

Chemerin in Liver Diseases

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Abstract

Chemerin is a chemoattractant protein and moreover has a role in adipogenesis, angiogenesis and glucose homeostasis. Chemerin is primarily synthesized and secreted by adipocytes and hepatocytes. Chemerin receptors chemokine-like receptor 1 (CMKLR1), G-protein coupled receptor 1 (GPR1) and CC-motif chemokine receptor-like 2 (CCRL2) are all expressed in the liver suggesting that chemerin may be relevant in liver physiology and pathophysiology. Non-alcoholic fatty liver disease (NAFLD) is associated with obesity and is the most common cause of chronic liver injury. NAFLD and chronic hepatitis C virus infection are risk factors for hepatocellular carcinoma. Hepatic and serum chemerin have been analyzed in human and rodent NAFLD, in patients with chronic hepatitis C and patients with hepatocellular carcinoma. Chemerin, GPR1 and CMKLR1 deficient mice have been used to elucidate the role of these proteins in body weight gain and glucose homeostasis. The regulation of chemerin and CMKLR1 by adipokines, hormones and cytokines relevant in liver diseases has been studied in hepatocytes. The data published so far are briefly summarized herein. Current experimental findings do not provide evidence for a crucial role of chemerin in chronic liver diseases and further research is needed to evaluate a possible protective function of this protein in hepatocellular carcinoma.

Keywords: Hepatocellular carcinoma; NASH; Hepatitis C; Adipokines

Introduction

Chemerin has been initially identified as a retinoid (tazarotene)-responsive gene in the skin named tazarotene-induced gene 2 (TIG2) [1]. Chemerin is well known for its chemotactic activity. Plasmacytoid dendritic cells, macrophages and natural killer cells express the chemerin receptor chemokine-like receptor 1 (CMKLR1) and respond to chemerin [2]. Subsequently chemerin has been shown to be produced by adipocytes [3,4]. Inflammatory mediators like lipopolysaccharide (LPS) and tumor necrosis factor α (TNF α) strongly induce adipocyte chemerin synthesis [5,6]. Circulating chemerin levels are elevated in overweight/obese humans and rodents and this may be related to higher synthesis in fat tissues [3,5,7]. In healthy controls, a cohort of patients with stable chest pain and type 2 diabetic patients serum chemerin is positively associated with markers of inflammation. Levels correlate with body mass index (BMI), triglycerides, HDL-cholesterol and hypertension [3,7,8]. Most of the human studies identify positive correlations of serum chemerin with body weight, fat mass and insulin resistance [9].

Chemerin is synthesized as an inactive 163 amino acid precursor, the main form found in serum. Proteolytic cleavage of the carboxyl-terminus by serine proteases, cysteine proteases and carboxypeptidases generates proteins lacking 6 (Chem157), 8 (Chem155) or 9 (Chem154) amino acids. Among these isoforms Chem157 is most effective in attracting immune cells [2].

CMKLR1, G-protein coupled receptor 1 (GPR1) and CC-motif chemokine receptor-like 2 (CCRL2) function as chemerin receptors and bind to chemerin with similar affinities [2]. Chemerin activates GPR1 with a higher potency than CMKLR1 showing that GPR1 is a highly sensitive chemerin receptor [10,11]. GPR1 and CCRL2 receptors do not seem to have a role in cell migration [2]. Function of CCRL2 is to concentrate prochemerin and/or active chemerin at specific sites and present it to neighboring cells expressing CMKLR1 [2]. Chemerin is elevated in serum of CCRL2 deficient mice in accordance with the postulated role of this receptor [1].

Chemerin is well known to be expressed in the liver [10,12]. Hepatocytes secrete relatively high concentrations of chemerin which are similar to levels produced by adipocytes. Chemerin is also synthesized in hepatic stellate cells which release about 95% less

chemerin than human hepatocytes [13]. Importantly, it has been shown that at least rodent hepatocytes produce bioactive chemerin [12]. Whether chemerin released from the liver significantly contributes to circulating levels of total and active chemerin has not been clarified so far. In patients with liver cirrhosis hepatic vein chemerin is higher compared to portal vein levels [7]. Albeit this shows that chemerin is released from the liver at least in these patients this does not prove that higher hepatic chemerin synthesis translates to increased serum levels.

CMKLR1 is expressed by primary human hepatocytes, bile duct cells, hepatic stellate cells, endothelial cells and Kupffer cells [14]. Compared to white adipose tissue and skeletal muscle, expression of the chemerin receptors CMKLR1, GPR1 and CCRL2 is low in the rodent liver [10,15]. Chemerin may nevertheless influence the properties of all liver resident cells.

In this review article data on the regulation of hepatocyte chemerin/CMKLR1 levels and on hepatic and systemic chemerin in liver diseases of different etiologies are being summarized.

