Current Perspectives of Residual Ridge Resorption: Pathological Activation of Oral Barrier Osteoclasts

Takeru Kondo ^{a,b}, Keiichi Kanayama ^{a,c}, Hiroshi Egusa ^b, Ichiro Nishimura ^{a,*}

^a Weintraub Center for Reconstructive Biotechnology, UCLA School of Dentistry, Los Angeles, CA 90095-1668, USA

^b Division of Molecular and Regenerative Prosthodontics, Tohoku University Graduate School of Dentistry, Sendai 980-8575, Japan

^c Department of Periodontology, Division of Oral Infections and Health Science, Asahi University School of Dentistry, Gifu, Japan, 501-0296

Abstract

Purpose: Tooth extraction is a last resort treatment for resolving pathological complications of dentition induced by infection and injury. Although the extraction wound generally heals uneventfully, resulting in the formation of an edentulous residual ridge, some patients experience long-term and severe residual ridge reduction. The objective of this review was to provide a contemporary understanding of the molecular and cellular mechanisms that may potentially cause edentulous jawbone resorption.

Study selection: Clinical, *in vivo*, and *in vitro* studies related to the characterization of and cellular and molecular mechanisms leading to residual ridge resorption.

Results: The alveolar processes of the maxillary and mandibular bones uniquely juxtapose the gingival tissue. The gingival oral mucosa is an active barrier tissue that maintains homeostasis of the internal organs through its unique barrier immunity. Tooth extraction not only generates a bony socket but also injures oral barrier tissue. In response to wounding, the alveolar bone socket initiates regeneration and remodeling through coupled bone formation and osteoclastic resorption. Osteoclasts are also found on the external surface of the alveolar bone, interfacing the oral barrier tissue. Osteoclasts in the oral barrier region are not coupled with osteoblastic bone formation and often remain active long after the completion of wound healing, leading to a net decrease in the alveolar bone structure.

Conclusion: The novel concept of oral barrier osteoclasts may provide important clues for future clinical strategies to maintain residual ridges for successful prosthodontic and restorative therapies.

Keywords: Residual Ridge Resorption, Oral Barrier Tissue, Osteoclast, Tooth Extraction

Received 7 December 2021, Accepted 31 January 2022, Available online 21 February 2022

1. Introduction

Tooth extraction is a last resort treatment option that surgically removes the affected dentition as the source of oral microbial infection causing irreversible structural degradation of teeth by dental caries and exuberant inflammation of periodontal tissue by periodontitis. The latest U.S. National Health and Nutrition Examination Survey reported that 3.75% of adults aged 20 to 64 years and 27.27% of older adults over the age of 65 had total loss of teeth [1].

Tooth extraction creates an alveolar bone socket and gingival open wound, which normally undergoes uneventful healing, leading to the formation of a residual alveolar ridge. However, the volume of the residual ridge gradually decreases after a series of morphological changes, which have been described as residual ridge reduction [2,3]. Residual ridge reduction continues throughout life in some patients, leading to a large cumulative loss of jawbone structure that

significantly limits the quality of life. Therefore, it has been proposed that residual ridge reduction should be recognized as a pathological disease entity [4].

Tooth extraction can cause dimensional changes in the alveolar bone within the first six months, potentially limiting dental implant treatment. To maintain residual ridge morphology, various procedures have been postulated, such as socket or alveolar ridge preservation, with clinical success [5,6]. However, because the pathological mechanism of residual ridge resorption has not been fully established, current preservation methods may lack biological rationale or design principles.

There is an acute need to elucidate the mechanism of edentulous jawbone resorption to facilitate functional and esthetic dental restoration and craniofacial rehabilitation. The pathological mechanism has been examined from various perspectives, such as the patients' own anatomical structure [7-9], biomechanical contribution [10-16], and association with systemic diseases [17-22]. However, we still do not know how edentulous jawbone resorption continues even long after the tooth extraction wound is healed, and how some patients lose a large amount of jawbone structure. This review provides the current perspective on the pathology of residual ridge re-

DOI: https://doi.org/10.2186/jpr.JPR_D_21_00333

*Corresponding author: Ichiro Nishimura, Weintraub Center for Reconstructive Biotechnology, UCLA School of Dentistry.

