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Analysis of anti-diabetic exosomes secreted from beige adipocytes

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Abstract
Accumulation of excess fat in white adipose tissue is associated with an increase in risk for type 2 diabetes. Within white fat tissue resides a population of ‘beige’ adipocytes that are activated by cold exposure and expend energy contained in fats, which is released as heat. Increasing energy expenditure through beige adipocyte activation has been shown to reduce diabetic symptoms in rodent models of obesity. However, activation of beige adipocytes through exposure of humans to cold temperatures is uncomfortable and likely not a realistic strategy to control body weight. In addition to its fat burning potential, secreted factors derived from activated beige adipocytes may enter the circulation and reduce diabetic symptoms such as insulin resistance in other tissues. The mechanisms by which these secreted factors act on distant tissues may in part be due to their transport inside extracellular vesicles, known as exosomes. Exosomes carry a diverse array of signaling molecules, including microRNAs that are transported and released into recipient cells and tissues. The goal of this project was to determine if beige adipocytes grown in cell culture secrete exosomes that contain microRNAs that may harbor anti-diabetic properties. Unexpectedly, we found that during the activation of beige adipocytes, secreted exosomes contain elevated expression of a number of microRNAs known to be negative regulators of beige adipocyte activation, including mir-27. This suggests that exosome secretion may be a way to increase beige adipocyte activation by decreasing the expression of specific microRNAs. Future testing of these microRNA candidates may translate to improved therapies for obese patients that develop diabetes.

Background
During weight gain, periods of prolonged overeating result in fat storage in white adipocytes, which can lead to inflammation, cellular stress, insulin resistance and eventually T2D. Unlike the energy storage function of white adipose tissue, beige adipocytes, which can lead to inflammation, cellular stress, insulin resistance and eventually T2D. Unlike the energy storage function of white adipose tissue, beige adipocytes become metabolically activated in response to cold and burn calories by releasing energy stored in fats to generate heat, thereby providing mammals with the ability to respond to cold temperatures. Beige adipocytes are often referred to as “brite” adipocytes due to their ability to switch to a brown-like state, allowing for increased energy expenditure and heat production. Beige adipocytes are found in various tissues such as the liver, white adipose tissue and others. (B) Exosomes carry a diverse array of signaling molecules, including microRNAs that are transported and released into recipient cells and tissues. The goal of this project was to determine if beige adipocytes grown in cell culture secrete exosomes that contain microRNAs that may harbor anti-diabetic properties. Unexpectedly, we found that during the activation of beige adipocytes, secreted exosomes contain elevated expression of a number of microRNAs known to be negative regulators of beige adipocyte activation, including mir-27. This suggests that exosome secretion may be a way to increase beige adipocyte activation by decreasing the expression of specific microRNAs. Future testing of these microRNA candidates may translate to improved therapies for obese patients that develop diabetes.

An Alternative Hypothesis
Beige adipocyte activation is associated with rapid exosome-mediated clearance of mir-27, which promotes thermogenesis through increased mitochondrial biogenesis, membrane potential, and mitophagy-mediated clearance of damaged mitochondria.

Methods
1) Grow beige adipocytes in culture. 2) Isolate exosomes from conditioned medium. 3) Purify microRNA from isolated exosomes. 4) Make cDNA from exosomal microRNA. 5) Test expression of microRNAs previously shown to be present in exosomes secreted by beige adipocytes in vivo.

Results
(A) Liver cells treated with exosomes from activated beige adipocytes show decreased expression of known and predicted mir-27 target genes. (B) mir-27ab target gene expression is decreased in beige adipocytes activated in the presence of the exosome secretion inhibitor manumycin A (man-A).

Future directions
Hypothesized Role of mir-27 and Mitochondrial Fission Factor (MFF) in Mitochondrial Biogenesis and Degradation

Summary
Exosome secretion may provide a mechanism for down-regulation of negative regulators of thermogenesis. mir-27 may negatively repress activation of brown and beige adipocytes by targeting genes involved in promoting mitochondrial biogenesis and turnover. MFF may maintain mitochondrial homeostasis by removing those that are damaged. Exploitation of brown and beige adipocyte release of exosomes, their associated microRNAs or their target genes may be used to develop new therapies for the treatment of obesity and metabolic syndrome.

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