

## CD40L-CD40 fuel ignites obesity

Esther Lutgens<sup>1,2</sup>; Marjorie Poggi<sup>2</sup>; Christian Weber<sup>1,2</sup>

<sup>1</sup>Institute for Cardiovascular Research (IMCAR), RWTH Aachen, Aachen, Germany; <sup>2</sup>Cardiovascular Research Institute Maastricht (CARIM), University of Maastricht, Maastricht, The Netherlands

Obesity and its metabolic complications like insulin resistance and type II diabetes with their continuously increasing morbidity and mortality represent a challenge for global health care (1). Yet, detailed mechanistic understanding of the pathogenesis of obesity and its metabolic complications as well as effective treatment options are still lacking.

Inflammation is considered to have a pivotal role in the development of metabolic diseases (2–5). Obese adipose tissue shows hallmarks of chronic inflammation, with the involvement of T-cell subsets like Th1 and Th2 and regulatory T-cells (4–6), macrophage subsets (classically and alternatively activated macrophages) (7), but also other immune cells like mast cells (8). These immune cells, their cell-cell interactions, and their interactions with adipocytes have been found to alter adipose tissue function, thereby affecting insulin resistance and obesity. However, the exact immune cells and molecules involved, as well as the interplay between the different cell-types are still unclear (9).

Especially T-cells have been proven to be important in the development of insulin resistance and obesity (4, 5). Recently, obesity has been associated with T-cell accumulation in adipose tissue, which apparently precedes the appearance of macrophages (3, 10). Surprisingly, *Rag*<sup>-/-</sup> mice, which lack T- and B-cells, gain more weight, exhibit

more visceral adiposity and have a more disturbed insulin and glucose tolerance when fed a high-fat diet than their wild type counterparts (4). Reconstitution of CD4<sup>+</sup> T-cells improved their glucose tolerance, insulin sensitivity and lessened weight gain. These counterintuitive results can be explained by the shift in T-cell subsets: CD4<sup>+</sup> reconstituted *Rag*<sup>-/-</sup> mice exhibited a strong increase in the Th2 subset (4). Along this line, other papers show a detrimental role for CD4<sup>+</sup> T-cells, especially the interferon  $\gamma$ -producing Th1 subset (6). These data suggest that CD4<sup>+</sup> cells of the Th2 phenotype gradually fail to withhold the ever-expanding pro-inflammatory Th1 population, leading to a progressively pro-inflammatory environment, thereby promoting insulin resistance and obesity.

In addition, Nishimura et al. showed a pivotal role for CD8<sup>+</sup> T-cells in macrophage recruitment and tissue inflammation in obesity, indicating that also CD8<sup>+</sup> T-cells have an essential role in initiation and propagation of adipose inflammation (3).

T-cell proliferation, activation and subsequent adequate function of antigen presenting cells (APCs) require co-stimulation (11, 12). One of the co-stimulatory molecule dyads recently associated with obesity are the tumour necrosis factor (TNF)- and TNF-receptor family members CD40L (CD154) and CD40 (13, 14). CD40L-CD40 interactions play a substantial, multifaceted role in immunity and inflammation, and are far more ubiquitously expressed than expected (15, 16). Not only are CD40L-CD40 interactions required for CD4<sup>+</sup> cell proliferation and activation, and for inducing proper APC-function, they also induce endothelial cell activation, subsequent monocyte migration, as well as macrophage- and smooth muscle cell activation, characterised by the production of chemokines, cytokines and proteolytic enzymes, and are therefore involved in a

plethora of chronic diseases including atherosclerosis (14, 17, 18). In chronic inflammatory diseases, CD154-CD40 interactions are able to polarise T cells towards the Th1 subset (18), which suggests a detrimental role for this dyad in obesity.

Soluble CD40L (sCD40L) serum levels are not only associated with cardiovascular disease (19), but are also increased in obese (20) and diabetic (21, 22) individuals, as well as in individuals with metabolic syndrome (23). Moreover, Poggi et al. (13) showed that CD40 mRNA levels in adipose tissue were correlated with body mass index (BMI). She also showed that CD40 was expressed not only in the stromal adipose fraction, which contains immune cells, but also on the adipocyte itself. Adipocyte CD40 was biologically active, since its stimulation was able to induce MAPK and nuclear factor  $\kappa$ B activation, as well as inflammatory (adipo)cytokine production, and decreased insulin-induced glucose transport. These effects were mediated by T-cell CD40L and involve direct T-cell-adipocyte contact (13).

In this issue of *Thrombosis and Haemostasis*, Missiou et al. further highlight a role for the CD40-CD40L dyad in obesity (24). The authors confirm the functional expression of CD40 on adipocytes and stress its function in adipogenesis. The authors prove a functional relevance of the CD40-induced adipokines by applying the supernatant of CD40 activated adipocytes to endothelial cells, which subsequently express the activation marker ICAM-1. In addition, Missiou et al. show that stimulation of adipocytes with CD40L resulted in adipogenesis of pre-adipocytes that also contain CD40, into adipocytes, thereby accelerating obesity, and also confirmed the increased presence of sCD40L in obese individuals.

Based on these studies, controlling CD40 signalling in obesity portends an important therapeutic strategy for metabolic disease. However, until now, data on

### Correspondence to:

Esther Lutgens  
Institute for Molecular Cardiovascular Research (IMCAR)  
Pauwelsstraße 30  
52074 Aachen  
Germany  
Tel.: +49 241 808 0580, Fax: +49 241 808 2716  
E-mail: elutgens@ukaachen.de

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CD40L-CD40 signalling related to metabolic diseases are confined to correlative studies and *in vitro* experiments. Therefore, additional studies on the effect of CD40L-CD40 interactions on metabolic disease *in vivo* are required. Since CD40 is ubiquitously expressed, inhibition of CD40L-CD40 interactions in humans will not be without risk of immune-suppression and efforts are needed to unravel downstream 'obesity' associated CD40L-CD40 pathways for clinically applicable, CD40 targeting drugs for obesity.

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