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REVIEW ARTICLE

Soluble CD36– a marker of the (pathophysiological) role of CD36 in the metabolic syndrome?

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Abstract
CD36 is a class B scavenger receptor observed in many cell types and tissues throughout the body. Recent literature has implicated CD36 in the pathogenesis of metabolic dysregulation such as found in obesity, insulin resistance, and atherosclerosis. Genetic variation at the *CD36* loci have been associated with obesity and lipid components of the metabolic syndrome, with risk of heart disease and type 2 diabetes. Recently, non-cell bound CD36 was identified in human plasma and was termed soluble CD36 (sCD36). In this review we will describe the functions of CD36 in tissues and address the role of sCD36 in the context of the metabolic syndrome. We will also highlight recent findings from human genetic studies looking at the *CD36* locus in relation to metabolic profile in the general population. Finally, we present a model in which insulin resistance, oxLDL, low-grade inflammation and liver steatosis may contribute to elevated levels of sCD36.

Keywords: Obesity; insulin resistance; type 2 diabetes; inflammation; ox-LDL; NAFLD

Introduction

Type 2 Diabetes (T2D) is one of the most costly and burdensome chronic diseases of our time. It is associated with the development of devastating complications and a significantly higher risk for cardiovascular disease. Unfortunately, T2D is becoming gradually more common as life expectancy is increasing and obesity rates are rising. Increased expression of the class B scavenger receptor CD36 has been observed in many cell types and tissues throughout the body and has been implicated in the pathogenesis of atherosclerosis (Collot-Teixeira *et al.*, 2007; Silverstein, 2009) and metabolic disease (Glatz *et al.*, 2010). In addition, a region along chromosome 7q, containing the *CD36* gene, has been linked to components of the metabolic syndrome in several genome-wide linkage studies (An *et al.*, 2005; Arya *et al.*, 2002; Malhotra *et al.*, 2007). Variants in the *CD36* gene have now been shown to influence the susceptibility for the metabolic syndrome, and associate with risk of heart disease and Type 2 Diabetes (T2D) (Love-Gregory *et al.*, 2008, 2010).

Recently, non-cell bound CD36 was identified in human plasma and was termed soluble CD36 (sCD36) (Handberg *et al.*, 2006). sCD36 clusters with markers of insulin resistance and is progressively related to the severity of insulin resistance and atherosclerosis in the human population (Handberg *et al.*, 2006, 2008, 2010). Interestingly, sCD36 parallels the increased CD36 expression observed in multiple cell types and tissues in human and rodent models of insulin resistance and T2D (Aguer *et al.*, 2010, Bonen *et al.*, 2004; Griffin *et al.*, 2001; Koonen *et al.*, 2007; Luiken *et al.*, 2001; Sampson *et al.*, 2003). Indeed, results from association studies have led to the hypothesis that sCD36 reflects tissue CD36 expression level, and in particular monocyte and macrophage expression level (Handberg *et al.*, 2006, 2008, 2009). As elevated sCD36 may be a marker of increased CD36 expression derived from a number of tissues associated with the metabolic syndrome, this review will discuss the proposed (patho)-physiological role of CD36 in atherosclerosis and metabolic disease. We will highlight recent findings from human genetic studies that examined the *CD36* locus in relation to metabolic profile

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in the general population, and propose a model in which insulin resistance, oxLDL, low-grade inflammation and liver steatosis may contribute to increased soluble CD36 in the circulation.

