Malin C. Levin and Jan Borén

The Extracellular Matrix Protein MAGP1 Is a Key Regulator of Adipose Tissue Remodeling During Obesity

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COMMENTARY

In response to increases in fat mass, as seen in obesity, the adipose tissue undergoes distinct structural remodeling (1). Recent attention has focused on the importance of the extracellular matrix (ECM) in remodeling of adipose tissue during the development of obesity. The ECM not only provides structural support to the surrounding cells, but also plays a crucial role in the biological function of different organs. Components of the ECM include structural proteins, such as collagen and fibrillins, and various classes of adhesion proteins, such as fibronectin and proteoglycan.

Fibrillins are large proteins that form extracellular microfibril suprastructures ubiquitously found in elastic and nonelastic tissues. Constitutive components of the microfibrils also include the microfibril-associated glycoproteins (MAGPs) 1 and 2 (2,3). Microfibrils appear to have dual roles: They confer mechanical stability and limited elasticity to tissues and modulate the activity of members of the transforming growth factor-β (TGF-β) superfamily (4–6). The importance of microfibrils in regulating TGF-β activity is illustrated by the phenotype associated with fibrillin-1 mutations (e.g., Marfan syndrome), namely excess TGF-β activity resulting from an inability to sequester latent TGF-β in the ECM (7).

In obesity, it is believed that altered expression of ECM components may influence immune cell recruitment and activation, leading to increased inflammation in the adipose tissue. However, the exact mechanisms for these processes are still largely unknown. In this issue, Craft et al. (8) investigate how ECM components mediate metabolic pathways that are associated with obesity and identify MAGP1 as a key regulator. The MAGPs can bind the active form of TGF-β and thereby regulate its activity (4–6), and mice deficient in MAGP1 have a phenotype consistent with increased TGF-β activity (9). MAGP1-deficient mice have also previously been reported to display increased adiposity (9). The purpose of the study by Craft et al. therefore was to investigate if this increased adiposity and altered metabolic function results from increased TGF-β activity. Using MAGP1-deficient (*Mfap2*$^{-/-}$) mice, Craft et al. demonstrate that MAGP1 has the capacity to regulate growth factor availability, which is important for maintaining normal metabolic function, and provide further support for the role of TGF-β in the etiology of obesity-associated metabolic disease (Fig. 1). The results also highlight the contribution that accessory proteins, such as MAGP1, provide to overall microfibril function and tissue homeostasis.

The relationship between ECM components, adipocyte size, and inflammation has been investigated previously. Khan et al. (10) recently explored the role of collagen VI in metabolic dysregulation. They demonstrated that weakening of the adipose tissue ECM by genetic disruption of collagen VI resulted in considerable improvement of the metabolic phenotype in the context of a high-fat diet and in mice with the *ob/ob* mutation. In addition, a study by Vaittinen et al. (11) showed that the microfibrillar-associated protein 5 (MFAP5) is highly expressed in human adipose tissue and is correlated with markers of insulin resistance, suggesting that MFAP5 is related to ECM remodeling during the development of obesity. Kolehmainen et al. (12) recently studied the effect of weight loss on gene expression in the adipose tissue of obese individuals with impaired metabolic function and found that genes regulating the ECM and cell death showed a strong downregulation after long-term weight reduction.

Sahlgrenska Center for Cardiovascular and Metabolic Research, Wallenberg Laboratory, Sahlgrenska University Hospital, Gothenburg, Sweden; and Institute of Medicine, Department of Molecular and Clinical Medicine, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

Corresponding author: Jan Borén, jan.boren@wlab.gu.se.

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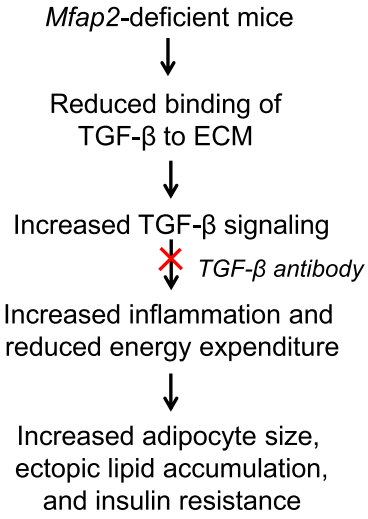

Figure 1—Lack of MAGP1 in *Mfap2*-deficient mice results in increased TGF-β signaling and obesity-associated metabolic disease. Treatment with a neutralizing TGF-β antibody enabled *Mfap2*-deficient mice to maintain normal metabolic function.

Several questions remain to be answered. Craft et al. show that MAGP1 mRNA expression is markedly increased in adipose tissue from obese humans. Why is this and what does it mean? In MAGP1-deficient mice, where MAGP1 expression is abolished, the mice display increased adiposity, suggesting that higher levels of MAGP1 are protective. It would be interesting to investigate if increased MAGP1 mRNA expression in obese human adipose tissue correlates with increased MAGP1 protein levels, or if increased mRNA levels are only compensatory. Would it be beneficial to induce expression of MAGP1 in obese human adipose tissue and would that result in a normalization of TGF-β activity? Furthermore, in contrast to proteins such as MAGP1 that inhibit TGF-β activity, other molecules are involved in releasing TGF-β from the ECM (13,14). How are these molecules regulated in adipose tissue and what are their roles in metabolic diseases?

In conclusion, the study by Craft et al. (8) highlights the fact that the ECM protein MAGP1 is extremely important in modulating adipocyte physiology. Further studies will be required to define the molecular mechanisms through which the ECM environment regulates adipocyte remodeling. It is likely that particular constituents of the ECM environment may provide possible targets for pharmacological intervention for the treatment of metabolic disorders.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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