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Commentary

Lysosome impairment as a trigger for inflammation in obesity: The proof is in the fat.

David R. Rawnsley[a,b], Abhinav Diwan[a,b,c,*]

[a] Cardiolovascular Division, Washington University School of Medicine, Division of Cardiology, 660 S. Euclid, CSRB 827 NTA, St. Louis, MO 63110, United States
[b] Center for Cardiovascular Research, Washington University School of Medicine, St. Louis, MO, United States
[c] John Cochran Veterans Affairs Medical Center, St. Louis, MO, United States

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ABSTRACT

Obesity is a global epidemic contributing to the rising prevalence of multiple disorders including metabolic syndrome, diabetes, fatty liver disease, cardiovascular and cerebrovascular disease, Alzheimer's disease and certain cancers. A renewed sense of urgency is required as obesity remains an intractable problem, despite a rapidly expanding armamentarium of behavioral, pharmacologic and surgical approaches which fall short of delivering sustained results

ATMs	adipose tissue macrophages
IP3Rs	inositol inositol 1,4,5-triphosphate receptor
TFEB	transcription factor EB
IP3R	inositol 1,4,5 tri-phosphate receptor
Ca^{2+}	calcium ions
Tregs	regulatory T lymptocytes
LSDs	lysosome storage diseases
PPARγ	peroxisome proliferator-activated receptor-gamma

Obesity is a global epidemic contributing to the rising prevalence of multiple disorders including metabolic syndrome, diabetes, fatty liver disease, cardiovascular and cerebrovascular disease, Alzheimer's disease and certain cancers. A renewed sense of urgency is required as obesity remains an intractable problem, despite a rapidly expanding armamentarium of behavioral, pharmacologic and surgical approaches which fall short of delivering sustained results. Activation of immune cell types in the adipose tissue, in particular in the visceral fat and in various organ systems, drives systemic inflammation which has been linked to the development of metabolic abnormalities. In this article of *EBioMedicine*, Luo et al. [1]. provide evidence pointing to lysosome dysfunction in pre-adipocytes as a trigger for inflammation in diet-induced obesity, presenting novel therapeutic targets to tackle obesity.

This study [1] demonstrates both upregulation of CD36 and reduced abundance of acidified lysosomes in stroma-resident pre-adipocytes in visceral adipose tissue obtained from obese humans or mice fed an obesogenic diet. In comparison, CD36 global null mice fed a high-fat diet had attenuated expansion of this pre-adipocyte population and also demonstrated increased abundance of acidified lysosomes in pre-adipocytes, reduced inflammatory markers, and improvements in glucose tolerance and insulin sensitivity. Cell culture studies demonstrated that fatty acids induced upregulation of CD36 in pre-adipocytes, and forced expression of CD36 was sufficient to trigger lysosomal pH abnormalities, inflammatory cytokine production and impaired lipophagy. Exogenously expressed wild-type CD36 demonstrated increased interaction with tyrosine kinase, Fyn, increased IP3R1 phosphorylation and co-localization of Ca^{2+} with lysosomes, and increased cytokine production as compared to its palmitoylation-deficient CD36 mutant. This phenotype was attenuated by pharmacologic inhibition of IP3R1 and Fyn, indicating that CD36/Fyn/IP3R1 signaling plays a role in increasing lysosomal Ca^{2+} content and pH impairment. These experiments provide evidence to support the contention that obesity provokes acquired lysosome dysfunction and, in turn, inflammation, which can be therapeutically targeted in cardio-metabolic disease (reviewed in [2]).

CD36 is a multifunctional transmembrane protein that functions as a scavenger receptor to facilitate uptake of lipids such as long chain fatty acids and lipoproteins. It is transcriptionally upregulated in pre-adipocytes via PPARγ signaling to drive adipose tissue expansion. CD36 expression was also found to be upregulated in hepatocytes (and other cell types such as macrophages and endothelial cells) with

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* Corresponding author.
E-mail address: adiwan@wustl.edu (A. Diwan).

