Perivascular Lipid Hubs: A New Player In Fatty Degeneration Of The Bone Marrow?

Sophie Morgani[1], Kevin Leclerc[1], Margaux Sambon[1], Philipp Leucht[1,2]
sophie.morgani@nyulangone.org

[1] Department of Orthopaedic Surgery, NYU Robert I. Grossman School of Medicine, New York, NY, United States of America
[2] Department of Cell Biology, NYU Robert I. Grossman School of Medicine, New York, NY, United States of America

ABSTRACT INTRODUCTION: Age-associated fatty degeneration of the bone marrow is accompanied by increased skeletal fragility and osteoporosis, impaired fracture healing, bone metastasis, and diminished skeletal and hematopoietic stem cell function [1-4]. Thus, regulating the level of marrow fat is a promising strategy for improving skeletal health and regenerative capacity. A major hurdle is that the cellular basis of bone marrow fatty degeneration is unclear, precluding the development of targeted therapies. While previous studies suggest that adipocytes are responsible [5], we found that the extent of adipocyte accrual is not sufficient to explain the increase in bone marrow fat, and hence other cell types must be involved. Our objective was to define the cell types involved in the accumulation of lipids within the BM during aging.

METHODS: To investigate the cellular lipid source, we combined fluorogenic lipid dyes with high-resolution confocal microscopy. We analyzed young (8-16-week-old) and middle-aged (52-week-old) mice. All animal experiments were performed in accordance with the guidelines of NYU Robert I. Grossman School of Medicine Institutional Animal Care and Use Committee (IACUC). Unpaired t-tests were used to determine statistical significance.

RESULTS SECTION: In addition to the previously described lipid-storing adipocytes within the metaphysis and epiphysis, we also observed concentrated lipid foci within the diaphysis. Diaphyseal "lipid hubs" comprise lipid-laden cells surrounded by extracellular lipid droplets. The number of lipid hubs significantly increases with age, pinpointing them as an uncharacterized player in bone marrow fatty degeneration. Preliminary single-cell RNA sequencing data indicate that these cells may be of vascular smooth muscle origin and reveal specific lipid metabolism genes that are transcriptionally perturbed within this population during aging.

DISCUSSION: Together these findings identify a non-adipocyte source of bone marrow lipids that could represent a novel cellular target to counteract bone marrow fatty degeneration. Lipid hubs are sinusoid-adjacent and hence, in addition to influencing the local bone marrow microenvironment, may be a source of circulating lipids that contribute to systemic inflammaging and organ degeneration [6].

SIGNIFICANCE/CLINICAL RELEVANCE: Weakening of the skeleton is one of the most common causes of age-associated impairments, and fractures significantly increase the risk of death in elderly individuals. Since the global population is rapidly aging, it is imperative to establish and treat the root of skeletal degeneration to prolong health span.

ACKNOWLEDGEMENTS: Sophie Morgani is a New York Stem Cell Foundation Druckenmiller Fellow. This research was supported by The New York Stem Cell Foundation.

REFERENCES:

1. Singh, L., et al., *Good, Bad, or Ugly: the Biological Roles of Bone Marrow Fat.* Curr Osteoporos Rep, 2018. **16**(2): p. 130-137.
2. Devlin, M.J., *Bone marrow composition, diabetes, and fracture risk: More bad news for saturated fat.* Journal of Bone and Mineral Research, 2013. **28**(8): p. 1718-1720.
3. Yeung, D.K.W., et al., *Osteoporosis is associated with increased marrow fat content and decreased marrow fat unsaturation: A proton MR spectroscopy study.* Journal of Magnetic Resonance Imaging, 2005. **22**(2): p. 279-285.
4. Wang, H., Y. Leng, and Y. Gong, *Bone Marrow Fat and Hematopoiesis.* Front Endocrinol (Lausanne), 2018. **9**: p. 694.
5. Nehlin, J.O., et al., *Aging and lineage allocation changes of bone marrow skeletal (stromal) stem cells.* Bone, 2019. **123**: p. 265-273.
6. Fontana, L., et al., *Visceral fat adipokine secretion is associated with systemic inflammation in obese humans.* Diabetes, 2007. **56**(4): p. 1010-1013.

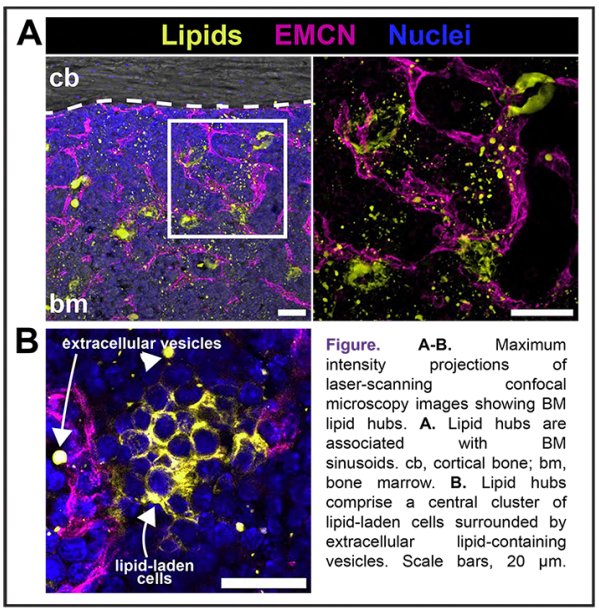

Figure. A-B. Maximum intensity projections of laser-scanning confocal microscopy images showing BM lipid hubs. **A.** Lipid hubs are associated with BM sinusoids. cb, cortical bone; bm, bone marrow. **B.** Lipid hubs comprise a central cluster of lipid-laden cells surrounded by extracellular lipid-containing vesicles. Scale bars, 20 µm.