MASTER 2 SUBJECT OF RESEARCH

Title of the Internship:
Impact of inflammation in the composition and function of skeletal muscle-released extracellular vesicles on macrophages

State of the art:
Skeletal muscle (SkM), the largest organ in the human body, is responsible for glucose and energy homeostasis, locomotion and serves as protein pool. It is a highly adaptable tissue responding to numerous environmental conditions (e.g.; physical activity/sedentarity) and physiological challenges (e.g.; nutrition, chronic inflammation) by changing its fiber size and composition. These modifications are associated with the secretion of myokines capable of modulating homeostatic adaptations into various peripheric tissues (e.g.; pancreas, adipose tissue, bone) or which are involved in the process of myogenesis. But during the last decade it has been shown that muscle cells also release lipid-derived extracellular vesicles (EVs) into the extracellular milieu, which represent new paracrine and endocrine signals, that have modified our conceptual basis to explain how muscles communicate with other tissues (PMID: 31447684). Once in the extracellular environment EVs can be incorporated into neighbouring cells where they promote phenotypic changes. As a result of their complex composition, EVs have a much more potent influence on the physiology of the recipient cells than single-molecule mediators (e.g.; lipids, hormones, cytokines). The numerous proteins, lipids, and nucleic acid components they carry can affect multiple signalling pathways inside the recipient cells.

Context of the study:
Increasing evidence suggests that inflammation occurs in SkM from obese patients. Muscle inflammation is manifested by increased immune cell infiltration and proinflammatory activation in intermyocellular and perimuscular adipose tissue. Coculture of differentiated human myotubes with macrophages in the presence of palmitic acid, to mimic an obese environment, revealed that macrophages in the presence of palmitic acid synergistically augment cytokine and chemokine expression in myotubes demonstrating a cross-talk between immune and muscle cells. But at present, the role of SkM-EVs in this cross-talk and in the development of the obesity-induced inflammation has never been studied. Two fundamental questions remain unanswered: whether inflammation modifies the release and the composition of SkM-EVs; whether SkM-EVs participate in maintaining the chronic inflammation observed in muscle from obese subjects.

Project:
During this Master training period, we will grow muscle cells in the presence of different inducers of inflammation (cytokines and fatty acids) and will determine how it affect the composition of the SkM-EVs (EV extraction & quantification, protein and lipid profiles). Then we will use these ‘inflammatory’ SkM-EVs, to treat recipient muscle cells and macrophages to see how they modify SkM cell homeostasis and polarize and play on macrophage migration. These data will clarify the role of SkM-EVs as endocrine signals, during chronic muscle inflammation in obese patients and other pathological situations associated with muscle inflammation.

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