Regulating of hepatocyte chemerin and CMKLR1

Inflammatory cytokines, LPS and adipokines regulate liver cell function and are involved in liver disease pathology [16-20]. TNF α , interleukin-6 (IL-6) and LPS which are elevated in obesity induce adipocyte chemerin expression [5,6,12] but do not upregulate its expression in hepatocytes [12,13,21]. Leptin does neither affect bovine adipocyte nor human hepatocyte chemerin levels [13,22]. Adiponectin ameliorates insulin resistance and liver injury and is reduced in obesity and NAFLD [16]. Adiponectin induces chemerin expression in bovine adipocytes [22] while cellular concentrations are not changed in human adipocytes and human hepatocytes [6,13]. Chemerin in the

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supernatants of cultured hepatocytes is reduced by adiponectin [13]. The profibrotic cytokine transforming growth factor beta increases chemerin in hepatocyte supernatants [13].

Prolonged food restriction decreases chemerin mRNA in rat white adipose tissue and its level increases upon refeeding. Hepatic chemerin expression is not affected by food restriction and food restriction-refeeding [23]. Adipocyte chemerin synthesis is upregulated by insulin but whether this contributes to higher serum chemerin levels is still a matter of debate [23-25]. Glucagon and insulin have no effect on hepatocyte chemerin expression [21].

Cultivation of hepatocytes in the presence of fatty acids is used as an in-vitro model for steatotic parenchymal cells. Regarding hepatocytes exposed to fatty acids contradictory results have been published. While palmitate and oleate do not alter chemerin in primary human hepatocytes, palmitate lowers chemerin production in HepG2 cells [13,21,26]. The antidiabetic drug metformin lowers hepatocyte chemerin levels [13]. Aspirin reduces serum chemerin does not influence adipocyte and hepatocyte chemerin expression directly [27].

The nuclear hormone receptors peroxisome proliferator-activated receptor (PPAR) α and γ , liver X receptor (LXR) and farnesoid X receptor (FXR) regulate glucose and lipid metabolism [28]. FXR agonists but not ligands of the other receptors reduce hepatocyte chemerin expression [26].

CMKLR1 in hepatocytes is not regulated by insulin, glucagon, palmitate, oleate, leptin, LPS, TNF α or cholesterol accumulation

[14,21]. TGFbeta shows a trend to reduce CMKLR1 protein. IL-6 induces CMKLR1 mRNA but not protein [14,21]. Adiponectin upregulates CMKLR1 in hepatocytes in line with low hepatic CMKLR1 protein in adiponectin deficient mice [14]. Data summarized in this paragraph are listed in Table 1. In summary, current experimental evidence reveals discordant results regarding chemerin / CMKLR1 regulation in hepatocytes. Whether this is related to different experimental conditions and / or the use of primary and tumor cells has to be clarified.

Non-alcoholic fatty liver disease (NAFLD)

NAFLD is a common cause for chronic liver diseases with a higher incidence in obesity. Dyslipidemia and insulin resistance are associated with NAFLD pathophysiology. Liver steatosis and non-alcoholic steatohepatitis (NASH) are the two entities of NAFLD. Fatty liver is a relatively benign condition and refers to the accumulation of triglycerides in liver parenchymal cells. NASH is characterized by inflammation and eventually liver fibrosis [16,20,29]. Diagnosis of NASH depends on liver biopsy and non-invasive markers have not been identified. Current treatment options are weight loss, resistance training and high dose vitamin E therapy [16,30]. NAFLD is closely associated with metabolic syndrome, which includes central obesity, hypertension, elevated blood glucose and dyslipidemia [16,31,32].

Serum chemerin and metabolic syndrome

Metabolic syndrome increases the risk of developing type 2 diabetes, cardiovascular diseases and NAFLD [33]. Adipose tissue

Substance	Cell	Chemerin	Ref	Substance	CMKLR1	Ref
IL-6 50 ng/ml	PHH	mRNA \leftrightarrow	[21]	IL-6 50 ng/ml	mRNA \uparrow	[21]
IL-6 5, 20 ng/ml	PHH	CP, SN \leftrightarrow	[13]	IL-6 5 ng/ml	CP \leftrightarrow	[14]
IL-6	Hep3B	mRNA \leftrightarrow	[27]			
IL-1beta 10 ng/ml	Hep3B	mRNA \leftrightarrow , SN \downarrow	[27]			
Glucagon 100 nM	PHH	mRNA \leftrightarrow	[21]	Glucagon 100 nM	mRNA \leftrightarrow	[21]
Insulin 100 nM	PHH	mRNA \leftrightarrow	[21]	Insulin 100 nM	mRNA \leftrightarrow	[21]
Palmitate 0.3 mM	PHH	mRNA \leftrightarrow	[21]	Palmitate 0.3 mM	mRNA \leftrightarrow	[21]
Palmitate 0.3 mM	PHH	CP \leftrightarrow , SN (\downarrow)	[12]	Palmitate 0.3 mM	mRNA, CP \leftrightarrow	[14]
Oleate 0.3 mM	PHH	CP, SN \leftrightarrow	[12]	Oleate 0.3 mM	mRNA, CP \leftrightarrow	[14]
Palmitate 0.1, 0.2, 0.5 mM	HepG2	mRNA, SN \downarrow	[26]			
FXR agonist 1, 2, 5 μ M	HepG2	mRNA \uparrow	[26]			
FXR agonist 1, 2, 5 μ M	PMH	mRNA \uparrow	[26]			
LXR agonist	HepG2	mRNA \leftrightarrow	[26]			
PPAR γ agonist	HepG2	mRNA \leftrightarrow	[26]			
PPAR α agonist	HepG2	mRNA \leftrightarrow	[26]			
Leptin 20 ng/ml	PHH	CP \leftrightarrow , SN \uparrow	[13]	Leptin 10, 20 ng/ml	CP \leftrightarrow	[14]
TNF α 2 ng/ml	PHH	CP \leftrightarrow , SN \downarrow	[13]	TNF α 0.5, 2 ng/ml	CP \leftrightarrow	[14]
TNF α 25 ng/ml	Hep3B	mRNA, SN \leftrightarrow	[27]			
TNF α 20 ng/ml	PMH	CP \leftrightarrow	[12]			
TGF β 5 ng/ml	PHH	CP \leftrightarrow , SN \uparrow	[13]	TGF β 5 ng/ml	CP (\downarrow)	[14]
APN 10 μ g/ml	PHH	CP \leftrightarrow , SN \downarrow	[13]	APN 10 μ g/ml	mRNA, CP \uparrow	[14]
LPS 10 μ g/ml	PHH	CP, SN \leftrightarrow	[13]	LPS 1, 10 μ g/ml	CP \leftrightarrow	[14]
	PHH			ACAT Inh + AcLDL	CP \leftrightarrow	[14]
Metformin 0.5, 1 mM	PHH	CP, SN \downarrow	[13]			
Aspirin 2, 20 mg/l	Hep3B	mRNA, SN \leftrightarrow	[27]			

