PhD position - INSERM U976 - Institut de Recherche Saint Louis - Paris

Lymphoid Development in Human Ontogeny

Hematopoiesis is organized as a complex developmental hierarchy with multipotent hematopoietic stem cells (HSCs) at the apex. HSC undergo a dynamic process of multi-lineage diversification giving rise to a series of intermediates progenitor cells with gradual fate restriction that ultimately generate mature blood cells. According the classical model of hematopoietic organization established in the mouse, HSCs differentiate into lineage-biased multipotent progenitors (MPPs) which segregate into common myeloid progenitors (CMPs) and common lymphoid progenitors (CLPs). CLPs define a founder lymphoid population that diversifies into early B cell precursors (EBPs), and natural killer and innate lymphoid cell precursors (NK/ILCPs), or into early T cell precursors (ETPs) leaving the bone marrow (BM) towards the thymus. The hosting laboratory which has been studying human thymus colonization for the last twenty years (Haddad et al., 2006) now focusses on defining the development trajectory and gene regulatory networks controlling the emergence of human lymphoid progenitors in ontogeny. In the last years we have demonstrated that human lymphopoiesis displays a bipartite architecture stemming from distinct populations of CD127/IL7R$^{-/+}$ early lymphoid progenitors (ELP) that differ as to both differentiation potentials and growth-factor dependency (Alhaj Hussen et al., 2017). From our recent studies it emerges that human ELPs originate from a lymphoid-restricted bipotent ancestor population and that their differentiation proceeds asynchronously and is subjected to distinct cell-intrinsic versus -extrinsic regulatory mechanisms (*manuscript in preparation*). Our data also indicate that the balance between CD127/IL7R$^{-/+}$ ELP differentiation is finely tuned across ontogeny, especially during the transition between fetal and postnatal life when B lymphocyte output reaches maximum levels.

The proposed thesis project will aim at investigating the epigenetic and transcriptional bases of lymphoid lineage specification during development and aging. We will follow the dynamic remodeling of human lymphopoiesis during development and aging : (1.) by spectral flow cytometry mapping of the changes in lymphoid architecture in fetal, neonatal and adult donors; (2.) by evaluating concomitant changes in HSCs and LMPPs lymphoid potential; (3.) by comparative transcriptional and epigenetic characterization of fetal, neonatal and aged HSCs, MPPs and CLPs; (4.) by evaluating the capacity of fetal, adult and aged HSCs to reconstitute lympho-myeloid lineages following transfer into immunodeficient mice.

This project addresses fundamental questions regarding the factors that modulate lymphoid potential and lymphocyte production patterns during ontogeny and with age. As well as the fundamental questions it is likely that this project will contribute to a better understanding of the differences in age incidence of acute myeloid versus lymphoid leukemias, and help optimizing transplantation and therapeutic strategies to reconstitute lymphoid subsets in disease and aging.

The selected candidate will be presented to the doctoral school entrance contests to be held in early July 2021

References :

Alhaj Hussen, K., Vu Manh, T.P., Guimiot, F., Nelson, E., Chabaane, E., Delord, M., Barbier, M., Berthault, C., Dulphy, N., Alberdi, A.J., et al. (2017). Molecular and Functional Characterization of Lymphoid Progenitor Subsets Reveals a Bipartite Architecture of Human Lymphopoiesis. Immunity 47, 680-696 e688.

Haddad, R., Guimiot, F., Six, E., Jourquin, F., Setterblad, N., Kahn, E., Yagello, M., Schiffer, C., Andre-Schmutz, I., Cavazzana-Calvo, M., et al. (2006). Dynamics of thymus-colonizing cells during human development. Immunity 24, 217-230.

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