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"Bone Breakers: The Osteoclasts That Shape Our Skeletons"

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Abstract: Osteoclasts are specialized, multinucleated cells responsible for bone resorption, playing a crucial role in bone remodeling and calcium homeostasis. Derived from the monocyte/macrophage lineage, these cells adhere to the bone matrix, creating an acidic microenvironment that facilitates the dissolution of mineral components and degradation of the organic matrix, primarily through the secretion of enzymes such as tartrate-resistant acid phosphatase (TRAP) and cathepsin K. The regulation of osteoclast differentiation and activity is mediated by various signaling pathways, including the receptor activator of nuclear factor kappa-B ligand (RANKL) and its decoy receptor osteoprotegerin (OPG). Dysregulation in osteoclast activity is implicated in several bone disorders, such as osteoporosis, where increased bone resorption leads to reduced bone mass and increased fracture risk. This abstract reviews the current understanding of osteoclast biology, emphasizing the molecular mechanisms governing their formation and function, as well as their role in pathological conditions. Further research into osteoclast regulation offers potential therapeutic targets for treating bone-related diseases.

"Bone Breakers: The Osteoclasts That Shape Our Skeletons

Introduction

Osteoclast is the primary cell responsible for bone resorption. With two to one hundred nuclei per cell, it is a multinucleated giant cell.

It's size ranges up to 100 micro meter in diameter and is located on the periosteal surface on the periosteum. Osteoclast are usually seen attached to surface of bone(1). Originating from haematopoietic cells, osteoclasts belong to the monocyte-macrophage lineage. The mononuclear cells that first adhere to the surface of the bone contain nonspecific esterase, and as they develop, tartrate-resistant acid phosphatase—a hallmark enzyme of osteoclasts—is produced, according to Baron and colleagues in TRAP. Eventually, these enzymes became multinucleated osteoclasts and lost their nonspecific esterase activity (2).Burger et al. determined that a monocytic lineage cell served as the progenitor for these osteoclasts.

Multinucleation, which results from the fusing of mononuclear osteoclasts, is the defining trait of osteoclasts. The fusion process between osteoclast cells is thought to be crucial for the reorganisation of the cytoskeleton, as demonstrated by the actin-ring and ruffuled border, which seal the resorbing area and secrete protons, respectively, to

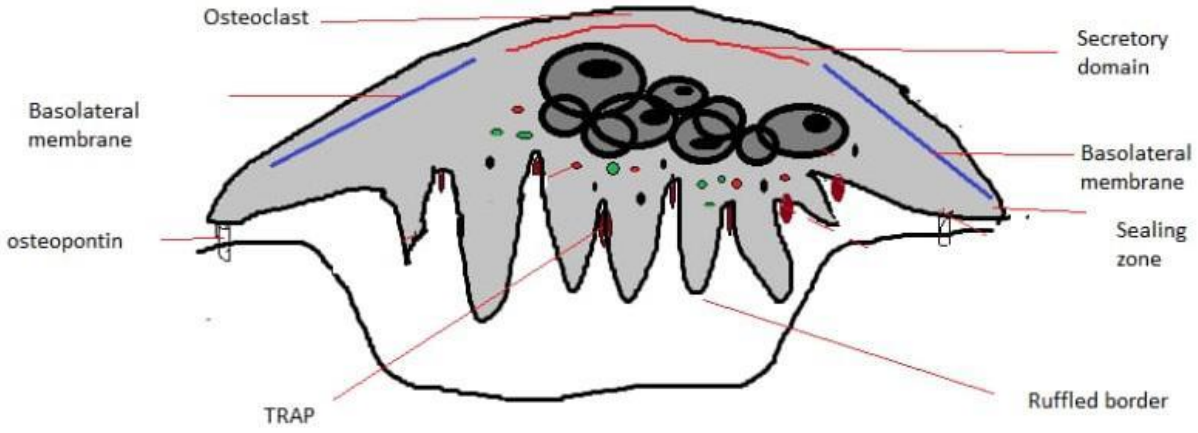
resorb bone.

Origin of osteoclast

Origin of osteoclast are mainly hematopoietic in origin .The early studies of Walker, using parabolic union of osteopetrotic mice with normal little mates demonstrated that osteopetrosis could be cured in these animals and that a marrow cavity formed (1). It is conformed that the osteoclast were host derived with the help of studies using quail chick chimeras.

Studies on patients with osteopetrosis and lethally irradiated rats have demonstrated that the osteoclasts are of haematopoietic origin. Haematopoietic tissue includes things like the spleen, bone marrow, and peripheral blood. These studies shows that the precursors of osteoclast present in bone marrow can be detectable in peripheral blood.

Baron and colleagues TRAP used an in-vivo model of osteoclast formation to show that non-specific esterase was present in the mononuclear cells that first adhered to the bone surface, and that these cells later expressed tertrate resistant acid phosphatase, an osteoclast marker enzyme (2). Afterwards, these cells developed into multinucleated osteoclasts and lost their non-specific esterase activity.



