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Chemerin in Non-Alcoholic Fatty Liver Disease – Up or Down?

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Chemerin (previously known as tazarotene-induced gene-2 or retinoic acid receptor responder-2) is an adipokine whose systemic levels are increased in human and rodent obesity [1-5]. Chemerin is an attractant for immune cells and may play a role in the recruitment of tissue macrophages [6]. This adipokine also regulates adipogenesis and glucose metabolism [2,7,8]. Chemerin is released as a proprotein with low biological activity, and extracellular C-terminal processing by distinct proteases generates bioactive polypeptides which exert pro- or antiinflammatory effects [6,7]. Hence, local and systemic levels of bioactive chemerin depend on proteolytic processing and are not simply related to chemerin protein concentrations determined by commercially available ELISAs or immunoblot techniques.

It is well known that chemerin is expressed in the liver and hepatocytes produce plenty of chemerin which is also secreted by these cells [2,9,10]. Hepatic stellate cells release low levels of this protein while chemerin mRNA is not detected in Kupffer cells [10]. Chemerin is a ligand of the chemokine-like receptor 1 (CMKLR1) which is expressed by hepatocytes, hepatic stellate cells and Kupffer cells suggesting that chemerin affects liver cell function [11]. Chemerin regulates adipogenesis, and insulin response of skeletal muscle cells and adipocytes, and future studies have to identify downstream targets of this protein in liver cells [8,12,13].

In adipocytes chemerin is induced by proinflammatory cytokines, Lipopolysaccharide (LPS), Free Fatty Acids (FFA) and insulin [12,14-17], which are all increased in obesity [18-20], and this may contribute to elevated systemic chemerin. Three studies recently published investigated whether these metabolites also regulate hepatocyte chemerin synthesis [9,10,21]. IL-6 has, however, no effect on chemerin mRNA, cellular and soluble protein, and LPS does not increase chemerin protein in Primary Human Hepatocytes (PHH) [9,10]. Chemerin mRNA expression, total and bioactive chemerin concentrations in the supernatants of mouse hepatocytes are not regulated by TNF [3]. In PHH TNF even lowers chemerin in cell supernatants without changing cellular levels [10]. Therefore, inflammation contributes to higher adipocyte chemerin synthesis but seems not to raise hepatocyte chemerin production.

Insulin increases adipocyte chemerin whereas mRNA expression is not induced in PHH [9,16,17]. FFA have no effect on chemerin mRNA and cellular protein levels in PHH while palmitate tends to lower chemerin in the respective supernatants [9,10]. Palmitate even strongly reduces chemerin mRNA and protein in the supernatants of HepG2 cells [21]. Thus, in contrast to adipocytes, increased lipid storage in hepatocytes, which is used as an in-vitro model for liver steatosis, does not induce chemerin in primary hepatocytes and may even reduce its level in hepatoma cells [9,10,14,21].

Leptin and TGFβ1, which play a central role in liver fibrosis, elevate soluble chemerin while cellular protein is not altered in PHH [10,20,22]. Farnesoid X receptor is reduced in NAFLD [23], and its agonist GW4064 increases chemerin in HepG2 cells and in the liver of mice [21]. Food restriction and refeeding do not affect hepatic chemerin mRNA while adipose tissue expression is reduced upon prolonged fasting and increased by refeeding [24].

These data suggest that adipocyte chemerin is upregulated by metabolites with a function in obesity associated metabolic complications while hepatocyte chemerin is mostly not affected or even reduced. The in-vitro data further surmise that hepatic chemerin synthesis might be not grossly changed in non-alcoholic fatty liver disease (NAFLD).

NAFLD is a common liver disease with a higher incidence in obesity. NAFLD is associated with insulin resistance and is referred to as the hepatic manifestation of the metabolic syndrome. The term NAFLD encompasses liver steatosis, Non-alcoholic Steatohepatitis (NASH), liver cirrhosis and hepatocellular carcinoma. Excess storage of fat in the liver is believed to sensitize the organ to further insults and to promote inflammation and fibrosis [20,25-27].

Chemerin mRNA expression has been determined in fatty liver of db/db and ob/ob mice and was found unaltered or induced, respectively [2,13]. Mice fed a high fat diet have increased hepatic chemerin mRNA while protein is unchanged in the liver of these animals and in the liver of ob/ob mice [10]. Hence, raised mRNA levels may not translate to higher cellular protein while released chemerin may very well be increased. In humans hepatic chemerin mRNA expression positively correlates with BMI, and steatosis grade [9] and mRNA levels tend to be higher in patients with liver steatosis compared to controls [9,10]. Anyway, decreased hepatic chemerin mRNA in db/db mice, animals fed a high fat diet for two months and human fatty liver has also been described [21].

Fatty liver may progress to NASH in a subgroup of patients [20,26] which is characterized by inflammation and eventually liver fibrosis. An animal model widely used to study NASH is feeding rodents a methionine choline deficient diet (MCD) which causes massive hepatic triglyceride storage, inflammation and fibrosis [27]. While one study has found increased hepatic chemerin protein, a second study describes reduced mRNA levels in this animal model. Serum chemerin is shown to be lower in MCD fed animals in accordance with reduced body weight while systemic chemerin is also found to be similar compared with chow fed animals [10,21]. Mice fed an atherogenic diet known to cause hepatic steatosis, inflammation and fibrosis have a trend to higher hepatic chemerin protein while serum chemerin is increased most likely because of higher body weight [10,14]. In humans liver chemerin mRNA positively correlates with NAFLD activity score, and is induced in patients with NASH [9,28]. Serum chemerin is found increased and unchanged in human NASH, and elevated levels are partly associated with higher BMI of the NAFLD patients [9,28-30].

Higher levels of chemerin in hepatic venous serum compared to portal venous serum of patients with liver cirrhosis indicate that chemerin is released by the cirrhotic liver [5]. It has not been clarified yet whether chemerin is also secreted by the liver of healthy

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probands or NAFLD patients. Further studies are needed to find out whether the liver contributes to circulating chemerin. In patients with chronic hepatitis C serum chemerin is strongly increased and this may be related to higher hepatic and/or adipocyte synthesis and / or inappropriate clearance of this protein from the circulation. Of note, in these patients systemic chemerin is even negatively associated with hepatic necro-inflammatory grade [31].

Hepatocellular carcinoma (HCC) develops in patients with chronic liver diseases [20,25]. Chemerin protein is significantly lower in HCC tissue compared with paracarcinomatous liver tissue and is associated with the number of dendritic and natural killer cells [32]. It is suggested that chemerin contributes to recruitment of immune cells in HCC, and lower levels of this adipokine are associated with poor prognosis [32].

In summary, data published so far are inconclusive concerning abundance of chemerin in NAFLD, thus, additional studies are needed regarding this subject. Although discrepant findings on the protein level may be partly related to the use of different antibodies with divergent affinities for chemerin isoforms, discrepant data on mRNA expression showing increased and decreased chemerin in NAFLD can´t be explained by the different specificities of the applied techniques. Chemerin might be differentially expressed according to steatosis, fibrosis and inflammation grade in NAFLD. Species-specific differences may also exist. Of note, CMKLR1 is found decreased in rodent NASH liver while mRNA is increased in human NASH liver [9,11] and further research is necessary to clarify hepatic expression and function of chemerin and CMKLR1 in NAFLD. Chemerin is activated by proteolytic processing [6,7], and assays to measure local bioactivity have to be performed. Several studies found that serum chemerin is similar in males and females while others show that adipose tissue expression and serum levels are associated with gender suggesting that sex may also be relevant when studying expression of chemerin in NAFLD [4,5,33,34].

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