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HYPOTHESIS

Could platelet-derived growth factor α mediates hepatitis C-induced insulin resistance and hepatic fibrosis?

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DOI: 10.21040/eom/2018.4.2.2

Received: April 24th 2017
Accepted: May 29th 2018
Published: June 29th 2018

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Funding: None.

Conflict of interest statement: The authors declare that they have no conflicts of interest.

Data Availability Statement: All relevant data are within the paper.

Abstract

Hepatitis C virus (HCV) infection represents an important risk factor for Type 2 diabetes mellitus (T2DM) development. Although the HCV diabetogenic potential depends on its genotype, it is probably due to dysglycemia and dyslipidemia promotion, visceral obesity, and genetic predisposition. Hepatic steatosis represents a common feature of chronic HCV infection as well as T2DM. Thus, we hypothesize that these two conditions might share a common mechanism in hepatic steatosis pathogenesis. Lipid accumulation in the hepatocytes represents the "first hit" that increases the liver vulnerability to many factors that constitute the "second hit" and promote hepatic injury, inflammation, and fibrosis. Many inflammatory cytokines and growth factors are released during liver injury, including platelet-derived growth factors (PDGFs). It was recently demonstrated that elevated hepatic PDGF-A gene expression and increased secretion of PDGF-A are associated with hepatic steatosis and fibrosis in patients with T2DM. Since HCV infection is often accompanied with systemic insulin resistance, we hypothesize that chronic hyperinsulinemia might lead to increased secretion of PDGF-α and thus mediate the HCV-related hepatic steatosis and fibrosis.

Key words: Hepatitis C infection; insulin resistance; hepatic steatosis; platelet-derived growth factor α

1. The Hypothesis

Hepatitis C virus (HCV) infection affects approximately 64–103 million people worldwide and represents one of the major causes of chronic liver disease [1]. Although an acute infection might resolve spontaneously in a certain number of patients, 75%–85% fail to clear the virus and become chronically infected [2]. Hepatocytes represent the primary host cells for HCV. Once internalized through the low-density lipoprotein receptor pathway [3], HCV interferes with hepatic lipid metabolism through its life cycle [4], consequently leading to hepatic steatosis, cirrhosis, and eventually to hepatocellular carcinoma, which represents the HCV-related end-stage liver disease [2].

Although it might occur in any HCV genotype [5,6], genotype type 3 is associated with the most pronounced steatosis [5]. Its severity, however, results from the combination of several host and viral factors that directly interfere with lipid metabolism within the hepatocytes [6]. Host factors include insulin resistance (IR)/hyperglycemia, dyslipidemia, hypertension, visceral obesity, alcohol consumption, medication use, and genetic predisposition (e.g., interleukin 28B polymorphism), while viral factors include the before mentioned genotype, HCV RNA load, and gene mutations [5,6].

The inability of insulin to suppress lipolysis in white adipose tissue is defined as IR. It leads to increased plasma concentrations of free fatty acids (FFA), which then disrupts the hepatic balance of FFA influx and oxidation and therefore becomes the main source of hepatic triglycerides in steatosis [7]. Therefore, IR in white adipose tissue might contribute to hepatic fat accumulation. However, the accumulation of saturated fatty acids and triglycerides hepatocytes in HCV-related steatosis cannot all be contributable not only to the increased FFA influx [8] but also to the *de novo* lipogenesis in the liver which is significantly increased in HCV-related steatosis [6]. The influence of HCV on the cholesterol and lipogenesis pathways of hepatocytes is a crucial part of its life cycle. The HCV core protein plays a major role in the replication process by inducing lipid accumulation, as well as lipogenic gene and protein activity [9]. The main mechanisms contributing to HCV-induced hepatic steatosis include promotion of lipogenesis by activating the transcription factor sterol regulatory element binding protein-1c, impairment of mitochondrial lipid oxidation, and decreased microsomal triglyceride transfer protein activity [10-12].

Lipid accumulation in the hepatocytes represents the "first hit" that increases liver vulnerability to many factors that constitute to the "second hit" and promote hepatic injury, inflammation, and fibrosis [13]. To date, there is no effective treatment for patients with HCV-related liver fibrosis, so a better understanding of the pathways that regulate fibrosis has great clinical and therapeutic potential.

Many inflammatory cytokines and growth factors are released during liver injury, including platelet-derived growth factors (PDGFs), which are potent mitogens for hepatic stellate cells [14,15]. The PDGF family of ligands and receptors plays a central role in repair after injury and are key regulators of connective tissue formation [16,17]. Elevated PDGFR expression is detected in human heart disease and pulmonary and kidney fibrosis [18,19], and blocking of PDGFR signaling decreases collagen deposition after myocardial infarction, as well as pulmonary and kidney fibrosis [19-22]. Although the association of PDGF-B gene polymorphism and the development and progression of hepatic fibrosis are known [23], the regulatory mechanism in the PDGF-related fibrosis pathway has not been elucidated. A recent study demonstrated that elevated hepatic PDGF-A gene expression and increased PDGF-α secretion are associated with hepatic steatosis and fibrosis in patients with type 2 diabetes mellitus [23]. Moreover, Mendelian randomization confirmed a direct effect of fasting serum insulin levels on PDGF-α expression [24].

Thus, since HCV infection is often accompanied with systemic IR, we hypothesize that chronic hyperinsulinemia might lead to increased PDGF- α secretion and thus mediate the HCV-related hepatic steatosis and fibrosis; therefore, there is an urgent need for research in the field.

2. Authors' Contributions

All the authors contributed equally to the paper: Kristina Blaslov and Anna Mrzljak participated in the conception

and design of the study, and Davorka Dušek collected the data. All the authors participated in the literature review, drafted the manuscript, and gave their final approval of the submitted version.

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