Acetylated LDL, AcLDL; adiponectin, APN; cellular protein, CP; farnesoid X receptor, FXR; liver X receptor, LXR; primary human hepatocytes, PHH; primary mouse hepatocytes, PMA; Inhibitor, Inh; peroxisome proliferator-activated receptor, PPAR; reference, Ref; supernatant, SN; not regulated, \leftrightarrow ; upregulated, \uparrow ; downregulated, \downarrow ; when arrows are given in brackets this indicates a trend.

Table 1: Regulation of chemerin and CMKLR1 in hepatocytes.

	Hepatic chemerin	Serum chemerin	Hepatic CMKLR1	References
Steatotic Liver in obesity	↔, ↑, ↓	↔, ↑	↑, ↓	[13-15,21,26,43-45]
NASH	↑, ↓	↔, ↑	↑, ↓	[13,14,21,26,43-45]
Hepatitis C	↔	↑	↔	[17,54,56,57]
Hepatocellular carcinoma	↓	n.d.	n.d.	[59,61]

Table 2: Hepatic and serum chemerin and liver CMKLR1 expression in patients with chronic liver diseases. normal ↔; higher than controls ↑; lower than controls ↓; not defined to our knowledge so far n.d.

insulin resistance is increased in the metabolic syndrome and correlates with systemic chemerin [34]. A recent study analyzed chemerin in first-degree relatives of type 2 diabetic patients and found that triglycerides and homeostatic model assessment insulin resistance (HOMA-IR) are independent risk factors that influence systemic chemerin [35]. In hypertension patients HOMA-IR, TNF α and triglycerides are independently related to chemerin level after multiple regression analysis. Chemerin is independently associated with hypertension after adjustment for age, gender and metabolic risk factors [36]. In overweight and obese type 2 diabetes patients chemerin levels are positively correlated with HOMA-IR and fasting insulin and negatively with insulin sensitivity index (ISI). Changes in the chemerin concentration during 12 weeks intensive lifestyle modification are independently and negatively correlated with changes in ISI and positively with changes in fasting plasma glucose and total cholesterol [37]. Weight-loss is mostly found to reduce chemerin and to improve insulin sensitivity [38]. The majority of studies have identified positive correlations of chemerin and serum triglycerides, LDL cholesterol and blood pressure and negative correlations with HDL cholesterol [39]. Therefore, chemerin appears to be related to features of the metabolic syndrome which is closely associated with the pathogenesis of NAFLD.

Chemerin and CMKLR1 in fatty liver

Liver steatosis is commonly observed in obesity. In the fatty liver of leptin deficient ob/ob mice chemerin, CCRL2, GPR1 and CMKLR1 are normally expressed. In the db/db mice with mutated leptin receptors liver chemerin mRNA but not protein is induced while GPR1 is strongly decreased [15]. In mice fed a high fat diet for 24 weeks hepatic chemerin and CMKLR1 are similar to mice fed a control chow [10]. Krautbauer et al. show that chemerin mRNA is induced in the liver of mice fed a high fat diet while protein is not upregulated. Leptin deficient ob/ob mice develop markedly steatotic liver without an effect on hepatic chemerin protein [13]. In patients with liver steatosis chemerin mRNA tends to be higher while protein is not induced [13]. Doecke et al. analyzed chemerin and CMKLR1 in human NAFLD. In this cohort hepatic expression of chemerin and CMKLR1 are increased in patients with higher BMI. While CMKLR1 is not associated with liver steatosis chemerin is elevated in patients with a higher degree of liver fat [21]. Wanninger et al. studied CMKLR1 in human healthy and fatty liver and mRNA as well as protein is reduced in the latter. Of note, CMKLR1 is diminished in the liver of adiponectin deficient mice and adiponectin induces CMKLR1 in hepatocytes (Table 1) suggesting that low adiponectin in NAFLD may contribute to reduced hepatic CMKLR1 expression [14]. Deng et al. demonstrate that liver chemerin is reduced in db/db mice and mice fed a high fat diet. Similarly, human fatty livers express less chemerin mRNA than normal livers. FXR but not LXR, PPAR α or PPAR γ agonists induce chemerin in hepatocytes (Table 1) and low FXR activity in rodent NAFLD is suggested to contribute to reduced hepatic chemerin expression [26].

