,21]. Likewise, since environmental exposure to phthalate-ester plasticizers, industrial solvents, herbicides and other synthetic peroxisome proliferators also poses risk, it became imperative to systematically evaluate the potential risk to humans [12,13,32]. Our work on the induction of hepatocellular carcinomas in acatalasemic mice treated with nafenopin, a hypolipidemic peroxisome proliferator (Fig. 1), strongly suggested