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The micro-Managing Fat: Exosomes as a New Messenger

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Abstract

Brown fat secretes endocrine factors and exerts metabolic effects beyond thermogenesis. In addition to protein factors and bioactive lipids, recent work has revealed brown fat-derived microRNAs carried by exosomes as a new means of interorgan crosstalk with potentially important implications for metabolic physiology and disease.

The adipose tissue plays a pivotal role in energy homeostasis, by acting as the storage depot for excess energy (white fat) and the site of fuel oxidation and thermogenesis (brown and beige fat). Brown and white fat also function as endocrine organs by secreting protein hormones and bioactive lipids that act on other peripheral tissues and the central nervous system. A recent study by Thomou et al. discovered that microRNAs (miRNAs) from the adipose tissue, delivered by the exosomes, provide yet another important form of communication between fat and other tissues such as the liver [1].

As post-transcriptional modulators of gene expression, miRNAs fine-tune the turnover and translation of mRNAs and are integral to the regulation of diverse biological processes. Besides residing within cells, miRNAs can be readily detected in circulation either in complex with Argonaute 2 or within the exosomes, the membrane-bound vesicles released by numerous cell types [2–4]. In mice with adipose tissue specific ablation of Dicer (ADicer KO), a key endoribonuclease in miRNA biogenesis, Thomou et al. observed a marked reduction of most circulating exosomal miRNAs in the serum [1]. Similar reduction was also observed in human lipodystrophy patients, further implicating the adipose tissue as the major source of circulating miRNA carried by the exosomes. ADicer KO mice developed lipodystrophy and insulin resistance, accompanied by increased hepatic expression and serum levels of fibroblast growth factor 21 (FGF21). In an effort to determine the tissue source of exosomal miRNAs, the authors transplanted different fat pads into ADicer KO mice and examined miRNA profile in serum exosomes. Interestingly, transplant of brown

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fat, but to a lesser extent epididymal and subcutaneous white fat, restored the profile of circulating exosomal miRNAs. Brown fat transplant also improved glucose intolerance and reduced plasma FGF21 levels in ADicer KO mice. Suppression of hepatic FGF21 mRNA could be achieved with serum exosomes isolated from normal but not those from ADicer KO, leading to the identification of miR-99b as a likely candidate which recognizes the 3'-UTR of FGF21 mRNA and suppresses its secretion by the liver. This adipose-hepatic crosstalk via exosomal miRNAs was further demonstrated using a "bio-orthogonal" pair of miRNA and target gene of human origin. When expressed in mouse brown fat, the human miRNA suppressed its cognate reporter construct in the liver, presumably via the exosomes secreted by brown fat.

Recent studies have demonstrated that exosomes contain regulatory information important for metabolic crosstalk among different cell types. Exosomes isolated from adipose tissue explants from obese ob/ob mice were actively taken up by monocytes, leading to macrophage activation toward a proinflammatory phenotype and their accumulation in the adipose tissue [5]. Remarkably, injection of exosomes isolated from obese mouse adipose tissue promoted insulin resistance in lean wild type mice, indicating that fat-derived exosomes contain metabolic cues that are sufficient to disrupt whole body glucose homeostasis. In a separate study, extracellular vesicles isolated from human adipocytes or adipose tissue explants promoted differentiation of monocytes into macrophages characteristic of adipose tissue macrophages [6]. In addition to adipocytes, other metabolic tissues, such as the liver, skeletal muscle, and pancreas, also release and take up exosomes [7]. These studies provide compelling evidence for a potential role of exosomes in mediating the paracrine and/or endocrine crosstalk between different cell types. However, the significance of exosome-mediated metabolic signaling and the function of exosomal miRNAs in physiology and disease remain to be more conclusively established.

