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Single-cell genome analyses determine the trajectory of osteoclast differentiation in healthy subjects and osteoporosis patients

Background and Significance
Osteoporosis is a systemic bone disorder causing low bone mass and compromised bone strength, leading to an increased risk of fracture. Osteoporosis is more prevalent in the aging population and provides significant health challenges to the elderly. Even a single fracture in the elderly results in impaired quality of life, significant morbidity, and mortality. Osteoporosis can be preventable if it is treated. However, osteoporosis is a silent disease, and there are no symptoms until fractures occur. Thus, the early diagnosis of osteoporosis is important. One important cause of osteoporosis is the dysregulation of osteoclast activities. Our previous study identified human circulating osteoclast precursor cells (cOCPs) that have higher osteoclastogenic potential. We hypothesize that cOCPs travel to bone marrow and then fuse with mature osteoclasts, which can be used as a biomarker for in vivo osteoclast activity. Our goal is to identify relevant marrow OCPs (mOCPs) within the bone marrow and blood of patients with osteoporosis.
Methods
Single-cell RNA sequencing (scRNA-seq) data and bulk RNA sequencing data were obtained from both our lab and publicly available datasets. scRNA-seq analysis was performed using Seurat, an R package for single-cell analysis. Seurat calculated highly variable genes across the single cells and found ~2,000 variable genes. Gene expressions of the target populations were characterized and analyzed for osteoclastogenic potential. Cells were also analyzed by flow cytometry analysis and were cultured with M-CSF and RANKL to test osteoclastogenesis.
Results
Through the combined use of flow cytometric and functional analyses, we have identified a population of circulating osteoclast precursor cells (cOCPs). The frequency of cOCPs is affected by bone diseases and their response to anti-resorptive medications. We have also discovered that cOCPs have a unique transcriptomic signature. To further investigate their res