



CD36: the common soil for inflammation in obesity and atherosclerosis?

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This editorial refers to ‘A CD36-dependent pathway enhances macrophage and adipose tissue inflammation and impairs insulin signalling’ by D.J. Kennedy et al., pp. 604–613, this issue.

Insulin resistance, a decreased metabolic responsiveness of peripheral organs and tissues to insulin, is considered the central mechanism of metabolic syndrome, a cluster of cardiovascular risk factors, including abdominal obesity, hypertension, a pro-atherogenic lipid profile, a pro-thrombotic, pro-inflammatory state, and dysglycemia. Studies in recent years have revealed the causal role of chronic low-grade inflammation in development of obesity-associated insulin resistance in animal models.¹ Since chronic inflammation also plays a pivotal role in atherosclerotic cardiovascular disease,² it is therefore considered to be the fundamental mechanistic link between insulin resistance and increased cardiovascular prevalence in obesity. Compelling evidence from numerous studies in animal models demonstrates that monocytes are recruited to adipose tissue during obesity and become macrophages through interaction with dysfunctional adipocytes.³ Moreover, resident adipose tissue macrophages may switch their phenotype from the anti-inflammatory ‘alternative’ (M2) to pro-inflammatory ‘classical’ (M1) macrophages during expansion of adipose tissue in obesity.⁴ Accumulation of macrophages and phenotypic switch from M2 to M1 macrophages has been suggested to play a determinant role in insulin resistance in obesity at least in mouse models.³ Increased adipose tissue inflammation and macrophage infiltration have been confirmed in human obesity.⁵ However, subset macrophage accumulation in human adipose tissue in obesity requires further characterization.

There is much interest in the question of what are the micro-environmental changes in adipose tissue in obesity that initiate and regulate adipose tissue inflammation. Adipocytes are highly active in secretion of numerous bioactive hormones called adipokines that exert profound endocrine and/or paracrine effects on different types of cells including macrophages and vascular wall cells, i.e. endothelial cells or smooth muscle cells.⁶ It is proposed that adipocyte dysfunction reflected by imbalanced secretion of pro-inflammatory and anti-inflammatory adipokines contributes to insulin resistance,

metabolic disorders, and cardiovascular disease.⁶ Crosstalk between perivascular adipocytes and the vascular wall or adipocytes and macrophages through paracrine secretion of adipokines has been reported in many studies in recent years.³ It has been demonstrated that adipocytes or perivascular adipose tissues release relaxing factors causing vascular smooth muscle relaxation, and secrete smooth muscle cell growth inhibitors such as adiponectin as well as growth promoters, which could play a role in vascular remodelling under disease conditions.^{6,7} Moreover, increased perivascular adipose tissue inflammatory cell infiltration in atherosclerosis has also been demonstrated in patients,⁶ which is similar to the phenomenon in obesity. To what extent the perivascular adipose tissue inflammation contributes to cardiovascular disease remains to be determined. Also, regulatory mechanisms of crosstalk between adipocytes and macrophages and other cells in obesity and cardiovascular disease are largely unknown.

The study by Kennedy et al.⁸ explored the crucial role of CD36 in mediating crosstalk between adipocytes and macrophages *in vitro* and also *in vivo* in mouse models of obesity. CD36, first discovered in platelets 30 years ago, is now characterized as a membrane glycoprotein that is widely expressed on the surface of a variety of cell types, including cardiomyocytes, vascular endothelial cells, smooth muscle cells, macrophages, adipocytes, and hepatocytes.⁹ CD36 functions as a class B scavenger receptor and fatty acid translocase that binds long-chain fatty acids and facilitates their transport into cells. CD36 also binds and scavenges a wide spectrum of endogenous molecules, including oxidized lipids from LDL, advanced glycosylated proteins, components of apoptotic cells, and cell-derived microparticles.⁹ It seems not surprising that the previous work of this research group and others demonstrated multiple cellular functions of CD36.^{9,10} For example, CD36 functions as a negative regulator of angiogenesis and promotes endothelial apoptosis; it promotes oxidative stress by down-regulation of antioxidant enzymes peroxiredoxin-2 and haem oxygenase-1 in vascular smooth muscle cells under conditions of vascular injury; it renders platelets hypersensitive to aggregation stimuli and thereby promotes platelet aggregation and secretion; it promotes lipid uptake in macrophages and facilitates foam cell formation. It appears that CD36-mediated effects on a variety of cell types are through similar signal transduction pathways, i.e. activation of the non-