The observations that fat tissue, particularly brown fat, provides a major source of exosomal miRNAs in circulation were intriguing and unexpected. In fact, inactivation of Dicer in adipocytes did not significantly alter the abundance of exosomes in circulation; instead, miRNAs residing in serum exosomes were markedly reduced in ADicer KO mice, supporting the notion that adipose tissue disproportionately contributes to the biogenesis of exosomal miRNAs in circulation. Membranes of adipocytes are enriched with lipid rafts, which have been suggested as a preferred source of exosome membrane. Whether this facilitates packaging of miRNAs into exosomes in adipocytes remains to be determined. The adipose tissue is dynamically regulated by hormonal, nutritional, circadian, and stress signals, which would likely alter the profile of adipocyte-derived exosomal miRNAs. As such, dissecting the qualitative and quantitative nature of adipose tissue-derived exosomes and exosomal miRNAs is expected to reveal important insights into their endocrine functions.

The identification of brown adipose tissue as an important source of exosomal miRNAs in circulation adds a new dimension to its role as an endocrine organ (Figure 1). Brown fat releases secreted protein factors and bioactive lipids that act on other metabolic tissues, such as the liver, skeletal muscle, and the central nervous system to maintain energy homeostasis [8, 9]. Two important features of endocrine signaling by protein hormones are their highly

regulated release and exquisite specificity due to the restricted expression of receptors on target tissues. Exosomes carry diverse potentially bioactive cargo molecules including proteins, lipids, and RNAs. These extracellular vesicles also contain a unique set of proteins such as the tetraspanins that serve as exosomal markers and are important for exosome formation, cargo selection, and function [10]. Whether tetraspanins and other exosomal proteins contribute to the selection and sorting of miRNAs into adipocyte exosomes is an important area for future exploration. It is possible that the exosomes released by adipocytes may be heterogeneous both in their cargo content and target tissue specificity. The latter can be theoretically achieved by the inclusion of specific proteins on the exosome membranes that can be recognized by receptors present on target tissues. Regardless of the exact molecular mechanisms involved, the presence of such cellular zip codes for exosomes is likely critical for fulfilling their role in endocrine metabolic crosstalk.

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References

1. Thomou T, et al. Adipose-derived circulating miRNAs regulate gene expression in other tissues. *Nature*. 2017; 542(7642):450–455. [PubMed: 28199304]
2. Arroyo JD, et al. Argonaute2 complexes carry a population of circulating microRNAs independent of vesicles in human plasma. *Proc Natl Acad Sci U S A*. 2011; 108(12):5003–8. [PubMed: 21383194]
3. Chen X, et al. Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. *Cell Res*. 2008; 18(10):997–1006. [PubMed: 18766170]
4. Valadi H, et al. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nat Cell Biol*. 2007; 9(6):654–9. [PubMed: 17486113]
5. Deng ZB, et al. Adipose tissue exosome-like vesicles mediate activation of macrophage-induced insulin resistance. *Diabetes*. 2009; 58(11):2498–505. [PubMed: 19675137]
6. Kranendonk ME, et al. Human adipocyte extracellular vesicles in reciprocal signaling between adipocytes and macrophages. *Obesity (Silver Spring)*. 2014; 22(5):1296–308. [PubMed: 24339422]
7. Huang-Doran I, et al. Extracellular Vesicles: Novel Mediators of Cell Communication In Metabolic Disease. *Trends Endocrinol Metab*. 2017; 28(1):3–18. [PubMed: 27810172]
8. Lynes MD, et al. The cold-induced lipokine 12,13-diHOME promotes fatty acid transport into brown adipose tissue. *Nat Med*. 2017
9. Wang GX, et al. The brown fat secretome: metabolic functions beyond thermogenesis. *Trends Endocrinol Metab*. 2015; 26(5):231–7. [PubMed: 25843910]
10. Andreu Z, Yanez-Mo M. Tetraspanins in extracellular vesicle formation and function. *Front Immunol*. 2014; 5:442. [PubMed: 25278937]

Figure 1. Endocrine signaling by brown fat

Brown adipocytes secrete protein hormones, bioactive lipids, and miRNA-containing exosomes to relay metabolic signals to other tissues. The presence of membrane receptors for protein hormones defines the tissue specificity of their action, whereas whether and how exosomal miRNAs exert biological effects on selective target tissues remain to be elucidated.