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Physiology and pathophysiology of the RANKL/RANK system

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The bone resorption activity of osteoclasts is regulated at many levels, including differentiation of their monocytes precursors, fusion into multi-nucleated cells, migration to the resorption site, polarization of the mature osteoclasts and assembly of a podosome-based sealing zone. Another function of osteoclasts is relative to the integrity of the actin cytoskeleton, depending on the substratum upon which the osteoclasts are spread. There are two different structures of actin known as podosomes and sealing zone, actived in specialized matrix contacts and delimiting the membrane domain, where the ruffled border is formed.

When a dual coculture of murine osteoblasts and murine mononuclear monocytes, in absolute absence of exogenous cytokines and other growth factors, was cultured on glass, the basic architecture of podosomes units and ruffled border was maintained regularly (1). We studied the osteoclast morphology and its behaviour in adhesion and in vesicle traffic by combination of light microscopy immunohistochemistry and transmission electron microscopy (TEM) immunolabeling. The adhesion and the fusion of preosteoclasts were observed by scanner electron microscopy (SEM).

The osteoclasts produced by our physiological dual co-culture (without interaction of specific cytokines) are functionally and biologically active TRAP + and multinucleated cells. In fact the role of RANK, expressed by osteoblasts, controls the modulation of OPG bioavailability in the extracellular compartment.

The fusion of monocytes is influenced by the presence of osteoblasts, that is based on RANK-RANKL interaction and communication between osteoblasts and preosteoclasts mediated by several molecules (2). Osteoclasts and osteoblasts can make direct contact, allowing membrane-bound ligands and receptors to interact and initiate intracellular signalling. RANKL-RANK complexes are likely internalized via rafts and then degraded in lysosomes. A recent study has shown that membrane-bound RANKL complexes to OPG is internalized by endocytosis process. A potential interaction of RANKL with clathrin components prior to the OPG binding, as shown by the kinetic results, OPG is intracellularly degraded after being internalized: our observation of osteoclast membrane at TEM has shown that immunogold labelled RANKL colocalizes with immunoglod labelled clathrin via the clathrin-coated-pit-mediated (3) pathway and both proteins are degraded by lysosome and proteasome pathway.

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