The same relationship has not been described in more obese individuals where the predictive ability and pathophysiological importance of fat cell size may differ.

## Resistin Receptor Mediates Inflammatory Actions

Written by **Brian Hoyle**

Hyo-Soo Kim, MD, PhD, Seoul National University Hospital, Seoul, South Korea, reported on the cloning of the receptor for resistin, and its involvement in chronic inflammation and cardiometabolic disease.

Cardiometabolic disease is the collective term used to describe events that occur due to cardiovascular disease, diabetes, and obesity. Proinflammatory and proatherogenic pathways are also related to obesity and can contribute to insulin resistance and atherosclerosis. Chronic lipid loading and cellular stress may also lead to enlargement of adipocytes. The hypertrophic cells respond to inflammation by becoming insulin resistant, driving the metabolic syndrome.

One of the implicated molecules is resistin, a cytokine that is secreted from cells such as adipocytes in mice and human monocytes and macrophages. Resistin increases the level of low-density lipoprotein cholesterol leading to the development of atherosclerosis. Increased resistin production has also been linked with obesity in a mouse model [Steppan CM et al. *Nature* 2001]. In humans, elevated resistin is associated with chronic inflammation [Kaser S et al. *Biochem Biophys Res Commun* 2003; Silswal N et al. *Biochem Biophys Res Commun* 2005], vascular inflammation [Jung HS et al. *Cardiovasc Res* 2006] and arterial atherosclerosis. Yet, the cell receptor has remained unknown and has not been described.

In order to characterize the resistin receptor, a fusion protein was constructed that contained human resistin with mouse Fc, allowing expression of resistin in transfected HEK cells. Used as a ligand, the human resistin bound to a 55 kDa protein in human monocytes. The protein was identified as adenylyl cyclase-associated protein 1 (CAP1). Immunofluorescence staining showed the membrane localization of CAP1 in THP-1 human monocytes. Fluorescence-activated cell sorting revealed increased CAP1 in monocytes exposed to resistin. Finally, immunofluorescent antibodies to CAP1 and resistin were found to be co-localized in the monocyte membrane.

The physical association between CAP1 and resistin was determined conclusively using a variety of experimental approaches. The site of resistin binding in the 3 functional domains of CAP1 was determined using deletion mutants lacking the adenylyl cyclase-binding domain, proline-rich SH3 binding domain, and actin-binding domain. The proline-rich domain was implicated as the active site.

THP-1 monocytes treated with resistin displayed a time-dependent increase in the levels of cAMP, consistent with the known role of CAP1 in the yeast adenylyl cyclase complex. Resistin increased the production of protein kinase A (PKA) and nuclear factor-kappa B (NF-κB) in monocytes, and upregulated the protein level of integrin β1 and the mRNA expression of the cytokines interleukin-6, -1β, and tumor necrosis factor-alpha. All responses could be abolished by a small interfering RNA that targeted CAP1.

These results support a scenario involving crosstalk between the monocyte cAMP, PKA signaling and NF-κB pathways, in which CAP1 acts as a receptor for resistin and regulates the resistin-induced activity of monocytes.

In support of this hypothesis, inhibition of PKA activity *in vitro* abolished resistin-induced activation of NF-κB and expression of inflammatory cytokines. *In vivo*, expression of human resistin in mice demonstrated that CAP1 overexpression significantly enhanced monocyte migration to resistin, macrophage infiltration, and expression of cytokines. All were abrogated by curtailed CAP1 expression. Further work is needed to define the cellular pathways associated with this receptor; however, CAP1 may become a novel target in the treatment of inflammatory diseases such as atherosclerosis.

## Storage of Dietary Fatty Acids in Type 2 Diabetes

Written by **Mary Mosley**

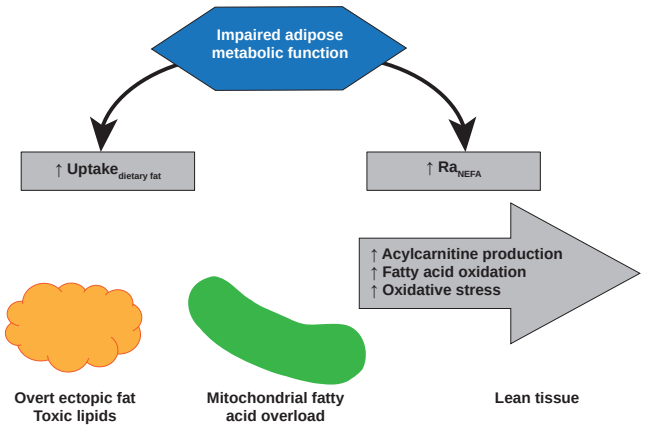
White adipose tissue is thought to be critical in controlling the amount of fat in lean tissue because it takes up excess dietary fat to prevent potentially toxic dietary fatty acids from being metabolized by lean tissue. Dietary fatty acid spillover drives, at least in part, regulation of ectopic fat, which plays a role in insulin resistance and metabolic abnormalities related to the metabolic syndrome. At least 4 different mechanisms are thought to contribute to the deposition of ectopic fat: increased dietary fat, increase uptake of nonesterified fatty acids from white adipose tissue lipolysis, impaired fatty acid oxidation, and increased lipogenesis (Figure 1).

