

## **ROUND VERSUS FLAT: MORPHOLOGY, RHEOLOGY, and MECHANOSENSING BY BONE CELLS**

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There is increasing evidence that cell function and mechanical properties are closely related to morphology. However, most *in vitro* studies investigate flat adherent cells, which might not reflect physiological geometries *in vivo*. Osteocytes, the mechanosensors in bone, reside within ellipsoid containment, while osteoblasts adhere to flatter bone surfaces. It is unknown whether morphology difference, dictated by the geometry of attachment is important for cell rheology and mechanosensing. We studied the rheology and mechanosensitivity of bone cells under different morphologies using atomic force microscopy and our two-particle assay for optical tweezers. We found that the elastic modulus of MLO-Y4 osteocytes when flat and adherent (> 1kPa) largely differed when round but partially adherent (< 1kPa). The elasticities of round suspended MLO-Y4 osteocytes, MC3T3-E1 osteoblasts, and primary osteoblasts were similarly < 1kPa. The mechanosensitivity of round suspended MLO-Y4 osteocytes was investigated by monitoring nitric oxide (NO) release, an essential signaling molecule in bone. These cells were stimulated by oscillatory undulations of the integrin-bound spheres upto 30pN force. Interestingly, the NO released increased in response to 5pN force stimulation, in contrast with flat cells, which required higher force stimulation while releasing lesser NO. Our results suggest that a round cellular morphology supports a less stiff cytoskeleton configuration compared with flat cellular morphology. This implies that osteocytes take advantage of their ellipsoid morphology *in vivo* to sense small strains benefiting bone health. Our assay provides novel opportunities for *in vitro* studies under a controlled suspended morphology versus commonly studied adherent morphologies.