The data regarding chemerin and CMKLR1 levels in fatty liver are not concordant (Table 2). Further studies have to address the expression of chemerin and CMKLR1 in steatotic liver.

Chemerin and CMKLR1 in NASH liver

The Paigen diet is supplemented with cholesterol and cholate and causes body weight gain, liver steatosis, mild inflammation and fibrosis in the liver of mice [40]. Liver chemerin protein tends to be higher in mice fed this chow. Methionine choline deficient diet (MCD) fed animals display increased chemerin protein and reduced CMKLR1 protein in the liver [13,14]. In contrast Deng et al. demonstrate lower chemerin in the liver of MCD fed rats [26].

In human NASH liver chemerin mRNA tends to be increased compared to controls [13]. Chemerin in the liver of NAFLD patients is positively associated with hepatic lobular inflammation and ballooning degeneration. In subjects suffering from significant liver fibrosis chemerin is higher than in those with absent or mild fibrosis. Patients with NASH have about 3 fold elevated chemerin mRNA expression and about 2 fold increased CMKLR1 mRNA than subjects not suffering from NASH. CMKLR1 is upregulated by IL-6 in hepatocytes (Table 1) and this may contribute to increased CMKLR1 in NASH [21].

Most of the findings summarized above show increased chemerin in NASH liver (Table 2). Future studies have to examine the expression of CMKLR1, GPR1 and CCRL2 in NASH.

Serum chemerin in NAFLD

Serum chemerin is diminished in MCD fed mice and rats [26]. MCD diet strongly lowers body weight and when adjusted to body weight serum chemerin is even increased [13]. Yilmaz et al. analyzed serum of 54 patients with biopsy-proven NAFLD and 56 age- and sex-matched controls and found increased chemerin in NAFLD [41]. This group also analyzed serum of 99 patients with biopsy-proven NAFLD and 75 control subjects and found elevated serum chemerin in the first cohort [42]. BMI of the NAFLD patients was significantly higher compared to controls and this may partly contribute to elevated serum chemerin. These findings are nevertheless in accordance with the study by Kukla et al. where chemerin in serum is found increased in patients with liver steatosis and NASH [43]. Serum chemerin is associated with hepatocyte ballooning degeneration, total cholesterol and diastolic blood pressure but not HOMA-IR [43]. Sell et al. identified elevated circulating chemerin in morbidly obese patients with hepatic portal- and fibroinflammation. Chemerin concentrations correlated positively with HOMA-IR and negatively with HDL. The strong decrease of chemerin in the serum of patients three months after surgery is associated with the decrease in HOMA-IR and blood glucose [44]. Ye et al. measured serum chemerin levels in 467 controls and 436 patients with B-mode ultrasound-proven NAFLD. Chemerin correlates positively with insulin resistance and inflammation in the whole cohort but is not induced in NAFLD [45]. In line with this study Doecke et al published that systemic chemerin is not different in patients with a high and a low NAFLD activity score. Further, liver chemerin mRNA levels do not correlate with circulating chemerin [21].

In all of these studies total chemerin has been analyzed and data on the ratios of active chemerin are not available. Total and bioactive chemerin in serum of mice increase in parallel suggesting that levels of active chemerin may be partly related to total circulating chemerin [15].

In conclusion, inflammation, BMI, blood pressure and insulin resistance are associated with NAFLD and serum chemerin levels [3,7,8]. Variations in these parameters most likely explain inconsistent results regarding systemic chemerin in NAFLD (Table 2).

Role of chemerin / CMKLR1 in NAFLD pathophysiology

A few studies analyzed whether CMKLR1 and chemerin are involved in the pathogenesis of obesity, insulin resistance and NAFLD in mice. Ernst et al. describe that injection of recombinant, human chemerin exacerbates glucose intolerance, reduces serum insulin and tissue glucose uptake in ob/ob and db/db mice. There is no effect on glucose homeostasis of normoglycemic animals [15]. In mice with whole-body chemerin deficiency and mice where human chemerin is overexpressed in the liver body weight is not affected. Chemerin knock-out mice have impaired glucose uptake in skeletal muscle, increased hepatic glucose production and reduced insulin secretion. Chemerin transgenic mice subsequently display improved glucose tolerance [46]. Becker et al. expressed human chemerin in LDL-receptor knock-out mice using adenovirus associated virus 8. Human chemerin in serum reaches the level of endogenous murine chemerin. There is no effect on body weight during the 16 weeks of follow up. Skeletal muscle but not the liver shows impaired insulin sensitivity. The animals expressing human chemerin do not display altered total cholesterol, triglycerides, HDL cholesterol and non-HDL cholesterol levels [47].