Role of CD36 in foam cell formation, platelet activation and fatty acid uptake

CD36 is a heavily glycosylated membrane protein containing two predicted transmembrane areas, two short intracellular domains and a large extra-cellular loop (Rac *et al.*, 2007; Su and Abumrad, 2009). CD36 is involved in many different functions depending on cell-type and ligand-specific binding. Membrane CD36 in monocytes and macrophages bind and internalize oxLDL (Kunjathoor *et al.*, 2002; Podrez *et al.*, 2002). In addition, CD36 expression is up-regulated by oxLDL, and thus CD36 plays an important role in formation of foam-cells, which may eventually turn into atherosclerotic plaques in the arterial wall (Febbraio *et al.*, 2000; Podrez *et al.*, 2000). In platelets and endothelial cells CD36 functions as an adhesion molecule, and through interaction with anionic phospholipids present in, for example, oxLDL, CD36 is involved in platelet activation (Podrez *et al.*, 2007, Valiyaveettil and Podrez, 2009). In metabolically active tissues CD36 has been shown to bind long-chain fatty acids (LCFA) and facilitate LCFA uptake across the plasma membrane (for review, see Glatz *et al.*, 2010). Increased recruitment of CD36 from intracellular storage sites towards the plasma membrane has been shown to regulate fatty acid (FA) metabolism under various physiological conditions, however, is also associated with enhanced efficiency of FA uptake and lipid accumulation in rodent and human muscle (Aguer *et al.*, 2010, Bonen *et al.*, 2004, Holloway *et al.*, 2009, Smith *et al.*, 2007), and may therefore contribute to the aetiology of insulin resistance.

Obesity, low-grade inflammation, and the metabolic syndrome

The metabolic syndrome describes a cluster of factors associated with an increased risk of T2D and atherosclerosis. Among many definitions, the newly published IDF criteria include: abdominal obesity and two out of the following four components: elevated triglyceride, reduced HDL-cholesterol, elevated systolic blood pressure or diastolic blood pressure, and increased fasting glucose (Alberti *et al.*, 2006).

Increased adiposity and lipid accumulation in liver and skeletal muscle have strongly been associated with the development of insulin resistance and T2D. Intracellular lipid metabolites, including fatty acyl-CoA and diacylglycerol, have been shown to interfere with normal insulin signalling at the level of insulin receptor-mediated tyrosine phosphorylation and at downstream sites within the insulin signalling cascade (Hegarty *et al.*, 2003).

Insulin resistance and T2D are, like atherosclerosis, associated with systemic low-grade inflammation (for review, see Shoelson *et al.*, 2007 and Rocha and Libby, 2009). Abdominal and visceral obesity in particular has been proposed to induce a low-grade inflammatory condition. The prevailing understanding is that distension of fat cells above a critical level influence vascularization of fat tissue through an adipokine dependent mechanism. The resulting fat cell necrosis is followed by infiltration of macrophages and a local low-grade inflammation, which may become systemic (Kloting *et al.*, 2010; Shoelson *et al.*, 2006). Cytokines like TNFalpha induce insulin resistance in muscle, fat and liver, and inflammation and insulin resistance stimulate atherosclerosis development through associated dyslipidaemia, per-oxidation of lipoproteins, local influences on the vessel wall among other mechanisms (Holvoet *et al.*, 2008; Rocha and Libby, 2009; Shoelson *et al.*, 2007).

Elevated expression of CD36 associated with T2D and metabolic syndrome

Over the years evidence has accumulated that implicate CD36 in the development of atherosclerosis and metabolic disease. Lipid accumulation in human obesity and T2D is associated with increased rates of skeletal muscle FA transport and increased CD36 expression due to enhanced membrane recruitment of CD36 (Aguer *et al.*, 2010; Bonen *et al.*, 2004). CD36 expression is increased in adipose tissue and skeletal muscle in human obesity and T2D (Bonen *et al.*, 2004, 2006), and in liver biopsies from non-alcoholic liver disease (NAFLD) patients correlating with the degree of steatosis (Greco *et al.*, 2008). CD36 is also upregulated in vascular lesions derived from hyperglycaemic patients and in human monocyte-derived macrophages differentiated in the presence of high glucose, providing a mechanism for accelerated atherosclerosis in diabetic patients (Griffin *et al.*, 2001). In addition, recent data provided new evidence to support the atherogenic property of CD36 by demonstrating that lipid-induced insulin resistance following a 24-h Intralipid/heparin infusion is associated with increased monocyte expression of CD36 and internalization of oxidized LDL in healthy subjects (Kashyap *et al.*, 2009). Consistent with this idea, a delay in atherosclerosis development was observed in CD36-deficient mice bred on an ApoE-/-background compared to Apo-E-/- mice, whereas re-introduction of CD36 into the double-knockout mice resulted in a significant increase in the degree of atherosclerosis (Febbraio *et al.*, 2000).