Differentiating markers of osteoclast

The osteoclast have unique different phenotypic feature that distinguish them from Other multinucleated cell. The osteoclast have high level of acid hydrolases that detected by immunohistochemical studies. Tactrate resistant acid phosphatase (TRAP) (purple acid phosphatase, type 5 acid phosphate) Is expressed extra high level in osteo class 10 present in lysosome, golgi bodies, extracellular channels of the Ruffled border and the space between cells and bone(1).

The RT- PCR technique, shows that TRAP is expressed in a variety of tissue including the gut, kidney and lung. TRAP is save as a marker enzyme for osteoclast in bone the cloned product of mucine and TRAP is save as a marker enzyme for osteoclast in bone the cloned product of mucine and TRAP is a promoters for these genes characterized.

Positive and negative regulatory elements, together with two promoters, one of which is located within an intron, are present in the 5³- flanking region of the TRAP gene (1). Two promoters found in the TRAP gene are utilized to cause the targeted gene to express in transgenic mice. An essential part in osteoclast bone resorption is played by TRAP. Recent research using the technique of homologous recombination has produced a non-functional TRAP gene in mice, showing that the absence of this gene causes abnormalities in the axial and appendicular skeletons, plays a significant role in the formation of endochondral bone, and prevents osteopetrosis in these animals.

This show that TRAP is not involved primarily in bone resorption but as tyrosine phophatase, must have other important functions that are not as yet delineated(1).

Pathology

In relation to periodontitis

It is characterised by the progressive breakdown of supportive Periodontal tissues, especially the loss of alveolar bone(4).As the lesion develop the height of the alveolar bone reduces and gradual weakening of bone occurs along with root exposure and mobility of tooth.

If it is left untreated further more that leads to tooth loss. Periodontitis is closely related to multiple systemic diseases, such as atherosclerosis (5), diabetes mellitus (DM) (19), rheumatoid arthritis (RA) (12) and osteoporosis (13), and some Patient with these conditions were reported to present more severe bone loss.

If an osteoclast get activated they will get attached to bone surface and produce protons and proteases that will lead degeneration of bone matrix this was regulated by mineralisation process of osteoblast and stabilize the volume of alveolar bone but in case of Periodontitis the virulence factors of pathogens will disrupt the oral mucosal defencive barrier and leads to apical migration of epithelium to the root surface , that result to the formation of periodontal pocket.

Inflammatory cytokines are released by resident cells in the tissue, such as fibroblasts, keratinocytes, and dendritic cells. These cells encourage the migration of various inflammatory cells, including neutrophils, macrophages, and T/B cells, to the site of inflammation and eventually infiltrate deeper into the periodontal connective tissue, including alveolar bone (4).

These inflammatory cells produce antimicrobial agents, reactive oxygen species, and enzymes to eliminate pathogens but also disrupt the normal activity of alveolar bone remodeling (22,23). A decrease in bone volume results from the imbalance between bone resorption and regeneration caused by the induction and activation of osteoclasts and the inhibition of osteoblasts (24).

Factors affecting osteoclast function and formation

Systemic hormones

PTH : PTH can induce bone resorption, increase bone formation and inhibit osteoblast activity, depending on it's mode of administration (1). When administered consistently, osteoclastic bone resorption increases and bone growth is prevented. One of the byproducts of vitamin D, calcitrol is a strong inducer of osteoclastic bone resorption and osteoclast development.The most active metabolite of vitamin D3, 1,25-dihydroxy D3, functions as a fusigen for released osteoclast precursors.

According to Yasuda et al. (6), 1,25-(OH)2 D3 can cause osteoblasts to produce the RANK ligand, which is a factor that promotes osteoclastic bone resorption (2)

Calcitonin: The thyroid gland's parafollicular cells release this hormone. It is a strong inhibitor of osteoclastic bone resorption and a peptide hormone. It inhibits the development of new osteoclasts and the ability of old osteoclasts to resorb bone (1). It operates at several stages in a single osteoclast lineage. Prostaglandins: Depending on the assay system and dose administered, prostaglandins can have different effects on bone production and resorption.

In the human system, PGE2 inhibits the development and resorption of osteoclastic bone. According to Chambers et al., isolated osteoclasts treated with PGE2 behave similarly to osteoclasts treated with calcitonin in terms of contracting and pulling away from the bone surface (1).

Factors that enhance osteoclast activity

Interleukin 1: It can promote bone resorption both in vivo and in vitro and is produced by osteoclasts, marrow stromal cells, and monocyte macrophages. All phases of osteoclast formation are impacted by IL-1, which could account for its strong effects on bone turnover in vivo(1).Additionally, IL-1 has been linked to a number of clinical disorders that are linked to accelerated bone loss. It is produced by a number of tumours linked to hypercalcemia, including lymphoma and squamous cell carcinoma (1).

