MAGP1, the extracellular matrix, and metabolism

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Adipose tissue and the extracellular matrix were once considered passive players in regulating physiological processes. Now, both entities are acknowledged for their capacity to engage signal transduction pathways, and for their involvement in maintaining normal tissue homeostasis. We recently published a series of studies that identified a novel mechanism whereby an extracellular matrix molecule, MAGP1 (microfibril associated glycoprotein 1), can regulate energy metabolism in adipose tissue. MAGP1 is a component of extracellular microfibrils and plays a support role in maintaining thermoregulation by indirectly regulating expression of the thermogenic uncoupling proteins (UCPs). The focus of this commentary is to draw attention to the role of the extracellular matrix in regulating the bioavailability of signaling molecules, like transforming growth factor β (TGFβ), and exemplify that a better understanding of the extracellular matrix’s biological properties could unveil a new source of therapeutic targets for metabolic diseases.

The extracellular matrix (ECM) of adipose tissue is a milieu of basement membrane components, fibrillar and non-fibrillar collagens, fibronectin, SPARC, microfibrils, and numerous other proteins. Once considered an inert structure, the ECM is now considered a dynamic regulator of cellular processes. The ECM influences cellular processes through 2 broad mechanisms: mechanical force and biochemical cues.

ECM protein composition and cross-linking determines the physical properties (i.e. rigidity) of the ECM network, which in turn dictates the constraint on adipocyte expansion. When metabolic conditions change, such as weight gain or loss, the ECM must remodel to accommodate the change in adipocyte size and number. Inactivation of adipose-associated ECM genes in mice has demonstrated that changing the composition of the ECM in ways that alter its physical properties has functional consequences for adipose integrity. For example, overexpression of fibrillar collagens (mainly types I, III, and V), or preventing the remodeling of fibrillar collagens by inactivating collagen-degrading proteases, leads to a stiffer, fibrotic matrix that restricts tissue function. In contrast, decreasing ECM rigidity by reducing collagen I content (as occurs in the SPARC-null mouse) or by subtracting collagen VI from the mix, results in a permissive environment that supports adipose tissue expansion.

The ECM can interact with cells by directly engaging cell surface receptors or by regulating the delivery of signaling molecules to cells. Microfibrils are an example of ECM structures that do both: they provide mechanical stability to tissues and regulate the bioavailability of several growth factors. The microfibril core consists of polymers of fibrillin proteins. Fibrillin polymers then associate with several additional “accessory” proteins that confer functionality to the fiber. For example, fibrillin-1 interacts with latent TGFβ binding proteins (LTBPs) to covalently anchor the large latent complex (LLC) of TGFβ into the ECM where it is sequestered away from the cell. Loss of fibrillin-LTBPs binding increases free “active” TGFβ levels, causes aberrant TGFβ signaling, and is pathologic.

MAGP1 and Growth Factor Regulation

We recently demonstrated that the ECM, and microfibrils in particular,
there is an increase in basal TGFβ activity (determined by smad-2/-3 phosphorylation), indicating that MAGP1 supports sequestration of active TGFβ in vivo (Fig. 1B).

MAGP1’s ability to influence TGFβ signaling is particularly interesting in the context of obesity. Body mass index (BMI) positively correlates with serum and adipose TGFβ-1 concentration, and elevated TGFβ-1 is a risk factor for type-2 diabetes. TGFβ drives inflammation and fibrosis, and supports adipocyte expansion by reducing energy utilization. Specifically, TGFβ interferes with PGC-1α (peroxisome proliferative activated receptor-γ coactivator 1α) and UCP-1 (uncoupling protein-1) expression in brown and beige adipose tissue.23-26 MAGP1 transcript can be detected in white, “beige,” and brown adipose tissue depots in mice.14 Adipose tissue fibroblasts are a major source of MAGP1 transcript (unpublished data), and stromal cells isolated from adipose tissue can assemble MAGP1 into a 3-dimensional extracellular matrix (Fig. 2). Thus, MAGP1 is appropriately positioned to regulate TGFβ bioavailability in adipose tissue.