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receptor tyrosine kinase Src family (Fyn and Lyn) and the serine/threonine kinase MAPK family (JNK and p38 MAPK).⁹

In this study, Kennedy *et al.*⁸ further demonstrated that CD36 deficiency in several backgrounds protects mice from chronic adipose tissue inflammation induced by high fat diet (HFD) feeding. Although obesity was protected in CD36^{-/-} mice fed HFD when compared with wild-type controls, no difference in body weight was observed between ApoE^{-/-} and ApoE^{-/-}/CD36^{-/-} mice. The results demonstrate a direct anti-inflammatory effect of CD36 deficiency that is independent of reduced obesity. The authors further elucidated the underlying mechanisms involved in adipose tissue inflammation and insulin resistance. By using several specific genetic knockout mice and through analysing adipocyte-macrophage interactions, they demonstrated that CD36 in adipocytes interacts with Fyn and Lyn tyrosine kinases, resulting in JNK activation and impaired insulin signalling. The dysfunctional adipocytes secrete adipokines and thereby stimulate macrophage migration. On the other hand, CD36 also impairs insulin signalling in macrophages from mice fed HFD, resulting in enhanced production of pro-inflammatory cytokines and reactive oxygen species accompanied by increased inducible NO synthase expression and decreased arginase activity, which resembles the M1 phenotype. Co-culture experiments further showed that CD36-positive but not CD36-deficient macrophages impair insulin signalling in adipocytes. The authors proposed a model of crosstalk between adipocytes and macrophages through CD36 to explain the protection against insulin resistance by CD36 deficiency (see Figure 6 in their published study⁸).

This study has shed new light on the role of CD36 in obesity-associated inflammation that links obesity to increased risk of atherosclerotic cardiovascular disease. It is of note that the contribution of CD36 to insulin resistance as well as to atherosclerosis in the literature is controversial. Both CD36-mediated contribution to and CD36-mediated protection from insulin resistance have been reported.^{9,11} The phenotype of CD36 deficiency seems also dependent on the type of diet. It has been reported that in mice, CD36 deficiency enhances insulin responsiveness on a high starch, low-fat diet, and it predisposes to insulin resistance induced by high fructose diet.¹² One should consider whether CD36 deficiency is indeed beneficial or detrimental for the whole organism even under conditions where a protective metabolic profile can be achieved. For example, CD36 deficiency may be detrimental for the heart because fatty acid uptake in cardiomyocytes, the major energy source for the heart, is impaired. Indeed, a link between CD36 deficiency and hypertrophic cardiomyopathy in humans has been proposed.¹³ Another important consideration is that if arginase activity were increased in vascular endothelial cells by CD36 deficiency, as shown in this study for adipose tissues or macrophages, the endothelial NO production would be expected to decrease,¹⁴ which could also have a

negative impact on insulin sensitivity and cardiovascular function, as endothelial dysfunction, i.e. decreased endothelial NO bioavailability, plays a role in insulin resistance, obesity, and atherosclerosis.¹⁴ There is a report showing that CD36 is required for eNOS activation by certain free fatty acids;¹⁵ however, whether these aspects could partly explain the controversial results of CD36 deficiency on insulin resistance and atherogenesis requires further investigation. In addition, interaction of CD36 polymorphisms with other genetic determinants could also affect the phenotypes.

Nevertheless, it appears that more recent studies support the beneficial effects of CD36 deficiency on inflammation and metabolic profile.⁹ More disease-associated endpoints such as heart function, endothelial function, and survival rate would be required to determine the final benefit of CD36 deficiency in obesity and atherosclerosis.

Conflict of interest: none declared.

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