

Review

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Cell-specific regulation of insulin action and hepatic fibrosis by CEACAM1

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Abstract

The incidence of metabolic dysfunction-associated steatotic liver disease (MASLD) has reached an epidemic rise worldwide. The disease is a constellation of a broad range of metabolic and histopathologic abnormalities. It begins with hepatic steatosis and progresses to metabolic dysfunction-associated steatohepatitis (MASH), including hepatic fibrosis, apoptosis, and cell injury. Despite ample research effort, the pathogenesis of the disease has not been fully delineated. Whereas insulin resistance is implicated in the early stages of the disease, its role in hepatic fibrosis remains controversial. We have focused our studies on the role of carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) in hepatocytes and endothelial cells in the metabolic and histopathological dysregulation in MASH. Patients with MASH exhibit lower hepatic CEACAM1 with a progressive decline in hepatocytes and endothelial cells as the fibrosis stage advances. In mice, conditional deletion of CEACAM1 in hepatocytes impairs insulin clearance to cause hyperinsulinemia-driven insulin resistance with steatohepatitis and hepatic fibrosis even when mice are fed a regular chow diet. In contrast, its conditional deletion in endothelial cells causes inflammation-driven hepatic fibrosis without adversely affecting metabolism (mice remain insulin-sensitive and do not develop hepatic steatosis). Thus, this review provides *in vivo* evidence that supports or discards the role



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of insulin resistance in liver injury and hepatic fibrosis.

Keywords: Insulin action, insulin resistance, insulin clearance, hepatic steatosis, hepatic fibrosis, liver injury

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease (NAFLD)^[1], is a heterogeneous disease^[2]. Its broad spectrum spans simple steatosis to steatohepatitis to hepatic fibrosis, which marks its progression to metabolic dysfunction-associated steatohepatitis (MASH), together with apoptosis and cell injury. If uncontrolled, liver fibrosis can progress to cirrhosis and hepatocellular carcinoma^[3]. In fact, this disease has topped the list of abnormalities that lead to liver transplant in the US and its incidence has grown in children and adolescents, especially of Mexican descent^[4-7].

MASLD/MASH is spreading worldwide in parallel to the increasing incidence of metabolic syndrome (MetS), a constellation of diseases that include visceral obesity, hyperinsulinemia/type 2 diabetes, hypertension, and atherosclerosis^[8]. The reasonably high degree of overlap in its mechanistic underpinning with atherosclerosis has led to their identification as twin diseases^[9,10].

Liver fibrosis evolves when hepatic stellate cells (HSCs) are activated to produce collagen fibers that escape fibrolysis^[11]. Its rapid spread stems in part from our limited understanding of its pathogenesis, which has slowed down progress in developing Food and Drug Administration (FDA)-approved targeted therapies. Lifestyle changes (diet, exercise and restricted alcohol intake) remain the cornerstone of treatment of this disease, at least at its early stages^[2]. More recently, progress has been made and several metabolism-improving drugs have been developed and are now at stage 2a/3 clinical trials. These include thyroid hormone receptor beta-selective agonists and fatty acid synthase (FASN) inhibitors^[12]. With insulin resistance playing a major role in the pathogenesis of MetS^[13,14], repurposing insulin sensitizers and incretins glucagon-like-peptide-1 receptor (GLP-1R)-agonists has become an accepted therapeutic strategy, particularly at the early stages of the disease^[15]. However, their use in curbing hepatic fibrosis remains controversial. Whereas GLP-1R agonists (exenatide, liraglutide, semaglutide) improve glucose disposal in response to increased insulin secretion, reduce food intake and body weight, and ameliorate insulin resistance and hepatic steatosis^[16], their efficacy in late stages of metabolic liver injury remains questionable^[17]. To date, phase 2 clinical trials have excluded an antifibrotic effect for liraglutide^[18] and semaglutide^[19]. The limited efficacy of these drugs in the resolution of hepatic fibrosis is consistent with the fact that not all patients with advanced hepatic fibrosis are insulin-resistant^[20-24]. In fact, hepatic fibrosis in some patients likely stems from genetic predisposition, inflammatory diseases, and others.

If MASLD/MASH is a prominent feature of MetS, with insulin resistance being at its foundation, it is logical to assign a significant role for insulin resistance in its pathogenesis. Because MASLD/MASH is the liver manifestation of MetS, we will focus this review on hepatic insulin resistance. In the liver, hepatic insulin clearance plays a critical role in regulating insulin and lipid metabolism and subsequently, insulin action. This is bolstered by the emergence of reduced insulin clearance as a risk factor for MetS, especially among African Americans, Native Americans, and Hispanics^[25,26].

