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IMMUNE CELL REGULATION BY MUSCLE CELLS: RESPONSES TO CONTRACTION AND HIGH FATS

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KEY WORDS: myotube contraction; saturated fatty acids; myokines; monocyte chemoattraction

Obesity-induced insulin resistance and its consequent type 2 diabetes correlate with by whole body low-grade inflammation and a gain in pro-inflammatory macrophages in the expanding adipose tissue. Yet, skeletal muscle is the tissue determining insulin-dependent glucose disposal and hence the insulin response of muscle is key to whole-body insulin resistance. Therefore we asked whether skeletal muscles undergo macrophage infiltration during obesity and if so, by which mechanism. Our first two aims were to determine whether skeletal muscle gains pro-inflammatory macrophages in mice fed high fat diet (enriched in saturated fats), and whether myotubes grown in cell culture would respond to saturated fat exposure by attracting monocytes.

Exercise is a major strategy to improve whole-body insulin action, causing changes in skeletal muscle metabolism and requiring immune cell participation to aid in ongoing muscle repair, but the cues emanating from the working muscle that attract monocytes were not fully understood. Hence, our third aim was to investigate how contracting myotubes would impact on immune cells.

In mice, three days of high fat feeding sufficed to elevate skeletal muscle markers of inflammation (TNF α , CCL2) and by 1 week pro-inflammatory macrophages (CD11c⁺, F4/80⁺) were elevated in the tissue, with total macrophages representing 55% of the immune cell population within the tissue. Similarly, glucose intolerant obese individuals with documented insulin resistance of muscle showed higher Cd68 and CD11 expression compared to similarly obese but glucose tolerant individuals, which correlated with whole-body insulin resistance. Conversely, across all patients, whole-body insulin sensitivity correlated positively with gene markers of anti-inflammatory macrophages.

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In myotubes in culture, exposure to the saturated fatty acid palmitate (PA) increased cell-autonomous gene expression of CXCL2, CCL2, IL-1a, TNFa, IL6 whereas there was no effect of the monounsaturated fatty acid palmitoleate (PO) of equivalent carbon chain length. PA-treated myotubes chemoattracted monocytes and this was mediated via ATP release from myotubes, liberated through pannexin channels. PA treatment elevated the expression of pannexin-3, downstream of NFkB activation. PA-treated myotubes also polarized macrophages towards a more pro-inflammatory orientation.

Electrical pulse stimulation (EPS) induced myotube contraction and medium from these myotubes attracted monocytes, but in this case the chemoattracting factor is a protein. EPS also increased glucose uptake into the contracting myotubes, but this response was independent of exogenously secreted factors. In contrast, short-term tetanic contracture of myotubes released ATP via existing pannexins channels that acted autocrinely to promote glucose uptake. Hence, depending on the strength and type of muscle contraction/contracture, myotubes regulate their metabolism, and possibly the immune system, by distinct mechanisms.

Overall, our studies reflect the intense communication between the muscle metabolic state and surrounding immune cells.