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ODONTOCLAST: A BRIEF OVERVIEW

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ABSTRACT

Odontoclasts are responsible for resorption of dental hard tissues in various physiological and pathological oral conditions. These cells are usually studied and compared with osteoclasts because of some overlapping morphological and biochemical characteristics. However, there are still some differences. Some studies had shown that, similar to osteoclastogenesis RANK, RANKL and OPG are involved in odontoclastogenesis. Also, similar pathways [alpha(v)beta(3) integrin pathway and c-Fms pathway] seem to operate during activation of both odontoclasts and osteoclasts. According to certain contradictory studies response of odontoclasts to parathyroid hormone extract and certain drugs was found to be different from that of osteoclasts. Thus, it can be proposed that there might be additional pathways involved in formation and activation of odontoclasts. Physiological root resorption is seen only during shedding of deciduous teeth. Whereas pathologic root resorption can be due to various causes like trauma as in orthodontic treatment, hormonal imbalance, various cysts and tumors affecting jaw bones and periodontal disease. Pathways for formation and activation of odontoclasts can vary slightly among these pathologies. Thus, further studies are necessary to have a clear molecular insight in formation and activation of odontoclasts which might help to develop modalities to prevent pathological dental resorption.

KEYWORDS: Odontoclast, Alpha(v)beta(3) integrin pathway c-Fms pathway, root resorption.

INTRODUCTION

Resorption of soft and hard tissues is an important aspect of many physiological and pathological processes in human.[1] As clastic cells are responsible for resorption of bone and dental hard tissues, these cells play important role in calcium homeostasis, skeletal growth and tooth movement. Imbalance of these cells may result in disturbed resorptive activity causing local or systemic diseases.[2] This article covers physiological and pathological aspects of odontoclasts which are responsible for resorption of dental hard tissues.

Origin of odontoclast

There are different views regarding the origin of odontoclasts. According to some, odontoclasts originate from tartarate-resistant acid phosphatase (TRAP) positive circulating monocytes.[3] Some consider origin of these cells from circulating progenitor cells residing in dental pulp and periodontal ligament.[4,5]

Structure of odontoclast

Ultrastructural and functional characteristics of odontoclasts are thought to be similar to osteoclasts.[6] Fully differentiated odontoclasts are multinucleated large cells with numerous mitochondria, golgi apparatus, endoplasmic reticulum, variously sized cytoplasmic vesicles and vacuoles, prominent cell polarity at resorbing surface, clear zone at periphery and well developed ruffled border.[4]

Odontoclast possess similar biochemical characteristics as osteoclasts such as cathepsin K, cathepsin D, tartarate resistant acid phosphatase, H^+-ATPase and matrix metalloproteinases (MMPs) like MMP-9 and membrane type 1 MMP expression.[5]

However, there are some differences between odontoclasts and osteoclasts. Odontoclasts are smaller than osteoclasts and also possess fewer nuclei. They form smaller resorption lacunae than osteoclasts.[6]

Formation, differentiation, activation and function of odontoclast (Fig. 1)

The process of formation of odontoclasts is referred as 'odontoclastogenesis'. Stellate reticulum and dental follicle of underlying permanent tooth seems to initiate and regulate odontoclastogenesis by secretion of cytokines and transcription factors.[1]

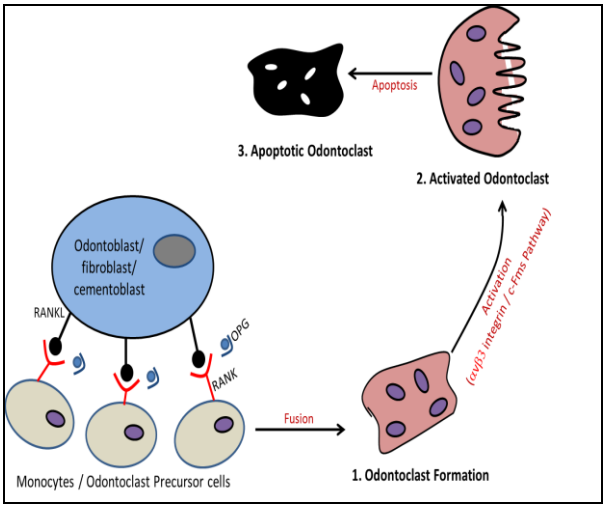

Fig. 1: Overview of process of odontoclastogenesis, activation and fate.

