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Identificación del proyecto:

Función de la vía de Notch en la adquisión del potencial de célula madre hematopoyética, heterogeneidad y latencia (Notch-hetHSC)

Descripción del proyecto:

Hematopoietic stem cells (HSC) have served as a model for developing knowledge about the biology of stem cells. We now know that what was initially defined as a homogeneous population of HSC is much more complex and includes different cell types. Various studies carried out over time have shown that there is a rare population of quiescent cells that are responsible for reconstituting long term hematopoiesis in transplantation assays. In addition to these cells, there are HSC populations that can enter a dormant state and are only activated in response to specific stimuli, as well as HSCs that are biased in their ability to differentiate to the myeloid or lymphoid lineage. In addition, the population defined as HSC, its differentiation potential and self-renewal activity, as does its resistance to cellular transformation varies with age. HSCs are generated during embryonic life and go through different waves of development that take place at specific locations. In the embryo they are generated in the Aorta/Gonad/Mesonephros (AGM) and then go to the fetal liver where they expand. Finally, HSCs migrate to the bone marrow that constitute their definitive niche in the adult.. Nevertheless, it is not yet known if HSCs are specified as a homogeneous population that progressively acquires different characteristics, if they are generated directly as heterogeneous population of cells, and which are the signals that control this process.

The Notch signaling pathway is essential for the generation of cellular heterogeneity from groups of equipotent cells. Previous work in our laboratory has shown that Notch plays an essential role in the generation of HSCs in the mouse embryo, as well as in neoplastic transformation. In addition, the type of ligand that Notch activates determines the degree of activation of the pathway with a direct impact on the production of functional HSCs. Recent results suggest that Notch is involved in the generation of heterogeneity of HSCs by modulating their epigenetic memory and their subsequent ability to respond to specific signals.

The main objective of this project is to elucidate the origin of the HSC heterogeneity in terms of latency and the generation of biased lineages in the mouse embryo and the adult organism. In addition, we will determine whether and how Notch activity influences the potential response of the HSCs to specific signals at different stages of development, which may impact in their susceptibility to oncogenic transformation.

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