15 de Novembro de 2019 12h00 | Auditório 1

JUNIOR LECTURE

UNCODING THE HEMATOPOIETIC STEM CELL NICHE IN ACUTE LEUKEMIAS

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The majority of acute myeloid leukemia (AML) patients and relapsed T-cell lymphoblastic leukemia (T-ALL) patients have a poor response to conventional chemotherapy. Leukemia-bone marrow (BM) microenvironment interactions are emerging as potential therapeutic targets. Yet, the *in vivo* role of BM niches in leukemia is poorly understood.

Using intravital microscopy of mouse calvarium BM and pre-clinical mouse models, we have shown that T-ALL expansion and chemoresistance is independent from particular niches (Hawkins ED*, Duarte D* et al. Nature. 2016). Contrarily to the current dogma, we observed that chemoresistant T-ALL cells are highly migratory. We also questioned whether leukemia itself remodels the HSC-supportive microenvironment. We reveal a previously unappreciated vascular remodeling hierarchy during progression of AML. We show that AML outcompetes non-malignant hematopoiesis by gradual elimination of stroma cells, endosteal endothelium and osteoblastic cells.

In contrast, central marrow remains vascularized, while vascular niches expand in the spleen. We further demonstrate that blood vessels in AML are more cell-permeable and contribute to loss of hematopoietic cells. We show that the endosteal endothelium represents a unique microenvironment in AML.

This environment rescues HSC loss and promotes chemotherapy efficacy (Duarte et al. Cell Stem Cell. 2018). More recently, our work highlights the role of inflammation and iron in the vascular changes induced by AML. Together, these data suggest therapies targeting the endosteal vasculature could potentially improve existing AML therapeutic regimes.