E-mail address: inishimura@dentistry.ucla.edu

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Fig. 1. Edentulous jawbone. A. Immediately after tooth extraction. Extraction sockets are visible in the alveolar process of the mandible (bracket). B. Long after tooth extraction of the same patient as A. The alveolar bone was largely lost while the mandibular body (arrow) is well maintained. C. D. Panoramic radiographs of edentulous patients that similarly exhibit the loss of the edentulous alveolar bone, while mandibular body (arrows) remained less affected.

Fig. 2. Clinical reports repeatedly confirmed that the residual ridge formed after tooth extraction underwent size reduction of the width and the height over time. This is thought to be due to active osteoclastic bone resorption from the external surface of the alveolar process of the edentulous jawbone.

sorption and provides the biological rationale for a clinical means to reduce dental disability after tooth extraction.

2. Clinical characterization of residual ridge reduction

Residual ridge reduction following tooth extraction has been characterized using standardized lateral cephalographs (**Fig. 1A, B**) [7-10,13,14,16,21,23-29] and panoramic radiographs (**Fig. 1C, D**) [20,30] to evaluate underlying jawbone structural changes. More recently, alveolar bone reduction has been characterized by cone beam computed tomography (CBCT), and the residual ridge contour has been examined by digital impression, possible due to technological progress [31-33].

After tooth extraction, the buccolingual width of the residual alveolar bone was reduced more than the height. The rate of height reduction, calculated as the percentage of vertical linear reduction over the distance between the bottom of the socket and the crest of alveolar bone before tooth extraction, was 15% and 11-22% at 3 and 6 months, respectively. The rate of buccolingual width reduction, calculated as the percentage of horizontal linear reduction over the distance between the buccal and lingual borders of the alveolar bone before tooth extraction, was 32% and 29-63% at 3 and 6 months, respectively [34]. However, crestal bone height change varied depending on the site [34,35]. These results from clinical observations suggest that the structural change in the edentulous jawbone is unidirectional and is primarily induced by resorption of the residual alveolar bone by osteoclasts (**Fig. 2**).

Fig. 3. A. Bone resorbing osteoclasts (OC) in bone marrow (mouse mandible; HE staining) associate closely with bone-forming osteoblasts (OB), which together organize the bone multicellular unit (BMU). B. After tooth extraction, osteoclasts are abundantly observed on the external surface of the alveolar bone interfacing the oral barrier tissue and within the remodeling bone in the socket (mouse maxillary 1st molar; TRAP staining). C. Extraction socket osteoclasts appeared to form BMU with osteoblasts (HE staining). D. Unlike bone marrow BMU, oral barrier osteoclasts do not associate with osteoblasts; however, they often juxtapose oral barrier inflammatory cells, likely lymphocytes (arrows) (HE staining).

3. Osteoclasts and bone remodeling

Osteoclasts are multinuclear, large cells capable of secreting an acidic milieu to dissolve bone minerals, and strong proteinases, such as cathepsin K, to digest organic bone collagen extracellular matrices [36]. Unlike bone-forming osteoblasts of mesenchymal stem cell origin, osteoclasts are derived from monocytes/macrophages, myeloid immune cells, or osteoclast progenitor cells. Macrophage colony-stimulating factor (M-CSF) promotes the fusion of osteoclast progenitors [37]. Receptor activator of nuclear factor kappa-B ligand (RANKL) is also an essential factor for osteoclastogenesis and survival [38]. Extensive studies have demonstrated that osteoblasts are a cellular source of RANKL during bone remodeling [39–44]. More recently, osteocytes were found to be the primary cellular source of RANKL during physiological bone remodeling [45]. Osteoprotegerin (OPG), a decoy receptor of RANKL, can bind to RANKL and inhibit its activity, resulting in inhibition of osteoclastogenesis and bone resorption [46,47]. Therefore, the RANKL/OPG ratio is crucial for osteoclastogenesis [48].