CMKLR1 deficiency does not markedly affect body weight, inflammation, glucose tolerance and dyslipidemia in mice when fed a standard chow or a high fat diet [48]. A second study reports reduced food uptake, body weight and body fat in CMKLR1^{-/-} mice regardless of feeding a low or high fat diet. Hepatic and adipose tissue inflammation is reduced.

CMKLR1^{-/-} mice are glucose intolerant and this is associated with decreased glucose stimulated insulin secretion, lower skeletal muscle and white adipose tissue glucose uptake [49]. A high fat, high cholesterol diet does not affect body weight, food intake, insulin resistance, hepatic inflammation and hepatic expression of fibrotic genes in CMKLR1^{-/-} mice [50].

Resolvin E1 is an omega-3-polyunsaturated fatty acid derived lipid and a ligand of CMKLR1 [51]. This lipid exerts anti-steatotic and insulin-sensitizing effects in ob/ob mice. Whether these effects depend on CMKLR1 or are explained by the induction of adiponectin has not been clarified [52].

Heterozygous and homozygous Gpr1 knockout mice on a high-fat diet display more severe glucose intolerance than wild type animals partly because of low insulin levels. Body weight, adiposity and energy expenditure are, however, normal [10]. Studies on the role of GPR1 in NAFLD have not been published to our knowledge so far.

In summary, chemerin / CMKLR1 do not grossly affect body weight but seem to have a role in glucose homeostasis. There is no evidence that chemerin and / or CMKLR1 have a major function in liver physiology, lipid metabolism and NAFLD pathophysiology.

Chemerin and CMKLR1 expression and serum levels in chronic hepatitis C

Kukla et al. found strongly increased serum chemerin levels in patients chronically infected with the hepatitis C virus genotype 1b. Chemerin is not related to HOMA index. Surprisingly, serum levels decline with increasing hepatic necroinflammatory activity. Therefore, chemerin is suggested to bind to its receptors at sites of inflammation and attract further immune cells including natural killer cells which

help to eradicate the virus [17]. Chemerin may be also proteolyzed to generate small peptides shown to exert anti-inflammatory activities [53].

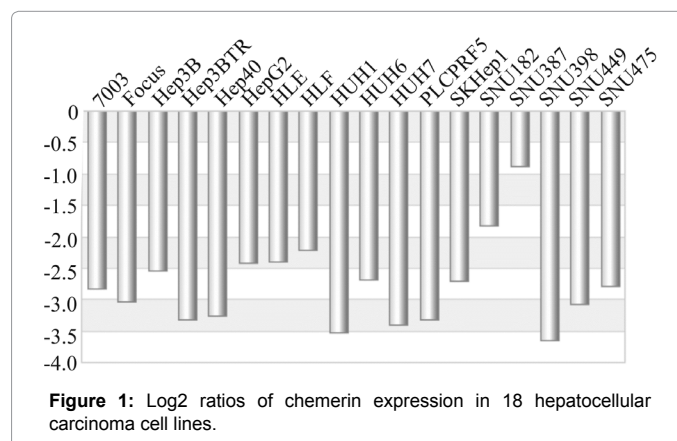
Serum chemerin tends to be higher in patients with more advanced fibrosis. Most of the patients enrolled had less severe liver fibrosis and cirrhosis was only diagnosed in one patient. Thus the potential association of serum chemerin with liver fibrosis has to be confirmed in suitable cohorts [54]. Angiogenesis in chronic hepatitis C patients is positively associated with the stage of fibrosis, grade of inflammatory activity and steatosis [55]. Serum chemerin is, however, not associated with the formation of new blood vessels in lobules and portal tracts in the liver [56]. There is a positive correlation of serum chemerin and leptin levels [54,56]. Analysis of chemerin and CMKLR1 expression in the liver of 63 non-obese chronic hepatitis C patients shows no association with necroinflammatory activity and steatosis grade, fibrosis stage and metabolic abnormalities. Of note, a negative association between serum chemerin and hepatic chemerin expression has been found [57]. Serum chemerin is higher in the patients compared to 30 healthy, age and BMI matched controls [57] (Table 2).

Chemerin expression and serum levels in hepatocellular carcinoma

Chronic hepatitis B and C infections and increasingly NAFLD are underlying risk factors for hepatocellular carcinoma [58]. Lin et al describe reduced expression of chemerin protein in hepatocellular carcinoma tissues of 72 patients compared with paracarcinomatous liver tissue (Table 2). Chemerin correlates with tumor size, histological grade and the infiltration of dendritic cells and natural killer cells. Patients with low hepatic chemerin have poorer survival and liver chemerin expression is of prognostic value [59].

CellMinerHCC is a freely accessible database of microarray expression profiles of currently 18 different hepatocellular carcinoma cell lines [60]. Expression of chemerin is reduced in the 18 different hepatocellular carcinoma cell lines when compared to normal liver (Figure 1). In the liver chemerin is mainly expressed by hepatocytes [13] suggesting that levels are lower in these cell lines when compared to normal hepatocytes. Therefore, these cell lines may be used to evaluate a possible role of chemerin on proliferation, survival and migration in liver tumor cells.

