Live and Let Die

Critical regulation of survival in normal and malignant hematopoietic stem and progenitor cells

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Hematopoietic stem cells (HSCs) are multipotent cells that give rise to all blood cells throughout an individual’s lifetime. The interaction to other cells in a specialized microenvironment in the bone marrow, known as the stem cell niche, provides HSCs with signals important for their self-renewal, survival, migration and differentiation. The hematopoietic stem cell niche is thought to be located in a low-oxygen (hypoxic) milieu, which is suggested to play a fundamental role in maintaining stem cell activity. In this thesis, entitled Live and Let Die critical regulation of survival in normal and malignant hematopoietic stem and progenitor cells, I highlight our recent findings of the importance of a balanced regulation between survival and cell death in normal and leukemic HSCs and progenitors. Acute myeloid leukemia (AML) is an example of a disturbance in the regulation of the cell fate where specific mutations cause uncontrolled survival and proliferation. Molecular abnormalities of tyrosine kinase receptors, in particular the FLT3 receptor, are implicated in the molecular pathology of AML. We have paid special attention to survival pathways downstream of the mutated FLT3 receptor. Furthermore, I discuss how hypoxia regulates proliferation and survival of normal HSCs and HSCs exposed to oxidative stress. This thesis is recommended for anyone who is curious to read more about recent research focused on the significance of maintaining a balance between survival and death in hematopoietic stem cells.