Bone remodeling plays a critical role in the repair and replacement of damaged bone and involves osteoclastic bone resorption followed by osteoblastic bone formation. The balance between coupled bone resorption and formation maintains the net volume and structure of bone. It has been hypothesized that osteoclastic bone resorption releases embedded growth factors in the bone marrow to differentiate osteoblasts [49]. Osteoclasts and osteoblasts are closely associated with the transient structure of basic multicellular unit (BMU) (Fig. 3A). It is believed that coupled bone remodeling occurs within the BMU canopy [50]. However, the behavior of osteoclasts on

the external surface of the alveolar bone socket appears to be distinctly different from that of bone remodeling osteoclasts and lacks coupled osteoblastic bone formation (Fig. 3B).

4. Osteoclasts associate with oral barrier tissue

Clinical observations have repeatedly shown the abnormal behavior of post-tooth extraction alveolar bone, which decreases in height and width over time (Fig. 1, 2, Table 1). It is well established that residual alveolar bone does not increase in size. However, the mechanism of residual ridge reduction is not well understood. The unique aspect of residual ridge resorption is aberrant osteoclastic activity at the bony margin of the socket and the external surface of the alveolar bone [51,52]. Aberrant osteoclastogenesis on the external alveolar bone surface is not a part of physiological bone remodeling, but may be regulated by the oral barrier tissue and function. We propose that osteoclasts associated with oral barrier tissue are primarily responsible for residual ridge resorption because oral barrier osteoclasts reside in the resorption pits on the external surface of the alveolar bone without coupled osteoblastic bone formation, resulting in the net loss of bone structure.

Tooth extraction not only creates defects in the alveolar bone but also causes trauma to the gingival tissue. The external alveolar bone surface closely interfaces with the gingiva or oral barrier tissue. Barrier tissues such as the skin, intestine, and gingiva/oral mucosa are equipped with a tissue-specific barrier immune system and protect internal tissue homeostasis from external physical, thermal, and microbial insults [53–55]. Disruptions of barrier tissue and cell membrane microbarriers release multiple signaling molecules, including

Table 1. Clinical Reports of Residual Ridge Reduction

Tissue	Site		Dimensional change	Duration	Reference
Alveolar bone	Height	Mid-buccal	-1.24 mm	6 months	[34]
		Mid-lingual	-0.5 mm	6 months	[129]
		Mesial	-0.84 mm	6 months	[34]
		Distal	-0.8 mm	6 months	
		All	-15.7%	3 months	[130]
	Width	All	-11-22 %	6 months	[34]
			-3.2 mm	3 months	[131]
			-32 %	3 months	[34]
			-3.79 mm	6 months	
Soft tissue	Height	Buccal	-0.1mm	3 months	[132]
			+0.4 mm	12 months	
		Lingual	-0.8 mm	3 months	
			-0.8 mm	12 months	[133]
		All	-0.1 mm	3 months	
			-0.5 mm	12 months	
	Width	All	-3.8 mm	3 months	[132]
			-6.1 mm	12 months	
	Thickness	Buccal	-0.4 mm	6 months	[129]
		Lingual	-0.5 mm	6 months	
		All	-0.1 - +4.8 mm	2 months	[31]

damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). These molecular danger signals are sensed by inflammatory cells through pattern recognition receptors, such as toll-like receptors. The resultant inflammatory response in the oral barrier tissue is designed to clear the molecular danger and induce tissue repair mechanisms of wound healing [56,57].

