29ème congrès du CHO
11 au 14 octobre 2023
Giens, Var, France

Role of JAM-C-mediated adhesion in the maintenance of stemness of acute myeloid leukemia cells

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JAM-C is an adhesion molecule belonging to the immunoglobulin superfamily and expressed by hematopoietic stem cells (HSCs). JAM-C can interact with itself or with JAM-B, its high-affinity ligand, expressed by bone marrow stromal cells (Arcangeli et al, Blood, 2011). In Acute Myeloid Leukemia, JAM-C is expressed by leukemic stem cells (LSCs), and high frequencies of JAM-C+ LSCs are associated with poor prognosis (De grandis et al, Cancer Research, 2017). This study aims to explore whether JAM-C plays an active role in the production and maintenance of the LSC compartment in the early phases of the disease. To address this question, we generated mice that can be conditionally deleted for JAM-C expression in HSCs before induction of AML disease thanks to expression of MLL-AF9 fusion gene (Stavropoulou et al, Cancer Cell, 2016). We also generated several LSC-like cell lines expressing or not JAM-C in order to develop in vitro models amenable to functional assays. We have shown that deletion of JAM-C in leukemic mice modifies the leukemia-initiating cell compartment by altering gene expression in LSCs. We identified 53 overexpressed genes belonging to the pro-inflammatory signaling pathways AP-1 and TNF-a that had a prognostic value for human disease outcome. Using a reporter system for AP-1 activity, we further show that AP-1 activation is partially controlled by JAM-C expression and cell differentiation state. Ongoing experiments aim at identify the molecular mechanisms by which loss of JAM-C expression could lead to increased AP-1 and TNF-a pathway genes expression.