Several independent studies have associated obesity traits in humans to a locus on chromosome 1p36 that includes the gene for MAGP1, MFAP2, and MFAP3, and we have since discovered that MAGP1 expression is altered in obese humans and mice.14 While additional studies are necessary to confirm a role for MAGP1 in human energy metabolism, we have demonstrated that MAGP1’s regulation of TGFβ influences the pathogenesis of obesity and metabolic syndrome in mice. As described in Craft et al.,14 MAGP1-deficient mice display increased adiposity that is associated with impaired glucose tolerance and reduced insulin sensitivity, even on standard chow diet. Increased adiposity and insulin resistance in MAGP1-deficient mice are preceded by reduced energy expenditure stemming from disruption of PGC-1α and UCP1 transcriptional regulation (thermogenesis). From these studies, we concluded that in MAGP1-deficient mice, reduced mitochondrial uncoupling leads to abnormal lipid accumulation, resulting in an overall increase in adiposity and eventually insulin resistance. In support of a MAGP1-mediated regulation of TGFβ in adipose tissue, we demonstrated aberrant activation of smad-2/3 (TGFβ’s downstream target), and increased fibrosis and inflammation. Importantly, blocking TGFβ signaling in MAGP1-deficient mice using TGFβ neutralizing antibody treatment increased core body temperature and prevented excess adiposity.

**MAGP1 and BMP Regulation**

Not discussed in Craft et al.,14 is the functional interaction between MAGP1 and bone morphogenetic proteins (BMPs). While TGFβ-1 appears to be a negative regulator of thermogenesis,23 BMP-7 has a positive regulatory role.20 Solid phase binding assays and surface plasmon resonance have demonstrated

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Figure 1. MAGP1 structure and hypothesized function. (A) Protein domain composition of MAGP1. (B) Schematic of MAGP1s proposed method of action. Fibrillin-1 self-associates to form the microfibril backbone. The N-terminus of fibrillin-1 contains a binding site for TGFβs large latent complex (LLC). This interaction allows fibrillin-rich microfibrils to sequester inactive TGFβ in the ECM. Fibrillin-1 also has 2 binding sites for MAGP1. We hypothesize that MAGP1 functions to prevent aberrant TGFβ signaling by capturing liberated-active TGFβ.
that MAGP1 interacts with both TGFβ-1 and BMP-7 with high affinity. Interestingly, TGFβ-1 has much faster rates of association and dissociation relative to BMP-7, which may have functional consequences on how these growth factors signal once released from the cell. In Craft et al., we demonstrate that treating MAGP1-deficient mice with a TGFβ neutralizing antibody significantly improves their core body temperature, however, MAGP1-knockout mouse temperatures did not completely revert to WT values. It is possible that thermoregulation requires a balance of BMP(-7) and TGFβ (-1) signaling, and neutralizing TGFβ in MAGP1-deficient mice improves this balance but does not completely restore it.

Marfan Syndrome

In humans, clinical correlations exist between microfibrils and energy metabolism. Mutations in fibrillin-1 give rise to the autosomal dominant disease Marfan syndrome. In addition to cardiovascular, ocular and skeletal abnormalities, a large percentage of individuals with Marfan syndrome have difficulty storing fat. Marfan syndrome is associated with elevated TGFβ signaling. TGFβ supports adipocyte hypertrophy and impairs energy expenditure by inhibiting thermogenesis. Therefore, it is interesting that individuals with Marfan syndrome have reduced fat mass when our current understanding of fibrillin-1 would predict these individuals to be predisposed to obesity and diabetes (similar to MAGP1-deficient mice). It is also interesting that mutations in fibrillin-1 and MAGP1, proteins that comprise the same extracellular fiber, can result in such contrasting phenotypes.

To understand this contradiction, it is necessary to remember the roles that fibrillin-1 and MAGP1 play in microfibril biology. MAGP1 is not a structural protein of the microfibril but a modifier of fibrillin function. Its deletion leaves the core microfibril intact, but disrupts sequestration of TGFβ by the microfibril. Fibrillin-1 mutations disrupt the assembly of microfibrils resulting in an overall decrease in microfibril number. Reduced microfibril number translates into a change in the relative composition, and therefore mechanical properties, of the extracellular milieu. Reducing the microfibril core infrastructure will also disrupt the localization of all the microfibril accessory proteins (MAGPs, LTBPs, emilins, fibulins, etc.). Reduced adiposity associated with Marfan syndrome could therefore be the consequence of altered ECM mechanics and/or disruption of another signaling molecule normally anchored to the microfibril in the ECM. Continued characterization of fibrillin and fibrillin-binding proteins will likely provide additional insight to the mechanical and biochemical pathways regulating energy storage.