Although the precise mechanism has not yet been elucidated, residual ridge osteoclasts appear to be influenced by oral barrier immunity. The close proximity of oral barrier tissue and, potentially, its immune cells to osteoclasts on the external surface of the alveolar bone (Fig. 3D) prompted us to investigate the role of oral barrier lymphocytes, which may initiate the recruitment of osteoclasts, as shown in the tooth extraction model [58-60]. In wild-type mice, osteoclasts were observed inside the extraction socket and on the external surface of the alveolar bone after tooth extraction (Fig. 4A). When the same tooth extraction was performed in *Rag2*^{-/-} mice, genetically lacking functional T and B lymphocytes, normal osteoclastogenesis was induced in remodeling the bone inside the socket. However, no osteoclasts were observed on the external surface of the alveolar bone interfacing the oral barrier tissue (Fig. 4B) [60]. Tooth extraction from *Rag2*^{-/-} mice demonstrated a total lack of osteoclasts interfacing oral barrier tissue, suggesting that oral barrier osteoclasts responsible for residual ridge resorption require an interaction with lymphocytes. To further examine the role of lymphocytes, *Rag2*^{-/-} mice were repopulated with human peripheral blood CD3⁺ T cells (hCD3⁺ T cells) by intraperitoneal injection. hCD3⁺ T cell repopulation resulted in the presence of oral barrier osteoclasts (Kanayama and Nishimura, unpublished, Fig. 4C, 4D). Thus, we propose that T cells in oral barrier tissue are responsible for the development of oral barrier osteoclast.

Similar to the long bones, the body of the jawbone is covered by the periosteum (Fig. 4C), which provides the blood supply and contains active cells capable of bone formation [61]. In adult bones, the periosteal reaction or abnormal bone formation can be found on the external bone surface associated with diseases such as osteomyelitis and bone tumors [62]. While rare, the jawbone can also develop a periosteal reaction [63,64]. Medication-related osteonecrosis of the jaw has been reported to develop the periosteal reaction at the jawbone body covered by the periosteum [65,66] (Fig. 4E). It must be noted that periosteal reaction has never been associated with alveolar bone. This observation further highlights the unique characteristics of alveolar bone interfacing the oral barrier tissue.

5. Cellular source of RANKL in the oral barrier tissue

Oral barrier tissue is composed of oral epithelial cells [67], distinct gingival and periodontal ligament fibroblasts [68], and oral immune cells [55]. In addition, osteoblastic progenitor cells are primarily localized in the periodontal ligament space [69]. Tsukasaki (2021) investigated the cellular source of RANKL in a mouse ligature-induced periodontitis model [70]. RANKL-encoding *Tnfsf11*-floxed mice were crossed with mice carrying *Mb1-Cre* (targeting B-cells), *CD4-Cre* (targeting T-cells), *Scx-Cre* (targeting fibroblasts), and *Sp7-Cre* (targeting osteoblasts). Ligature-induced bone resorption and osteoclastogenesis were significantly decreased in *Tnfsf11*. *CD4-Cre*, *Tnfsf11.Scx-Cre*, and *Tnfsf11.Sp7-Cre* mice, suggesting that the cellular source of RANKL was T cells, fibroblasts, and osteoblasts. Recently, Yang et al. (2018) induced a RANKL knockout mutation specific to type I collagen-expressing cells in *Col1a1.CreER.RANKL*^{f/f} mice and found that periodontal ligament osteoclasts significantly decreased during orthodontic tooth movement [71]. Since *Col1a1.CreER.ROSA*-positive cells were localized throughout the periodontal ligament space, oral fibroblasts were considered the cellular source of RANKL in response to orthodontic tooth movement.