M-CSF: research on an osteopetrotic mouse, which lacks osteoclasts and has a point mutation in the M-CSF gene, demonstrates the critical function M-CSF plays in the development of murine osteoclasts and severe osteoporosis.

Given that osteoclasts are haematopoietic, it is not unexpected that CSF, a haematopoietic growth factor, may function as an inducer of osteoclast development. CSF-1 is crucial for the formation of osteoclasts. Osteoclast precursors proliferate and differentiate when exposed to CSF-1. Transforming growth factor alpha, or TGF-a, is a polypeptide produced by a number of solid tumours linked to hypercalcemia in cancer. It is largely similar to epidermal growth factor.

By binding the epidermal growth factor receptor, TGF- may promote osteoclastic bone resorption in murine organ cultures. TGF-a, on the other hand, is a proliferative factor that promotes the proliferation of early osteoclast precursors but lacks the activity of colony-stimulating factors on its own. Interleukin-6: Numerous cells in the bone microenvironment, such as osteoclasts, osteoblasts, monocyte-macrophage, and marrow stromal cells, produce IL-6 (2).

It stimulates osteoclast development from osteoclast precursors (7,8). The effects of other hormones, such as parathyroid hormone-related protein, on osteoclastic bone resorption and calcium homeostasis in vivo are enhanced by IL-6 (9). In human marrow cultures, IL-6 can promote the development of osteoclast-like cells even in the lack of additional IL-6 receptor (8).

interleukin 2: IL-6 (10). Girasole et al. found that in a coculture of mouse bone marrow and calvarial cells, IL-2 stimulated the production of osteoclasts. On calcified matrices, osteoclasts generated in the presence of IL-2 had a high degree of ploidy and generated resorption lacunae.

This study also showed that the formation of osteoclasts caused by 1,25 (OH)2D3, parathyroid hormone (PTH), IL-1, or TNF was inhibited by a neutralising antibody against IL-2 (2). By stimulating the expression of RANK ligand on osteoblasts and marrow stromal cells, Il-2 has an effect on osteoclasts. The way that bone resorption works Osteoclasts resorb bone by breaking down proteases, which releases bone mineral into the extracellular space under the ruffled border. The regulators of bone resorption help control the amount of hydrogen ions that osteoclasts secrete.

For example PTH and prostaglandin E2 increase acid secretion by osteoclast (14) (1) while calcitonin decreases acid

secretion . Micro electrode based PH measurement at the ruffled border have shown PH level as 3-4 1(15) (1) for the acid secretion by osteoclasts requires a proton pump. This proton pump will transport the proton against concentration gradient.

Protons are supplied for the proton pump by the action of several enzymes including carbonic anhydrase 2 (16)(1). Studies on patients with congenital absence of carbonic anhydrase 2 and osteopetrosis (17)(1) have demonstrated the vital role that this enzyme plays in the osteoclast. Osteoclastic bone resorption can also be inhibited by acetozolamide (18)(1), an inhibitor of carbonic anhydrase.

Lysosomal hydrolases, which are active at acid PH, resorb the organic matrix(1). Due to the high MMP-9 level of osteoclasts, collagenase and osteoclasts may work together to break down the collagen matrix. Recent research indicates that the osteoclasts secrete enzymes that have the ability to actively break down collagen.

Apoptosis of osteoclasts

The nuclear and cytoplasmic condensation and fragmentation of nuclear DNA into nucleosomal-sized units is the basis of osteoclast. Fragmentation of DNA can demonstrated using gel electrophoresis or in-situ labeling of fragmented DNA by the incorporation of labeled deoxyoligonucleotides at the single stranded ends of these DNA. Hughes and co-workers (25) have recently developed an in- vitro system for examining apoptosis in osteoclast (1).

Using this system Hughes et al. have shown that TGF beta can induce apoptosis in mature osteoclast (1). TGF beta can also induce apoptosis in a variety of other tissues, such as liver and hematopoietic cell lines, and will cause cell death in tumor cell lines derived from prostate, liver and kidney tumors (26).

Conclusion

Osteoclasts play an indispensable role in maintaining bone health through their bone-resorptive activities, which are essential for normal bone remodeling and calcium balance. The intricate regulation of osteoclast formation, function, and survival by various signaling molecule including RANKL and OPG, underscores the complexity of bone metabolism.

The pathophysiology of various bone illnesses, including osteoporosis, where excessive bone resorption threatens skeletal integrity, is largely attributed to dysregulation in osteoclast activity . Advancements in understanding the molecular pathways governing osteoclast biology have opened new avenues for therapeutic intervention, offering hope for more effective treatments for bone-related diseases.

Continued research is crucial to further unravel the complexities of osteoclast function and to develop targeted therapies that can restore balance in bone remodeling processes, ultimately improving patient outcomes

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