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Deep Human Bone Imaging and Learning Reveals a Composite Osteo-Sinusoidal Niche for Mesenchymal Stromal Cells

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Abstract
Human bone marrow mesenchymal stromal/stem cells (BM-MSCs) are widely used in clinical trials and tissue engineering applications. Physiologically, these cells reside within a highly complex microenvironment rich in three-dimensional structures, including blood capillaries, sinusoids, trabeculae, and nerves. Traditional two-dimensional techniques are insufficient to fully capture this complexity, limiting our understanding of both normal and pathological processes in human bone. To address this, we developed DeepBone, a method enabling simultaneous 3D mRNA and protein pattern mining when human bones age. Using DeepBone, we spatially mapped CXCL12+ mRNA-expressing BM-MSCs relative to key components such as blood capillaries, adipocytes, sinusoids, and bony trabeculae. Quantitative analysis revealed a close association between BM-MSCs and their CD271+ functional subsets with sinusoids and bone matrix in samples from young patients, but not in those from older individuals. The unsupervised neural network, trained to interpret intricate 3D structures, uncovered a novel triplex niche for MSCs formed by sinusoids coiling around trabeculae and enriched by a specific ADGRL+ R-vessel subtype. This study provides the first comprehensive 3D characterization of the BM-MSC microenvironment within human bone marrow, laying the groundwork for future tissue engineering applications of human MSCs.

Biography
Dr. Nelson Chu Tsz Long was graduated with a PhD from the University of Hong Kong in 2018 working with Professor Kathryn Cheah in Skeletal Biology, where he found cartilage derived osteoblasts as one of the major targets of Parathyroid Hormone for treating Osteoporosis (Elife, 2023). After that he moved to Karolinska Institute in 2020 for his postdoctoral training with Professor Andrei Chagin and in 2024 as a researcher (and PhD supervisor) in Gothenburg University. His latest work focuses on combining lightsheet microscopy and neural network analysis to study the microenvironment of Mesenchymal Stem Cells (MSCs) in human bones (under revision in Nature Biomedical Engineering). His second project uses single cell RNA sequencing(scRNA-seq) technology to unravel the mechanism of human bone growth during puberty where he found dormant epiphyseal stem cells(epSCs) as one of the direct targets of Growth Hormone (under revision in Science Translational Medicine).

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