POSTER 23: What are the signaling pathways downstream of JAM-C that maintain the sternness of LSCs ?

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Acute Myeloid Leukemia (AML) is a heterogeneous disease with a poor prognosis that originates in hematopoietic stem or progenitor cells (HSPC). Genetic alterations occurring in HSPC leads to abnormal proliferation and blockage of differentiation of sick hematopoietic cells that are replenished by leukemic stem cells (LSC). The latter are enriched in the immature CD34+CD38- leukemic compartment and are responsible for relapse in more than 50% of patients. Therefore, LSC frequencies determine the overall disease outcome and their localization in protective niches of the bone marrow contributes to chemo-resistance of LSC.

In the laboratory, it has been shown that the adhesion molecule JAM-C is expressed by LSC and interacts with JAM-B expressed by bone marrow stromal cells. Accordingly, high frequencies of JAM-C-expressing leukemic cells have been associated with poor AML prognosis, Increased proportions of JAM-C-expressing cells were found in relapsing samples suggesting that JAM-C may play an active role in the maintenance ofLSC in chemo-protective microenvironment

However, the link between JAM-C expression and adhesion of LSC to bone marrow microenvironment remained to be defined.

To answer this question, we set-up several leukemic model cell lines expressing JAM-C or not in order to study the biochemical modalities ofJAM-C signaling. We found that the intracellular domain of JAM-C (ICD) is cleaved, similar to Notch signaling, Identification of the intracellular sequence involved in JAM-C ICD release allowed us to establish HeLa cell models suitable for Crisp/Cas9 screenings. Cleavage of JAM-C is modulated by cell/cell interactions and by cell adhesion to ligands present in the bone marrow microenvironment Accordingly, JAM-B, the high affinity ligand of JAM-C, supported LSC adhesion and reduced JAM-C cleavage. Altogether, our data suggest that cleavage of JAM-C may switch LSC from extrinsic stromal dependent chemo-resistance to cell-autonomous signaling.