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Extracellular Matrix and Cellular Network on Bone Cell Mechanotransduction

X. E. Guo [1]

In this paper, two important aspects of bone cell mechanotransduction, influences of extracellular matrix (ECM) and cellular network, are discussed and emphasized. Osteoblast interactions with ECM proteins are known to influence many cell functions, which may ultimately affect osseointegration of implants with the host bone tissue. Some adhesionmediated events include activation of focal adhesion kinase, and subsequent changes in the cytoskeleton and cell morphology, which may lead to changes in adhesion strength and cell responsiveness to mechanical stimuli. We examined focal adhesion kinase activation (FAK), F-actin cytoskeleton reorganization, adhesion strength, and osteoblast responsiveness to fluid shear when adhered to type I collagen (ColI), glass, poly- L-lysine (PLL), fibronectin (FN), vitronectin (VN), and serum (FBS). In general, surfaces that bind cells through integrins (FN, VN, FBS) elicited the highest adhesion strength, FAK activation, and F-actin stress fiber formation after both 15 and 60 minutes of adhesion. In contrast, cells attached through non-integrinmediated means (PLL, glass) showed the lowest FAK activation, adhesion strength, and little F-actin stress fiber formation. When subjected to steady fluid shear using a parallel plate flow chamber, osteoblasts plated on FN released significantly more prostaglandin E_2 (PGE_2) compared to those on glass. In contrast, PGE_2 release of osteoblasts attached to FN or glass was not different in the absence of fluid shear, suggesting that differences in binding alone are insufficient to alter PGE_2 secretion. The increased adhesion strength as well as PGE_2 secretion of osteoblasts adhered via integrins may be due to increased F-actin fiber formation, which leads to increased cell stiffness.

Osteocytes are interconnected through numerous intercellular processes, forming extensive cell networks throughout the bone tissue. We successfully cultured bone cells into a micropatterned network with dimensions close to that of *in vivo* osteocyte networks using microcontact printing and self-assembled monolayers (SAMs). Bone cells patterned in these networks were able to form gap junctions with each other, shown by immunofluorescent staining for the gap junction protein connexin 43, as well as the transfer of gap-junction permeable calcein-AM dye. We have demonstrated, for the first time, that the intracellular calcium response of a single bone cell indented in this bone cell network, can be transmitted to neighboring bone cells through multiple calcium waves. Furthermore, the propagation of these calcium waves was diminished with increased cell separation distance. Thus, this study provides new experimental data that support the idea of osteocyte network memory of mechanical loading similar to memory in neural networks. The formation of neural network circuits in the brain is the key to permanent memory in cognitive functions. Osteocytes in mineralized bone tissue also form elaborate cellular networks. It is well known that mechanical usage modulates the shape, mass, and microstructure of bone. Does the osteocyte network hold the key to cellular memory of mechanical loading history in bone tissue? This is an interesting hypothesis, which may have a profound implication in cellular and molecular mechanisms of bone adaptation to mechanical loading. We provide new experimental data that support the idea of osteocyte network memory of mechanical loading similar to memory in neural networks.

[1]Columbia University, New York, New York 10027, USA

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