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Title: Metabolic Regulation of Hematopoietic Stem Cells and their Niche

Abstract:

Hematopoietic Stem Cells (HSCs) reside within the bone marrow (BM) where they are responsible for producing almost $10^{12}$ blood cells per day. In order to appropriately maintain their stemness while continuously producing astonishing numbers of mature cells, HSCs and their progeny establish an intricate crosstalk with the BM stroma that constitutes the HSC microenvironement or “niche”.

Although often ignored, adipocytes constitute the most abundant cell type within the human BM stroma, but little is known about their biological function or how they relate to other adipose depots in the body. BM adipocytes are most abundant in the long bones of the skeleton, and they increase dramatically in all locations with age, after chemo- or radiotherapy, or in obese individuals. Indeed, we were first to demonstrate that adipocytes are not passive space fillers of the marrow space, but that they actively inhibit the proliferation of blood progenitors. Given that NAD+ boosting strategies can revert the metabolic effects of high-fat induced obesity, we tested whether NAD+ boosters could increase blood progenitors in the BM, and found that Nicotinamide Riboside efficiently accelerates hematopoietic recovery through increased mitochondrial recycling.

Current work in the laboratory focuses on understanding how specific populations of BM adipocytes induce HSC quiescence. Given the fragility of mature adipocytes and the added challenge of isolating them from within the bone compartment, the laboratory has also focused on quantitative tool development for the study and isolation of BM adipocytes. Overall, our work has the potential to generate new niche-directed strategies to decrease the high mortality associated to the slow blood recovery after HSC transplantation for leukemia, and to unravel more general mechanisms of organ plasticity via reversible adipocyte infiltration.