Insulin-resistant M2-CD163^{+} macrophages release extracellular vesicles affecting lipid metabolism in muscle cells

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Skeletal muscle (SkM) is a major regulator of systemic glucose homeostasis. An excessive dietary intake of lipids and/or glucose can induce muscle IR. Natural residents SkM macrophages are involved in IR. It has been demonstrated that in addition to cytokines, macrophages also release extracellular vesicles (EVs) [1]. We tested whether muscle-resident macrophages, treated with an excess of fatty acids release EVs affecting SkM homeostasis.

For this purpose, small and large EVs (sEV and lEV) were collected from macrophages treated with palmitate + oleate (FFA) with or without 15 mM D-glucose (FFA/G15). Moreover, C2C12 myotubes were treated with sEV or lEV to determine their effects on muscle lipid composition and insulin-induced AKT phosphorylation.

We found that FFA-treated macrophages polarized into M2-CD163+ which released pro-/anti-inflammatory cytokines, accumulated triacylglycerols (TAG), fatty acids, phospholipids, and had reduced insulin sensitivity compared to untreated macrophages. Myotubes treated with lEV-FFA accumulated TAG and fatty acids and had reduced insulin sensitivity compared to untreated cells. sEV-FFA reduced the expression of genes involved in lipid oxidation and mitochondrial respiration and induced TAG accumulation without affecting muscle insulin resistance. The macrophage FFA/G15 condition reduced CD163+ and IL-10 and increased IFNα, IL-1β, and IL-8. In conclusion, the biological effects of EVs mirror the phenotype plasticity of the releasing macrophages recapitulating the different events leading to SkM insulin resistance in obesity-induced diabetes.