In a cohort of 44 patients with any stage of hepatocellular carcinoma systemic chemerin correlates with albumin, platelet count and prothrombin time. Interestingly, serum chemerin is inversely related to Child-Pugh score, serum alanine aminotransferase and total bilirubin. Chemerin in serum is not associated with survival [61].



Summary

Chemerin and its receptors are expressed in the liver. From current data it is unclear whether hepatic levels of chemerin and CMKLR1 are induced or suppressed in NAFLD. Animal studies suggest a minor if any role of chemerin and CMKLR1 in metabolic liver disease. Further, serum chemerin may be elevated or similar to controls in NAFLD patients. Circulating chemerin is increased in patients with chronic hepatitis C and is even negatively associated with inflammatory grade. In hepatocellular carcinoma serum chemerin is associated with severity of liver injury defined by the Child-Pugh score. Chemerin is reduced in carcinomatous liver tissue and hepatic chemerin expression is associated with survival. Further studies are needed to evaluate whether chemerin plays a role in the pathophysiology of liver tumors.

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References

- Nagpal S, Patel S, Jacobe H, DiSepio D, Ghosn C, et al. (1997) Tazarotene-induced gene 2 (TIG2), a novel retinoid-responsive gene in skin. *J Invest Dermatol* 109: 91-95.
- Zabel BA, Kwitniewski M, Banas M, Zabieglo K, Murzyn K, et al. (2014) Chemerin regulation and role in host defense. *Am J Clin Exp Immunol* 3: 1-19.
- Bozaoglu K, Bolton K, McMillan J, Zimmel P, Jowett J, et al. (2007) Chemerin is a novel adipokine associated with obesity and metabolic syndrome. *Endocrinology* 148: 4687-4694.
- Goralski KB, McCarthy TC, Hanniman EA, Zabel BA, Butcher EC, et al. (2007) Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism. *J Biol Chem* 282: 28175-28188.
- Bauer S, Wanninger J, Schmidhofer S, Weigert J, Neumeier M, et al. (2011) Sterol regulatory element-binding protein 2 (SREBP2) activation after excess triglyceride storage induces chemerin in hypertrophic adipocytes. *Endocrinology* 152: 26-35.
- Sell H, Laurencikienė J, Taube A, Eckardt K, Cramer A, et al. (2009) Chemerin is a novel adipocyte-derived factor inducing insulin resistance in primary human skeletal muscle cells. *Diabetes* 58: 2731-2740.
- Weigert J, Neumeier M, Wanninger J, Filarsky M, Bauer S, et al. (2010) Systemic chemerin is related to inflammation rather than obesity in type 2 diabetes. *Clin Endocrinol (Oxf)* 72: 342-348.
- Lehrke M, Becker A, Greif M, Stark R, Laubender RP, et al. (2009) Chemerin is associated with markers of inflammation and components of the metabolic syndrome but does not predict coronary atherosclerosis. *Eur J Endocrinol* 161: 339-344.
- Ernst MC, Sinal CJ (2010) Chemerin: at the crossroads of inflammation and obesity. *Trends Endocrinol Metab* 21: 660-667.
- Rourke JL, Muruganandan S, Dranse HJ, McMullen NM, Sinal CJ (2014) Gpr1 is an active chemerin receptor influencing glucose homeostasis in obese mice. *J Endocrinol* 222: 201-215.
- Barnea G, Strapps W, Herrada G, Berman Y, Ong J, et al. (2008) The genetic design of signaling cascades to record receptor activation. *Proc Natl Acad Sci U S A* 105: 64-69.
- Parlee SD, Ernst MC, Muruganandan S, Sinal CJ, Goralski KB (2010) Serum chemerin levels vary with time of day and are modified by obesity and tumor necrosis factor- α . *Endocrinology* 151: 2590-2602.
- Krautbauer S, Wanninger J, Eisinger K, Hader Y, Beck M, et al. (2013) Chemerin is highly expressed in hepatocytes and is induced in non-alcoholic steatohepatitis liver. *Exp Mol Pathol* 95: 199-205.
- Wanninger J, Bauer S, Eisinger K, Weiss TS, Walter R, et al. (2012) Adiponectin upregulates hepatocyte CMKLR1 which is reduced in human fatty liver. *Mol Cell Endocrinol* 349: 248-254.
- Ernst MC, Issa M, Goralski KB, Sinal CJ (2010) Chemerin exacerbates glucose intolerance in mouse models of obesity and diabetes. *Endocrinology* 151: 1998-2007.
