POSTER 22: Unravelling the role(s) of micro-environmement in myelodysplastic syndromes: from stromal cells to human ossicles in mice

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Introduction:

Myelodysplastic syndromes (MDS) are clonal disorders of hematopoietic stem cells. In some cases, MDS can be diagnosed after a stage of clonal hematopoiesis (CH), an entity described in healthy elderly individuals. The mechanisms involved in the evolution of CH to MDS remain to be characterized. Numerous studies have highlighted the role of the bone marrow microenviromnent (BMME) in the pathophysiology of MDS [1]. Mesenchymal stromal cells (MSC), a key component of BMME, have the ability to develop in viva hematopoietic niches, called human ossicles (hOss), that mimic human BMME in immune-deficient (ID) mice [2]. Here, we aimed to fully characterized MSC from MDS patients, compared to age-matched healthy patients, by combining in vitro and in viva approaches, and better decipher the role of pathological hOss on the development of normal hematopoiesis.

Methods:

Human MS Cs were isolated from bone marrow (BM) of MDS patients and femoral head (FH) of age-matched healthy patients. After an extensive in vitro characterization (morphology, proliferation rate, senescence, flow cytometry, and gene expression), normal and pathological MSC were used to generate hOss in ID mice. Notably, we studied the level of engraftment of long-term normal hematopoiesis following intravenous injection of human cord blood (CB) CD34+ cells in hOss and mouse BM.

Results:

Slight differences were observed in vitro between normal and pathological MSCs, especially in terms of proliferation rates. Results ofRNA-Seq analysis indicated an up-regulation of HOXB7, HOXA2 and HOXB6 genes in MSCs from patients with MDS, results that are being validated in a larger cohort of MSCs. In ID mice, MSCs from MDS patients and FH controls were able to generate hOss, with similar weight and size. Long-term hematopoiesis developed in all MDS/FH-derived hOss and in mouse BM, without major differences in lineage distribution. Engrafted human CD34+ cells were detectable in all generated hOss, with no major differences observed with respect to MSC origin. LTC-IC and RNA sequencing of sorted human CD34+ from hOss and mouse BM cells are in progress.

Conclusion:

Although MSC from MDS patients and from FH controls are different in vitro, MSC from both origins are capable of generating hOss, which are capable of supporting normal hematopoiesis. Based on this model, we aim at investigating if and how the MDS microenvironment modulates CH development.

[1] J.-C. Jann et al., « Bone marrow derived stromal cells from myelodysplastic syndromes are altered but not clonally mutated in viva », Nat Commun, vol. 12, no 1, p. 6170, act. 2021, doi: 10.1038/s41467-021-26424-3.

[2] A. Reinisch et al., « A humanized bone marrow ossicle xenotransplantation model enables improved engraftment of healthy and leukemic human hematopoietic cells», Nat Med, _vol. 22, no 7, p.812-821,juill. 2016, doi: 10.1038/nm.4103.