INSULIN ACTION

Insulin is secreted from pancreatic β -cells in response to stimuli and exerts its effects on several target tissues, including classically known targets: the liver where it suppresses endogenous glucose production,

skeletal muscle where it promotes glucose uptake, and adipose tissue where it mainly promotes fat storage and contributes to glucose uptake.

Insulin action is mediated by insulin binding to the α -subunit of its receptor (IR α) followed by trans-activation of the tyrosine kinase of its β -subunit (IR β). This initiates a cascade of phosphorylation/dephosphorylation that leads to a myriad of insulin actions in a cell- and tissue-specific manner^[27-30]. Whereas insulin signaling mediates insulin action, this process is regulated by circulating insulin level, which is determined by the net balance of insulin secretion from pancreatic β -cells and its clearance from the circulation, mainly in liver and to a lower extent in kidney^[31,32].

INSULIN CLEARANCE

We and others have presented several reviews on insulin clearance and its role in regulating insulin action^[31,33-35]. In brief, receptor-mediated insulin uptake and degradation constitute the main mechanism of insulin extraction. Endogenous insulin is cleared mostly in hepatocytes and, to a lower extent, in renal proximal tubule cells. In response to stimuli, insulin is secreted in pulses from pancreatic β -cells into the portal vein to passively and rapidly reach hepatocytes via fenestrae in the capillaries in the liver sinusoid. This leads to the binding of insulin to its receptor and its delivery to its degradation processes. Up to 70%-80% of insulin is cleared during its first pass through hepatocytes. In this manner, hepatic insulin clearance regulates the amount of insulin reaching its peripheral targets, such as skeletal muscle and white adipose tissue, where its delivery is tightly controlled by endothelial cells lining systemic vessels^[33,36,37].

Insulin binding to its receptor causes its dimerization and trans-activation of its tyrosine kinase in the intracellular domain to phosphorylate, among other substrates, the carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1). CEACAM1 is a ubiquitous plasma membrane glycoprotein with a predominant expression in the liver, but not in skeletal muscle or adipose tissue, among classical insulin target tissues. In hepatocytes, it is expressed as two alternatively spliced isoforms differing by the presence or absence of 60/71 amino acids (based on the rat sequence) and 60/73 amino acids (based on the mouse sequence) of its well-conserved intracellular tail that harbors its phosphorylation sites^[38,39] [Figure 1]. The long isoform (CEACAM1-4L) is expressed on both the sinusoidal and the bile canalicular domains of hepatocytes, whereas the short isoform (CEACAM1-4S) that lacks Serine503 and Tyrosine513 in the rat (or 515 in the mouse) is expressed exclusively in the bile canalicular domain^[40].

Upon its phosphorylation by IR β in response to acute insulin pulses, CEACAM1-4L (hereafter referred to as CEACAM1) takes part in the insulin-IR complex to stabilize it and increase the rate of its cellular uptake and insulin's delivery to the degradation process^[33,41] [Figure 2]. For insulin to undergo degradation in the acidic environment of late endosomes, it must dissociate from its receptor. This is achieved by the dissociation of CEACAM1 from the endocytosis complex following its reciprocal binding to FASN that is highly expressed in the perinuclear region. The receptor undergoes recycling, whereas the CEACAM1/FASN association mediates the repression of FASN activity in response to insulin^[42,43]. In this manner, we demonstrated a novel acute negative effect of insulin on *de novo* lipogenesis (DNL) linked to promoting insulin clearance in hepatocytes in response to acute rises of insulin in the portal vein. In other words, CEACAM1 phosphorylation by IR β bestows protection against the otherwise lipogenic effect of the physiologic high insulin level in the portal circulation^[27] and this is achieved by promoting insulin clearance and suppressing DNL. This negative acute physiologic effect of insulin on DNL is in contrast to its permissive chronic effect when supraphysiologic levels of insulin activate SREBP-1c to induce the transcription of lipogenic genes, such as FASN^[44] and, subsequently, promote DNL. Together with diminished pulsatility of insulin and downregulated insulin receptor number, chronic hyperinsulinemia

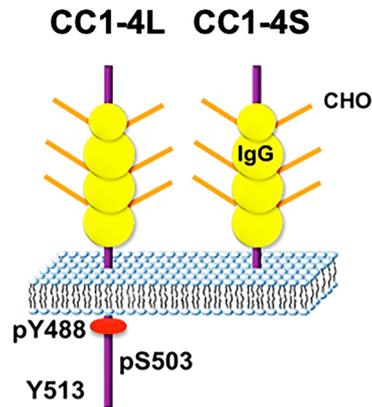


Figure 1. Alternative spliced variants of CEACAM1. In the liver, CEACAM1 is expressed as 2 spliced isoforms resulting from deletion or inclusion of Exon 7. The long isoform, denoted CC1-4L, contains a longer intracellular tail than the short (CC1-4S) (71 vs. 11 a.a.). Its cytoplasmic tail includes serine and tyrosine phosphorylation sites. Serine503 residue must be intact for Tyrosine488 to undergo phosphorylation by the insulin receptor tyrosine kinase. Both forms have 4 IgG loops and several CHO on their extracellular domains. CEACAM1: Carcinoembryonic antigen-related cell adhesion molecule 1; CEACAM1-4L: CC1-4L; CHO: carbohydrate chains.