RANKL is present in the gingival crevicular fluid, and thus gingival sulcus-lining oral epithelial cells are postulated to express RANKL [72]. RANKL is selectively expressed in the intestinal mucosa by sub-epithelial stromal cells (fibroblasts), which play an important role in organizing intestinal Peyer's patches and other organized mucosal lymphoid tissues [73]. The function of gingival sulcus epithelial RANKL, including its role in osteoclastogenesis, has not yet been elucidated. After tooth extraction, the periodontal ligament initially provides bone-regenerating cells in the extraction socket and progressively disintegrates. The resultant edentulous oral mucosa has been associated with chronic inflammation and changes in connective tissue structure particularly with the use of removable dentures [74,75]. In this review, we discuss the molecular and cellular mechanisms of residual ridge resorption, focusing on oral barrier immune cells and fibroblasts.

6. Oral barrier Th17 cells respond to mechanical stimulation

The immune system of the oral barrier tissue can adapt well to constant external stimuli and plays a crucial role in immune surveillance while tolerating commensal microbes and harmless antigens without excessive inflammation [76]. Tissue injury results in the synthesis of local cytokines and guides naïve helper T (Th) cells to differentiate into Th1, Th2, Th17, and regulatory T (Treg) cell subunits [77].

Fig. 4. Unique behaviors of the alveolar bone interfacing with oral barrier tissue. A. After maxillary first molar extraction of wild type (WT) mice, the bony socket was filled with active bone regeneration and remodeling, including osteoclasts (blue arrows). A separate cluster of oral barrier osteoclasts (red arrows) was observed on the external surface of the alveolar bone (TRAP staining). B. The maxillary molar extraction of *Rag2*^{-/-} mice lacking functional lymphocytes induced bony socket bone regeneration and remodeling with osteoclasts; however, oral barrier osteoclasts were not observed. Lymphocytes are required for the development of oral barrier osteoclasts (TRAP staining). C. *Rag2*^{-/-} mice were repopulated with human peripheral blood CD3⁺ T cells (hCD3⁺ T cells). Bone resorption lacunae were observed in the alveolar bone interfacing with oral barrier tissue (the enclosed area; also black arrows in Fig. 3D) (HE staining). The maxillary body was covered by the periosteum (Kanayama and Nishimura, Unpublished). D. Magnification images of the square in Fig. 3C (upper panel: HE staining, lower panel: TRAP staining). While the bone remodeling with osteoclasts (blue arrow) in the extraction socket was maintained, *Rag2*^{-/-} mice repopulated with hCD3⁺ T cells showed a new sign of bone resorption on the external surface of the alveolar bone, with TRAP⁺ osteoclasts (red arrows) (Kanayama and Nishimura, Unpublished). E. Mandibular CBCT image of an MRONJ patient depicted periosteal reaction or abnormal bone formation in the periosteum covering the mandibular body (Courtesy of Dr. Sil Park).

Interactions between T cells and osteoclasts have been reported in pathological osteolytic diseases and have been described as osteoimmunology [78]. Activated T cells can regulate osteoclastogenesis by expressing RANKL and other cytokines that have either stimulatory or inhibitory effects [79,80]. RANKL secreted by activated T cells explains the mechanism of disease-induced bone resorption in autoimmune diseases [81], cancers [82], and peri-implant osteolysis [83]. Therefore, osteoclastic alveolar bone resorption during tooth extraction wound healing may be caused by a similar mechanism involving an injury-induced oral barrier immune reaction. However, the long-term presence of oral barrier osteoclasts needs to be addressed.

Among Th cell subunits, Th17 cells are involved in promoting osteoclastogenesis. Th17 cells are characterized by the expression of IL-17A, IL-17F, IL-21, and IL-22 [84,85]. In a mouse model of rheumatoid arthritis, IL-17 expressed by Th17 cells promoted osteoclastogenesis by inducing RANKL expression in synovial fibroblasts and mesenchymal cells. In addition, IL-17 stimulated innate immune cells to express inflammatory cytokines, such as TNF- α , IL-1 β , and IL-6, which enhance the expression of RANKL in mesenchymal cells and activate RANK signaling in osteoclasts [86]. It has also been reported that Th17 cells directly expressed RANKL [86]. Thus, Th17 cells are closely associated with bone resorption.

