POSTER 9: Exploring the role of the bone marrow microenvironment in pediatric Acute Myeloid Leukemia

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Introduction. ~40% of pediatric acute myeloid leukemia (pedAML) patients relapse due to different chemoresistance mechanisms. Hematopoietic bone marrow (BM) niches, that are key effectors of normal blood system regulation, are among the known drivers of treatment resistance in leukemia. In accordance, a recent study has described alterations of BM mesenchyrnal stem cells (MSC) in pedAML 1. Here we aimed at deciphering the contribution of pedAML stroma in leukemic cell expansion and how it impacts normal hematopoiesis. Methods. BM MSC isolated from pedAML patients or healthy contrais were cocultured with human CB CD34+ cells for a week. The phenotype of recovered CD34+ cells and their CFU/LTC-IC contents were explored. The ability of pedAML MSC to produce human BM niches in vivo (humanized ossicle, hOss)2 and the impact of the pedAML MSC-derived hOss on human hematopoiesis after human CD34+ cell transplants was studied. Moreover, the role of pedAML hOss on leukemic cell growth after pedAML blast cell transplants was also assessed, in autologous and heterologous conditions.

Results. In coculture experiments, pedAML MSC were supportive of normal hematopoiesis but showed a trend to decrease granula-macrophage progenitors and to enhance CFU-GM number. PedAML MSC were able to generate hOss that supported long term normal hematopoiesis. However, a significant diminution of hematopoietic stem cells (HSC) and clonogenic progenitors was observed in human CD34+ cells recovered from pedAML MSC-derived hOss, without impact on mature cell production. Preliminary results reveal a better leukemic support for autologous AML MSC-derived hüss, similar to control MSC, compared to heterologous pedAML hOss. Secondary transplantation of AML cells recovered from hOss in NSG mice confirmed this superior support. Genetie alterations of

leukemic cells recovered from pedBM MSC ossicles were similar to input ce lis regardless of MSC origin, suggesting no impact on the clonai evolution.

Conclusions: These first results suggest that PedAML MSC harbor a specific ability to support normal hematopoietic and leukemic development compared to healthy pedBM MSC. The benefit of autologous BM/leukemic context may rel y on the secretion of specific factors or BM structures that merit further investigation. AML stromal cells also induce in vitro and in vivo dysregulated early myelopoiesis that may contribute to leukemic process or limit post-treatment hematopoietic reconstitution at long term.

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