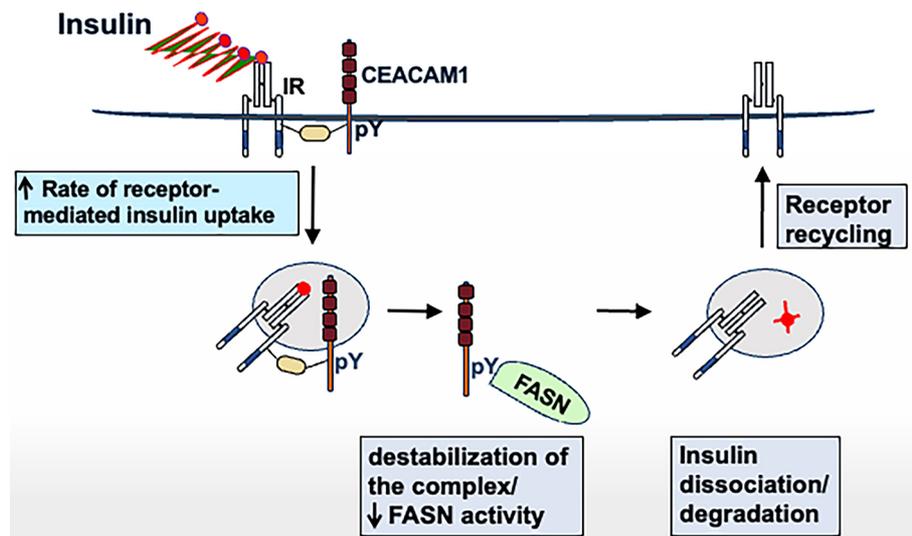


Figure 2. The double role of CEACAM1 in hepatocytes. In response to stimuli, insulin is released from pancreatic β -cells in pulses. This would stimulate CEACAM1 phosphorylation by the activated IR in hepatocytes. Phosphorylated CEACAM1 stabilizes the IR-insulin endocytosis complex and induces the rate of its uptake and insulin delivery to lysosomal degradation. By binding to FASN, expressed at high levels in the perinuclear region, CEACAM1 dissociates from the complex to allow the detachment of insulin from its receptor in the acidic environment of endosomes to undergo degradation. This also leads to suppression of FASN activity. In this manner, FASN activity in hepatocytes is kept at minimal under normal physiologic conditions despite its high levels resulting from increased transcription by the physiologic high insulin in the portal circulation. Thus, the pulsatility of secreted insulin and ensuing CEACAM1 phosphorylation by activated insulin receptors protect the liver against the otherwise lipogenic effect of physiologic high insulin in the portal vein. The upward arrow \uparrow indicates an increase, and the downward arrow \downarrow indicates a decrease. CEACAM1: Carcinoembryonic antigen-related cell adhesion molecule 1; IR: insulin receptor; FASN: fatty acid synthase.

increases DNL and causes hepatic insulin resistance. Thus, we posited that hepatic insulin resistance is inclusive of the inability of insulin to acutely suppress lipogenesis as well as gluconeogenesis. Thus, we propose that hepatic insulin resistance is not as selective for gluconeogenesis as commonly believed. This is supported by a recent report showing that in patients with MASLD, hepatic insulin resistance is not pathway-selective^[45].