Th17 cells of the intestinal and skin barrier tissues are activated by commensal microbial interactions [87,88]. Unlike these barrier tissues, oral barrier Th17 cells do not respond to oral commensal microbes [89]. When mice were fed soft food, Th17 cells were not detected in the oral barrier tissue. In contrast, hard pellet food or other mechanical stimuli to the palatal gingival tissue significantly increased the number of Th17 cells in the oral barrier [89]. These results indicate that Th17 cell development in oral barrier tissue requires crucial molecular signals from mechanical stimuli. It may be proposed that oral barrier Th17 cell development by excessive mechanical stimulation may cause oral barrier osteoclastogenesis affecting the external surface of the alveolar bone.

7. Prostaglandin E2 synthesis in oral barrier fibroblasts by mechanical stimulation

Orthodontic tooth movement exerts mechanical stimuli on the periodontal ligament space and induces osteoclastic bone resorption. Fibroblasts are the major cell type occurring in the periodontal ligament, which attaches teeth to the alveolar bone [90,91]. During orthodontic tooth movement, the loading pressure induced RANKL expression in fibroblasts, which were localized in the compressed site, as well as osteocytes and osteoblasts [92-95]. Prostaglandin E2 (PGE2), which is known to induce inflammation [96] and bone resorption [97], was synthesized by fibroblasts in response to mechanical stress [98-101]. Therefore, PGE2 is a key factor in osteoclastogenesis during tooth movement. When mechanical force was applied to periodontal ligament fibroblasts, PGE2 was produced via the cyclooxygenase pathway [102]. Compressive force significantly increased the RANKL/OPG ratio of periodontal ligament fibroblasts at both the gene and protein levels, with increased secretion of PGE2 [103]. Exogenous PGE2 induced RANKL expression in fibroblasts [98] and stimulated fibroblasts to produce IL-6 and IL-8 [104] which activates M-CSF and RANKL production, resulting in bone resorption.

An increase in PGE2 levels of 50% and 90% at 1 and 14 days of orthodontic treatment, respectively, at compression sites in

orthodontically treated cats has been reported [105]. Yamasaki et al. showed that indomethacin, a specific inhibitor of PG synthetase, suppressed the number of osteoclasts and alveolar bone resorption during experimental tooth movement [97]. Nishimura et al. examined the role of PGE2 in edentulous jawbone resorption in rats and found that indomethacin treatment decreased long-term residual alveolar bone resorption, which was, in part, reversed by continuous infusion of PGE2 by an osmotic pump [106]. It has been proposed that mechanical stress to the oral barrier tissue may be sensed by fibroblasts and enhances osteoclastogenesis by increased secretion of PGE2, as well as increased RANKL/OPG ratio and M-CSF production. Indeed, Akashi et al. recently demonstrated that conditioned media obtained from human gingival fibroblasts cultured under cyclic pressure promoted osteoclastogenesis [107].

8. Excessive wearing of removable dentures increases the residual ridge resorption

Over seven decades, numerous clinical investigations have addressed local and systemic factors linked to severe residual ridge reduction. In 1960, Campbell et al. reported that the denture-wearer group had shorter and narrower residual ridges than the non-denture-wearer group in a cross-sectional study of institutionalized edentulous patients [108]. Atwood and Coy (1971) similarly addressed the time of denture wearing in edentulous subjects and reported an insignificant but strong trend for longer denture wearers to have a more severe residual ridge reduction [7]. A series of prospective studies monitored patients with complete maxillary edentulism opposing partial edentulism in the posterior segments of the mandible [16,109]. Mandibular posterior residual ridge resorption was documented in subjects wearing maxillary complete dentures and mandibular distal extension removable partial dentures (RPD), whereas the morphology of the mandibular posterior ridge remained relatively unchanged in subjects who did not wear RPD. More recently, Alsaggaf and Fenlon (2020) reported that excessive denture wearing for more than five years significantly increased residual ridge resorption compared to non-denture-wearing edentulous patients [110]. Furthermore, Pham et al. reported in a systematic review that two implant-assisted overdenture treatments increased the rate of posterior residual ridge resorption compared to four implant-supported overdenture treatments, indicating that increasing mechanical pressure on the posterior edentulous gingiva might promote residual ridge resorption [111].