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high fat diet feeding [3]. In such cells, CD36 was demonstrated to signal pleiotropically to negatively regulate autophagy by inhibiting AMP kinase (AMPK) via Fyn-induced phosphorylation of LKB1. Indeed, CD36 deficiency induced lipophagy and protected mice against high fat diet-induced obesity [3], mimicking the findings presented in this article by Luo et al. [1]. Furthermore, CD36 deficiency was associated with increased nuclear translocation of TFEB [6] (a master regulator of the lysosome biogenesis program [4]), suggesting a role for stimulation of lysosome function in the observed benefits. Conceivably, the autophagic impairment observed in various tissues in obesity may be regarded as a 'symptom' of lysosomal impairment, as demonstrated by Luo et al. [1], which necessitates the need to develop experimental tools to evaluate lysosome function *in vivo* to comprehensively understand both autophagy as well as non-autophagy related lysosomal functions in obesity.

Conceivably, homeostatic lysosome function in adipocytes may couple lipolysis to exosome release that signals to adipose-tissue macrophages (ATMs), that also upregulate the lysosome biogenesis program with nutrient stress to stimulate lipolysis; to maintain homeostasis and modulate inflammation [5]. Indeed, inborn errors of metabolism resulting from loss of lysosomal enzymes and proteins, termed lysosome storage diseases (LSDs), are uniformly characterized by loss of adipose tissue [6], resulting in excess lipid deposition in other organs as with complete absence of lysosomal acid lipase (*LIPA*) activity. Moreover, LSDs are characterized by inflammation in various tissues [4], paralleling the mechanistic link between impaired lysosome function and pro-inflammatory signaling observed in mice with diet-induced obesity [1]. Conversely, stimulation of lysosome biogenesis and function in adipocytes with activation of TFEB, a master transcriptional regulator of the lysosome biogenesis program, was sufficient to attenuate the development of diet-induced obesity and improve insulin sensitivity [7]. Taken together, the study presented by Luo et al. [1] therefore supports an approach for harnessing the lysosome biogenesis program to attenuate obesity-induced inflammation and its downstream sequelae.

While regulation of lysosome calcium levels is critical to lysosome function [4], the etiology of how IP3R activation forces lysosome Ca^{2+} overload in pre-adipocytes requires experimental delineation. Increased release of Ca^{2+} at ER-lysosome contact sites may act locally to trigger lysosome calcium overload, affect the function of lysosome membrane-associated proteins including the LYNUS complex, or cause lysosome membrane permeabilization. Alternatively, elevated cytosolic Ca^{2+} may affect cellular ATP availability that indirectly affects lysosome pH via reduced proton pump activity. Indeed, while the paradigm presented by Luo et al. is intriguing, further work is also required to understand the role of Pref-1-expressing pre-adipocytes via-a-vis other adipocyte precursors [8], which will require cell-type specific targeting approaches to dissect the multiple mechanisms whereby global CD36 ablation attenuates lysosome dysfunction, inflammatory markers and diet-induced obesity. Furthermore, the CD36/Fyn/IP3R1-mediated Ca^{2+} release may also regulate adipogenesis. Therefore, the effects of CD36 upregulation on lysosome function are likely to be complex, resulting from direct effects of saturated fatty acid uptake and lipid overload with the cells, and the effects of lysosomal Ca^{2+} overload as described by Luo et al. [3].

The current study provides a strong rationale for developing pharmacotherapies to inhibit CD36 signaling to prevent the metabolic complications of obesity. However, such approaches will need to be carefully designed to avoid harmful effects. For example, regulatory T cells have also been demonstrate to upregulate CD36 in a PPARγ dependent fashion, suggesting that inhibiting CD36 globally could abrogate benefits obtained from its actions in these immunomodulatory cell types [9]. Moreover, CD36 plays critical roles in tissue homeostasis (reviewed in [10]). In light of these findings, it will be also be important to evaluate whether lysosome function is a determinant of metabolic health in obese individuals, and whether their individual proclivity to develop metabolic disorders is determined by genetic and environmental determinants of lysosome function.

Declaration of Competing Interest

Abhinav Diwan reports that he provides consulting services for the interpretation of echocardiograms for clinical trials to ERT (Biomedical systems). This relationship does not affect his research efforts and did not affect the content of this manuscript. David R. Rawnsley has nothing to disclose.

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Authors' contribution

David R. Rawnsley and Abhinav Diwan drafted the manuscript.

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