MICRO-ENVIRONMENTAL SIGNALS IN HEMATOPOIETIC DEVELOPMENT

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Hematopoietic development in the mammalian embryo is remarkably complex, taking place in asynchronous waves at different anatomical sites and involving a specific hierarchy of progenitors, different from the adult. The micro-environmental factors orchestrating the establishment of a functional hematopoietic system are still poorly understood, especially using in vivo approaches. Using transgenic mouse models, we have shown that endothelial-derived Kit ligand (Kitl) is required for erythro-myeloid progenitors (EMP) and macrophage development, as well as for maturation and survival of hematopoietic stem cell (HSC) precursors. Hematopoietic development is intertwined with the establishment of a functional vascular system, both being formed almost at the same time; however, it is still unclear how the two systems interact and influence each other. We have employed different genetic mouse models to study the role of blood flow derived signals in HSC development. Using embryos lacking blood flow, we found that pro-HSCs that developed in a circulation-free environment were emerging at a normal frequency but were severely impaired in their function. We also found that blood flow is instrumental in directing the establishment of a normal hematopoietic niche. Next, we have used single cell gene expression profiling and functional assays to identify an early role for the Notch pathway in HSC precursors development, and linked it with signals originating from the circulation. Currently, we are starting a new line of research aimed at establishing a novel mouse model of pediatric acute myeloid leukemia. We plan to use this model to study its cellular origins in the embryo, to identify pre-leukemic stages and associate them with a gene expression signature, and to understand how (pre-)leukemic cells shape their microenvironment.