REDUCED HEPATIC INSULIN CLEARANCE, INCREASED LIPOGENESIS AND HEPATIC INSULIN RESISTANCE: CEACAM1 IS A MOLECULAR LINK

Insulin resistance, manifested by chronic hyperinsulinemia, is the hallmark of MetS. It occurs when insulin response in target tissues is compromised. It has been established that chronic hyperinsulinemia in insulin resistance implicates both β -cell dysfunction and impaired insulin clearance^[46]. However, the cause-effect relationship remains a subject of debate. It is commonly believed that primary insulin resistance, when associated with visceral obesity, is compensated for by increased insulin secretion and reduced insulin clearance; the latter serves to limit compensatory insulin release and prolong the life/function of the β -cell^[47]. Alternatively, it is also possible that reduced hepatic insulin clearance causes chronic hyperinsulinemia, which, in turn, leads to downregulation of the insulin receptor, and subsequently hepatic insulin resistance^[48-50]. Hyperinsulinemia also induces DNL followed by the assembly of very-low-density lipoprotein (VLDL)-triglycerides and redistribution to white adipose tissue for fat storage. Eventually, the release of adipokines and excessive lipolysis-derived free fatty acids (FA) together cause systemic insulin resistance [Figure 3]. Accordingly, it is conceptually possible that reduced hepatic insulin clearance could cause hyperinsulinemia-driven hepatic insulin resistance and fat accumulation in the liver (hepatic steatosis). This paradigm is in line with the emergence of reduced insulin clearance as a risk factor for metabolic dysregulation^[51-53].

As detailed below, this alternative paradigm has been bolstered by the phenotype of mice with liver-specific loss-of-function of *Ceacam1*, the gene encoding CEACAM1 (L-SACC1 and *AlbCre+CC1^{fl/fl}* mutants)^[54,55], and by the reversal of systemic insulin resistance and hepatic steatohepatitis in global *Ceacam1* null mice when CEACAM1 is exclusively reconstituted in hepatocytes^[56]. This highlights a key role for CEACAM1-dependent insulin clearance pathways in maintaining insulin sensitivity and limiting hepatic steatosis by promoting hepatic insulin clearance and mediating the anti-lipogenic effect of acutely released insulin in hepatocytes.

According to this paradigm, reduced hepatic insulin clearance causes secondary hepatic insulin resistance and steatosis. However, delineating this paradigm in patients has been challenged by at least two main factors: 1) both insulin action and clearance depend on the rapid insulin binding to its receptor, and 2) in the Western world, most patients exhibit systemic insulin resistance with prominent abdominal obesity that could prohibit a fair assessment of an earlier onset of reduced insulin clearance. Accordingly, studies in Japanese subjects who exhibit milder abdominal obesity showed that impaired insulin clearance causes hepatic insulin resistance and steatosis^[57]. Moreover, Bril *et al.* from the University of Florida reported that hyperinsulinemia in patients with MASLD is caused primarily by reduced insulin clearance rather than increased insulin secretion^[58]. Thus, clinical research employing a more sensitive assessment of insulin clearance is needed to determine in human subjects that reduced insulin clearance can cause insulin resistance and is not just a consequence thereof.

IMPAIRED INSULIN CLEARANCE PRECEDES INFLAMMATION IN THE PATHOGENESIS OF DIET-INDUCED INSULIN RESISTANCE

High-fat feeding causes a progressive decline in hepatic CEACAM1 expression by a peroxisome proliferator-activated receptor alpha (PPAR α)-dependent mechanism^[59]. This provides a positive feedback mechanism on fatty acid β -oxidation (FAO) while maintaining intact insulin clearance and insulin sensitivity within the first 2 weeks of diet initiation in parallel to $\leq 50\%$ loss of *Ceacam1* expression^[59]. The mild decrease in hepatocytic CEACAM1 expression relieves FASN from the negative effect of CEACAM1 to lower malonyl-CoA level and its inhibition of carnitine palmitoyltransferase I (CPT1) activity and promote mitochondrial transport of long chain fatty acyl-CoA for FAO. Sustained high fat intake for > 3 weeks

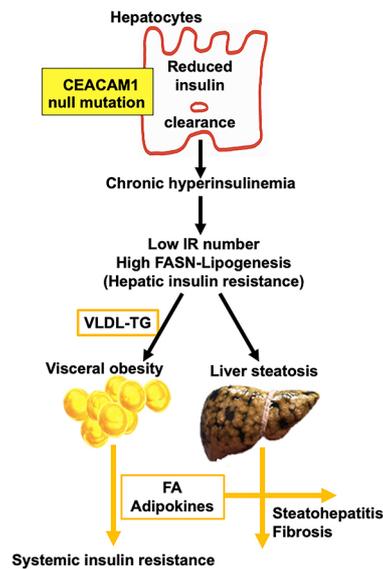


Figure 3. Loss of CEACAM1 in hepatocytes causes insulin resistance and hepatic fibrosis. Loss of CEACAM1 in hepatocytes impairs insulin clearance, which causes hyperinsulinemia-driven hepatic insulin resistance and *de novo* lipogenesis (steatosis). Redistribution of VLDL-triglycerides to white adipose tissue causes visceral obesity and, eventually, excessive release of FA and adipokines, both of which could lead to systemic insulin resistance. In addition to fat accumulation in the liver, adipokines can alter the inflammatory milieu of the liver and steatohepatitis emerges. Both FA and IL-6 could transactivate EGFR in HSCs to mediate their activation and cause collagen production and hepatic fibrosis [Cf Figure 4]. CEACAM1: Carcinoembryonic antigen-related cell adhesion molecule 1; FA: fatty acids; EGFR: epidermal growth factor receptor; HSCs: hepatic stellate cells; IR: insulin receptor; FASN: fatty acid synthase.

