Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Generating an *ex vivo* system to asses how ovaries communicate with adipose tissue

Synopsis:

Within multicellular organisms, different cell populations can have fundamentally different metabolic needs. A challenging task faced by animals is that tissue-specific metabolic requirements need to be coordinated at the whole-organism level. To achieve this task, animals use extensive networks of inter-organ cross-talk, that allow the organism to maintain homeostasis. Inter-organ communication is at the core of most aspects of physiology. Female fertility has emerged as a highly relevant paradigm to study the integration of metabolism, inter-organ communication, and dietary nutrient availability. Because it is critical for animal fitness, the function of the germline needs to be tightly regulated, ensuring the reliable and timely production of high-quality oocytes. Furthermore, the production of oocytes by the germline requires a high and balanced nutrient provision. **Which molecular processes in the germline impact animal physiology, what are the signaling molecules underlying the communication between the germline and other tissues, and how these are modulated by nutrient availability, are key questions that our lab will approach.**

Using Drosophila as a model organism, I have recently described the activity of the metabolic pathway pentose phosphate pathway (PPP) in the germline as a novel integration node in the regulation of animal physiology and reproduction. In early oogenesis the germline undergoes metabolic rewiring through the upregulation of the PPP, a process that is critical for oogenesis and requires the provision of dietary sugars. Furthermore, the PPP in the germline defines a new axis of communication, required for the transcriptional regulation of a satiety factor, fit, in the fly's adipose tissue, the fat body (FB). In turn, Fit acts on the central nervous system (CNS) to regulate the appetite for sugar-rich food, which fuels PPP in the germline.

Communication between organs is often achieved via metabolites or peptides, which are secreted by one tissue into the circulating system to be delivered and act at the organ of destination. The fat body adipokine *fit*, which I showed to be regulated by the metabolic status of the germline, is expressed in the head FB supporting the hypothesis that signaling molecules are secreted from the ovaries into the hemolymph to act at a distance on the FB. However, whether this communication is direct and what is the nature of the molecules mediating the communication between these two organs is still unknown. In this project we aim to establish an *in vitro* tissue co-culture system which will allow to test if the ovary-FB communication is direct. In combination with in vivo experiments, this novel system will be used to test the hypothesis that one or multiple metabolites are sufficient to direct ovary-FB communication in the regulation of nutrient appetite and fertility. Simultaneously, we will ask how the metabolic state of the gremline, broadly affects adipose tissue functions. To achieve this, we will use a combination of approaches, taking advantage of the power of genetics of Drosophila to generate reporters, mutants, gene knockdowns and combine that with tissue morphology imaging, transcriptomics analysis and monitoring animal nutrient appetites using state of the art feeding behavior setups and fertility by measuring egg production.

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Webpage of the group

Bibliography: Carvalho-Santos, Z.; Cardoso-Figueiredo, R.; Elias, A. P.; Tastekin, I.; Baltazar, C.; Ribeiro, C. Cellular Metabolic Reprogramming Controls Sugar Appetite in Drosophila. Nat Metab. 2020, 2 (9), 958–973.