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POSTER 15: Spatial profiling of bone marrow endothelial cells in patients with myeloproliferative neoplasms

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Introduction: Myeloproliferative neoplasms (MPNs) are a group of heterogeneous hematopoietic stem cell disorders, characterized by the increase in myeloid lineages in the bone marrow (BM). MPNs are caused by driver mutations (JAK2, CALR and MPL genes) together with other genetic and cellular (niche alterations and inflammation) factors. Increased myeloid counts have been associated with cardiovascular outcomes, such as thrombosis and angiogenesis, two mayor vascular complications in MPNs. These clinical features suggest an important contribution of BM endothelial cells (BMECs) to the chronic inflammation and angiogenic activity within the marrow niche of MPN patients. However, BMECs impact on MPN pathogenesis remains unclear, partly due to the complexity to study them in the BM niche. The aim of our study is to combine spatial context and transcriptomics to assess the role of BMECs within the MPN marrow microenvironment and their impact on two cell lineages, monocytes and megakaryocytes, involved in MPN inflammatory response and fibrosis/thrombosis.

Methods: Four slides with BM biopsies from 9 MPN (Primary Myelofibrosis and Essential Thrombocythemia) patients positive for JAK2V617F and 3 healthy controls were examined using the

human World Transcriptomic Atlas (WTA) on the Nanostring GeoMx Digital Spatial Profiling (DSP) platform. We profiled 112 regions of interest (ROI) in total, selected throughout each biopsy by cell specific surface staining and by spatial location (Vascular or Endosteal areas) defined by the pathologist. Normalized matrix of all ROIs' spatial transcriptome, allowed to define specific gene signatures of the vascular and endosteal areas that were analyzed using bioinformatics tools.

Results: Gene regulatory network analysis of these gene signatures identified two distinct gene modules positive for vascular region with endothelial labeling, and notably deregulated in MPN patients compared to healthy controls. In parallel, supervised Elastic net analysis was performed. Overlap genes between both supervised analyses highlighted 82 common genes, of which 15 were associated to EC and MPN literature, confirming their relevance in endothelial functions, and vessel development in these pathologies.

Conclusion/Perspectives: Our study suggests a deregulation of the BM vascular niche in MPN patients and support further molecular analysis of the most relevant targets identified in an EC model to validate their function in an MPN context.