THE ROLE OF NEW ADIPOKINES IN THE PATHOGENIC MECHANISMS OF CHRONIC HEPATITIS C

Rădulescu Mihaela Andreea1,2, Popescu Cristina1,2, Aramă Victoria1,2, Streinu-Cercel A.1,2

1 Prof. Dr. Matei Bals National Institute of Infectious Diseases, Bucharest
2 Carol Davila University of Medicine and Pharmacy, Bucharest

Abstract. Hepatitis C virus (HCV) infection is an important problem of public health in our country and worldwide. HCV infection leads to cirrhosis and in some cases to hepatocarcinoma. In the past years, HCV was associated with metabolic disturbances, including hepatic steatosis, dyslipidemia and insulin resistance, on the other hand these metabolic factors were identified to accelerate progression to cirrhosis and hepatocarcinoma. Also in patients with chronic hepatitis C (CHC), the endocrine activity of fat tissue is disturbed and a large number of adipokines seem to be involved in the pathogenic mechanisms of CHC progression, including liver inflammation, steatosis, fibrogenesis, insulin resistance and angiogenesis. In this paper we summarize published data regarding the role of two novel adipokines: Visfatin and Chemerin in the pathogenesis of HCV infection.

Key words: hepatitis C, adipokines, Visfatin, Chemerin, pathogenic mechanisms

Background

WHO estimates[1] that about 150 million people are chronically infected with hepatitis C virus (HCV), and over 350 000 deaths are attributed each year to HCV-related liver diseases. Romania is considered a country with high prevalence (3.23%- 4.26%), and it is estimated that 600000 to 800000 Romanians are infected with hepatitis C virus [2,3].

There are a few factors responsible for an accelerated progression to cirrhosis, of which metabolic factors came to attention in the past years. It is considered that HCV is associated with a number of metabolic disturbances, including hepatic steatosis, dyslipidemia, insulin resistance and type 2 diabetes mellitus. Also, in patients with HCV infection, the endocrine activity of adipose tissue is perturbed. The fat tissue, initially considered a non-active tissue with energy storage role, subsequently came to attention as an active tissue, with important secretory function, the source for a large number of bioactive molecules. Some of these molecules are mainly involved in glu- cidic and lipid metabolism, some of them are involved in immunity and inflammation mechanisms and other have different other functions in tissue repair, vasoco- nstriction, regulation of other hormones including cortisol and aldosteron. Most of these adipokines belong to more than one of the categories mentioned above and most of them are also synthesized in other cells than adipocytes. In table I we listed the most studied adipokines and their prevalent function. Serum levels of some adipokines are altered in some viral infections associated with chronic inflammation, such as HIV and HCV [4]. Some adipokines are involved in the pathogenic mechanisms of HCV infection, including inflammatory response, insulin sensitivity, fibrogenesis and liver steatosis, and they seem to play an important role in the evolution of chronic hepatitis C (CHC) to cirrhosis and hepatocarcinoma.

Among adipokines, Leptin, Resistin and Adiponectin are the first studied in CHC and their role is relatively well known. In this paper we intend to summarize published data regarding some relatively new adipokines, Visfatin and Chemerin, and their role in hepatitis C pathogenesis.

Physiological role of Visfatin

Visfatin is an adipokine first described in 1994 as a Pre-B cell colony enhancing factor by Samal et al [5]. It has been shown to have immunomodulatory and proinflammatory effects, with a role in innate immunity by activating B-cells, dendritic cells (DC) and macrophages, stimulating synthesis of a large number of cytokines, including interleukin 1β.
Visfatin in CHC

There are only a few studies which evaluated Visfatin in CHC patients. Serum levels of Visfatin are higher in CHC patients [24,25], regardless of genotype 1 or 3 [25]. It has been suggested that Visfatin could have a protective role against inflammatory liver injury, since its levels are higher in patients with low grade necroinflammatory activity [24]. Its role in the fibrogenesis process in CHC patients is controversial. Both Kukla and Baranova found no correlation to liver fibrosis or steatosis [24,25], while Huang reported a positive association to fibrosis grade and histological activity index scores. Huang also evaluated the association with antiviral treatment response and found no correlation between Visfatin levels and treatment response rates [26].

Although its role remains incompletely clarified, all the data available suggest that Visfatin is involved in important pathogenic mechanisms of CHC.

