Do Extracellular Vesicles Mediate the Muscle Insulin Resistance of Obesity and Type 2 Diabetes?

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Modest weight loss causes well-established beneficial changes to metabolism and physiology. As reported in this issue of *Diabetes Care*, Samovski et al. (1) have shown that 10 volunteers with obesity and type 2 diabetes who accomplished substantial (16–20%) weight loss accompanied by a 50% improvement in insulin sensitivity had significant, robust alterations in adipose tissue (AT) pathways and composition. The authors confirmed many of the previously and extensively reported beneficial effects of weight loss. Using RNA sequencing analysis of AT before and after weight loss, they found a reduction in transcripts associated with extracellular matrix remodeling. They also found alterations in AT immune cell populations after weight loss, with an increase in T cells and little alteration to resident macrophage populations.

The most novel and interesting part of this article is the characterization of the extracellular vesicle (EV) changes in response to weight loss. These changes include reductions in the quantity and quality of microRNA (miRNA) cargo and effects of EVs before weight loss on insulin signaling ex vivo. EV is an umbrella term for a group of small membranous structures, generally 50–500 nm in size, that are derived from diverse cell types (reviewed in van Niel et al. [2] and Zaborowski et al. [3]). EVs are secreted from cells and are taken up by other cells, either local or in distant tissues, to facilitate interorgan and intraorgan cross talk. These EVs carry a diverse set of cargo, including proteins and enzymes, nucleic acids such as miRNA, and signaling molecules. This facilitates transfer of cell type–specific communication cargo such as miRNA that would otherwise be degraded in circulation. In AT (AT-specific exosomes are reviewed in Zhao et al. [4]), both adipocytes and nonadipocyte resident AT cells such as macrophages secrete EVs. Estimates from murine models of AT contribution to the plasma EV pool vary (5,6). In humans, adipocyte-derived EVs have been identified (7), as have EVs from primary differentiated human adipocytes in culture (8). The relative contribution of AT-derived EVs to the pathology of obesity and metabolic dysfunction is unknown.

Samovski et al. (1) report a reduction in (small) EV plasma abundance following weight loss, in line with previous work by Nakoa et al. (9). As has been the case for virtually all human studies, Samovski et al. (1) could not determine the origin of the circulating EVs in their volunteers. They attribute the reduction in plasma EVs following weight loss to a reduction in adipose-derived EVs. However, the data shown in Supplementary Fig. 5 suggest that most of the changes to plasma EV are not from adipocytes directly, although the data shown cannot rule out EVs derived from the nonadipocyte fraction of AT. The plasma EV concentrations decreased in response to weight loss in these individuals, yet the decrease in EV concentrations was not associated with a concomitant reduction in EV protein markers (FABP4, RBP4, and adiponectin) that mark EVs originating from AT. This suggests the decrease in EV abundance following weight loss is the reduced release of EV from a different cell type or tissue bed. This is of interest, because alterations in EV physiology in tissues other than AT might be an underappreciated source of some of the beneficial effects of weight loss. As noted, Nakoa et al. (9) also found decreased plasma EV load following significant weight loss via bariatric surgery, but they used an antibody-based EV detection approach and concluded the reduction was due to a reduction in hepatocyte-derived EVs. In addition to the decrease in absolute numbers of plasma EVs, the profound reduction in numerous miRNAs from the isolated EVs certainly confirms that weight loss was sufficient to induce significant alterations in EV cargo in this cohort

Given the inherent difficulties in performing certain measurements in humans in vivo, Samovski et al. (1) elected to use an ex vivo study design to test the hypothesis that alterations in plasma EVs before and after weight loss affect muscle insulin signaling. They found that plasma EVs obtained from people with obesity and diabetes prior to weight loss reduced the phosphorylation of key canonical insulin signaling proteins in L6 rat myotubes and that this reduction was offset by the addition of EVs obtained from these same volunteers after weight loss.