Increased CD36 expression, enhanced efficiency in FA uptake and increased FA esterification has also been observed in animal models of insulin resistance and T2D, including high-fat feeding and obesity (Coort *et al.*, 2004a; Han *et al.*, 2007; Hegarty *et al.*, 2002; Holloway *et al.*, 2009; Luiken *et al.*, 2001). In heart and skeletal muscle, CD36 was found in excess on the cell surface, which was demonstrated to be due to a permanent relocation of CD36

from its intracellular storage pool towards the membrane (for review, see Glatz *et al.*, 2010). This permanent relocation towards the cell membrane was shown to be an early event in the development of insulin resistance (Coort *et al.*, 2004b; Ouwens *et al.*, 2007). Interestingly, CD36 turnover is abnormally slow in macrophages from insulin resistant ob/ob mice reflecting a defect in CD36 receptor trafficking in response to altered insulin signalling (Liang *et al.*, 2004). In liver, increased CD36 expression in response to diet-induced obesity was shown to be sufficient to exacerbate hepatic triglyceride storage and secretion, confirming a role for CD36 in the pathogenesis of metabolic disease (Koonen *et al.*, 2007).

Interestingly, a combination of metformin and exercise was shown to reduce muscle CD36 expression and lipid accumulation and blunt the progression of high-fat diet induced hyperglycaemia in rats (Smith *et al.*, 2007). Moreover, green tea polyphenols and cinnamon extract had a similar reducing effect on CD36 expression in heart and adipose tissue from high fructose-fed rats (Qin *et al.*, 2010a, b), suggesting that CD36 might represent a potential therapeutic target for the prevention and/or treatment of insulin resistance.

Although the mechanisms are still under investigation, not one single factor is likely to explain the altered CD36 expression seen in atherosclerosis and metabolic disease. Some of those factors are inter-related, such as glucose, plasma lipids and insulin resistance, inflammation and oxidative stress, most of which are predisposing for atherosclerosis. Therefore, defective CD36 expression might reflect an intricate mechanism involving the interaction of multiple factors at different stages in time.

Genetic variation at the CD36 locus and metabolic profile in humans

Other strategies for the investigation of CD36 in metabolic diseases in humans include the study of naturally occurring genetic variants in population-based data. Several genome-wide linkage studies identified a region along chromosome 7 (7q11.2–7q21.11), containing the *CD36* gene, that was linked to components of the metabolic syndrome (An *et al.*, 2005; Arya *et al.*, 2002; Malhotra *et al.*, 2007). In other, more focused, candidate gene studies of the *CD36* locus, investigators gather information on the metabolic and cardiovascular consequences of lifelong exposure to genetic variants that may produce CD36 gene-products with differential functionality. Already, several single nucleotide polymorphisms (SNPs) at the *CD36* locus have been found to be associated with parameters of lipid metabolism, insulin sensitivity, and cardiovascular disease. Studies in Europeans found *CD36* SNPs associated with adiponectin (Lepretre *et al.*, 2004a, b), serum free FA and triglyceride levels (Ma *et al.*, 2004), fasting plasma glucose, insulin resistance, risk of T2DM (Corpeleijn *et al.*, 2010), and levels of high-density and low-density lipoprotein cholesterol (HDL-C and LDL-C) (Goyenechea *et al.*, 2008). Recently a group of publications have explored the role of genetic variants in *CD36* in relation to adiposity. One study suggested that four SNPs, known from the previous studies of lipid traits, were associated with adolescent obesity without any evidence for an association with plasma lipids (Bokor *et al.*, 2009). However, in the largest study to date, a meta-analysis of almost 10,000 participants neither supported the evidence for the previously indicated SNPs, nor suggested any other SNPs captured on their genome-wide arrays, to play a role in early onset obesity in European adolescents (Choquet *et al.*, 2010). Conversely, a simultaneous publication of six genotyped *CD36* SNPs in 1790 non-diabetic Germans found associations with measures of body-mass index and waist circumference, and no associations with detailed measures of glucose tolerance, insulin sensitivity, triglycerides, HDL-C, and LDL-C (Heni *et al.*, 2010). Some studies have indicated that the impact of *CD36* variants may differ across population characteristics (Corpeleijn *et al.*, 2010). So far, there has been no detailed investigation of context-dependent effects of the *CD36* SNPs on the metabolic traits of interest but certainly the discrepancy in the findings between studies conducted within populations with differences in population-characteristics that might play a role for the observed association between genotype and metabolic outcomes (such as age, gender, obesity and smoking), highlight that exploration of gene-environment interacts will be of interest for future studies.

