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Role of proteases, cytokines, and growth factors in bone invasion by oral squamous cell carcinoma

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Oral squamous cell carcinoma (OSCC) is the most common oral malignancy and an increasing global public health problem. OSCC frequently invades the jaw bone. OSCC-induced bone invasion has a significant impact on tumor stage, treatment selection, patient outcome, and quality of life. A number of studies have shown that osteoclast-mediated bone resorption is a major step in the progression of bone invasion by OSCC; however, the molecular mechanisms involved in OSCC bone invasion are not yet clear. In this review, we present the clinical types of OSCC bone invasion and summarize the role of key molecules, including proteases, cytokines, and growth factors, in the sequential process of bone invasion. A better understanding of bone invasion will facilitate the discovery of molecular targets for early detection and treatment of OSCC bone invasion.

Keywords: Oral squamous cell carcinoma, Bone invasion, Growth factors, Cytokines, Proteases

Introduction

Cancer of the lip and oral cavity is a rising problem worldwide with around 300,000 new cases per annum [1]. Squamous cell carcinoma (SCC) is detected in most patients with oral cancer [2]. Oral squamous cell carcinoma (OSCC) often happens at the gingiva and tongue and contributes above 90% of all oral cancers [3,4]. Genetic aspects and environmental factors, including alcohol abuse, smoking, viral infection, and chronic inflammation, have been associated with the pathogenesis of OSCC [5,6]. Due to the close anatomical structure of the oral mucosa and jaws, OSCC cells may frequently invade bone tissues. Tumors derived from the floor of the mouth, the retromolar zone, and the tongue invade the mandible in 62%, 48%, and 42%, respectively [7]. The patients with oral cancer generally have severe dysfunctions of speaking, chewing, and/or swallowing. Treatment and rehabilitation are particularly difficult in the patients with bone invasion. Thus, early detection and accurate prediction of bone invasion is important to plan surgical ablation and minimize the spread of tumor cells, especially to induce maxillary or mandibular conservative surgery.

In general, OSCC bone invasion shows histologically two distinct patterns. One is the less aggressive erosive pattern with a tumor mass that invades on a broad pushing front and is detached from the bone by the connective tissue layer. The other is the invasive pattern in which the connective tissue layer is destroyed and the islands of tumor penetrate the bone [7–9] (Fig. 1). The formation of two patterns is affected by regional anatomic aspects of exposed bone, particularly whether the progressing front of the neoplasm contacts cancellous bone, by

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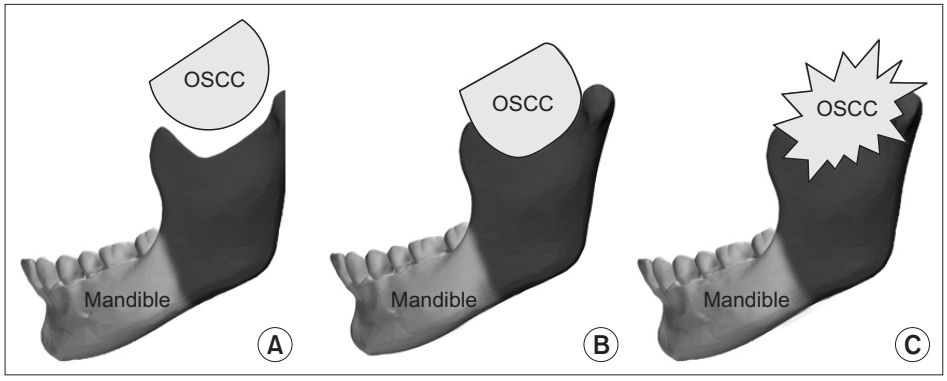

Fig. 1. Distinct patterns of oral squamous cell carcinoma (OSCC) bone invasion. (A) OSCC without bone invasion. (B) Erosive pattern of bone invasion with clear interface between mandible and OSCC. (C) Invasive pattern of bone invasion with irregular front and residual bone islands within OSCC.

the inherent properties of the malignant cells, and by the properties of tumor stroma and unidentified factors [10]. In spite of developments in OSCC treatment, recurrence and mortality rates are continuously increasing in patients with bone invasion [11].

To promote the quality of life and survival, it is necessary to improve diagnosis and therapy for OSCC patients with bone invasion based on molecular mechanisms by which OSCC invades bone. Therefore, we will focus on critical molecular markers associated with bone invasion by OSCC.

