10.1.1

Mechanisms of Bone Remodeling

Watch the video Osteoclast and Osteoblast Regulation

Bone remodeling is a lifelong process where mature bone tissue is broken down and new bone tissue is formed within the skeleton. It is important in the reshaping and replacement of bone following microdamage we acquire daily or due to injury like a fracture. Bone remodeling is also important in changing the strength of bones in response to structural and mechanical stresses. Bone remodeling is carried out by the **bone multicellular unit (BMU)**. The cells involved in the BMU are **osteoblasts**, which produce the bone matrix, and **osteoclasts**, which are responsible for bone breakdown/resorption. Osteoclasts originate from macrophage-type cells that fuse together to make a large osteoclast cell with multiple nuclei.

BMU activity is regulated by important cell to cell interactions; specifically the **RANK/RANKL/OPG signaling pathway** plays a key role in regulating osteoclast differentiation and activation. This pathway starts with osteochondral progenitor cells, which are a type of stem cell that is found in the bone marrow. These cells have the ability to differentiate into osteoblasts or chondroblasts. The osteochondral progenitor cells express a ligand called **RANKL** (which they continue to express when they differentiate into osteoblasts). Osteoclast precursor cells express a receptor for RANKL called **RANK**. RANK stands for 'receptor activator of nuclear factor κ.' If the RANKL of the osteoblast binds with the RANK of the osteoclast precursor, then the signaling of the RANK will activate a transcription factor known as NF-κB which is important for the production and survival of osteoclasts. The osteoclast precursor will then develop into an osteoclast and increase bone breakdown. Therefore, regulation of osteoclast development is largely determined by signaling from osteoblasts.

Osteoprotegarin (OPG) is a decoy receptor that will bind to RANKL and prevent it from interacting with the RANK on osteoclast precursor cells. This means OPG prevents the production of new osteoclasts, thus decreasing osteoclast activity and favoring bone retention. OPG is produced by osteoblasts and osteochondral progenitor cells. Its production is increased in response to mechanical strain, sex hormones such as estrogen and testosterone, and the thyroid-derived hormone, calcitonin. OPG is decreased by parathyroid hormone (PTH) and glucocorticoids. On the other hand, osteoblast RANKL expression is increased by PTH and glucocorticoids and decreased by estrogen and testosterone, as well as calcitonin. Overall, this means that mechanical strain, calcitonin, and the sex hormones favor bone retention while PTH and glucocorticoids favor bone breakdown and remodeling.

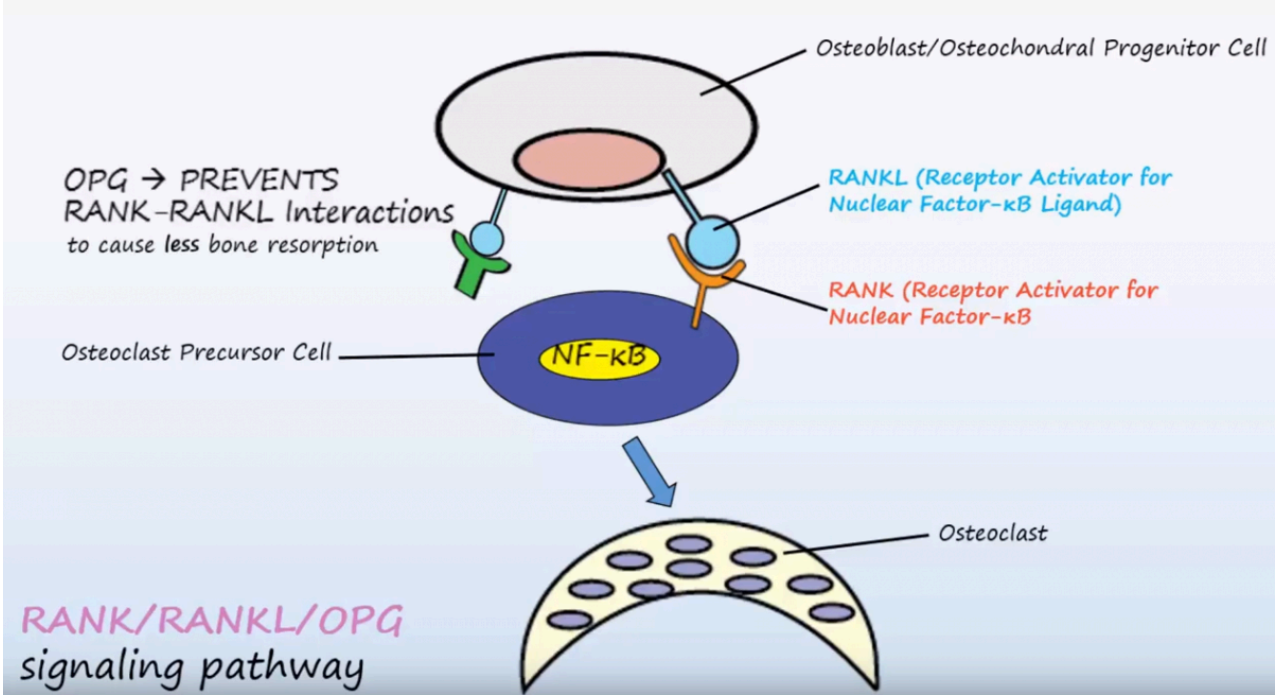

Image by Lanning Baker S17