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## Metabolically stressed adipocytes: mediators of cardioprotection via extracellular vesicle-mediated transport of oxidatively damaged mitochondria

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Obesity is a known risk factor for cardiovascular disease (CVD), including heart failure and ischemia. However, although the incidence of CVD is higher in obese humans, numerous studies have found that obese individuals with CVD have a better prognosis than lean individuals, a phenomenon known as the “obesity paradox” (1). Adipose tissue has a well-defined role as an endocrine organ that differs by anatomical location [e.g., inguinal white adipose tissue (WAT), perigonadal WAT, interscapular brown adipose tissue (BAT), etc.] as well as adipocyte cell content (white vs. brown vs. beige), and recent work has focused on the adipose-cardiac signaling axis to decipher the endocrine mechanisms of adipocytes. We and others have recently reviewed adipose tissue-derived signals that are known to directly impact the myocardium (2–4). Some of these adipose-derived endocrine signals are mediated by small extracellular vesicles (sEVs) that can deliver diverse cargo, including RNA, protein, and lipids (4). However, the cardiac effect of adipose-derived sEVs is not always consistent. Multiple recent studies describe EV-mediated delivery of specific microRNA (miRNA) from adipose-derived stem cells that impact mouse models of cardiac ischemic injury (5–9). BAT-derived EVs blunt obesity-induced declines in cardiac function, but their delivered EVs were shown to accumulate mainly in the liver, spleen, and lungs, and the direct effects on the myocardium were not investigated (10). Conversely, EVs secreted from WAT in response to PPAR $\gamma$  activation induce hypertrophic signaling in neonatal cardiac myocytes via transport of miRNA (11). sEVs isolated from epicardial adipose tissue were associated with atrial fibrillation in humans, were sufficient to induce cardiac fibrosis when injected into rats, and implicated sEV-mediated delivery of pro-fibrotic miRNAs as a potential mechanism (12).

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In a recent issue of *Cell Metabolism*, Crewe *et al.* (13) examined the role of sEVs released by energetically stressed adipocytes, and their effects on cardiomyocytes. They have previously shown that mice with an adipocyte-specific overexpression of mitochondrial ferritin (adipo-FtMT), when placed on high fat diet (HFD), display dysfunction in multiple organ systems, including mitochondrial oxidative stress in the heart (14). As cardiac oxidative stress is also observed in obese humans, they extended these prior observations in this work to specifically examine circulating sEVs as endocrine mediators in adipo-FtMT mice (13). They first demonstrated that adipo-FtMT mice produce more sEVs than their wild-type counterparts, and that inhibiting sEV release via neutral sphingomyelinase ablates the observed cardiac oxidative stress. Isolated circulating sEVs from adipo-FtMT mice also induced an increase in oxidative stress in healthy (wild-type) primary cardiomyocytes in culture, compared to cardiomyocytes treated with sEVs from healthy mice. Additional models of mitochondrial stress in stromal vascular fraction (SVF)-derived adipocytes, including palmitate treatment, electron transport chain inhibitors, and HFD feeding of the mice prior to SVF isolation, were also seen to increase sEV release, confirming that sEV release is a general response to oxidative stress. Furthermore, sEVs derived from oxidatively stressed adipocytes were found to be respiration-competent and enriched for mitochondrial proteins. Importantly, injection of these stressed sEVs into wild-type mice 2 hours prior to cardiac ischemia/reperfusion (I/R) injury reduced acute myocardial infarct size, resulting in less cardiac hypertrophy and increased ejection fraction at seven days post-infarct. Thus, the authors concluded that the mild sEV-induced oxidative stress in the myocardium serves as a cardioprotective preconditioning effect against subsequent I/R injury.

This work is novel in that it shows a direct endocrine-driven cardioprotective signal being generated by adipose tissue through the sEV-mediated transfer of mitochondria. Interestingly, this work links metabolically stressed adipose tissue, potentially through a mechanistic mediator of the obesity paradox, with long-standing evidence that increasing ROS signaling in the heart prior to I/R elicits a protective preconditioning response. ROS generation within the myocardium was first shown to be a mediator of cardioprotection via ischemic preconditioning by Sun *et al.* (15) in 1996, and it was later shown that mitochondria were a likely key source of this ROS (16). Prior work by Haar *et al.* (17) also showed that acute feeding of HFD elicited a cardiac preconditioning phenotype in mice, but the role of sEVs was not explored in this model, and the cardioprotective effect of HFD was fleeting and waned after 6 weeks of HFD. Many cardiac preconditioning stimuli are accepted to mediate an acute (early—minutes to hours) and/or more sustained (late—hours to days) phase of preconditioning. In light of this, it would be interesting to see whether sEVs derived from metabolically stressed adipocytes provide chronic protection, or display a distinct window of cardioprotection as observed from HFD by Haar *et al.* (17). This may be difficult to achieve via chronic sEV injection, but could possibly be done using an sEV secretion inhibitor in HFD-fed mice or directly in adipo-FtMT mice, for which cardiac infarct data was not reported.

There is little doubt from their work that the transfer of mitochondria is a mechanistic driver of the observed effects, but the work by Crewe *et al.* (13) also raises additional questions. For example, adipose-derived sEVs are known to elicit cardioprotection by transport of functional RNAs, such as miRNAs. Differential stress-induced sEV loading of RNA cargo

was not characterized in this model. Application of an ROS scavenger, or alternative means to directly reduce ROS production in the heart prior to or during I/R, would have also allowed for conclusive demonstration that sEV-induced ROS generation within the myocardium is responsible for initiating the observed cardioprotection.

This work is also of particular interest to my laboratory as we recently demonstrated that adipocyte-specific deletion of the RNA binding protein HuR (Adipo-HuR<sup>-/-</sup>) elicits spontaneous cardiac hypertrophy and fibrosis (18), and additionally have expertise in the field of cardiac preconditioning (19) and ischemic injury (20,21). Results from our Adipo-HuR<sup>-/-</sup> mice are suggestive of an endocrine EV driven mechanism of cardiac pathology, and work is ongoing to characterize the HuR-dependent cargo loading of Adipo-EVs from these mice, but given its nature as an RNA binding protein, the mediating factors are likely to be RNA.

This work by Crewe *et al.* (13) is likely just the tip of the iceberg with regard to how adipose tissue-derived endocrine signaling via EVs affects physiological homeostasis in other organ systems. The mechanisms that mediate adipo-EV protein and RNA cargo selection and how these pathways are altered under pathophysiological conditions such as obesity or metabolic syndrome remain largely unexplored.

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