English description

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Principal activities:
The exploitation of the data collected (RNA-Seq and mi-RNA) represents an essential step for the project. The objective is to develop tools to bring together in an integrative strategy the data from these two approaches to extract hypotheses about the molecular mechanisms involved, hypotheses that will then be biologically evaluated by functional tests conducted in vitro.

Scientific context
An increase in bone marrow adiposity has been demonstrated in different types of osteoporosis, notably post-menopausal or age-related, corticosteroid-induced (review: Hardouin P et al, 2016) and even linked to anorexia nervosa (Legroux-Gérot I et al, 2018; Bredella MA et al, 2009). Indeed, anorexia nervosa represents a unique osteoporotic situation, particularly in view of its non-inflammatory and metabolic context, the very early occurrence of its occurrence and the low number of studies devoted to it. Its multiple consequences include major neuroendocrine disturbances and low bone mineral density (BMD) associated with a fracture rate of 44% in patients as well as increased bone marrow adiposity which is strongly suspected of participating in the observed bone alterations. This bone fragility is often only partially corrected by weight gain and recovery from amenorrhea, leading to a high risk of bone fracture throughout life.

Our team has developed a mouse model mimicking the physiological consequences of anorexia nervosa (SBA model: Separation-Based Anorexia) in order to study the role of bone marrow adipocytes in the development of osteoporosis related to anorexia nervosa (Zgheib et al, 2014).
The hypothesis of the involvement of bone marrow adipocytes is supported by the fact that osteoblasts and bone marrow adipocytes come from a common progenitor, the skeletal stem cell (formerly mesenchymal stem cell), which is part of the stromal cells, and the existence of an inverse relationship between osteogenesis and adipogenesis supported by numerous studies. Among the pathways that regulate osteoblastic differentiation, it has been shown that sirtuin type 1 (Sirt1 - histone deacetylase) has a pro-osteogenic effect and an anti-adipogenic effect (Shakibaei M et al, 2012).

Furthermore, in our mouse model mimicking anorexia nervosa, we have shown a lasting decrease in Sirt1 expression in bone marrow stromal stem cells of SBA mice compared to the same cells of control mice (CT). Indeed, after 48 hours of culture (standard proliferation medium) or after 14 days of co-differentiation, stromal stem cells of SBA mice have a Sirt1 mRNA level 80% lower than that of stem cells of CT mice. This is accompanied on the one hand by an acceleration and increase in adipogenesis to the detriment of osteogenesis and on the other hand by a strong acetylation of the transcription factors Runx2 and Foxo1. All of these results were published in 2020 by Dr. Louvet in the journal Bone (Louvet L et al, 2020) thanks to postdoctoral funding from ULCO in 2017.

In order to determine the factors causing bone damage in our SBA model, we carried out, as part of V. Avilkina's thesis (thesis defended in February 2023 under the co-supervision of Prof. C. Chauveau and Dr. O. Ghali), in collaboration with the CNRS UMR-1283-8199 and the UMR 8199 genomics platform (European Genomic Institute on Diabetes (EGID), University of Lille), a transcriptomic analysis of mRNA (RNA-Seq) of stromal stem cells from SBA and control mice in order to determine the genes responsible for the decrease in Sirt1 expression and consequently the alteration observed in our SBA model mimicking anorexia nervosa. The RNA-Seq data were the subject of a preliminary study that allowed an initial demonstration of gene disruptions potentially linked to the regulation of Sirt1 and consequently to the bone impact in our SBA model mimicking anorexia nervosa.

In view of these promising results, our efforts are currently focused on identifying key genes and signaling pathways activated or repressed in stromal cells. In addition, as part of our thesis project (starting in October 2024), which recently received ULCO-Région Haut de France funding, we are planning an epigenetic study focusing on the determination of micro-RNAs (mi-RNAs), which are known as key post-transcriptional regulators of the expression of Sirt1 and consequently of the decrease in bone formation observed in our mouse model mimicking anorexia nervosa.