Increased Fibro-Adipogenic Progenitors and Intramyocellular Lipid Accumulation in Obesity-Related Skeletal Muscle Dysfunction

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COMMENTARY

The obesity epidemic is one of the most serious public health problems in the world. Today, about two out of three adults (69%) are overweight or obese in the U.S. In healthy persons, peripheral subcutaneous fat tissue makes up 80% of total body fat (1), and another 10% of adipose tissue is present as either abdominal visceral fat tissue or that in and around organs, including the vasculature, heart, and skeletal muscle (2). Skeletal muscle is the primary site of glucose uptake and is responsible for approximately 80% of glucose uptake in the postprandial state in healthy individuals (3). Skeletal muscle is also an important organ in the storage and release of lipids in response to physiological changes in fatty acid supply and demand (4). Once fat tissue mass expands, excess lipids form small lipid droplets and are stored in nonadipose tissues such as skeletal muscle (4). Therefore, excess lipids increase the total intramyocellular (IMC) lipid content and ectopic fat storage in skeletal muscle, resulting in skeletal muscle lipotoxicity, insulin resistance, and dysfunction (Fig. 1).

The deposition of excess IMC lipids is regarded as an important abnormality in overweight and obese individuals (4). Excess plasma lipids with resultant lipid overflow augments the accumulation of IMC lipid and fat infiltration into skeletal muscle (5). Further, fibro-adipogenic progenitors (FAPs), a population of mesenchymal interstitial cells, can differentiate to adipocytes and contribute to increased IMC fat accumulation (6) (Fig. 1). In skeletal muscle, myofibers are multinucleated and surrounded by satellite cells and multipotential cells (FAPs), which are positive for stem cell antigen 1 and platelet-derived growth factor receptor α but lack paired box protein Pax-7 expression (7). While FAPs readily differentiate into adipocytes under various conditions such as obesity, satellite

cells are generally resistant to adipogenic differentiation (7). Increased IMC lipid content in skeletal muscle is associated with insulin resistance, inflammation, and functional impairment. For example, increase in the sphingolipid ceramide induces release of inflammatory cytokines and promotes insulin resistance in skeletal muscle through up-regulation of nuclear factor-κB activity (8). Elevated muscle diacylglycerol levels are associated with increases in the θ form of protein kinase C, which promotes phosphorylation of insulin receptor substrate 1 at serine 1101, thereby inhibiting insulin metabolic signaling in skeletal muscle tissue (9). Clinical studies further support the notion that increased IMC lipid content may contribute to defective glucose uptake in skeletal muscle and thus represents an early abnormality in the pathogenesis of insulin resistance and type 2 diabetes (10).

The increased insulin resistance promoted by fatty infiltration in skeletal muscle is linked to muscle dysfunction and deconditioning in many diseases, including myopathies, type 2 diabetes, sarcopenia, and chronic obstructive pulmonary disease (11). To this point, the diaphragm is the primary skeletal muscle for supporting gas exchange and normal respiratory function. Recent data indicate that diaphragm skeletal muscle wasting is involved in inspiration dysfunction in the Zucker diabetic fatty rat (12). In their study in this issue of *Diabetes*, Buras et al. (13) further investigated whether fibro-adipogenic diaphragm remodeling occurs in obesity-associated respiratory impairment and whether FAPs contribute to skeletal muscle dysfunction in a clinically relevant mouse model of high-fat diet–induced obesity and associated respiratory dysfunction. This chronic high-fat feeding induced complex temporal responses, with impairment of skeletal muscle contractile function that paralleled

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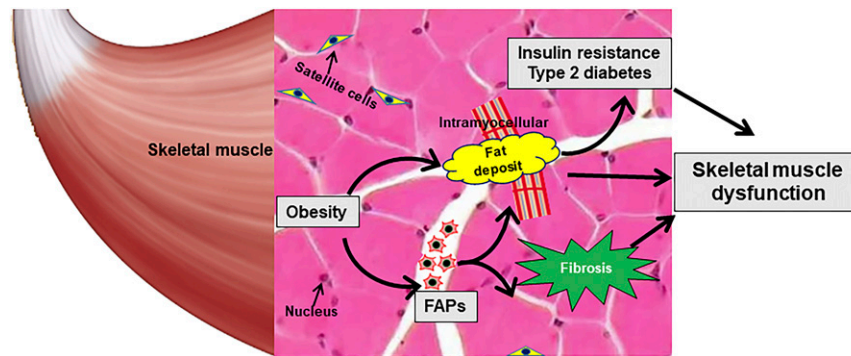
Figure 1—Proposed mechanisms of increased FAPs and intramyocellular lipid accumulation in diet-induced muscle adiposity, fibrosis, and remodeling as well as skeletal muscle dysfunction.

progressive adipose tissue expansion and collagen deposition within the diaphragm. This basic research highlights the increasing risk of obesity-associated respiratory dysfunction observed clinically with higher BMI. Meanwhile, 6 months of high-fat feeding also induced intradiaphragmatic FAP proliferation, increased adipocytes, and type I collagen-depositing fibroblasts. Furthermore, thrombospondin 1 (THBS1), a circulating adipokine increased in obesity, induced FAP proliferation. Thus, increased FAPs may represent a novel driver in abnormal diaphragm remodeling and skeletal muscle dysfunction in obesity-related respiratory dysfunction.

The study by Buras et al. (13) provides new insights into the role of increased FAPs in obesity-induced fibro-adipogenic diaphragm remodeling and respiratory dysfunction. This is translationally relevant as therapeutic targeting of FAPs has a potential application for prevention of diaphragm skeletal muscle dysfunction and maintenance of normal diaphragm structure and respiratory function. These data (13) highlight a role for FAP proliferation in the development of intradiaphragmatic adiposity, fibrosis, and associated diaphragm contractile compromise in a translational obese mouse model (Fig. 1). Indeed, FAPs have multiple remarkable properties. In the condition of skeletal muscle injury, FAPs produce trophic factors to induce myoblast differentiation and skeletal muscle regeneration. Indeed, if the efficiency of skeletal muscle regeneration is low, FAPs readily differentiate into adipocytes in skeletal muscle tissue (14). It has recently been shown that FAPs can also be differentiated to a myofibroblast phenotype by upregulation of the transforming growth factor β family (15). Therefore, FAPs have the ability to differentiate into adipocytes and fibrotic cells and thus are regarded as potential effectors of these maladaptive processes in response to environmental stimulation. One of limitations in this study is that the authors did not exclude the role of other tissue fat in development of diaphragm muscle dysfunction. To this point, inflammatory adipokines released from other adipose tissues may also have a negative impact on diaphragm muscle function (8–10). Further, the role of obesity-induced abnormalities in insulin metabolic signaling and insulin-mediated muscle glucose uptake is not clear in relation to diaphragm skeletal muscle dysfunction.

In conclusion, data in this important study (13) define the role of diaphragm skeletal muscle and respiratory dysfunction during the development and progression of intradiaphragmatic adiposity and fibrosis in diet-induced obesity. This study demonstrates an important role for increased FAP proliferation and IMC lipid accumulation in the pathogenesis of fibro-adipogenic diagram remodeling and associated respiratory dysfunction. These findings suggest that controlling FAPs may be a potential novel therapeutic strategy in prevention of obesity-induced diaphragm dyfunction and respiratory compromise in obese individuals. Further studies are warranted to more definitively understand the relative role of FAPs and IMC lipid accumulation in diet-induced obesity, insulin resistance, and type 2 diabetes.

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