causes a loss of CEACAM1 by > 60%, at which point, insulin clearance is impaired and hepatic insulin resistance develops preceding inflammation^[60]. At this point, re-esterification dominates over FAO and DNL contributes to hepatic steatosis. These observations were bolstered by the reversal of diet-induced insulin resistance and hepatic steatosis by acute adenoviral-mediated delivery of wild-type CEACAM1 to the liver^[61] or by forced liver-specific over-expression of rat transgene using human Apolipoprotein A1 promoter that is induced by high-fat feeding^[60].

LOSS OF CEACAM1 IN THE LIVER OF PATIENTS WITH MASH

Hepatic CEACAM1 levels were significantly reduced in 29% of South Korean obese subjects with insulin resistance and hepatic steatosis independently of diabetes^[62]. Likewise, in collaboration with Drs. A. Zarrinpar and S. Duarte from the University of Florida, we have shown that hepatic CEACAM1 levels are lower in liver biopsies of patients with MASH than normal subjects regardless of gender, ethnicity and race^[63]. Furthermore, hepatic CEACAM1 levels progressively decline with the advancement of hepatic fibrosis stage in patients with MASLD/MASH^[63].

CEACAM1 is expressed in all liver cells, which are all virtually involved in hepatic stellate cell activation to cause fibrosis. Thus, we have begun by deleting the *Ceacam1* gene individually in murine hepatocytes and endothelial cells (highest and second highest site of CEACAM1 expression, respectively) to evaluate its cell-specific role in the pathogenesis of hepatic fibrosis and delineate the underlying mechanisms. We summarize these findings below.

LOSS OF CEACAM1 IN HEPATOCYTES LINKS HEPATIC INSULIN RESISTANCE AND STEATOSIS TO FIBROSIS AND LIVER INJURY

Recapitulating the human disease, mice with global deletion of *Ceacam1* ($Cc1^{-/-}$) exhibited hyperinsulinemia-driven insulin resistance, steatohepatitis and hepatic fibrosis even when fed a regular chow diet^[60]. Fed a high-fat diet, hepatic fibrosis was amplified, and mice developed liver injury and apoptosis^[64-67].

Deleting CEACAM1 exclusively in hepatocytes (as in *AlbCre+Cc1^{fl/fl}* mice) impaired hepatic insulin clearance at 2-3 months of age, followed by hyperinsulinemia-driven hepatic insulin resistance and steatosis at ~6 months of age. Pair-feeding experiments showed that the increase in food intake of *AlbCre+Cc1^{fl/fl}* mice at 7 months of age (partly driven by elevated hyperinsulinemia-driven induction of hypothalamic FASN level and activity) contributed to their visceral obesity and excessive release of free FA and adipokines, ultimately causing systemic insulin resistance starting at 8-9 months of age^[54].

Histological analysis showed that in addition to increased accumulation of fat droplets, there was also an increase in inflammatory infiltration in the parenchyma of liver sections of 8-month-old *AlbCre+Cc1^{fl/fl}* mice. In addition to steatohepatitis and hepatic injury, Sirius Red staining indicated hepatic fibrosis in these mice, even when they were fed a regular chow diet^[63]. High fat intake caused apoptosis and amplified liver injury^[63]. These observations were corroborated by the reversal of the metabolic dysfunction and hepatic fibrosis together with other features of MASLD/MASH in global $Cc1^{-/-}$ nulls by liver-specific reconstitution of *Ceacam1* even when mice were fed a high-fat diet^[56,66].

Hepatic fibrosis is characterized by initial deposition of perisinusoidal collagen, followed by portal and bridging fibrosis^[68]. This results from the activation of HSCs situated in the Space of Disse between hepatocytes and liver sinusoidal endothelial cells (LSECs). When quiescent, HSCs store vitamin A^[69] in response to activated peroxisome proliferator-activated receptor gamma (PPAR γ). Following their transdifferentiation into proliferative, inflammatory myofibroblasts with enhanced extracellular matrix production, HSCs lose their PPAR γ and retinoids^[70], while they reciprocally gain PPAR β/δ ^[71,72] that undergo activation by the released FA (all-trans retinoic acid^[73] and polyunsaturated FA^[74]).

