Targeting the Lysosomal-Methylation Signaling Axis in Cystinotic Bone and Kidney Disease

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Cystinosis is a devastating genetic disease that causes bone and kidney disease. Bone function is a central aspect of systemic health and cystinotic bone presents as increased fracture risk, fragility, and abnormal mineralization. Previously, efforts have focused on uncovering the molecular details of osteoblasts and osteoclasts, which are responsible for bone formation and breakdown, respectively. Our lab investigated bone tissues from cystinotic patients and evaluated the protein levels of lysosomes, the primary subcellular organelle impacted by *CTNS* mutations in cystinosis. Surprisingly, we uncover a new bone cell population is dysregulated specifically in *CTNS* bone relative to healthy control tissues. This bone cell population, known as osteocytes, reside within the calcified bone matrix where they normally function to sense mechanical stress and respond by secreting factors that control bone turnover rates. We find that lysosomes are absent from osteocytes of *CTNS* patient bones. These findings suggest that therapies aimed at targeting molecular pathways downstream of lysosomes could open a new potential avenue. As a specific example, we focused our studies on a single osteocyte secreted factor that is controlled by the lysosome, named sclerostin. In physiology, osteocytes secrete sclerostin to replenish circulating calcium by stimulating bone turnover and degradation. Once calcium levels are normalized in circulation, lysosomes in the osteocyte specifically inhibit sclerostin secretion, which maintains bone at normal densities. In cystinotic patient biopsies, we find that the absence of lysosomes in osteocytes caused a constitutive sclerostin secretion which is known to drive osteoporosis. Importantly, FDA-approved antibody therapeutics have been developed in age-related osteoporosis that bind and deactivate elevated sclerostin in circulation. Our ongoing efforts further explore the role of osteocyte secreted factors in the CTNS bone defects using biochemical markers and high-powered microscopy based approaches. Together, our findings identify a new player in bone disease and could open a window for circulating, non-invasive biomarkers and disease progression in addition to new molecular targets for therapies, using currently available, FDA approved treatments that specifically target osteocyte secreted factors.