In vitro experiments showed that osteoclasts cultured can resorb dental hard tissues indicating that same signaling pathways might be involved in both odontoclastogenesis and osteoclastogenesis.[4,7,8,9,10] Various immunohistochemical studies showed expression of Receptor activator of nuclear factor kappa-beta (RANK) receptor in odontoclasts and Receptor activator of nuclear factor kappa-beta ligand (RANKL) expression by odontoblasts, fibroblasts and cementoblasts.[11,12] There was also a positive expression for Macrophage colony stimulating factor (M-CSF) and negative expression for osteoprotegerin (OPG) in odontoblast, ameloblast and dental pulp cells. All these finding suggest that role of RANK, RANKL, OPG and M-CSF is important for odontoclastogenesis.[3]

Similar to osteoclasts, after formation odontoclast activation and function is carried out via different signaling pathways. The best studied pathways are alpha(v)beta(3) integrin pathway and c-Fms pathway.[5] (Fig. 2) alpha(v)beta(3) and growth factor receptors co-ordinately regulate odontoclast and osteoclast adhesion, migration and membrane activity.[13] Characteristic features of activated odontoclasts are ruffled border and sealing zone. Integrins here are important in cell and extracellular matrix interactions for formation of sealing zone. Beta3 integrin is essential for formation of the actin ring and ruffled membrane. Several receptor tyrosine kinase activating cytokines such as M-CSF, hepatocyte growth factor and fibroblast growth factor might contribute to odontoclastogenesis and activation of odontoclasts.[5]

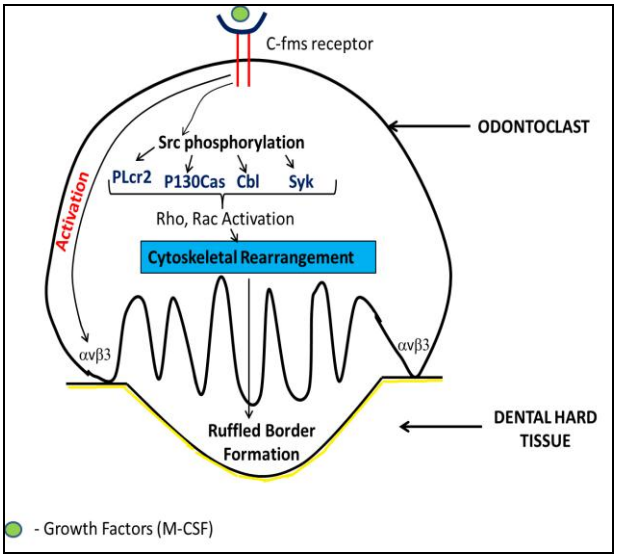

Fig. 2: Overview of alpha(v)beta(3) integrin and c-Fms pathways for odontoclast activation and function.

Upon alpha(v)beta(3) activation or c-Fms binding to M-CSF, Src which is a tyrosine protein kinase is phosphorylated. Downstream targets of Src are phospholipase C gamma 2 (PLc gamma$_2$), scaffold molecule P_{130}Cas, immunoregulatory protein Syk and ubiquitin ligase Cbl. These downstream targets form a signaling complex ultimately leading to Rac and Rho activation leading to cytoskeletal rearrangement.[14]

Odontoclasts have similar metabolic and enzymatic characteristics as that of osteoclasts. Odontoclasts release hydrolytic enzymes in resorption lacunae, lysosomes for degradation of collagenous and non-collagenous organic matrices. They demineralize the apatite crystals of the dental hard tissues by means of an H^+-ATPase and subsequently they degrade dentin proteins by the action of cathepsin K and MMP-9. Thus, they can resorb dentin as well as predentin.[3]