Physiological role of chemerin

Chemerin is a chimeric protein synthesized mainly in hepatocytes and fat tissue [27,28], with both pro-inflammatory and anti-inflammatory effects. Chemerin acts as a chemoattractant for macrophages, dendritic cells (DC), and NK cells [29,30] and it stimulates macrophage adhesion to vascular cell adhesion molecule 1 (VCAM1) and fibronectin [31]. On the other hand, Cash et al reported anti-inflammatory properties of Chemerin-derived protein C15 in a mouse peritonitis model, by inhibiting TNFα and IL6 [32], although later on the C15 protein it was described as an inactive compound on cells expressing ChemR23 - the principal receptor of Chemerin. However, the same authors reported ChemR23-dependent anti-inflammatory properties of Chemerin in a mouse pneumonia model [33].

Chemerin role in glucidic metabolism is also controversial. High serum levels of Chemerin were reported in humans with both type 1 and type 2 diabetes mellitus or impaired glucose tolerance[34-36].

### Visfatin in nonalcoholic fatty liver disease (NAFLD)

High serum concentrations of Visfatin were reported in patients with nonalcoholic fatty liver disease (NAFLD) [20,21]. Kukla et al reported a positive correlation of Visfatin serum levels with liver fibrosis, and no association with inflammatory liver activity and steatosis [22]. Lack of correlation with liver inflammation was also reported by Dahl [17]. On the other hand Aller found a positive correlation between Visfatin levels and liver inflammation in patients with NAFLD, and no correlation with liver steatosis [23].
It was shown to increase glucose intolerance in mouse models [37] and to inhibit glucose intake and accentuating glucose intolerance in human skeletal muscle cells by acting on insulin receptor substrate 1 [38]. However, other authors reported a positive effect of Chemerin in the sense of increasing glucose intake in mouse adipocytes [39]. Although both Bozaoglu and Kaur studies concluded that Chemerin stimulates angiogenesis by acting as an endothelial growth factor [40,41], which might suggest a role in carcinogenesis, Kukla found no relation between Chemerin levels and angiogenesis in portal tract [18]. Moreover, Chemerin acts as a chemoattractant for DC and NK cells, with role in antitumor immunity, which suggests a protective role against cancer. Lin et al found low serum levels of Chemerin correlated with tumor size, histological grade and poor survival rates in patients with hepatocarcinoma [42] and Zhao et al reported chemerin levels positively correlated to histological grade, NK infiltration and better survival rates in patients with non-small cell lung cancer [43].

The role of chemerin in NAFLD and CHC

High levels of Chemerin were found in NAFLD patients [44-46], and it seems to be correlated to NAFLD activity score, portal inflammation, fibrosis [45] and ballooning degeneration of hepatocytes [46]. There are few data published regarding the role of Chemerin in CHC. Kukla et al reported high levels of Chemerin in CHC patients compared to controls, and found a negative association to necroinflammation grade, and no correlation with fibrosis scores, although, as the authors themselves pointed, the study did not include patients with advanced fibrosis [47]. Subsequently the same authors reported no association of Chemerin levels with hepatic angiogenesis in CHC patients [18].

These findings suggest that Chemerin is an important element in the pathogenesis of CHC, especially in the inflammatory mechanisms, although further investigations are required to clarify its role.

Discussions

Multiple studies reported the contribution of different adipokines to the development of metabolic abnormalities in (NAFLD) and CHC and their role in fibrogenesis and angiogenesis, and some of them seem appropriate for predictive models and even as target molecules for future treatments against fatty infiltration, fibrosis and insulin resistance. Moreover, the serum level of some adipokines seems to be correlated with higher or lower rates of sustained response to antiviral treatment and they might prove useful in the future as response predictors. Although in the past 15 years numerous articles in this field were published, some results seem to be contradictory and the complex interactions between HCV, adipocyte secretion, inflammatory response and pathogenic mechanisms of chronic hepatitis remain insufficiently clarified.

ACKNOWLEDGEMENT: This paper is supported by the Sectoral Operational Programme Human Resources Development (SOP HRD) 2007-2013, financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/107/1.5/S/82839.

References


28. Murugananandam S, Parlee SD, Rourke JL, Ernst MC, Goralski KB, Sinal CJ. Chemerin, a novel peroxisome proliferator-activated receptor g (PPAR g) target gene that promotes mesenchymal stem cell adipogenesis. J. Biol Chem. 2011;286:23982–95.


42. Lin W, Chen YL, Jiang L, Chen JK. Reduced Expression of Chemerin is Associated with a Poor Prognosis and a Lowed Infiltration of Both Dendritic Cells and Natural Killer Cells in Human Hepatocellular Carcinoma. Clinical Laboratory. 2011; 57:11-12: 879-885.