CD36 is also a receptor for *Plasmodium falciparum* infected erythrocytes and therefore linked to malaria susceptibility. Thus, the polymorphisms' in *CD36* differ in frequency and position between European and non-European populations due to selection. Investigations of a *CD36* SNP that encodes a truncated protein (rs3211938) found in African and Asian populations, suggests that decreased CD36 expression as found in heterozygotes is more advantageous for metabolic traits as compared to complete CD36 deficiency as observed in the homozygous carriers of this variant (Love-Gregory *et al.*, 2008). In addition, the HyperGen population sample of 2020 African-Americans found 15 other *CD36* SNPs that were also associated with HDL-cholesterol. Recently this investigator group followed up their initial HDL-related *CD36* SNPs with detailed assessments of CD36 expression on monocytes and platelets (Love-Gregory *et al.*, 2010). Here they observed that the SNPs that were associated with an advantageous metabolic profile were also associated with less CD36 expression. It is of equally great interest to address whether such kind of functionality can also be established for the above-mentioned metabolically relevant SNPs that were identified in European populations.

sCD36, a novel marker for insulin resistance, atherosclerosis and inflammation

Recently, non-cell bound CD36 (soluble CD36; sCD36) was identified in the human population and a simple

sandwich ELISA suitable to measure sCD36 in plasma was developed (Handberg *et al.*, 2006). This is convenient as compared to tissue CD36– both in terms of sample accessibility and the methodological procedure. This new measure of plasma CD36 has been investigated in studies of sCD36 in T2D, insulin resistance, and atherosclerosis where altered expression levels of CD36 could play an important pathophysiological role. In particular enhanced CD36 in monocytes and macrophages induced by hyper-glycaemia and insulin resistance is believed to be an important link between T2D and atherosclerosis. Consistent with this hypothesis, sCD36 is up to 4-fold higher in plasma from obese T2D-patients compared with lean healthy control subjects and tightly associated with insulin resistance (Handberg *et al.*, 2006). Likewise, in chronic kidney disease (CKD) elevated sCD36 in serum was associated with the presence of T2D (Chmielewski *et al.*, 2010). Furthermore, insulin resistance in non-diabetic obese individuals as well as in women with polycystic ovarian syndrome (PCOS) was associated with increased sCD36 (Glintborg *et al.*, 2008; Handberg *et al.*, 2006). In addition to the consistent correlation between insulin resistance and sCD36, pioglitazone treatment reduced sCD36 while improving insulin-sensitivity in PCOS (Glintborg *et al.*, 2008). Interestingly, the correlation between sCD36 and insulin resistance was independent of BMI or alternatively, abdominal obesity (Glintborg *et al.*, 2008; Handberg *et al.*, 2006). Factor analysis of data from a diabetes prediction study propose that sCD36 is associated with the insulin resistance component in a model of the metabolic syndrome, comprising blood pressure, lipids, glucose, inflammation, and obesity/insulin resistance, and is associated with elevated risk of diabetes (Handberg *et al.*, 2010).

