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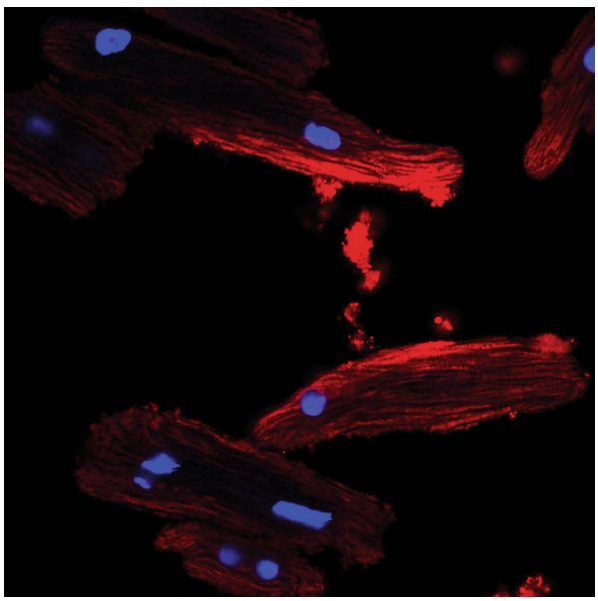
ADIPOSE TISSUE

Mitochondria transported from adipocytes in extracellular vesicles

> this is the first case to demonstrate interorgan mitochondrial transfer in mammals

Dysregulated mitochondria in adipocytes are known to be associated with increased oxidative stress in the heart; however, the mechanisms underlying this connection were unclear. New research published in *Cell Metabolism* has now demonstrated that, under conditions of mitochondria-specific stress, adipocytes release small extracellular vesicles that contain mitochondrial fragments. These vesicles enter the circulation and are taken up by cardiomyocytes, where they elicit the production of free radicals.

"We have previously shown that there is an intense exosomal exchange between the endothelium and the adipocyte," explain authors Philipp Scherer and Clair Crewe. In the present study, the researchers used an inducible, tissue-specific mouse model of mitochondrial ferritin overexpression (the adipo-FtMT mouse), in which FtMT overexpression is induced by feeding the mice doxycycline.



Heart cells that have taken up red-coloured adipocyte-derived extracellular vesicles. Image courtesy of Philipp Scherer, University of Texas Southwestern Medical Center.

Adipo-FtMT mice fed a high-fat diet (HFD) with doxycycline had higher cardiac levels of protein carbonylation adduct formation (a measure of protein damage by reactive oxygen species) than control mice on the same diet, with no changes seen in adipo-FtMT mice fed a chow diet with doxycycline. The authors also demonstrated that the reactive oxygen species seen in the adipo-FtMT mice were probably specific to mitochondria. The response seen in the adipo-FtMT mice was similar to that seen in wild-type mice fed a HFD, suggesting that there could be an endocrine mechanism relaying information from adipocytes to cardiomycocytes.

Next, the researchers assessed whether extracellular vesicles were mediators of the observed cardiac response. They found that adipo-FtMT mice fed a HFD with doxycycline had higher circulating levels of small extracellular vesicles than control mice. In addition, small extracellular vesicles from adipo-FtMT mice had increased levels of small extracellular vesicle markers, as well as of FABP4 (an adipocyte enriched protein).

Next, the researchers injected the mice with GW4869, an inhibitor of exosome production. GW4869 prevented the rise in small extracellular vesicles in the serum of adipo-FtMT mice fed a HFD with doxycycline, and also prevented cardiac oxidative stress in these mice. These findings suggest that small extracellular vesicles carry a pro-oxidant signal from adipocytes to the heart.

The researchers also conducted proteomics analyses of the small extracellular vesicles. "To our surprise, we found mitochondrial components packaged in these exosomes," explain Scherer and Crewe. In addition, more mitochondrial components were seen in exosomes from dysfunctional adipocytes than in those from functional adipocytes. "While this could be simply a disposal mechanism for dysfunctional cellular components, it seemed to us that there was more to it," say Scherer and Crewe. The authors found that the cardiomyocytes that took up the small extracellular vesicles became pre-conditioned by exposure to low levels of oxidative stress so that they were better able to survive more severe oxidative stress situations, such as ischaemia–reperfusion injury. "As dysfunctional mitochondria in adipocytes are observed more frequently in the obese setting, this finding might offer a partial explanation for the 'obesity paradox', in which individuals with obesity are better protected from the negative consequences of an ischaemic event in the heart than lean individuals," say Scherer and Crewe.

"From a cell biological perspective, this is the first case to demonstrate interorgan mitochondrial transfer in mammals, adding to the remarkable ways by which adipocytes communicate with other organs, beyond adipokines, signalling lipids and nutrients," comment Scherer and Crewe.

The authors now hope to develop additional models to genetically and selectively intervene with the formation of exosomes in adipocytes, which will enable them to determine the in vivo consequences of eliminating this aspect of communication in adipocytes. "Ultimately, this work highlights the potency of these exosomal preparations in influencing key pathways in select tissues," conclude Scherer and Crewe.

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