Among other mechanisms, we have recently shown that these FA activate the epidermal growth factor receptor (EGFR) on the surface membrane of HSCs to cause their myofibroblastic transformation^[63,75,76] [Figure 4]. In addition to FA^[75], IL-6 also transactivates EGFR^[77]. Consistently, deleting CEACAM1 from hepatocytes caused steatosis and visceral obesity, both of which could partially alter the inflammatory milieu of the liver through the release of IL-6 among other interleukins^[78]. Visceral obesity leads to lipolysis-derived FA that could activate EGFR in liver cells following their passage through the portal vein^[79]. Moreover, hyperinsulinemia caused by deleting CEACAM1 in hepatocytes induced the production of Endothelin-1, which transactivates EGFR via Src kinase, as we have shown^[63]. Consistently, plasma Endothelin-1 levels were elevated in *AlbCre+Cc1^{fl/fl}* mice starting at 6 months of age preceding hepatic fibrosis. Additionally, media transfer experiments demonstrated that Endothelin-1 release from mutant hepatocytes played a significant role in activating wild-type HSCs^[63]. As summarized in Figure 4, both IL-6 and FA activate EGFR in HSCs. With FA suppressing *Ceacam1* expression in HSCs by activating PPAR β/δ , as we have recently shown^[75], sequestration of Shc by CEACAM1 upon its phosphorylation by EGFR is diminished, leading to its amplified coupling to EGFR. This activates Shc/MAPK proliferation and Shc/NF- κ B inflammatory pathways. The latter leads to increased autocrine expression of several transcriptional targets of NF- κ B such as TNF α and IL-6 adipokines^[63] and of PDGF-B and its receptor. Together, these contribute to the activation of HSCs and their myofibroblastic transformation. This was demonstrated by

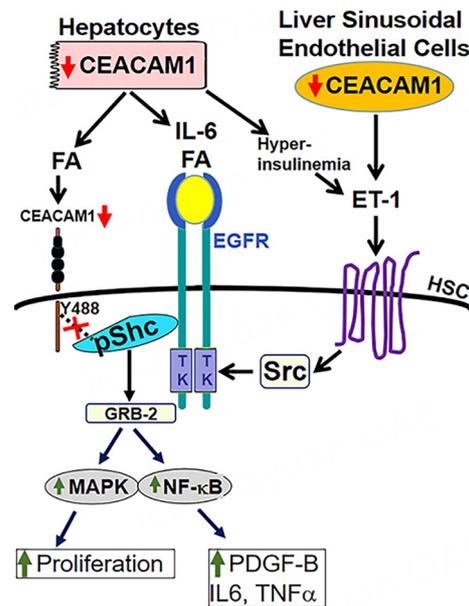


Figure 4. Loss of CEACAM1 in hepatocytes and endothelial cells activates HSCs. As in the legend of Figure 3, the loss of CEACAM1 in hepatocytes causes the release of FA, IL-6 and ET-1 that could activate EGFR in HSCs. Moreover, FA activate PPARβ/δ to reduce the transcription of CEACAM1, which, upon its phosphorylation by EGFR, sequesters Shc to counter cell proliferation. Reduced levels of CEACAM1 in HSCs would consequently elevate the coupling of Shc to the activated EGFR and amplification of Shc/MAPK and Shc/NF-κB downstream signaling. The latter leads to the transcriptional activation of several cytokines and to PDGF-B pro-fibrogenic factor. Loss of CEACAM1 in endothelial cells leads to increased production of ET-1, a vasoconstrictor that applies its pro-fibrogenic effects by binding to its A receptor on the surface membrane of HSCs to transactivate EGFR via Src kinase. Thus, the loss of CEACAM1 in hepatocytes and endothelial cells merges at the level of activation of EGFR to cause myofibroblastic transformation of HSCs and hepatic fibrosis. The upward green arrow ↑ indicates an increase, and the downward red arrow ↓ indicates a decrease. CEACAM1: Carcinoembryonic antigen-related cell adhesion molecule 1; HSCs: hepatic stellate cells; FA: fatty acids; IL-6: interleukin-6; ET-1: endothelin-1; EGFR: epidermal growth factor receptor; PDGF-B: platelet-derived growth factor subunit B.

the activation of wild-type HSCs by conditioned media from hepatocytes isolated from *AlbCre+Cc1^{fl/fl}* mice independently of other cells and without injuring endothelial cells^[63].

Similarly, L-SACC1 mice with liver-specific inactivation of CEACAM1 (overexpressing a dominant-negative phosphorylation-defective S503A isoform that evades sinusoidal localization)^[40] displayed visceral obesity, insulin resistance, steatohepatitis and spontaneous hepatic fibrosis^[55] in addition to exaggerated hepatic fibrosis when fed a high-fat diet^[80]. On the other hand, overexpressing CEACAM1 in hepatocytes protected mice against the metabolic and liver histological abnormalities caused by high-fat feeding for 4 months^[60]. It also protected mice from developing fibrosis in adipose tissue in response to long-term high fat intake^[81].

