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POSTER ABSTRACTS

506.BONE MARROW MICROENVIRONMENT

Protective Function of Human Skin Mesenchymal Niches for Acute Myeloid Leukemia-Initiating Stem Cells

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Leukemia cutis (LC) or leukemic cell infiltration in skin is one of the common extramedullary manifestations in acute myeloid leukemia (AML) and signifies a poorer prognosis. However, the pathogenesis and maintenance of LC have been understudied, limiting our understanding of its impact on AML progression and relapse. We recently have shown that the AML cells infiltrated in the mouse skin during steady state and after chemotherapy were capable to regenerate AML after serial transplantation (Sandhow et al., J. Exp. Med, 2023). Further characterization of the skin mesenchymal stem cells (MSCs) suggests that skin MSCs could maintain AML-initiating stem cells (LSCs) and protect them from chemotherapy, even to a greater degree than their bone marrow (BM) counterparts. These data suggest the protective role of skin mesenchymal niche in AML LSCs during chemotherapy. However, it remains unexplored whether human skin MSCs exert the same functional impact on human AML cells.

We here have explored the role of human skin MSCs in AML maintenance and survival during chemotherapy by RNA sequencing and *in vitro* co-culture of patient-derived AML cells with primary human skin MSCs in comparison with BM MSCs. We first by prospective characterization identified human skin MSCs with a phenotype of CD45-CD235a-CD31-CD44+CD146- from healthy donors. RNA sequencing and Q-PCR revealed expression of key hematopoietic stem cell (HSC) regulatory genes including *THPO*, *SCF*, *CXCL12* and *LAMA4* in human skin MSCs. Interestingly, while HSC maintenance genes such as *THPO* and *KITLG* were significantly upregulated in skin MSCs ($p<0.0001$ and $p<0.05$, respectively), HSC negative regulator *SPP1* was downregulated ($p=0.05$), pointing to a possible better hematopoiesis-supportive function of skin MSCs. In line with this, our functional studies indicated that skin MSCs displayed a superior protective effect on human AML cell line THP-1 than their BM cell counterparts during cytarabine (Ara-C) treatment in the *in vitro* co-culture. There were more residual chemo-resistant AML cells, reflected in the higher number of CD36+ AML cells after treatment with Ara-C in cocultures with skin MSCs, compared to that with BM MSCs ($p=0.0065$). This result was confirmed by functional assays showing the increased number of cobblestone area-forming cells ($p=0.0298$) and colony-forming units ($p=0.038$) within the residual AML cells co-cultured with skin MSCs.

To investigate the mechanisms involved in the protective function of human skin MSCs, we have performed RNA-sequencing of the human skin and BM MSCs before and after co-culture with AML cells. This has revealed potential unique molecular pathways between AML and skin MSCs. Furthermore, there were dramatically less altered genes in the skin MSCs compared to BM MSCs after 3 day-coculture with THP1 AML cells (221 vs 1761 altered genes with adjusted p values <0.05). These data indicate that skin MSCs are likely more resistant to AML-remodeling, which could in turn maintain AML cells in quiescence status, thereby protecting AML cells from Ara-C treatment. This speculation is currently under validation. In addition, gene set enrichment analysis showed upregulated genes associated with fatty acid metabolisms and ribosome in skin MSCs compared to BM MSCs, providing molecular evidence for a potential better metabolic support of skin MSCs for AML cells.

Taken together, our preliminary data indicate an important role of human skin MSCs in supporting and protecting AML cells during Ara-C treatment. We are further investigating the underlying mechanisms.

Disclosures No relevant conflicts of interest to declare.

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