In line with the important role of CD36 in atherosclerosis development sCD36 in serum was found to predict cardiovascular mortality in a cohort of CKD stage 5 patients (Chmielewski *et al.*, 2010). Moreover, the use of HMG-CoA reductase inhibitors (statins) reduced serum concentrations of sCD36 (Chmielewski *et al.*, 2010). sCD36 is associated with triglyceride, LDL, and inversely with HDL but not oxLDL in several patient populations (Glintborg *et al.*, 2008; Handberg *et al.*, 2006, 2010). In addition, a modest correlation between intima-media-thickness determined by ultra-sound, and sCD36, independent of gender and age, was reported in healthy individuals (Handberg, submitted). We found that in patients with severe carotid artery atherosclerosis, sCD36 level was higher in patients that reported recent cerebral symptoms, compared to those who did not have symptoms in the previous two months (Handberg *et al.*, 2008) In contrast, levels of hsCRP were not different between these two group of patients. In the same patients, elevated CD36 expression found in unstable (symptomatic) atherosclerotic plaques was correlated with higher plasma sCD36 levels.

In terms of the relationship between inflammatory markers and sCD36 this was reported in glucose intolerant men, where fat-free mass and IL-6 independently contributed to sCD36, possibly through decreased insulin action (Handberg *et al.*, 2010). sCD36 has also been identified in rat plasma where is correlates with adverse lipid profiles and increased TNFalpha and IL-6 cytokine levels in plasma in rats fed a high-fructose diet (Qin *et al.*, 2010b). Moreover, addition of green tea polyphenols to the high-fructose diet completely restored sCD36 levels and alleviated the insulin-resistant cardiac phenotype in these rats (Qin *et al.*, 2010b). Ameliorations in plasma lipid profiles, sCD36 expression and insulin sensitivity were also observed in high-fructose fed rats following supplementation with cinnamon extract for 8 weeks (Qin *et al.*, 2010a).

So far, the relationship between the degree of liver fat accumulation and inflammation and sCD36 has not been investigated. However, sCD36 correlates positively with liver amino-transferase activity in subjects with glucose intolerance, indicating that sCD36 might also be a marker of liver injury (Fernandez-Real *et al.*, 2009). Indeed, even in healthy individuals, risk of non-alcoholic liver disease as scored by the fatty liver index was associated with an increase in sCD36 (Handberg, submitted). The validation of sCD36 as a risk marker of insulin resistance, inflammation and atherosclerosis is only in its beginning. However, the introduction of this easily accessible biomarker represents a promising tool for future risk stratification and monitoring of components of the metabolic syndrome.

Proposed model of CD36 release into the circulation

Despite the fact that sCD36 has been shown to cluster with markers of the metabolic syndrome, the mechanism(s) of CD36 release into the circulation are not known.

As elevated sCD36 may be a marker of increased CD36 expression known from a number of tissues that are associated with the metabolic syndrome, single factors (hyperglycemia, oxLDL) or a combination of factors (insulin resistance, low grade inflammation) that induce CD36 expression are likely to promote CD36 release into the circulation (Figure 1). Therefore, CD36 could be released into the circulation as part of the low-grade inflammatory state commonly seen in atherosclerosis and insulin resistance (Handberg *et al.*, 2006). Alternatively, increased plasma concentration of sCD36 could be directly related to apoptosis following cholesterol accumulation in foam-cells or to ectopic fat accumulation in general (Fernandez-Real *et al.*, 2009; Handberg *et al.*, 2006). However, given the wide-spread tissue expression of CD36 and its broad range of functions it is difficult to foresee which specific pathological processes may reflect alterations in sCD36, or alternatively, may induce. In addition, limited information is available about the structure of sCD36 in the circulation. To date, it has not been studied whether sCD36 consists of full-length CD36 or represents a proteolytic fragment of CD36 (i.e. the