Denture stomatitis is described as oral mucosal inflammation within the area covered by the denture, primarily caused by poor denture hygiene as well as continual and nighttime wearing of removable dentures [112]. Based on these empirical observations, patients are advised to remove dentures and facilitate daily rest of the residual ridge. Although the exact mechanism of residual ridge resorption associated with excessive denture wearing has not been fully elucidated, we hypothesize that the disproportionate force applied from the denture base may cause the activation of underlining oral barrier immunity, leading to edentulous jawbone loss (Fig. 5).

9. Oral barrier connective tissue contraction as a mechanism of residual ridge resorption

Compared with skin wounds, oral wounds are associated with less inflammatory cell infiltration [113] and less proinflammatory cytokine expression [114]. Oral fibroblasts isolated from the tooth extraction site of rats caused a much faster contraction of the floating

Fig. 5. Proposed molecular and cellular mechanism of denture-induced residual ridge resorption involving oral barrier osteoclasts.

Fig. 6. Proposed mechanism of post-tooth extraction and long-term residual ridge resorption influenced by oral barrier connective tissue contraction.

collagen gel *in vitro* than skin fibroblasts [115,116]. Accelerated floating collagen gel contraction by oral fibroblasts is a consistent and reproducible observation [117-119]. Fibroblasts migrate through the wound collagen connective tissue lattice and contribute to wound contraction by generating tensile strength. Therefore, the intrinsic force within the oral barrier tissue may result from accelerated oral wound closure and contraction, even long after tooth extraction.

The edentulous maxilla of female patients with osteoporosis exhibit a characteristically highly resorbed morphology and are covered by a thin oral mucosa [20], whereas the edentulous mandible tends to be a knife-edge ridge covered by a thick bundle of oral mucosa [21,120]. In a rare pathological condition, oral submucosal fibrosis, was reported to be associated with highly resorbed edentulous ridges [121]. The pattern of edentulous jawbone resorption may be

closely associated with the morphology and thickness of the overlying oral barrier tissue. It is conceivable that the intrinsic mechanical force induced by oral barrier tissue contraction may stimulate the osteoclastogenic oral barrier tissue environment (Fig. 6).

10. Conclusion and future perspectives

This review discusses the biological and pathological roles of oral barrier tissue, potentially influencing the closely associated alveolar bone of the edentulous jaw. We propose that osteoclasts responsible for residual ridge resorption should be considered oral barrier cells and are not coupled with subsequent osteoblastic bone formation. Given their monocyte/macrophage myeloid immune cell origin, oral barrier osteoclasts may also have immune regulatory characteristics [122,123]. Continuous induction of oral barrier osteoclasts is a

primary concern for the prevention of residual ridge resorption. Mechanical stimuli to oral barrier tissue may play a pathological role. We propose a novel biological rationale for socket preservation by preventing or reducing intrinsic oral barrier tissue contraction and the resultant tensile strength. Clinical studies of the edentulous jawbone demonstrated a wide variation among our patients, which masked the effect of postulated causal factors contributing to edentulous jawbone resorption. Increasing investigations into genetic polymorphisms [124-128] may shed light on the mechanisms of individual variations in the future.

Acknowledgements

Research support related to this review was in part from NIH/NIDCR R01 DE022552 (IN) and JSPS Research Fellowship for Young Scientists (19J117670) (TK).

Conflicts of interest

IN reports his role as a consultant of FUJIFILM Corp and BioVinc LLC. All other authors declare no competing interests.

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