- Buechler C, Wanninger J, Neumeier M (2011) Adiponectin, a key adipokine in obesity related liver diseases. *World J Gastroenterol* 17: 2801-2811.
- Kukla M, Mazur W, BuÅdak RJ, Zwirska-Korcza K (2011) Potential role of leptin, adiponectin and three novel adipokines--visfatin, chemerin and vaspin--in chronic hepatitis. *Mol Med* 17: 1397-1410.
- Shen C, Zhao CY, Zhang R, Qiao L (2012) Obesity-related hepatocellular carcinoma: roles of risk factors altered in obesity. *Front Biosci (Landmark Ed)* 17: 2356-2370.
- Soares JB, Pimentel-Nunes P, Roncon-Albuquerque R, Leite-Moreira A (2010) The role of lipopolysaccharide/toll-like receptor 4 signaling in chronic liver diseases. *Hepatol Int* 4: 659-672.
- Tilg H (2010) The role of cytokines in non-alcoholic fatty liver disease. *Dig Dis* 28: 179-185.
- Döcke S, Lock JF, Birkenfeld AL, Hoppe S, Lieske S, et al. (2013) Elevated hepatic chemerin mRNA expression in human non-alcoholic fatty liver disease. *Eur J Endocrinol* 169: 547-557.
- Suzuki Y, Hong YH, Song SH, Ardiyanti A, Kato D, et al. (2012) The Regulation of Chemerin and CMKLR1 Genes Expression by TNF- α , Adiponectin, and Chemerin Analog in Bovine Differentiated Adipocytes. *Asian-Australas J Anim Sci* 25: 1316-1321.
- Stelmanska E, Sledzinski T, Turyn J, Presler M, Korczynska J, et al. (2013) Chemerin gene expression is regulated by food restriction and food restriction-refeeding in rat adipose tissue but not in liver. *Regul Pept* 181: 22-29.
- Bauer S, Bala M, Kopp A, Eisinger K, Schmid A, et al. (2012) Adipocyte chemerin release is induced by insulin without being translated to higher levels in vivo. *Eur J Clin Invest* 42: 1213-1220.
- Tan BK, Chen J, Farhatullah S, Adya R, Kaur J, et al. (2009) Insulin and metformin regulate circulating and adipose tissue chemerin. *Diabetes* 58: 1971-1977.
- Deng Y, Wang H, Lu Y, Liu S, Zhang Q, et al. (2013) Identification of chemerin as a novel FXR target gene down-regulated in the progression of nonalcoholic steatohepatitis. *Endocrinology* 154: 1794-1801.
- Herová M, Schmid M, Gemperle C, Loretz C, Hersberger M (2014) Low dose aspirin is associated with plasma chemerin levels and may reduce adipose tissue inflammation. *Atherosclerosis* 235: 256-262.
- Hansen MK, Connolly TM (2008) Nuclear receptors as drug targets in obesity, dyslipidemia and atherosclerosis. *Curr Opin Investig Drugs* 9: 247-255.
- Kamada Y, Takehara T, Hayashi N (2008) Adipocytokines and liver disease. *J Gastroenterol* 43: 811-822.
- Chalasanani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, et al. (2012) The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology* 55: 2005-2023.
- Buechler C, Bauer S (2012) ATP binding cassette transporter A1 (ABCA1) associated proteins: potential drug targets in the metabolic syndrome and atherosclerotic disease? *Curr Pharm Biotechnol* 13: 319-330.
- Gruben N, Shiri-Sverdlov R, Koonen DP, Hofker MH (2014) Nonalcoholic fatty liver disease: A main driver of insulin resistance or a dangerous liaison? *Biochim Biophys Acta* 1842: 2329-2343.
- Lim S, Eckel RH (2014) Pharmacological treatment and therapeutic perspectives of metabolic syndrome. *Rev Endocr Metab Disord* 15: 329-341.
- Adams-Huet B, Devaraj S, Siegel D, Jialal I (2014) Increased adipose tissue insulin resistance in metabolic syndrome: relationship to circulating adipokines. *Metab Syndr Relat Disord* 12: 503-507.
- Zhuang XH, Sun FD, Chen SH, Liu YT, Liu W, et al. (2014) Circulating chemerin levels are increased in first-degree relatives of type 2 diabetic patients. *Clin Lab* 60: 983-988.
- Gu P, Jiang W, Lu B, Shi Z (2014) Chemerin is associated with inflammatory markers and metabolic syndrome phenotypes in hypertension patients. *Clin Exp Hypertens* 36: 326-332.
- Kim SH, Lee SH, Ahn KY, Lee DH, Suh YJ, et al. (2014) Effect of lifestyle modification on serum chemerin concentration and its association with insulin sensitivity in overweight and obese adults with type 2 diabetes. *Clin Endocrinol (Oxf)* 80: 825-833.