Together, this demonstrates that CEACAM1 in hepatocytes plays a key role in maintaining insulin sensitivity by promoting insulin clearance. It also prevents hepatic steatohepatitis as well as fibrosis and liver injury. Mice with hepatocytes-specific deletion (*AlbCre+Cc1^{fl/fl}*) or inactivation (L-SACC1) of *Ceacam1* provide an *in vivo* demonstration that hepatic inflammation and fibrosis can be associated with visceral obesity, insulin resistance, and hepatic steatosis. This supports a potentially significant role of reduced insulin clearance as a risk factor for hepatic fibrosis associated with MetS.

LOSS OF CEACAM1 IN ENDOTHELIAL CELLS CAUSES ENDOTHELIN-1–DRIVEN HEPATIC FIBROSIS IN THE ABSENCE OF HEPATIC INSULIN RESISTANCE OR STEATOSIS

In contrast to *AlbCre+ Cc1^{fl/fl}*, *VECadCre+ Cc1^{fl/fl}* mice with exclusive loss of *Ceacam1* in endothelial cells did not display impairment of insulin clearance or insulin resistance^[82]. Consistent with normo-insulinemia, *VECadCre+ Cc1^{fl/fl}* mice did not develop hepatic steatosis^[82]. However, like hepatocytes, loss of endothelial CEACAM1 restricted Shc sequestration to increase its reciprocal coupling to VEGFR and activation of downstream NF-κB pathways. This led to hepatic and systemic inflammation in *VECadCre+ Cc1^{fl/fl}* mice, as manifested by a remarkable rise in plasma IL-6 and TNFα levels at 8 months of age^[76]. Activation of NF-κB also led to increased transcription of Endothelin-1 and its autocrine production, followed by a spike in its circulating levels. In light of the pro-fibrogenic role of Endothelin-1, *VECadCre+ Cc1^{fl/fl}* mice developed hepatic fibrosis with bridging chicken-wire deposition of collagen fibers in their liver parenchyma at 8 months of age even when fed a regular chow diet^[76]. The role of Endothelin-1 in this phenotype was bolstered by the reversal of fibrosis in *VECadCre+ Cc1^{fl/fl}* mice with combined endothelial loss of *Ceacam1* (*Cc1*) and *Endothelin-1* (*Et1*) genes. Moreover, conditioned media from *VECadCre+ Cc1^{fl/fl}*, but not *VECadCre+ Et1. Cc1^{fl/fl}* primary liver endothelial cells, activated wild-type HSCs^[76]. In keeping with the predominant expression of CEACAM1 in LSECs relative to the general endothelial pool in the liver, LSECs of *VECadCre+ Cc1^{fl/fl}* single, but not *VECadCre+ Et1. Cc1^{fl/fl}* double mutants, manifested cell injury, characteristic of hepatic fibrosis^[76]. This was accompanied by increased Endothelin-1 production from LSECs. It is likely that Endothelin-1 exerted its pro-fibrogenic effect by transactivating EGFR in HSCs derived from *VECadCre+ Cc1^{fl/fl}* single, but not *VECadCre+ Et1. Cc1^{fl/fl}* double mutants^[76]. Together, these data demonstrated that endothelial CEACAM1 plays a key role in preventing hepatic fibrogenesis by reducing autocrine Endothelin-1 production. Thus, *VECadCre+ Cc1^{fl/fl}* mice provided an *in vivo* demonstration that hepatic fibrosis can result from inflammation in the absence of insulin resistance and hepatic steatosis.

Recapitulating the phenotype in mice, immunohistochemical analyses of liver tissue biopsies from patients with MASH diagnosis receiving liver transplant revealed lower endothelial CEACAM1 levels than adult patients undergoing bariatric surgery^[76]. Moreover, endothelial CEACAM1 expression gradually declined with the advanced hepatic fibrosis stage and in parallel to the progressive increase in plasma Endothelin-1 levels of patients with MASH^[76]. Furthermore, single-cell sequencing analysis of liver cells showed lower CEACAM1 and, reciprocally, higher Endothelin-1 mRNA levels in LSECs of patients with advanced fibrosis as compared to normal subjects^[76].