Proteases

Bone tissue consists of several distinct cell types and a mostly mineralized bone matrix. Osteocytes are integrated within bone and participate in the bone remodeling process with various cell types, including osteoprogenitor cells, osteoclasts, osteoblasts, marrow fibroblasts, and undifferentiated cells [12,13]. Bone-tropic tumor cells produce a variety of enzymes to directly destroy extracellular matrix (ECM) and then migrate into the surrounding tissues [14]. In addition, tumor-derived proteolytic enzymes stimulate differentiation and maturation of bone cells, especially osteoclast precursors, resulting in osteolysis. Matrix metalloproteinases (MMPs) and cathepsins have been considered pivotal proteases in OSCC-mediated bone invasion.

MMPs are the proteolytic enzymes responsible for degradation of fibrillar and non-fibrillar collagens, gelatin, elastin, and proteoglycans. Some MMPs are detected at high levels in cartilage and bone of mammals, including humans and mice, and are able to cleave native, non-denatured collagens by potentially functioning as collagenases *in vivo* [15]. MMP-1 and MMP-9 were strongly expressed in highly differentiated BHY OSCC cells [16]. In another study, 9 of the 24 buccal SCC with mandibular invasion were intensely stained for active MMP-7 but not 15 without bone invasion, representing that MMP-7 is connected with mandibular invasion [17]. MMP-7 secreted from breast and prostate cancer cells cleaved the receptor activator of nuclear factor-κB (RANK) ligand (RANKL) to its active soluble form, which triggers osteoclast differentiation and bone resorption [18,19]. In addition, high expression of MMP-9 is detected in the cytoplasm of invading OSCC cells [20].

Cathepsins are lysosomal proteases that degrade proteins at acidic pH. In normal cells, cathepsins modulate the immune responses and signaling pathways. Abnormal cathepsin activity is commonly implicated for altered immunologic and physiological behavior that is caused by cancers [21,22]. Cathepsins, including cathepsin D, E, K, and L, play a crucial role in bone resorption by osteoclasts [23]. Procathepsin L was secreted from BHY cells in large amounts and the active cathepsin L degraded the demineralized bone matrix [24]. The injected BHY cells on the masseter muscle of nude mice developed into highly differentiated SCC invading the mandible, demonstrating that cathepsin L might support to degrade the bone matrix [24]. Cathepsin B and D were intensely expressed in all 78 SCC of tongue, gingiva, or floor of mouth and the labeling indices of the two cathepsins were closely correlated with the degree of bone invasion [25]. Furthermore, the survival period in patients with high serum levels of cathepsin B and D was short, indicating that these molecules could be useful as prognostic indicators.

Cytokines

Osteoclasts are actually hematopoietic cells, originated from the macrophage/monocyte lineage. The differentiated osteoclasts attach to the bone matrix and then secrete protons to resorb inorganic components and soluble enzymes to degrade organic components of bone matrix [26]. Two hematopoietic factors are required for differentiation of osteoclast precursors

to mature osteoclasts (osteoclastogenesis): RANKL and macrophage colony-stimulating factor (M-CSF). Tumor necrosis factor (TNF) receptor/TNF-like proteins, including RANKL, its receptor RANK, and osteoprotegerin (OPG), regulate osteoclast differentiation [27]. RANKL functions a key inducer of bone resorption by binding to RANK but OPG acts as a soluble decoy receptor [28]. Osteoclastogenesis and activation of bone-resorbing osteoclasts appears to be the most important factor in OSCC bone invasion [29,30]. In OSCC-induced bone invasion, tumor-derived cytokines, including TNF-α, can directly or indirectly induce osteoclast formation by stimulating RANKL or M-CSF expression [3,31].

Interleukins (ILs), a family of pleiotropic cytokines derived from osteoblasts, osteoclasts, and stromal cells, play an important role in controlling the metabolism of bone [12]. Osteoclasts share many regulatory molecules with immune cells, thereby several immune cells differentiate as the osteoclasts in bone microenvironment [32]. The discovery that cultured human peripheral blood leukocytes can absorb bone supports the connection between immune system and bone metabolism [33]. IL-1β has been recognized as a primary mediator [34] but IL-6, IL-11, and IL-15 as well promote bone resorption [35]. Parathyroid hormone-related peptide (PTHrP), another key molecule of bone homeostasis, plays a role in preventing apoptosis of osteoblasts and recruiting osteoclasts, and is upregulated in the tissues of OSCC patients [36]. The binding of PTHrP to its receptors stimulates osteoclast activity and facilitates bone destruction [37]. High expression of PTHrP messenger RNA (mRNA) was detected in BHY cells and PTHrP mRNA was observed from tumor tissues in 7 of 11 patients with the lower alveolar and gingival carcinoma, showing an invasive pattern of bone invasion.