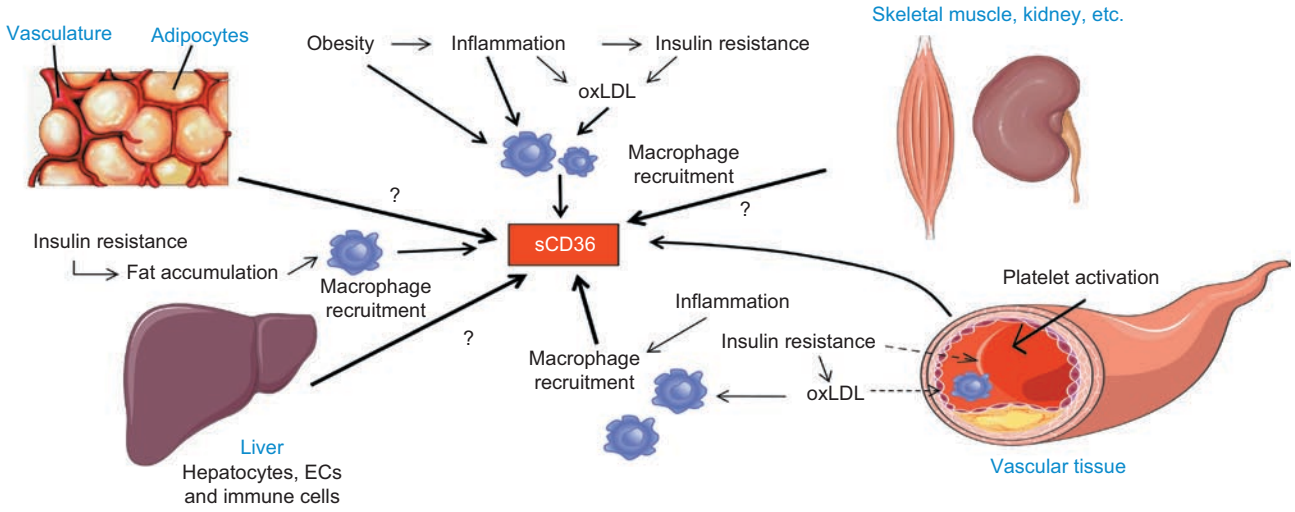

Figure 1. Proposed model of the pathophysiology behind elevated sCD36 in plasma in the metabolic syndrome. sCD36 reflects tissue CD36 expression level, and in particular monocyte and macrophage expression level. Elevated sCD36 may be a marker of increased CD36 expression known from a number of tissues that are associated with the metabolic syndrome; macrophage infiltration and low-grade inflammation in abdominal obesity, which may lead to dyslipidemia and peroxidation of lipoproteins, and liver steatosis. A combination of these factors influence atherosclerosis development and induces increased CD36 in the vessel wall. Insulin resistance, oxLDL, low-grade inflammation and liver steatosis stimulate CD36 expression in monocytes and macrophages in fat, liver, and arteries, which lead to elevated plasma sCD36. In addition, the involvement of CD36 in ectopic fat accumulation associated with insulin resistance, dyslipidemia and inflammation in liver and skeletal muscle may result in elevated circulating sCD36.

extracellular part of CD36). Detection and measurement of sCD36 in plasma have been based on immunological approaches, and all of the antibodies used for these experiments were directed against the predicted extracellular part of CD36. Since only a minor part of CD36 is located in the intracellular or trans-membraneous areas, and since the extracellular part of CD36 is heavily glycosylated, the size of the extracellular part and that of full length CD36 can not be discriminated by Western blotting. Therefore, more research is warranted to unravel the mechanism(s) involved.

Conclusion

The scavenger receptor and FA transport protein CD36 has been shown to play an important role in early atherosclerosis and insulin resistance. Non-cell bound CD36 (sCD36) has recently been identified in human plasma and is tightly related to risk factors of accelerated atherosclerosis in T2D such as insulin resistance and glycaemic control. Results from association studies suggest that sCD36 reflects tissue CD36 expression level, and in particular monocyte and macrophage expression level. Insulin resistance, oxLDL, low-grade inflammation and liver steatosis stimulate CD36 expression in monocytes and macrophages in fat, liver, and arteries, which lead to elevated plasma sCD36. While genetic variation at the *CD36* locus has also been associated with lipid levels, free fatty acids, insulin resistance, obesity, and risk of coronary heart disease, so far evidence linking the genetic variants to plasma concentrations of sCD36 is lacking. sCD36 may thus in future studies have a potential as marker of processes central in the development of insulin resistance and atherosclerosis related to the metabolic syndrome.

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Declaration of interest

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