38. Chakaroun R, Raschpichler M, Klötting N, Oberbach A, Flehmig G, et al. (2012) Effects of weight loss and exercise on chemerin serum concentrations and adipose tissue expression in human obesity. *Metabolism* 61: 706-714.
39. Rourke JL, Dranse HJ, Sinal CJ (2013) Towards an integrative approach to understanding the role of chemerin in human health and disease. *Obes Rev* 14: 245-262.
40. Shockley KR, Witmer D, Burgess-Herbert SL, Paigen B, Churchill GA (2009) Effects of atherogenic diet on hepatic gene expression across mouse strains. *Physiol Genomics* 39: 172-182.
41. Yilmaz Y, Kurt R, Gurdal A, Alahdab YO, Yonal O, et al. (2011) Circulating vaspilin levels and epicardial adipose tissue thickness are associated with impaired coronary flow reserve in patients with nonalcoholic fatty liver disease. *Atherosclerosis* 217: 125-129.
42. Yilmaz Y, Yonal O, Kurt R, Alahdab YO, Eren F, et al. (2011) Serum levels of omentin, chemerin and adiponin in patients with biopsy-proven nonalcoholic fatty liver disease. *Scand J Gastroenterol* 46: 91-97.
43. Kukla M, Zwirska-Korcza K, Hartleb M, Waluga M, Chwist A, et al. (2010) Serum chemerin and vaspilin in non-alcoholic fatty liver disease. *Scand J Gastroenterol* 45: 235-242.
44. Sell H, Divoux A, Poitou C, Basdevant A, Bouillot JL, et al. (2010) Chemerin correlates with markers for fatty liver in morbidly obese patients and strongly decreases after weight loss induced by bariatric surgery. *J Clin Endocrinol Metab* 95: 2892-2896.
45. Ye Z, Wang S, Yang Z, He M, Zhang S, et al. (2014) Serum lipocalin-2, cathepsin S and chemerin levels and nonalcoholic fatty liver disease. *Mol Biol Rep* 41: 1317-1323.
46. Takahashi M, Okimura Y, Iguchi G, Nishizawa H, Yamamoto M, et al. (2011) Chemerin regulates I^2 -cell function in mice. *Sci Rep* 1: 123.
47. Becker M, Rabe K, Lebherz C, Zugwurst J, Göke B, et al. (2010) Expression of human chemerin induces insulin resistance in the skeletal muscle but does not affect weight, lipid levels, and atherosclerosis in LDL receptor knockout mice on high-fat diet. *Diabetes* 59: 2898-2903.
48. Rouger L, Denis GR, Luangsay S, Parmentier M (2013) ChemR23 knockout mice display mild obesity but no deficit in adipocyte differentiation. *J Endocrinol* 219: 279-289.
49. Ernst MC, Haidl ID, Zúñiga LA, Dranse HJ, Rourke JL, et al. (2012) Disruption of the chemokine-like receptor-1 (CMKLR1) gene is associated with reduced adiposity and glucose intolerance. *Endocrinology* 153: 672-682.
50. Gruben N, Aparicio Vergara M, Kloosterhuis NJ, van der Molen H, Stoelwinder S, et al. (2014) Chemokine-like receptor 1 deficiency does not affect the development of insulin resistance and nonalcoholic fatty liver disease in mice. *PLoS One* 9: e96345.
51. Arita M, Ohira T, Sun YP, Elangovan S, Chiang N, et al. (2007) Resolvin E1 selectively interacts with leukotriene B4 receptor BLT1 and ChemR23 to regulate inflammation. *J Immunol* 178: 3912-3917.
52. González-Pérez A, Horrillo R, Ferré N, Gronert K, Dong B, et al. (2009) Obesity-induced insulin resistance and hepatic steatosis are alleviated by omega-3 fatty acids: a role for resolvins and protectins. *FASEB J* 23: 1946-1957.
53. Yoshimura T, Oppenheim JJ (2008) Chemerin reveals its chimeric nature. *J Exp Med* 205: 2187-2190.
54. Kukla M, Zwirska-Korcza K, Gabriel A, Waluga M, Warakomska I, et al. (2010) Chemerin, vaspilin and insulin resistance in chronic hepatitis C. *J Viral Hepat* 17: 661-667.
55. Gabriel A, Kukla M, Wilk M, Liszka A, Petelenz M, et al. (2009) Angiogenesis in chronic hepatitis C is associated with inflammatory activity grade and fibrosis stage. *Pathol Res Pract* 205: 758-764.
56. Kukla M, Berdowska A, Gabriel A, Sawczyn T, Mazur W, et al. (2011) Association between hepatic angiogenesis and serum adipokine profile in non-obese chronic hepatitis C patients. *Polish journal of pathology: official journal of the Polish Society of Pathologists* 62: 218-228.
57. Kukla M, Adamek B, Waluga M, Zalewska-Ziob M, Kasperczyk J, et al. (2014) Hepatic chemerin and chemokine-like receptor 1 expression in patients with chronic hepatitis C. *Biomed Res Int* 2014: 517820.
58. Kirstein MM, Vogel A (2014) The pathogenesis of hepatocellular carcinoma. *Dig Dis* 32: 545-553.
59. Lin W, Chen YL, Jiang L, Chen JK (2011) Reduced expression of chemerin is associated with a poor prognosis and a lowered infiltration of both dendritic cells and natural killer cells in human hepatocellular carcinoma. *Clinical laboratory* 57: 879-885.
60. Staib F, Krupp M, Maass T, Itzel T, Weinmann A, et al. (2014) CellMinerHCC: a microarray-based expression database for hepatocellular carcinoma cell lines. *Liver international: official journal of the International Association for the Study of the Liver* 34: 621-631.
61. Imai K, Takai K, Hanai T, Shiraki M, Suzuki Y, et al. (2014) Impact of serum chemerin levels on liver functional reserves and platelet counts in patients with hepatocellular carcinoma. *Int J Mol Sci* 15: 11294-11306.