These types of studies are challenging to design. In addition to including the obvious control experiments that examine the effect of insulin on L6 myotube

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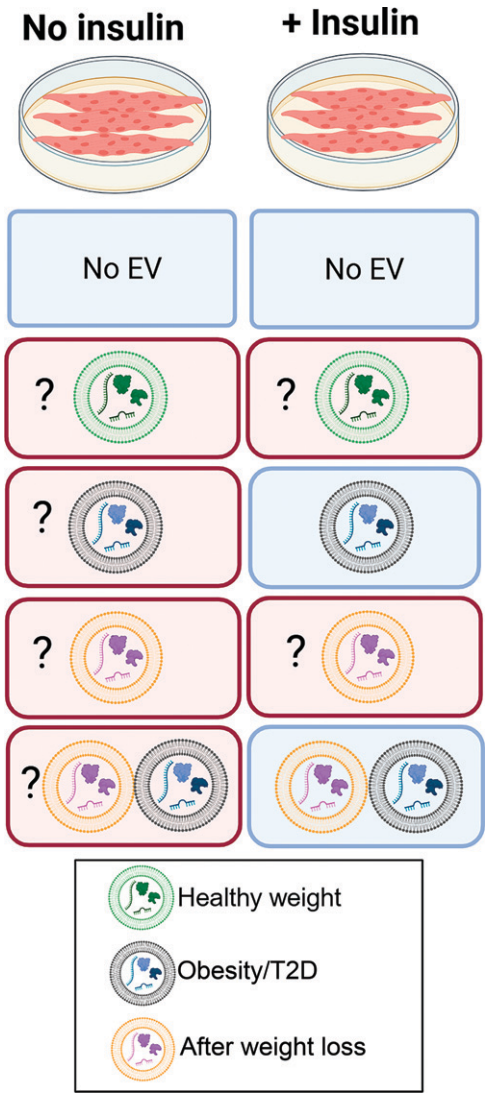

Figure 1—Proposed study design to test the hypothesis that EVs regulate muscle insulin signaling in cultured myotubes. Blue boxes denote groups tested by Samovski et al. (1), and red boxes denote additional experimental groups that would inform the interpretation of the effect of EVs on muscle insulin signaling. Image created with BioRender.com.

signaling proteins in the non–EV-exposed state, it would be helpful to know whether EV exposure per se alters the phosphorylation states of proteins. For example, do EVs from healthy, normal-weight individuals affect the signaling responses? We would also need to know whether EVs collected from the volunteers before and after weight loss affect the phosphorylation of these proteins in the basal state, not just the insulin-stimulated state. It might be that the presence of EVs alone (from adults who have normal weight, have obesity, or have had weight loss) significantly alters the basal insulin signaling response. The authors use the data from the noninsulin, non–EV-exposed condition as the baseline against which the other conditions (insulin alone, insulin plus EVs before weight loss, and insulin plus EVs before and after weight loss) are compared. If EVs affect the basal phosphorylation states of signaling proteins in L6 myotubes, this could alter the interpretation of these experiments. We propose a more robust design to examine the effects of obesity-related EVs on insulin signaling in Fig. 1. This approach would test the effects of control EVs on basal and insulin-stimulated signaling protein phosphorylation as well as the effects of EVs before weight loss, after weight loss, and before plus after weight loss on insulin responsiveness in L6 myotubes. Of course, this approach depends on having enough EVs from the volunteers who had obesity, which is not easy in a study such as that by Samovski et al. This information would allow us to determine if there is something unique about circulating EVs in people with obesity on muscle signaling or whether alterations are simply a response to the nonspecific presence of EVs. We also note that Samovski et al. (1) reported they used stored plasma to isolate EVs, which can cause contamination of their isolated EVs from platelets. Platelet release of exosomes and EVs has been studied in detail in the context of isolation procedures (10). Thus, the use of stored plasma rather than platelet-poor plasma may have resulted in platelet-derived contamination of the EVs they used for analysis and the ex vivo insulin signaling studies. If so, the interpretation of the findings might also be affected. As it stands, the data provided by these investigators indicts, but does not convict, EVs as culprits in impairing muscle insulin signaling in obesity.

In conclusion, Samovski et al. (1) provide preliminary yet intriguing evidence that muscle insulin resistance in the context of obesity and weight loss might be due to alterations to extracellular vesicle physiology and miRNA cargo. We look forward to future studies that will elucidate the relationship between EVs, obesity, and muscle insulin resistance.

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