**MAGP1, a Therapeutic Target for Obesity?**

The extracellular matrix has been considered an obstacle to drug delivery rather than a therapeutic target. However, nutrients, hormones and growth factors must first navigate the ECM before reaching their target cell. Many ECM proteins can either facilitate or restrict these agents’ access to the cell. This “gatekeeper” function allows the ECM to regulate key cellular processes.

The findings described in Craft et al. are of significance because the ECM has been largely unexplored for use in metabolic disease therapies, and we now have evidence that MAGP1 regulates adipocyte “browning,” a process that increases the thermogenic potential of white adipocytes. White adipocyte “browning” increases energy expenditure by converting lipid-storing white adipocytes to lipid-burning brown-like (or beige) adipocytes, a process involving PGC-1α and UCP-1. Independent rodent studies have demonstrated that impaired thermogenesis is associated with increased adiposity and diabetes, and stimulating thermogenesis is protective against diet-induced obesity and diabetes. Adult humans have brown adipose tissue (BAT); however, it is significantly less than white adipose tissue (WAT) depots. Consequently, stimulating thermogenesis in the white adipose tissue represents a therapeutic approach for the treatment of obesity.

Subcutaneous WAT (scWAT) in mice is enriched with adipocytes that have the capacity to store lipids and the potential to dissipate energy in the form of heat. MAGP1 transcript expression was significantly higher in scWAT, relative to BAT, and impaired transcriptional regulation of PGC-1α/UCP-1 appears worse in the
scWAT of MAGP1-deficient mice.14 These findings suggest that in rodents MAGP1s primary role may be in supporting mitochondrial uncoupling in beige adipocytes (versus brown adipocytes). If the presence of MAGP1 in adipose tissue ECM creates a microenvironment that fosters energy expenditure,14 then perhaps MAGP1 or MAGP1-derived biologicals can be used therapeutically to reduce energy storage. MAGP1 is a favorable therapeutic target due to its localization around cells, rather than inside; this feature allows MAGP1 to restrict (or facilitate) signaling molecules’ access to cell surface receptors rather than regulate specific members of the intracellular signaling cascade. Further, MAGP1s growth factor binding capacity is highly specific. Surface plasmon resonance bindings studies indicate that MAGP1 has selective affinity for some, but not all, members of the TGFβ superfamily. Further, several growth factors outside the TGFβ superfamily have also been tested and shown to not interact with MAGP1.19 In Werneck et al.,38 infusion of recombinant MAGP1 improved thrombocytic occlusion in mice following vessel wall injury, indicating our recombinant MAGP1 has biological activity. We are now conducting experiments to determine whether MAGP1 or a MAGP1-derived biologicals can be used to enhance energy utilization in adipose tissue.

It is important to highlight that MAGP1 is not the only protein regulating the bioavailability of signaling molecules outside the cell. Whether the signaling molecule is a paracrine or endocrine factor, once it is secreted from the originating cell it must navigate the extracellular milieu before reaching its target cell. Matrix-associated proteins interact with these signaling molecules to facilitate their presentation to cells or sequester them away from the cell to prevent aberrant signal transduction. Despite our vast knowledge of the hormones, growth factors, chemokines, adipokines, etc., these molecules, that influence energy metabolism, and often the intracellular signal transduction pathways they target, little attention has been paid to what controls the capacity of these molecules to initiate signal transduction. To truly understand how any physiological process is regulated, we must invest our energy into discovering how the extracellular matrix puppeteers signaling molecules.

**Summary**

The extracellular matrix is a critical component of all tissues. The goal of this article was to highlight the influence that the extracellular matrix, in general, and microfibrils, in particular, have on energy metabolism. By drawing attention to the ECM’s capacity to interact with signal transduction pathways important to metabolic diseases like obesity and diabetes, we hope to spur interest in extracellular matrix molecules as a resource for drug discovery.

Further, by demonstrating that a microfibril accessory protein (MAGP1) can influence energy metabolism and growth factor signaling, we hope to inspire research that addresses how fibrillin’s interaction with all accessory proteins modifies the fiber’s function, and whether phenotypes associated with Marfan syndrome are the direct consequence of fibrillin mutation alone or the consequence of loss of fibrillin’s interaction with another microfibril protein.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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