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P1414 MARROW ADIPOCYTE-ENRICHED NICHE HOSTS AND INFLUENCES A FRACTION OF HEMATOPOIETIC PROGENITORS IN ADULT HIP BONE

Topic: 23. Hematopoiesis, stem cells and microenvironment

Drenka Trivanovic[1, 2], Konstantin Horas[2, 3], Bianca Schlierf[1, 2], Maximilian Rudert[2, 3], Marietta Herrmann[1, 2]

[1] IZKF Research Group Tissue Regeneration in Musculoskeletal Diseases Orthopedic Center for Musculoskeletal Research, University Clinics Wuerzburg, Wuerzburg, Germany;[2] Bernhard-Heine-Center for Locomotion Research, University of Wuerzburg, Wuerzburg, Germany;[3] Department of Orthopaedic Surgery, Koenig-Ludwig-Haus, University of Wuerzburg, Wuerzburg, Germany

Background:

The hematopoietic process is tightly regulated by the bone marrow (BM) microenvironment. Emerging studies recognized a regulatory role of mouse BM adipose tissue (BMAT) on self-renewal and differentiation of hematopoietic stem cells (HSC) and progenitors, while results on human BMAT are still scarce.

Aims: Although hip arthroplasty-derived BM serves as an available resource for non-malignant hematopoietic cell research, the BMAT component of this BM and its' impact on hematopoietic progenitors is not yet revealed. Therefore, our aims were to explore the contribution of human BMAT to the maintenance of hematopoietic progenitors.

Methods: BM samples of acetabular bones were obtained from patients undergoing hip arthroplasty (n=13, 65.7±12.5 years, Ethical approval 187/18). Centrifugation was applied to separate the fatty layer containing BMAT from the BM cell suspension. The BM fraction was used for isolation of BM mononuclear (BMC) and expansion of BM mesenchymal stromal cells (BM-MSC). Digestion of BMAT was applied to separate the non-adipocytic cells of BMAT from mature adipocytes, expand them, and to investigate their functions and transcriptional activity by RNA sequencing. Multiparametric flow cytometry was applied to explore surface marker expression. Hematopoietic activity was investigated by short-term colony assays of cells *ex vivo* and *in vitro* upon co-culture with BM-MSC or sub-cultured BMAT adipocytes. Results are presented as mean ±SD and statistical significance was estimated by paired tests.

Results:

We found that the total colony forming cell number in BMC (0.147±0.068) was significantly higher than in BMAT-associated cells (0.0684±0.062%, p=0.0002, n=11). The strongest reduction within BMAT was observed in colony forming unit (CFU)-macrophages and CFU-granulocyte-erythroid-macrophage/monocyte-megakaryocytes. The content of $CD45^+CD34^+$ cells was higher in BMC (0.901±1.009%) than in BMAT (0.357±0.505%), while interestingly no differences were found in $CD33^+$ cell frequencies. Both, expanded BMAT and sub-cultured BMAT adipocytes showed stronger adipogenic potential than BM-MSC. When compared to BM-MSC, sub-cultured BMAT adipocytes showed weaker potential to support growth of committed hematopoietic progenitors within BMC *ex vivo*, favorizing the growth of early and late erythroid progenitors at the expense of other hematopoietic cells. Transcriptomic analyses showed that HSC niche factors (*Angptl4, Wnt5b, Il7, Dkk3*), but also *LepR* were upregulated in BM-MSC compared to expanded BMAT cells.

Summary/Conclusion:

Our findings indicate a yet unrevealed participation of the BMAT niche in compartmentalization of adult hip bone hematopoietic progenitors by hosting a set of hematopoietic cells and potentially, BMAT progenitors in the close proximity of BM adipocytes. Since a behavior of BM populations is dependent on local microenvironmental context

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and bone region, obtained results might reflect pathologic settings in arthroplasty patients. Further studies have to address the potential coupling of marrow adipogenesis and hematopoietic progenitor maintenance during aging and diseases.

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