POSTER 2: Cell quiescence and reprogramming are distinctive features of pre-leukemic stem cells in B-cell acute lymphoid leukemia

Vincent Fregona 1, Manon Bayet 1, Mathieu Bouttier 1, Laetitia Largeaud 1.2, Camille Hamelle 1, Laura Jamrog 1, Naïs Prade 1.2, Stéphanie Lagarde 1.2, Sylvie Hebrard 1, Marlène Pasquet 3, Christine Didier 1, Ahmed Amine Khamlichi 4, Cyril Broccardo 1, Éric Delabesse 1.2', Stéphane Mancini 5 and Bastien Gerby 1

1-Centre de Recherches en Cancérologie de Toulouse (CRCT), Université de Toulouse, Institut National de la Santé et de la Recherche Médicale (INSERM), Université Toulouse III Paul Sabatier (UPS), 31100 Toulouse, France.
2-Laboratoire d'Hématologie, Centre Hospitalier Universitaire (CHU) de Toulouse, 31000 Toulouse, France.
3-Department of Pediatric Hematology, CHU de Toulouse, 31000 Toulouse, France.
4-Institut de Pharmacologie et de Biologie Structurale (IPBS), Université de Toulouse, Centre National de la Recherche Scientifique (CNRS), UPS, 31077 Toulouse, France.
5-Microenvironment, Cell differentiation, immunology and Cancer (MICMAC), Inserm U1236, Rennes.

The development of B-cell acute lymphoblastic leukemia (B-ALL) is a multistep process characterized by the acquisition of diverse genetic alterations. Our group has reported a genetically engineered mouse model in which PAXS-ELN oncogene is specifically expressed in the B-cell compartment. This transgenic mouse model represents a rare and accurate B-ALL modeling that reveals a pre-leukemic phase and recapitulates the key features of the human disease. Therefore, this in vivo model gives us the opportunity to address the deregulation of normal B-cell development by PAXS-ELN in the early steps of the disease before malignant transformation. In normal hematopoiesis, cell quiescence and self-renewal activity are tightly regulated and are distinctive characteristics of normal hematopoietic stem cells (HSCs). Indeed, more mature cells including B-cell progenitors are devoid of these stem cell properties. However, several evidences indicated that primary genetic alterations should convert normal committed progenitors into pre-leukemic stem cells (pre-LSCs) by reprogramming stem cell-like properties. These pre-LSCs are described as resistant to chemotherapy agent and are involve in patient relapse. These observations support the idea that cellular plasticity, reprogramming and cancer initiation are tightly intertwined and represent key features to be studied to specifically target the molecular mechanism regulating the pre-LSCs activity. In this context, the questions of how and to what extent a primary oncogene reprograms stem cell-like properties in committed B-cells remains to be resolved. Here, we used the PAX5-ELN oncogenic model to demonstrate a causal link between the differentiation blockade, the self-renewal and the emergence ofpre-LSCs. First, through multi-parametric immunophenotyping, we show that PAXS-ELN oncoprotein disrupts the differentiation ofpre-leukemic cells by enforcing dependence to the IL7r/JAK-STAT signaling pathway. This disruption is associated with the induction of rare and quiescent pre-LSCs that sustain the leukemia-initiating activity, as assessed using the H2B-GFP model. Finally, the integration of transcriptomic and chromatin accessibility data reveals that those quiescent pre-LSCs Jose B-cell identity and reactivate an immature molecular program, reminiscent of human B-ALL chemo-resistant cells. Collectively, our study sheds new lights on the biological mechanisms underlying the cell-of-origin of leukemia.