Title of the PhD project: Role of extracellular vesicles released from skeletal muscle in the development of insulin-resistance associated with type 2 diabetes

Laboratory: CarMeN Laboratory, (INSERM1060/INRA1397), Faculty of Medicine LYON-SUD, Pierre-Bénéite, FRANCE (http://carmen.univ-lyon1.fr); Director: Dr. Hubert VIDAL

Doctoral school: Interdisciplinary Doctoral program in health-sciences (EDISS) - ED 205

Description: Scientific background and rationale: Exosomes represent a discrete population of 30-100 nanometer-sized vesicles formed in the endocytic compartments called multivesicular bodies (MVBs) during endosome maturation. They are released from the cell into the microenvironment following the fusion of MVBs with the plasma membrane. Exosomes are involved in the eradication of obsolete proteins, and can also play a role as modulators of the immune response. Recent data clearly indicated that exosomes not only convey information and signals between neighbour cells but likely between distant tissues. In agreement, exosomes have been found in blood. We have demonstrated that both myoblasts and myotubes secrete exosomes. We have then shown that myotubes transfer proteins and miRNAs through the exosomal route to myoblasts and thus can regulate myoblast proliferation and differentiation through this process. The mechanism involves a modulation of Sirt1 expression in recipient myoblasts by transferred miRNAs. Moreover, we found that during muscle cell differentiation miRNAs are selectively exported and regulated. Recently, we have demonstrated that insulin-resistance associated with a high-fat diet modified the miRNA and lipid compositions of exosomes released from skeletal muscle and likely the cross-talk between the skeletal muscle and pancreas, in mice. Aim: We want to determine, at the molecular level, which genes involved in MVB formation and exosome released, are affected by insulin-resistance in skeletal muscle and how the defects impact on the release of specific miRNAs. Moreover, we want to determine at the body level, the consequence of skeletal muscle insulin-resistance on the exosomal miRNA signature in plasma in order to identify a specific signature of insulin-resistance at the whole body level. Description of the project methodology: Year One: in vitro studies with muscle cells to determine the key genes from the MVB formation affected by insulin-resistance (use of lentivirus already available at the laboratory). Validation on skeletal muscle biopsies from animal models of insulin resistance (diet-induced obese mice), already available in the laboratory. Year two-three: in vivo studies with animal models of insulin resistance (diet-induced obese mice; DIO), to isolate exosomes from plasma during the development of insulin-resistance (4 different times) and determine to what extent, their miRNA signatures are biomarkers for alterations in skeletal muscle. In addition, exosomes from skeletal muscle from DIO mice will be injected into skeletal muscle or through the i.v route in order to determine whether their can transfer deleterious signals at the whole body level and might lead to the development of insulin-resistance. Expected results: Results from this thesis will give strong informations about the role of exosomes from skeletal muscle during the development of insulin-resistance associated with type 2 diabetes. Also, we will determine whether we can interfere or modulate exosome release from skeletal muscle. Perspectives: The development of new therapeutic approaches to prevent the development of type 2 diabetes.

Skills required:
microRNA quantification in biopsies and biofluids, extracellular vesicles isolation and characterization, molecular biology, bioinformatics, statistics (R package), metabolism and physiology

Bibliography: (Publications from the laboratory)

Key-words: microRNAs, extracellular vesicles, diabetes, insulin-resistance, skeletal muscle

Contact (Supervisor Name and email): Dr. SOPHIE ROME, srome@univ-lyon1.fr (e-mail only!)

Application should include: CV, application letter, Names and addresses of two references. The application file should be sent before May 14, 2017 to: (email of the supervisor). The open competitive recruitment process is in two steps: 1. Internal laboratory procedure.; 2. Interdisciplinary jury of EDISS.