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POSTER 7: Function of USP7 in normal hematopoiesis

Antoine Nouhaud[1], Vincent Fregona[1], Manon Bayet[1], Mathieu Bouttier[1], Pauline Enfedaque[1], Sylvie Hebrard[1], Stéphanie Lagarde[1,2], Laetitia Largeaud[1,2], Naïs Prade[1,2], Camille Hamelle[1], Esmaa Sellam[1], Marlène Pasquet[1,3], Cyril Broccardo[1], Bastien Gerby[1], Eric Delabesse[1,2] and Christine Didier[1].

1: Centre de Recherches en Cancérologie de Toulouse (CRCT) - Université Paul Sabatier - INSERM (U1037) - CNRS (UMR 5071)
2: Institut Universitaire du Cancer de Toulouse (IUCT) - CHU Toulouse
3: Département d'hématologie pédiatrique - CHU Toulouse

The ubiquitin-proteasome system catalyzes the addition of ubiquitin chains onto proteins to address for a part to the proteasome. These ubiquitin chains are regulated by deubiquitinating enzyme including the Ubiquin-Specific-Protease 7 (USP7). Due to its multiples substrates, USP7 plays roles in a large number of physiological processes but also participates in the oncogenesis and therapeutic resistance of several cancers including hematopoietic malignancies. Recently, USP7 mutations have been found in 12% of pediatric T-acute lymphoblastic leukemia (T-ALL)1 whose functions remain misunderstood. In addition, studies have shown that USP7 supports oncogenic programs notably in T-ALL2 and acute myeloid leukemia3. Moreover, the function of USP7 during normal hematopoiesis remains currently poorly understood. Using a USP7 haploinsufficient mouse model (USP7+/-), we describe here new function of USP7 in hematopoiesis. Phenotypic analyses of bone marrow cells reveal a significant reduction of hematopoietic stem and progenitor cells (HSPC) frequency in USP7+/- mice compare to wild type counterpart at steady state. However, these differences are not found in mature hematopoietic cells compartments. We also observed a significant reduction of quiescent cells among Hematopoietic Stem Cells (HSC) USP7+/- compare to wild type. Furthermore, to assess the impact of USP7 heterozygous invalidation on HSPC function, competitive syngeneic transplantation of USP7+/- and wild type HSPCs was performed and shows a decrease in engraftment capacity of USP7+/- HSPCs compare to wild type. Overall,

our results show that USP7 participates in the HSPC maintenance, quiescence and function. To go further, we plan to study the molecular mechanisms involved using transcriptomic and proteomic approaches.

1 : Liu Y, Easton J, Shao Y, et al. The genomic landscape of pediatric and young adult T-lineage acute lymphoblastic leukemia. Nat Genet. 2017;49(8):1211-1218.

2 : Jin Q, Martinez CA, Arcipowski KM, et al. USP7 Cooperates with NOTCH1 to Drive the Oncogenic Transcriptional Program in T-Cell Leukemia. Clin Cancer Res. 2019;25(1):222-239.

3 : Cartel M, Mouchel PL, Gotanègre M, et al. Inhibition of ubiquitin-specific protease 7 sensitizes acute myeloid leukemia to chemotherapy. Leukemia. 2021;35(2):417-432.