Chemokines, a superfamily of structurally associated cytokines, are classified into four subgroups based on the variations on a conserved cysteine motif in the protein sequences [38]. The CC and CXC are the larger subgroups, whereas CX3C and XC are smaller subgroups. Chemokines bind to their corresponding G-protein-coupled receptors and induce conformational changes in their transmembrane domain. Some chemokines in the bone matrix play a decisive role in osteoclast activation [39]. Additionally, chemokines produced by tumor cells regulate recruitment and mobilization of osteoclasts [40]. CXCL13 and its receptor CXCR5 promoted RANKL expression in OSCC cells and prevented bone invasion by OSCC through NFATc3 and c-Myc expression [41-43]. CXCL2 was found to be involved in bone destruction by expressing RANKL [44].

Growth Factors

Many growth factors influence function of osteoblasts and osteoclasts during bone remodeling. In the progression of the OSCC, osclast-mediated bone resorption induces secretion of growth factors from reservoirs within mineralized bone matrix, including transforming growth factor (TGF), epidermal growth factor, or connective tissue growth factor, which function as local managers of tumor growth and bone destruction [45]. Various growth factors advance the local microenvironment around tumor cells that express receptors for growth factors, promote tumor cell proliferation, and suppress their apoptosis [46-48]. TGF-β1 not only induces epithelial-mesenchymal transition to increase OSCC invasion capacity but also upregulates factors for prolonged osteoclast survival [49]. Recent studies have shown that TGF-β1 overexpression promoted invasiveness, migration, and angiogenesis of SCC9 cells by activating slug/MMP-9 axis [50].

Conclusions

OSCC bone invasion is an extremely coordinated process that can described in 'vicious cycle' of early, resorption, and ultimate stages, which is stimulated by interaction between

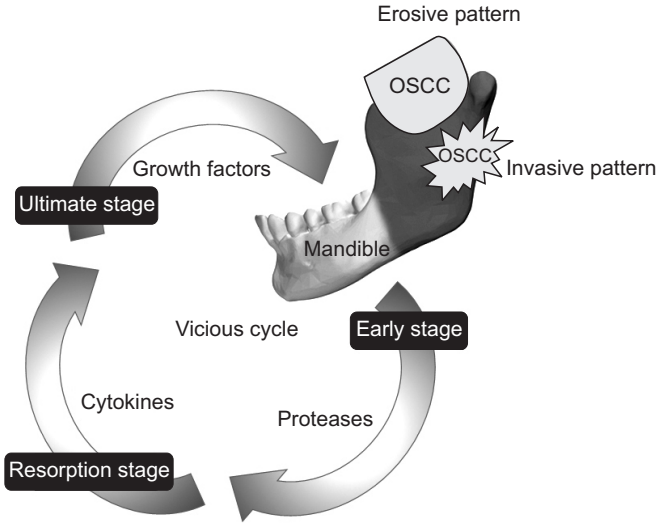

Fig. 2. Coordinated process of oral squamous cell carcinoma (OSCC) bone invasion. In the early stage, proteases degrade the surrounding extracellular matrix and stimulate OSCC cells to invade the bone tissue. In the resorption stage, cytokines regulate osteoclastogenesis and osteoclast-mediated bone resorption. In the ultimate stage, growth factors released from bone matrix promote OSCC growth. The bone invasion deteriorates by continuously repeating these stages.

OSCC cells, osteoblasts, osteoclasts, and bone matrix-derived factors (Fig. 2). In the early stage, proteases degrade the ECM of the adjacent soft tissues and promote the invasion of OSCC into the bone. The next step in bone invasion is the resorption stage, where osteoclasts play a major role in absorbing the mineral components of the bone. Osteoclast-mediated resorption leads to ultimate stage of bone invasion by secreting growth factors from bone matrix and consequently exacerbate OSCC bone invasion by promoting the growth of tumor cells.

Previous studies have reported molecular mechanisms associated with OSCC invasion, based on OSCC characteristics. Although many researchers are exploring molecular mechanisms of OSCC bone invasion, novel targeted markers are still needed to quickly predict bone invasion and to treat patients. The useful target molecules that can predict and serve to treat OSCC bone invasion will increase early diagnostic and therapeutic success and effectively reduce the morbidity and mortality associated with bone invasion by OSCC.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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