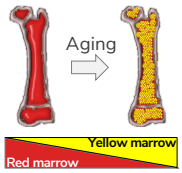
Direct and indirect osteogenesis by bone-resident MSCs during ageing is epigenetically regulated by FOXO1

German Institute of Human Nutrition Potsdam-Rehbrücke

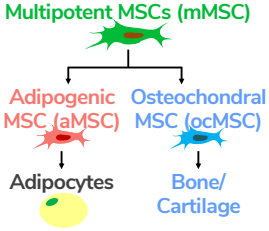
George Soultoukis, Marina Leer, Tim J. Schulz

Background

Ectopic bone marrow fat



- Bone marrow adipocytes (BMAds) accumulate with age, resulting in yellow marrow in adults >25 years.
- This correlates to loss of bone strength, impaired hematopoiesis, and systemic inflammation
- BMAd, bone, and cartilage formation stems from specialized mesenchymal stromal cells (MSCs)



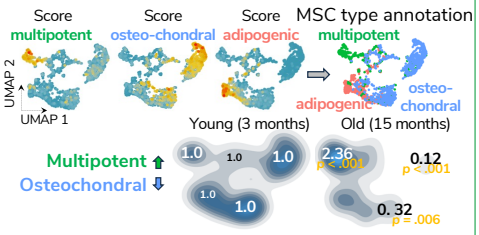
Aims

1. Analysis of the contribution of specialized mesenchymal stromal cells (MSCs) of the bone to the formation of the stem cell niche and their influence on bone regeneration.
2. Investigation of the effects of aging on chromatin organization mechanisms that regulate the specialization of MSCs into osteo-chondrogenic or adipogenic precursor cells.
3. Multimodal investigation of the FOXO1-mediated epigenetic organization in relation to bone health and regenerative processes.

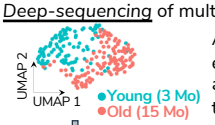
Results

1. MSC depletion due to pro-adipogenic age-related transcriptional re-programming

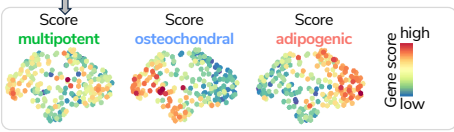
scRNA-Seq: Identification of distinct MSC subpopulations using gene module scoring.



Deep-sequencing of multipotent MSCs

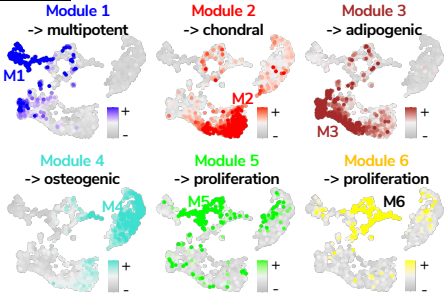


Aging multipotent MSCs exhibit an early pro-adipogenic specialization at the transcriptomic level.

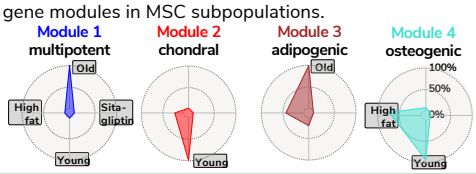


2. Co-expression of adipogenic genes in aging MSCs, and osteochondral genes in young MSCs

Weighted gene co-expression network analysis (WGCNA): Module enrichment of biological processes.

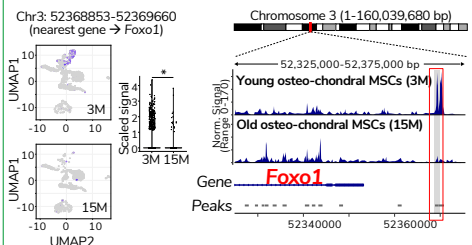


Aging reduces osteochondral and increases adipogenic gene modules in MSC subpopulations.

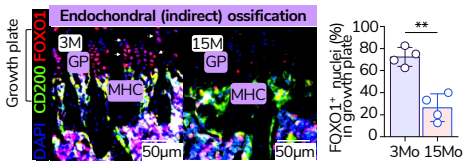


3. Mechanism: Pioneer transcription factor FOXO1 regulates MSC specialization.

scATAC-Seq: Mapping of accessible chromatin regions identifies reduced accessibility of a FOXO1 enhancer.

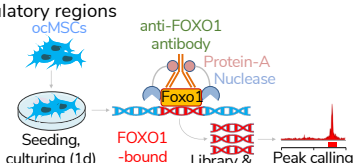


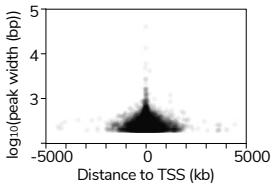
Loss of FOXO1⁺ nuclei in chondroblasts of the growth plate in aged mice.



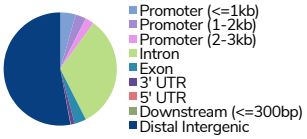
4. FOXO1 promotes osteochondral lineage commitment through chromatin remodeling

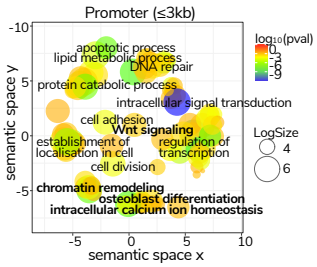
Cut&Run-Seq: ocMSC-specific chromosomal loci representing FOXO1-specific regulatory regions





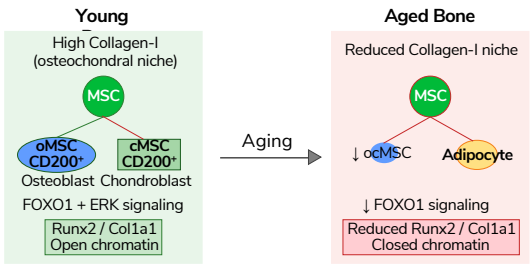
Promoter-specific gene set enrichment: FOXO1-bound promoters regulate genes related to chromatin remodeling and osteoblast differentiation





Summary & Outlook

Aging Disrupts MSC Osteogenic Commitment via Collagen-I / FOXO1 Axis



Outlook:

- determine presence or absence of mMSCs in the growth plate using Adipo-CRE mice
- clone FOXO1 enhancer into ocMSCs to validate effect of enhancer site on collagen type I-mediated FOXO1 activation
- Determine apigenetic effects of aging on adipogenic MSC commitment

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