Adipose Tissue Macrophages: Amicus adipem?

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Chronic overnutrition drives complex adaptations within both professional metabolic and bystander tissues that, despite intense investigation, are still poorly understood. Xu et al. (2013) now describe the unexpected ability of adipose tissue macrophages to buffer lipids released from obese adipocytes in a manner independent of inflammatory macrophage activation.

In its simplest archetype, obesity’s fundamental characteristic is a surfeit of caloric intake relative to energy expenditure. In lean individuals, these excess calories can be easily converted to lipid and stored in white adipose tissue without significant physiologic consequence. Chronic overnutrition, however, strains and eventually exhausts this storage capacity, allowing excess lipids to overflow into other physiologic compartments less well suited to nutrient handling, leading to significant cellular stress responses and, eventually, cellular dysfunction in both professional metabolic and bystander tissues (Odegaard and Chawla, 2013b). Despite its salience in metabolic dysfunction, our knowledge of the mechanisms underlying adipose tissue’s lipid buffering capacity—and, more importantly, how it fails in obesity—is surprisingly incomplete. In this issue of Cell Metabolism, Ferrante and colleagues identify a previously unknown mechanism by which triglycerides and nonesterified fatty acids released by overstretched adipocytes are buffered by macrophages resident within the adipose tissue, thereby partially shielding other tissues from potentially toxic levels of lipids (Xu et al., 2013) (Figure 1). Interestingly, this macrophage phenotype is enacted independently of traditional markers of inflammatory activation.

The authors begin with tissue-wide expression profiling of lean and obese adipose tissues, which demonstrate signatures for lipid uptake and lysosomal oxidation. Together these signatures describe a buffer into which adipocyte-derived lipids are drawn and at least partially catabolized (Xu et al., 2013). Unexpectedly, this buffering mechanism is located not within the adipocyte itself but within adipose tissue macrophages. Moreover, this program was not present in bone marrow-derived macrophages but was induced specifically upon exposure to adipose tissue-derived factors in vitro, suggesting a tissue-specific functional program similar to adipose tissue regulatory T cells’ ability to regulate adipocyte insulin signaling (Cipolletta et al., 2012). Macrophage lipid uptake itself, however, is not unique: macrophages have been widely implicated in both functional and dysfunctional lipid uptake in such varied contexts as atherosclerotic plaques, where lipid-engorged macrophages termed “foam cells” form the structural plurality of “fatty streak” lesions, and traumatic fat necrosis, where macrophages clear fatty debris following traumatic injury to adipose tissue such as that which occurs postsurgically.

Indeed, lipid-laden macrophages have also been previously described in nontraumatized adipose tissue itself, where they are found both as single cells and as multinucleated foreign-body giant cells within the crown-like structures surrounding dead adipocytes (Cinti et al., 2005; Prieur et al., 2011). Until now, functional explanations for these lipid-laden populations have largely invoked debris clearance and sequestration, often with little empiric support, which stands in sharp contrast to the active role in lipid buffering described by Xu et al. in the current issue. Interestingly, the ability of macrophages to buffer adipocyte-derived lipids also explains the previously enigmatic observations that macrophages are recruited to adipose tissue during weight loss (Mottillo et al., 2007), a highly lipolytic context in which the need for lipid buffering capacity is high, and that their depletion by liposomal clodronate results in increased levels of nonesterified fatty acids being released from the adipose tissue, a finding compatible with the loss of buffering capacity (Kosteli et al., 2010).

Although lipid levels and their dysregulation are unarguably critical in obesity-related metabolic dysfunction, inflammation of adipose and other tissue beds has emerged as a central mechanistic theme felt to be at least partially independent of derangements in nutrient concentrations (Odegaard and Chawla, 2013b). In the canonical model of obesitygenesis, the expansion of adipose depots is accompanied by a profound alteration in composition and inflammatory timbre of the tissue-associated leukocyte compartment. Numerically foremost among these leukocytes, the macrophage population expands from ~10% of all cells in lean adipose tissue to more than 50% in advanced obesity and, based on bulk tissue measurements, was thought to swap an alternative (M2) activation phenotype for a proinflammatory classical (M1) bias (Lumeng et al., 2007; Weisberg et al., 2003). Indeed, assessment of tissue levels of archetypal proinflammatory mediators such as TNF, IL1β, and iNOS appears to support this hypothesis; however, a growing body of recent reports focusing on per-cell measurements has begun to question the accuracy of this dogma. Indeed, Ferrante and colleagues also observe that the macrophage phenotype during obesitygenesis fails to conform to the accepted M2-M1 shift paradigm, instead eschewing TNF and many other canonical markers of M1 activation during obesity for a more complex immunophenotype that does not conform to either
traditional macrophage activation archetype (Xu et al., 2013).

It is important to note, however, that these findings do not conflict with the literature regarding the importance or contributions of classical (M1) and alternative (M2) macrophage activation; the evidence still strongly supports that relative loss of M2 activation potential (i.e., through genetic intervention) or gain of M1 exacerbates metabolic dysfunction in diet-induced obesity (Odegaard and Chawla, 2013b). Rather, it now appears that while macrophage activation programs do exert diametrically opposed influences on energy metabolism, their relative balance either changes less or, perhaps, shifts in a more complex way than previously thought. Indeed, with the more recent surveys ascribing significantly more diversity to the adipose tissue-associated leukocyte pool than initially appreciated (Odegaard and Chawla, 2013a), it is possible that the inflammatory evolution postulated from bulk tissue measurements reflects more the numeric and qualitative inflammatory shifts in nonmacrophage lineages than those in the macrophage compartment itself.

Collectively, the authors demonstrate that adipose tissue macrophages buffer lipids released from over-engorged adipocytes in a manner independent from canonical macrophage activation archetypes. These important findings challenge prevailing dogma regarding macrophage function in adipose tissue and raise many important questions. First and foremost, can this buffering mechanism be exploited for therapeutic effect? Current and previous studies suggest that augmentation of this pathway might ameliorate the lipotoxicity often seen in obesity-related metabolic dysfunction; however, how this might be accomplished or what the aggregate effects of such augmentation might be are entirely unclear. Furthermore, the increasingly complex picture of the adipose tissue macrophage in obesity has implications for the burgeoning efforts to therapeutically target this cell; given seemingly dualistic contributions, what might the effects of macrophage-targeted therapy be? Might inhibition of macrophage inflammation similarly squelch an important lipid buffer, leaving other tissues increasingly susceptible to lipotoxic sequelae? Or might augmentation of this lipid buffer unwittingly also augment inflammation in the macrophage or elsewhere, mitigating short-term consequences of the problem but perpetuating and exacerbating root causes? Clearly, the observations presented in this study represent an important advance and raise many interesting questions that bear heavily on the future of many antiobesity therapeutic approaches currently under development.

REFERENCES