However there are also some contradictory results. Odontoclastic activity is not observed in hyperparathyroidism.[15,16] Also parathyroid extract did not affected morphology of odontoclasts. Collagenase mRNA was evident in odontoclast and absent in osteoclasts. Some of the drugs also increase odontoclastic resorption but decreases osteoclastic resorption. This is might be due to difference in the mechanisms regulating the differentiation and activation of these two clastic cells.[4]

Fate of odontoclast (Fig. 1)

Odontoclasts are involved in resorption of dental hard tissues in physiological and pathological conditions. Once function is over there is loss of ruffled border in odontoclasts and they show degenerative changes.[3]

Physiological and pathological conditions involving odontoclasts

Root resorption is defined as a condition associated with either a physiologic or a pathologic process resulting in loss of dentin, cementum or bone.[17] The root is covered by collagen fibres, cementoblasts and a thin zone of cementoid under the cementoblasts. All of these are believed to protect the root from resorption. Additionally, cementum offers another layer of protection as it is more resistant to resorption than dentin.[6]

Root resorption can be discussed under following headings,

a) Physiological root resorption
b) Pathological root resorption.

Root resorption may be classified based on its location in relation to the root surface as,[18]

i. External root resorption
ii. Internal root resorption

a) Physiological root resorption

Physiologically, root resorption occurs only during the process of primary teeth exfoliation. When root resorption occurs in permanent dentition, it is considered as pathologic. Tooth eruption and exfoliation are complicated processes that involve tightly programmed events which co-ordinate functions of osteoblasts, osteoclasts and odontoclasts.[5]

It was believed that it is the pressure of erupting permanent tooth that causes the differentiation and activation of odontoclasts. Different studies showed that dental follicle and stellate reticulum are responsible for resorption of root of primary teeth.[19,20.21] Parathyroid hormone related protein (PTHrP) has been found to increase the RANKL and to downregulate the OPG expression levels on the dental follicle cells.[22] This indicates that the dental follicle cells can be responsible for differentiation and activation of monocytes to osteoclasts and/or odontoclasts. In fact, under non-resorbing conditions, PDL cells from deciduous teeth or permanent teeth, were found to express OPG and not RANKL.

At the critical time in the eruption process, cells from the stellate reticulum of developing tooth secrete PTHrP.[23] Secreted PTHrP then binds to the neighbour PTHrP receptors expressed by cells in the dental follicle.[22,24,25] Interleukin 1a is also secreted by the stellate reticulum and in the similar manner binds to the IL-1a receptors found on the dental follicle.[26] The stimulated dental follicle cells in turn, secrete monocyte recruiting factors (colony stimulating factor-1, monocyte chemotactic protein-1 or vascular endothelial growth factor).[26,27] Under the influence of these factors, monocytes are recruited into the dental follicle into its coronal region of tooth.[28,29] In the favourable environment, these monocytes fuse and subsequently differentiate into either osteoclasts or odontoclasts on contact with RANKL expressing cells.

While the primary roots are actively resorbed, the pulpal tissue initially does not seem to participate in the resorption process. Odontoclasts are not usually found inside the pulp until root resorption is close to completion.[30,31] During this phase, chronic inflammatory cells infiltrate the coronal pulp and odontoblasts begin to degenerate.[31,32] Following the degeneration of odontoblasts, odontoclast cells start resorbing the exposed dentin and predentin from the inner surface.[31]

The gingival epithelium and dento-gingival junction also participate in the resorption process of the primary teeth.[33] As root resorption advances, the gingival epithelium and dento-gingival junction migrate apically due to the inflammation at the dento-gingival junction.[34] Degradation of Periodontal ligament (PDL) precedes root resorption and specifically removal of collagen fibres. Collagen digestion is mediated by matrix degrading enzymes such as matrix metlloproteinases (MMPs) and their extracellular inhibitors, the tissue inhibitors of metalloproteinases (TIMPs). MMPs and TIMPs are produced by osteoblasts, PDL cells as well as by odontoclasts and osteoclasts.[35, 36, 37, 09] Thus, odontoclasts, osteoclasts seem to play an important role in normal and pathologic bone and connective tissue turnover as well as in physiologic root resorption process.