André C. Carpentier, MD, Université de Sherbrooke, Sherbrooke, Québec, Canada, reviewed research to understand abnormal organ-specific postprandial storage of dietary fatty acids, and the impact of lifestyle intervention to reduce this storage.

Using a novel approach with whole body positron emission tomography (PET), computed tomography (CT), and a fatty acid tracer (18F fluoro-6-thia-heptadecanoic acid [FTHA]), Prof. Carpentier and colleagues showed most dietary fatty acid uptake occurred 4 to 6 hours after eating. Dietary fatty acids first appear in the thoracic duct, and the

greatest uptake per tissue mass was found (in order) in the liver, heart, kidneys, visceral adipose tissue, white adipose tissue, and resting skeletal muscles [Labbe SM. *Am J Physiol Endocrinol Metab* 2011].

Figure 1. Mechanisms for Ectopic Fat Deposition




Reproduced with permission from AC Carpentier, MD.

Of the 9 subjects included in this study, those with impaired glucose tolerance (IGT), compared with those without IGT, were older (p<0.001), had higher body mass index (BMI; p<0.02) and waist circumference (p=0.008), more insulin resistance (p<0.001), fatty liver (p=0.10), and high triglycerides (TG; not significant). Postprandial metabolism was abnormal in patients with IGT. Persons with IGT had significantly less dietary fatty acid uptake in the anterior abdominal subcutaneous tissue (p=0.05). Predictors of less dietary fatty acid uptake were waist circumference, fasting TG, postprandial glucose area under the curve (AUC), and nonesterified fatty acid AUC (likely related to nonesterified fatty acid spillover associated with impaired white adipose tissue and dietary fatty acid uptake). In subjects with prediabetes, dietary fatty acid uptake was reduced in visceral and white adipose tissue. Dietary fatty acid spillover was clearly associated with impaired dietary fatty acid uptake by visceral adipose tissue.

A striking and consistent finding was a significant increase in dietary fatty acids. Uptake of dietary fatty acid by the myocardium appeared to be maintained over time in persons with IGT. However, there was no difference in liver uptake of dietary fatty acids in persons with and without IGT. Thus, Prof. Carpentier concluded, it does not appear that dietary fat is distributed to a greater degree in the liver in diabetes and does not seem to contribute to its ectopic fat deposition. The best predictors of increased dietary fatty acid uptake by the myocardium were IGT and insulin resistance, whereas there was an inverse relation between fasting TG and liver dietary fatty acid uptake.

To determine the effect of weight loss on organ-specific dietary fatty acid storage, persons with IGT in the imaging study were enrolled in a 1-year lifestyle intervention. Modest reductions were achieved in weight (-3.7 kg), BMI (-1.1 kg/m$^2$), and waist circumference (-5.0 cm). These reductions were associated with reductions in insulin resistance and postprandial insulin excursion, but IGT was not altered.

Subsequent imaging with FTHA showed that nonesterified fatty acids were significantly altered and TG were slightly reduced. Notably, dietary fatty acid uptake was decreased in the myocardium and increased in visceral adipose after weight loss. Prof. Carpentier hypothesized that weight loss is associated with at least partial normalization of impaired fat partitioning seen in IGT. In contrast, a 7-day hypocaloric diet (-500 kcal, saturated fats <7% of total calories) increased dietary fatty acid partitioning to the myocardium, but did not alter partitioning to the liver, white adipose tissue, or visceral adipose tissue.

Although there is clear evidence that impaired dietary fatty acid storage in adipose tissue is associated with risk of developing cardiometabolic disorders (high TG and increased waist circumference), it is less clear whether this association is mechanistically related to impaired dietary fatty acid storage in other organs. Thus, the local factors regulating cardiac metabolism of dietary fat require further investigation.

## Inflammation, Adipose Tissue, and Cardiometabolic Risk

Written by **Mary Mosley**

Inflammation that develops in obese persons is thought to play an important role in the development of type 2 diabetes. Epidemiological and clinical data have shown that low levels of omega-3 polyunsaturated fat (PUFA) consumption is related to cardiovascular disease, and that a higher ratio of omega-6 PUFA to omega-3 PUFA consumption increases this risk. André Marette, PhD, Université Laval, Québec City, Québec, Canada, reviewed research from his group that explored whether omega-3 is a link between obesity and inflammation.

A mouse model (Fat-1) was developed in which inflammatory markers were significantly reduced, resulting in improvements in fasting insulin and insulin resistance (IR), and partial improvement in glucose tolerance [Kang JX et al. *Nature* 2004]. In addition, there was greater production of PD1, a molecule that decreases levels of inflammation in muscle, liver, and adipose tissue, and an improvement in IR when Fat-1 mice were fed a diet high in omega-3. This increase in PD1, 1 of several anti-inflammatory mediators, is thought to be an important mechanism by which omega-3