Abstract: 76O

Liver-derived small extracellular vesicles regulate glycemic control through increased insulin secretion and enhanced glucose effectiveness

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Non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2D) are common co-morbidities. While the factors underpinning the relationship between NAFLD and T2D remain unclear, it is possible that factors secreted from NAFLD liver contribute to impaired glucose control. We hypothesised that NAFLD liver-derived extracellular vesicles (EVs) impair glycemic control, and that 'healthy' liver-derived EVs improve glycemic control in mice with NAFLD**.**
Secreted EVs were isolated from mouse liver slices (post-mortem), and proteomic evaluation identified 1741 proteins, with 91 upregulated and 66 down-regulated proteins in EVs from NAFLD compared to healthy liver. To evaluate the potential for liver secreted EVs to regulate glycemic control, mice were cross-injected intraperitoneally with saline or 30 µg liver-secreted EVs (i.e., healthy mice received liver EVs from NAFLD; NAFLD mice received liver EVs from healthy mice) 1 h prior to a glucose tolerance test (GTT), insulin tolerance test, or hyperinsulinemic-euglycemic clamp. Liver-secreted EVs, regardless of the donor, resulted in ~40% improvement in glucose tolerance and a ~2-fold increase in glucose-stimulated serum insulin levels during the GTT and directly in isolated mouse pancreatic islets (post-mortem), independent of changes in whole body or tissue-specific insulin sensitivity. These effects required EVs to be intact and the presence of EV surface proteins, as sonication of EVs and 'shaving' the surface proteins attenuated improvements in glycemic control and insulin secretion. Further, these responses were absent following the intraperitoneal injection of empty liposomes, adipose EVs (30 µg), or serum EVs (30 µg), indicating liver specific regulation. The improvement in glycemic control was maintained in the absence of circulating insulin through streptozotocin administration, suggesting improvements in glucose effectiveness (GE). Indeed, GE was specifically enhanced in isolated skeletal muscle and C2C12 cells in response to liver EVs. Collectively, we provide novel insight that liver secreted EVs communicate with the pancreas and skeletal muscle to regulate insulin secretion and glucose effectiveness to enhance glycemic control.