Lipotoxicity: a new role of lipid cargo in Extracellular Vesicles biology

Stefano TACCONI, *Carmen Laboratory, France*

Infertility, embryonic developmental defects, and abnormalities in offspring are common problems associated to obesity and type 2 diabetes. In particular, female obesity is a complex multifactorial condition in which multiple factors contribute to the development of these reproductive disorders, i.e., insulin resistance (IR), hyperinsulinaemia and hyperandrogenism, lipotoxicity and inflammation. Obesity- induced diabetes is associated with systemic inflammation, increased numbers of skeletal muscle (SkM) resident macrophages, and SkM-IR. Here, we determined whether the lipotoxicity affects the release and functions of macrophages-released extracellular vesicles (MEVs) and contributes to SkM-IR. To mimic in vivo lipotoxicity, THP-1-derived macrophages were treated with free fatty acids (FFA= palmitate+oleate). Polarization markers, lipid profile, insulin-induced AKT phosphorylation (IIAP) and oxidative stress were quantified in treated THP-1 macrophages. Small and large EVs (sEV and lEV), collected by differential centrifugations, were used for to treating C2C12 SkM cells. C2C12 lipid composition, insulin sensitivity and RNA sequencing were performed to determine whether MEVs biological action affect SkM homeostasis. FFA overload activated THP1 into a Lipid Associated Phenotype Macrophages (LAMs) phenotype. LAM macrophages released anti-inflammatory cytokines, accumulated triacylglycerols (TAG), FFA, and had altered IIAP vs untreated-THP-1 macrophages. The exposure to FFA overload affects the release of extracellular vesicles, with a reduction in refractosome release and a more heterogeneous population of TAG-filled lEVs. Furthermore, C2C12 treated with lEV-FFA accumulated TAG, FFA and had reduced insulin-sensitivity, mimicking FFA action on THP-1 macrophages. lEV-FFA also modulated component from extracellular matrix in muscle cells. sEV-FFA triggered TAG accumulation without affecting muscle insulin-sensitivity, reduced lipid oxidation and mitochondrial respiration. Thus, in a context of lipotoxicity, MEVs mirror macrophage phenotypic plasticity and participate in maintaining muscle integrity.