LOSS OF CEACAM1 RATHER THAN INSULIN RESISTANCE PLAYS A KEY ROLE IN THE PATHOGENESIS OF HEPATIC FIBROSIS

Our data demonstrated that whereas loss of CEACAM1 in hepatocytes causes hyperinsulinemia-driven hepatic insulin resistance and steatosis in addition to hepatic inflammation and fibrosis, its endothelial loss causes inflammation-driven hepatic fibrosis in the absence of insulin resistance and hepatic steatosis. This demonstrates that insulin resistance is likely implicated in the early stages of MASLD/MASH, and that the loss of CEACAM1 in the two most prominent cell populations in the liver constitutes a unifying mechanism underlying hepatic fibrosis (and inflammation) in the advanced stages of the disease. In support of this notion, insulin sensitizers, like PPARγ agonists, and incretins, like GLP-1 receptor agonists, individually or combined, have been used for the treatment of MASH, at least in the early stages of the disease. Both classes of drugs induced the transcription of *Ceacam1* by directly binding to the well-conserved PPRE/RXR sequence on its promoter, as shown by a chromatin immunoprecipitation assay in human hepatoma HepG2 cells treated with rosiglitazone, a PPARγ agonist, or exenatide, a GLP-1R agonist^[83]. Consistently, exenatide

treatment for 6 h induced GLP-1R mRNA levels in HepG2 cells, followed by inducing CEACAM1 and PPAR γ mRNA levels after 12 h of treatment. This positive effect of exenatide was mediated by its receptor, as demonstrated by the prevention of these effects by pre-incubating cells with exendin 9-39 GLP-1R antagonist^[83]. Moreover, treating mice with Exenatide reversed insulin resistance together with hepatic steatosis and fibrosis in wild-type but not in *AlbCre+Cc1^{fl/fl}* mice fed a high-fat diet. Thus, a CEACAM1-targeted therapeutic approach could constitute an effective strategy against hepatic fibrosis while it ameliorates insulin resistance in patients with this metabolic abnormality.

STRENGTHS AND LIMITATIONS

The data above demonstrate that the loss of CEACAM1 in hepatocytes and endothelial cells constitutes a unifying mechanism underlying hepatic fibrosis in mice independently of metabolic regulation. However, more studies are needed to delineate the independent role of CEACAM1 in other liver cells, such as Kupffer cells, before we could formulate a CEACAM1-based unifying mechanism against hepatic fibrosis. It is worth mentioning that CEACAM1 is at the crossroads of the regulation of metabolic and immune response in liver injury, as we have previously reviewed^[84]. Moreover, in both mice and humans, hepatic CEACAM1 expression correlated negatively with activation of innate and adaptive immune responses, demonstrating that CEACAM1 expression indicates donor liver quality and prevents early orthotopic transplantation injury^[85].

Because CEACAM1 is gradually lost in hepatocytes and endothelial cells in MASH patients with progressive fibrosis, the data promote CEACAM1 induction as a potential therapeutic strategy. Considering the potential confounding metabolic effects of PPAR γ and GLP-1R agonists, it would be of utmost importance to identify effectors that specifically induce *Ceacam1* promoter activity in an attempt to develop CEACAM1-targeted therapy with high efficacy against hepatic fibrosis and limited off-target effects.

CONCLUSION

In summary, loss of CEACAM1 in the two most dominant cells in the liver causes hepatic fibrosis with inflammation. In contrast to endothelial cells, its loss in hepatocytes also causes hepatic insulin resistance and steatosis, consistent with its role in promoting insulin clearance in these cells. Thus, loss of CEACAM1 provides an *in vivo* demonstration that hepatic inflammation and fibrosis can occur independently of insulin resistance and hepatic steatosis. On the other hand, most of the well-characterized therapeutic means against MASLD/MASH implicate induction of hepatic CEACAM1 expression. For instance, caloric restriction ameliorates MASH phenotype and hepatic fibrosis in rats with low aerobic capacity, partly by inducing their hepatic CEACAM1 expression^[86]. PPAR γ and GLP-1 receptor agonists induce hepatic *Ceacam1* transcription by their direct binding to the well-conserved PPRE-RXR consensus sequence on its promoter^[83]. This raises the possibility that inducing CEACAM1 could be a valid therapeutic target. Further studies are needed to explore whether hepatic fibrosis could similarly stem from deleting *Ceacam1* in other liver cells such as immune cells. This would ascertain a common underlying mechanism of CEACAM1's prevention of hepatic fibrosis marked by limited off-target effects.

DECLARATIONS

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Authors' contributions

Made substantial contributions to the conception, organization, and writing of the first draft of the review: Aldroubi BG, Najjar JA, Youssef TS
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Availability of data and materials

Not applicable.

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Conflicts of interest

Sonia M. Najjar is an Editorial Board member of the journal *Metabolism and Target Organ Damage*, and the Guest Editor of Special Issue: Altered Metabolism in Liver Injury. The other authors have declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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