b) Pathological root resorption

i. External root resorption

It is the common adverse complication of orthodontic treatment. Risk factors for root resorption include, patient gender, severity of malocclusion, apical displacement, treatment mechanics and duration as well as genetic disposition. The process involves two pathways.[38]

The first involves activation of odontoclastic cells through the ATP/P2XR7/IL-1beta□inflammation modulation pathway. Local damage of tissue may result in ATP release, which can activate the receptor P2xR7 on macrophages and other cell types leading to further release of cytokines including IL-1beta. Such cytokines can recruit more monocytes and macrophages to eliminate apoptotic cells and prevent further necrosis.[38]

The second pathway involves the RANK/RANKL/OPG osteoclast program. The excessive osteoclast activity induced by the inflammatory process will exacerbate root resorption. Any risk factors that interfere with osteoclast function may actually contribute to more root resorption. Thus, targeting osteoclast activation can modulate root resorption. Further research need to be done to elucidate how osteoclast activation can be modulated during orthodontic treatment to prevent root resorption.[5]

ii. Internal root resorption

Internal resorption is an inflammatory process initiated within the pulp space with loss of dentin and possible invasion of cementum. Various etiologic factors were proposed to play role in internal resorption. Among these, most common etiologic factors are trauma (43%) followed by carious lesions (25%).[39]

Persistent infection of pulp by bacteria causes the colonization of walls of the pulp chamber by macrophage like cells. The attachment and spreading of such cells is the primary pre-requisite for initiation of root resorption.[39] These cells fuse to form odontoclasts. Number of nuclei varies in odontoclasts. Odontoclasts with less than five nuclei are called as oligonuclear odontoclasts. It was seen that oligonuclear odontoclasts resorb more dentin per nucleus than do cells with a higher number of nuclei.[17]

Histologically, process of internal resorption can be divided into four stages. Pre-resorption stage, early resorption stage, later resorption stage and final resorption stage. Studies showed that, during pre-resorption stage wall of pulp chamber is covered with an odontoblast layer and no multinucleate odontoclast can be found in the pulp chamber. In early resorption stage, multinucleate odontoclast are detected on the pulp chamber wall, but the rest of the pulpal surface is still covered with an odontoblast layer. In later resorption stage, no odontoblast layer is found and entire surface of pulp chamber is lined with multinucleated odontoclasts. During final resorption stage resorbed dentin surface may be repaired partially or totally by the deposition of cementum- like tissue. Sometimes unique odontoclasts are formed with several clear zones besides those at the periphery region.[4]

c) Endocrine disorders

The RANK/OPG system is regulated by several hormones (i.e. growth hormone, thyroid hormone, glucocorticoids, oestrogen). Thus, decreased hormonal levels may decrease odontoclast as well as osteoclast differentiation by affecting RANK system. This results in retardation of tooth eruption. Most widely studied endocrine disorder is hyperparathyroidism. In hyperparathyroidism, bone resorption is seen due to increased osteoclastic activity. PTH causes activation of osteoclasts via PTH receptors. PTH receptors are absent on odontoclasts. Thus, root resorption was not evident in hyperparathyroidism.[40] In the case of over-retention of primary teeth, decreased odontoclast activity is observed

d) Cysts and Tumors

In case of cysts and tumors affecting jaw bones, external root resorption is evident due to pressure of growing tumor or cyst on external root surface. Here, molecular mechanism of resorption will be same as in external root resorption during orthodontic treatment.[41]

e) Periodontal Disease

Periodontal disease result in necrosis of tissue adjacent to exposed root dentin which causes stimulation of mononuclear precursor cells to differentiate into odontoclasts. These odontoclasts attracted to exposed root dentin and thus, result in external root resorption.[41]

CONCLUSION

Odontoclasts thus, are responsible for physiologic and pathologic root resorption. Though some molecular insight in the process of resorption is provided, further studies are required to provide a clear idea of molecular mechanism involved in formation as well as activation of these cells. It is also necessary to delineate the exact molecular differences between osteoclasts and odontoclasts as treatment modalities to inhibit odontoclast induced pathological root resorption might affect normal osteoclast function.

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