Crosstalk between muscle and immune cells in the generation of insulin resistance

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Insulin-resistance in obesity arises by both lipotoxicity and low-grade inflammation. Although inflammation is clearly recognized in adipose tissue, high fat-feeding is also responsible for a significant increase in pro-inflammatory cytokine expression in muscle. Strikingly, we found that muscle contains resident macrophages and recently reported infiltrating macrophages with a pro-inflammatory phenotype in muscle of high fat-fed mice. Conversely, in humans, markers of anti-inflammatory macrophages within muscle correlated with whole-body insulin sensitivity. We investigated the crosstalk between macrophages and muscle cells exposed to saturated and unsaturated fatty acids (palmitate vs palmitoleate), using a cell culture approach. Palmitate, but not palmitoleate, activated the TLR/NF-κB pathway to induce a significant expression of inflammatory cytokines and chemokines in L6 muscle cells. Strikingly, conditioned media (CM) from such palmitate-treated muscle cells induced THP-1 monocyte migration and confer to macrophages a pro-inflammatory polarization. Chemoattraction was not mediated by chemokines but, instead, by nucleotides, in particular ATP. Mechanistically, palmitate-treated myotubes increased expression of pannexin-3, a membrane channel, through which nucleotides were secreted to the CM. These findings constitute proof of concept that high levels of saturated fats may promote monocyte migration towards skeletal muscle in vivo, prompting the macrophage infiltration of this tissue that arises with fatty diets. They also predict that targeting chemokine production may be insufficient to reduce macrophage infiltration of muscle, as other factors such as nucleotides may significantly contribute to immune cell chemoattraction. Independently of the effect of muscle cells on immune cells, palmitate directly confers a pro-inflammatory polarization to macrophages, and conversely the mono-unsaturated acid palmitoleate conferred an anti-inflammatory polarization, mediated by AMPK. Palmitoleate also prevented the effects of palmitate, offsetting the pro-inflammatory action of the latter. These results suggest the exciting possibility that nutrient-activated AMPK may be engaged to counteract pro-inflammatory action of macrophages caused by diets rich in saturated fats. Finally, macrophages exposed to saturated fatty acids conferred insulin resistance to muscle cells, revealing a vicious cycle of inflammation and insulin resistance caused by saturated fatty acids on muscle and macrophages. Our studies of reconstitution of cellular crosstalk offer a platform to understand how macrophage infiltration and polarization within muscle occurs in obesity and diabetes, and how to possibly reverse their pro-inflammatory effects.

REFERENCES