POSTER 20: Stepwise GA T Al and SMC3 mutations alter megakaryocyte differentiation in a Down syndrome leukemia model

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Acute megakaryoblastic leukemia of Down syndrome (DS-AMKL) is a model of clonal evolution from a preleukemic transient myeloproliferative disorder requiring both a trisomy 21 (T21) and a GATA1s mutation to a leukemia driven by additional driver mutations. We modelled the megakaryocyte differentiation defect through stepwise gene editing of GATA1s, SMC3+/. and MPL^{w515K} providing 20 different trisomy or disomy 21 iPSC clones. GATA1s profoundly reshaped iPSC-derived hematopoietic architecture with gradual myeloid-to-megakaryocyte shift and megakaryocyte differentiation alteration upon addition of SMC3 and MPL mutations. Transcriptional, chromatin accessibility and GATA 1 binding data showed alteration of essential megakaryocyte differentiation genes, including NFE2 downregulation that was associated with loss of GATA1s binding and functionally-involved in megakaryocyte differentiation blockage. T21 enhanced the proliferative phenotype reproducing the cellular and molecular abnormalities of DS-AMKL Our study provides a unique array of human cell-based models revealing individual contributions of different mutations to DS-AMKL differentiation blockage, a major determinant of leukemic progression,