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Perspective Article

What do we know about alteration in the osteoblast phenotype with microgravity?

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The osteocyte is often viewed as the primary mechanosensor of the bone due to its placement and distribution in the three-dimensional labyrinthine syncytium included in the bone matrix, providing an intracellular and extracellular route for ions and signal molecules circulation. Surface cells are other candidates: the osteoblasts have attracted a lot of attention, they are the progenitors of osteocytes, their location means that they must generally sense strain through their supporting substratum and perhaps most importantly, they build the bone matrix. This synthesis is dependent on several environmental factors including not only soluble factors but also the mechanical environment. In such a polarized cell, the mechanical environment is not uniform all over the cell. It is conditioned by the physical properties of the thin layer of organic matrix covering the mineralized tissue where osteoblasts are seeded on, on the deformation of the matrix (probably less than 0.2%) and on pression of the marrow. Indirect fluid shear stresses are not excluded in view of the contact often seen between osteoblast layer and blood capillaries. So it has been far from clear to know what kind of forces is "physiological" to osteoblastic cells. In addition, adhesive forces on an osteoblast are three to four orders of magnitude larger than the gravitational forces at the earth's surface. On a first estimate it is thus difficult to understand how the small force change due to the reduction in gravity to microgravity could possibly be sensed by the cell itself and/or the extracellular compartment[1]. Despite these calculated considerations on a single cell, cultured cells in space conditions showed several types of alterations involving structures known to be implicated in the so-called mechanotransduction process. Thus osteoblastic cells change their cell shape, cytoskeletal and adhesion structures, signalling transduction pathways, and gene expression leading to possibly altered growth/differentiation[1-4]. These mechanotransduction-related events are able to interfere with other growth factor and cytokine signalling pathways.

Osteoblasts are sensitive to mechanical signals and adapt the matrix they form to their mechanical environment. They integrate and react to these signals via their connected structures: matrix/integrins/cytoskeleton. Osteoblasts adhere to the extracellular matrix (ECM) via integrin-mediated adhesions that link the ECM to the actin cytoskeleton. In cultured cells, integrin-based molecular complexes form discrete morphological entities of several types: focal complexes precursors of focal contacts or focal adhesions, streak-like structures associated with actin- and myosin-containing filament bundles (stress fibers). In addition to their function as adhesion sites, matrix adhesions participate in adhesion-dependent signaling. Thus, focal contacts function as both adhesion and signal transduction organelles, informing cells about the state of the ECM. An additional form of adhesion site, tensin-enriched fibrillar adhesions, is involved in the fibronectin fibrillogenesis conferring the mechanical properties of the ECM. A mechanical signal delivered to adherent cells leads to the development of tension forces applied to the focal and fibrillar adhesion sites. In a typical mechanotransduction sequence, a mechanical stimulus (or lack of mechanical stimulus) can be sensed by focal complexes and contacts, and ECM will be adapted to this stimulus by fibrillar adhesion dynamics. In return the physical state of the ECM can regulate protein composition of cell-matrix adhesions leading to modulation of proliferation/differentiation capabilities.

The details of the mechanosensory processes at focal adhesions are still elusive. There exists a positive feedback involving integrin ligation, assembly of the cytoplasmic plaque, Rho- and Rac-signaling to the cytoskeleton and reorganization of the cytoskeleton. In the case of Rho-signalling, an essential element of this feedback is generation of

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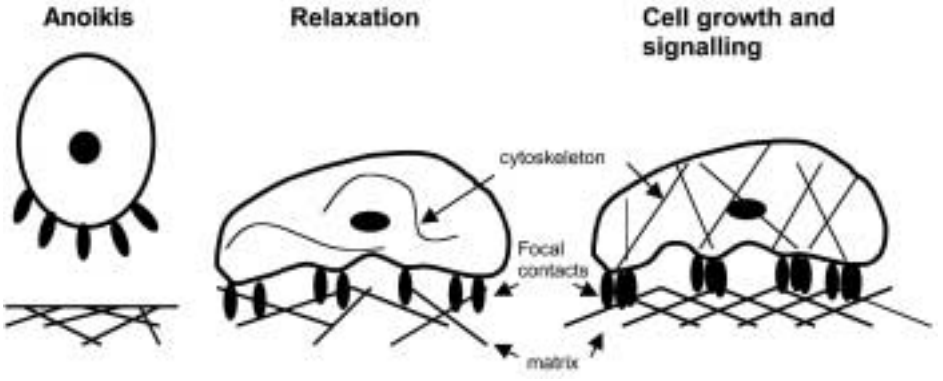

Figure 1. Different states of cell adhesion. **Left:** loss of cell adhesion or inappropriate cell adhesion induces a form of apoptosis called anoikis. **Center:** relaxation state (as in microgravity) is characterized by decreased adhesion and is thought to compromise cell survival, to impact gene expression and perhaps increase motility. **Right:** increased mechanical environment enhances cell attachment and promotes cell growth and differentiation. It may reduce motility.

stress through myosin II molecular motors and growth of focal adhesions under force. One of the future challenges in this field is a more complete and data-based description of the interplay between signalling and spatial organization of integrin-based adhesions and the actin cytoskeleton. In order to understand the role of force in the feedback loop between integrins and actin cytoskeleton, physical mechanisms have to be identified by which force affects the state of focal adhesions.

We will present results on cytoskeletal alteration in microgravity, and speculate on the matrix remodeling changes resulting from reduced tension of the cells (Figure 1).

These cellular events are mandatory to understand at the cell level because they might be part of the understanding of bone loss in space, which is still a serious limiting factor for long-term space mission and recovery on earth.

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