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Editorial on Sramkova et al., “Apolipoprotein M: a novel adipokine decreasing with obesity and upregulated by calorie restriction”

Chih-Wei Ko, Jie Qu, and Patrick Tso

Department of Pathology and Laboratory Medicine, University of Cincinnati, Cincinnati, OH

In this issue of the *Journal*, Sramkova et al. present novel data from 5 separate clinical trials as well as an in vitro study that uses human multipotent adipose-derived stem cell (hMADS) adipocytes (1). The goal of this study was to determine the relation between apolipoprotein M (apo M) and its participation in metabolic syndrome and insulin sensitivity. In an appealing complementary ex vivo study, the authors examined the regulation of apo M expression and secretion by adipose tissue during caloric restriction and resulting weight loss. This study is significant for the following reasons: 1) most studies on apo M have been conducted in the liver and kidney (2–4), but we know very little of apo M function in human adipose tissue; 2) this is a helpful example of how interdisciplinary studies can lead to a major advancement in our understanding of the physiology and function of human adipose tissue apo M; and 3) as with other outstanding research, the completion of this study not only greatly enhances our knowledge of human adipose tissue apo M production and secretion, but also stimulates us to ask additional questions, such as how apo M affects insulin sensitivity and what the relation and interaction are between apo M production and secretion by the liver, kidney, and adipose tissue.

Based on the use of a combination of microarray and proteomic analyses of the conditioned media from adipocytes and stromal vascular cells isolated from human adipose tissue, the authors identified apo M as a novel adipokine. The investigators then further validated apo M secretion from adipose tissue by detecting differential concentrations of apo M between arterial and venous blood in the subcutaneous abdominal adipose tissue. These observations provide the first evidence that apo M is produced and secreted by a tissue other than the liver and kidney. Although the liver produces significantly more apo M than the adipose tissue, the investigators present compelling evidence demonstrating that apo M expression in adipose tissue is inversely associated with obesity and its comorbidities such as metabolic syndrome and type 2 diabetes.

The authors then attempted to understand why apo M expression in adipose tissue is decreased with the progression of obesity and insulin resistance. They first reported that a proinflammatory cytokine, TNF α , downregulated apo M expression in hMADS adipocytes. Also, in a study involving both obese men and women in one of the cohorts (E), the investigators

found a negative correlation between apo M expression in adipose tissue and the level of plasma C-reactive protein. Treating the hMADS adipocytes with the insulin sensitizer rosiglitazone, on the other hand, increased apo M expression in adipocytes. Therefore, they suggested that apo M is negatively affected by obesity-associated inflammation, in contrast to most adipokines.

Diet restriction and weight loss are effective approaches to combat metabolic syndrome and insulin sensitivity in obese humans (5). Thus, the investigators reduced the food intake and caused weight loss in the obese subjects in their clinical studies. Contrary to most adipokines (6, 7), including adiponectin (8), the investigators found that the loss of fat mass in adipose tissue induced by caloric restriction increased the expression and secretion of apo M by the adipose tissue; however, this change apparently is not correlated with the changes in biochemical parameters other than plasma C-reactive protein.

Another important facet of the current study concerns the role of apo M as a lipocalin that carries a number of anti-inflammatory lipids such as sphingosine-1-phosphate (S1P) (2, 9, 10). S1P is a signaling sphingolipid, also known as lysosphingolipid, which is a bioactive lipid mediator (11). It has been demonstrated in other studies that the binding of apo M and S1P has important implications in atherosclerosis (9), glucose tolerance (12), and insulin sensitivity (13). However, whether these effects are due to apo M itself or S1P, or other bioactive molecules carried by apo M, remains an important question to be studied. Furthermore, the site and mechanism of apo M actions (either acting locally or targeting a remote site as an endocrine molecule) are still largely unanswered.

In summary, this novel paper reports the production of apo M by adipocytes and suggests how apo M may play a role in metabolism and insulin sensitivity in obesity. Essential findings

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Address correspondence to PT (e-mail: tsopp@ucmail.uc.edu).

Abbreviations used: apo M, apolipoprotein M; hMADS, human multipotent adipose-derived stem cell; S1P, sphingosine-1-phosphate.

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of this paper include the following: 1) the first demonstration of the production and secretion of apo M by adipose tissue; 2) apo M expression in adipose tissue is reduced in obesity; and 3) apo M appears to be a marker of healthy phenotype by serving as a beneficial adipokine. Although this study was well conducted and most of the conclusions are supported by the experimental data presented, it may be to some extent premature to propose apo M as a marker of healthy phenotype when we do not have a thorough understanding of the site and mechanism of apo M action. Specifically, relative to its predominant source from the liver, the contribution of apo M from adipose tissue to the circulating concentration may undermine the role of adipose tissue apo M as a marker for healthy phenotypes. The field of adipokine research moves steadily forward.

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