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Stewing in Not-So-Good Juices: Interactions of Skeletal Muscle With Adipose Secretions

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Derangements in both skeletal muscle and adipose tissue are clearly linked with obesity, type 2 diabetes, and insulin resistance. The complex mechanistic interactions between muscle and adipose tissue are, however, only recently beginning to be more fully understood in the pathogenesis of these epidemic metabolic diseases. White adipocytes are not homogenous but rather vary considerably in their metabolic and inflammatory profile, defined in part by adipose depot differences. For example, visceral adipocytes differ from subcutaneous adipocytes in their sensitivity to lipolytic stimuli and inflammatory and cytokine profiles (1). Yet, it has remained unclear how secreted factors from different types of adipocytes may uniquely impact skeletal muscle metabolism, and somewhat removed in primacy of contemporary interest, whether these affect muscle structure and contractile function.

In this issue of *Diabetes*, Pellegrinelli et al. (2) use elegant three-dimensional human primary cell culture experiments to examine the effects of secreted factors from both visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) on myocyte structure and the atrophy program within muscle. The secretory profile from adipocytes isolated from VAT was different from those isolated from SAT in lean subjects, while SAT from obese subjects manifested an intermediate pattern that was not as pronounced as VAT in negative repercussions. Myocytes cocultured with VAT were smaller, a morphology that seems consistent with a gene and protein expression profile indicative of, and predisposing to, muscle atrophy. Striking among this pattern was the suppression of key components of muscle contractile elements, notably troponin and other constituents comprising the sarcomere. Together with these, there was a repression of pathways of oxidative metabolism and protein synthesis. The authors conclude that VAT adipocytes create an environment in which the inflammatory cytokines interleukin (IL)-6 and IL-1β, which are deleterious to muscle, are prominent (Fig. 1).

This study advances our understanding in many important ways of the type of interactions between muscle and fat. The use of innovative three-dimensional cocultures using human cells provides an important methodological precedence and a framework for future studies in this area. This model system likely provides a more physiological context to examine both the release and impact of secreted factors in governing cell-to-cell interactions. The use of human primary cells—and adipocyte cultures from different regional adipose tissue depots—offers promise for more immediacy in translation to human biology than afforded from single tissue primary cultures; yet, one cannot imagine that a binary culture fully recapitulates in vivo physiology. Even so, it can be hoped that this type of platform will enable more fidelity in identifying novel targets for intervention.

Despite the important insights into the interaction between VAT and muscle that were achieved in this investigation, this study was limited in that muscle cell function was not actually measured. Thus, we cannot interpret the findings to firmly conclude that VAT or factors secreted from VAT directly affected muscle cell contractility function. Older obese humans have larger muscles (3) but reduced muscle strength and quality (strength per unit mass). Thus, there must be other factors at play in vivo (e.g., mechanical load, anabolic milieu, and others) that are important yet not adequately assessed ex vivo in cell culture systems. An area that we believe warrants additional consideration concerns increased expression of extracellular matrix in insulin-resistant skeletal muscle (4,5). It would have been of great interest in the studies by Pellegrinelli et al. (2) to have learned whether, in association with the effect of the

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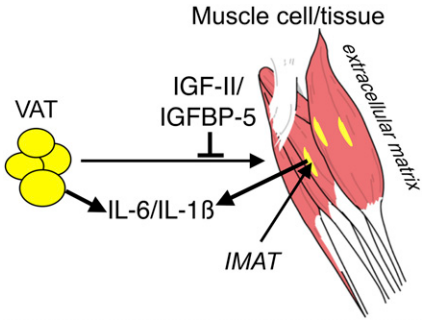

Figure 1—The simplified figure illustrates an important interface of secretory factors from VAT contributing to an atrophic myocyte phenotype as reported by Pellegrinelli et al. (2). These authors report that in response muscle expression of the myogenic growth factor IGF-II and its binding partner IGFBP-5 can be repressed contributing to an atrophy phenotype in muscle. In this figure, it is further suggested, though yet undetermined, that this model of interaction between adipose tissue and muscle may also include a contribution from IMAT similar to that from VAT.

adipocyte conditioned media to repress synthesis of contractile elements within myocytes, there was any effect, contralateral more specifically, on synthesis pathways of extracellular matrix. Regardless, the coculture findings raise interesting questions about the relative importance of adiposity affecting muscle mass and function (or quality) in obesity and aging. It might also be considered that the mice in this study were not old enough to examine whether these interactions between adipose tissue and muscle are worsened with advancing age; possibly this would be the case. The emerging concept of sarcopenic obesity is significant as a public health issue, as the worldwide obesity epidemic and the aging of the population likely represent a nasty confluence affecting self-sufficiency, public health, and economies worldwide.

The findings of the coculture of VAT with myocytes call to mind a potential interaction that seems likely to occur in vivo of another adipose tissue depot with muscle, that of intermuscular adipose tissue (IMAT) with adjacent skeletal muscle. Pellegrinelli et al. (2), to their credit, certainly raise a discussion of the potential importance of such proximity and the likelihood that these neighbors may be interacting in inharmonious ways in obesity. Although still conjecture at this point, might it be that in considering the proximity between muscle and IMAT what started as a halcyon interaction during lean youth turns sour with obesity and age? So, in a context of offering perspective upon this provocative article, we would like to take liberty and opine about the potential implications in considering the role of IMAT in cross talk with myocyte structure and function.

IMAT is an adipose tissue depot that has been identified in recent years to be yet another that is associated with insulin resistance (6) and increased cardiometabolic risk among older men and women (7). If one has had the opportunity to see IMAT within a cross-section image of a limb, or in more detail within a microscopy field of a muscle biopsy section, there can be the impression that this is a relatively small depot comprised of interspersed bits of adipose and that IMAT is outweighed as it were by VAT and overwhelmed by the size of SAT. The latter is certainly correct, but not so much the former. Detailed whole-body MRI studies have revealed that the collective mass of IMAT is higher in type 2 diabetes (8) and can be quite similar to that of VAT in African American subjects and not much smaller than VAT in others (9). Moreover, while weight loss can induce sizeable reduction in VAT, in the same individuals the amount of IMAT seems refractory to reduction (10). These are provocative findings that warrant continued study. Moreover, with aging, it is well known that characteristically IMAT increases while muscle mass declines (11), but whether these reciprocal trends represent adversarial interaction is uncertain. That the IMAT adipocytes would interact with adjacent muscles seems logical and the notion is encouraged conceptually by the findings presented by Pellegrinelli et al. (2), but unfortunately, at present, our knowledge about IMAT characteristics in humans is quite limited. The biological underpinnings for the observation between IMAT and muscle function in aging would extend this area of investigation in important ways (type of fat, endocrine vs. paracrine effects). We would certainly encourage those in the field to tackle this challenging yet potentially important area of adipocyte-myocyte cross talk.

In summary, the work of Pellegrinelli et al. (2) reporting that the secretome of obese adipocytes adversely affects the contractile complex of myocytes is an important contribution in furthering our understanding of adipocyte and myocyte interaction in metabolic illnesses. The platform of three-dimensional coculture that they used appears to offer unique value for these interrogations. Given the public health challenges of obesity and related insulin resistance and of sarcopenia, it can be hoped that further investigation of this interaction will begin to yield insights and impetus for effective intervention.

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