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Project title

ROLE OF ADIPOSE TISSUE IN AGE-ASSOCIATED DISEASES

Acronym/working title

AdAGE

Principal Investigator

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Registration number of the Ethical approval

Comitato Etico Interaziendale di Novara N° 10/21

Project summary

Metabolic syndrome (MetS) constitutes a cluster of at least three out of five of the conditions including central obesity, high blood pressure, high blood sugar, high serum triglycerides, and low serum high-density lipoprotein (HDL) which together raise the risk of an individual developing atherosclerotic cardiovascular disease, type 2 diabetes (T2D), vascular and neurological complications such as a cerebrovascular accident and even some cancers. Fat toxicity, chronic inflammation and oxidative stress play a key role in the pathogenesis of metabolic disorders causing an altered communication between different organs, such us liver, pancreas, adipose tissue (AT) and immune system, and their dysfunction that eventually progress to become irreversible clinical diseases.

Obesity is a major driving force in IR and in the pathogenesis of metabolic syndrome, T2D, cardiovascular disease, as well as various types of cancer. A positive energy balance between energy intake and energy expenditure results in weight gain and obesity and many factors, including genetics, epigenetics, and lifestyle factors, have been implicated in obesity pathogenesis. In obesity, when the storage capacity of subcutaneous white AT (WAT), the largest AT depot, is exceeded, further caloric overload leads to the fat accumulation in the visceral WAT depots as well as in ectopic tissues (liver, skeletal muscle, and heart) normally involved in energy homeostasis, an event commonly defined as "lipotoxicity". Lipotoxicity is associated with numerous deleterious consequences in AT, including inflammation, fibrosis, hypoxia, dysregulated adipokine secretion and disrupted mitochondrial function, each of which may present potential novel therapeutic avenues. Notably, obesity shares numerous biological similarities with the normal aging process such as chronic inflammation and multi-system alterations and represents an accelerated and exacerbated model of aging of AT. The progressive dysfunction of AT is, indeed, increasingly recognized as an important hallmark of the aging process, which in turn contributes to metabolic alterations, multi-organ damage and a systemic proinflammatory state (inflammaging). Accordingly, understanding the interplay between accelerated aging related to obesity and AT dysfunction is critical to gain insight into the aging process in general as well as into the pathophysiology of obesity and other related conditions that are typically associated with aging.

This project is based on the assumption that a deeper understanding of adipocytes pathophysiology will help to identify molecular pathways potentially targets for treatment not only of obesity-associated diseases but also of pathologic conditions frequently found in elderly. The general objective of the project is to gain insight into the role of AT in metabolic disorders and the consequences of aging on the functional properties of adipocytes and their precursors.

The primary objectives of the study are:

1) Evaluation of the role of aging, insulin resistance and obesity on vAT-MSC browning process, in order to identify signaling pathways and cellular processes as potential target for pharmacological interventions aimed at inducing browning of AT as a therapeutic approach to mitigate the alterations of energy metabolism associated with aging, obesity and IR.

2) Analysis of the role of irisin in the browning process of human visceral AT. In the mouse model irisin is able to promote energy expenditure thanks to its ability to promote the browning of WAT.
3) Identification of biomarkers of health or functional alterations of AT associated with obesity or aging through the characterization of EV released from adipocytes and their precursors.

Duration of Study

Study start: March 2021
Study end: December 2023

Total number of participants involved:

50

Biological samples collecte

- ✔ Plasma EDTA
- ✔ Buffy coat for nucleic acid extraction
- ✔ AT-derived mesenchymal stem cells