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Review

NF-κB acts as a multifunctional modulator in bone invasion by oral squamous cell carcinoma

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ABSTRACT

Oral squamous cell carcinoma (OSCC) is the most common malignant tumor in the oral cavity and the head and neck region. Gingival squamous cell carcinomas (SCCs) frequently invade the maxilla or the mandibular bone and are associated with poor prognosis. Recent findings suggest that osteoclasts, rather than OSCC cells, mediate invasion to the bone. Nuclear factor-κB (NF-κB) is constitutively activated in OSCCs and is involved in promoting the invasive characteristics of OSCC. NF-κB activation is also important for receptor activator of NF-κB ligand (RANKL)-induced osteoclastogenesis. NF-κB inhibitors suppress proliferation and stimulate apoptosis of OSCC cells in vitro and in vivo, as well as inhibit matrix metalloproteinase (MMP) production in OSCC. Furthermore, NF-κB inhibitors have been shown to suppress osteoclastogenesis by reducing RANKL expression in animal models. Thus, inhibition of NF-κB activity may constitute a promising therapeutic approach to treat bone-invasive OSCC. In this review, we discuss recent findings, which suggest that bone invasion in OSCC is mediated via NF-κB signaling and may be successfully prevented by NF-κB inhibition.
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1. Introduction

Oral squamous cell carcinoma (OSCC) is a malignant cancer of the head and neck region and is the sixth most common cancer in the world, with approximately 500,000 new cases projected annually [1]. Studies conducted in Japan demonstrated a dramatic increase in oral cancer incidence for both sexes with a 4.4-fold increase observed in males and 3.8-fold increase observed in females between 1965 and 1999 according to the Osaka Cancer Registry database [2]. The treatment of OSCC involves surgical resection, radiotherapy, chemotherapy, or a combination of these treatments. Despite advances in treatment, the 5-year survival rate for OSCC has not improved significantly and remains at 50–55% [3,4]. In particular, gingival squamous cell carcinoma frequently invades the maxilla or the mandible bone, which is a critical factor for poor prognosis as it leads to metastasis [5]. The presence of mandibular invasion is an important criterion for deciding whether mandibulectomy is necessary. According to the American Joint Committee on Cancer Classification, mandibular invasion is the most advanced primary stage (T4) and overall stage (IV) for these tumors. The treatment outcomes of these lesions are typically poor, with nearly 70% of cases recurring at the primary lesion site and ultimately leading to death [6].

The transcription factor nuclear factor-κB (NF-κB) regulates the expression in a wide variety of genes that are involved in immune and inflammatory responses, proliferation, tumorigenesis, and cell survival [7,8]. Accumulating evidence suggests that the NF-κB signaling pathway contributes to carcinogenesis and the acquisition of malignant characteristics, such as increased invasion, survival, chemoresistance, and angiogenesis in a number of cancer types, including OSCC [9–11]. The activation of NF-κB induces epithelium–mesenchyme transition (EMT) in OSCC [12]. Constitutive activation of NF-κB has been reported in oral cancer, and elevated expression of NF-κB correlates with enhanced invasion and metastasis in OSCC [9–11]. NF-κB has been reported to selectively enhance the expression of pro-inflammatory cytokines, such as interleukin (IL)-1α, IL-6, and IL-8 as well as the expression of degradation enzymes, such as matrix metalloproteinase (MMP)-9 [13,14], suggesting that NF-κB may significantly contribute to tumor progression and metastasis in OSCC via either direct or indirect mechanisms.

Recent studies have established that bone resorption by osteoclasts is an important step in the process of bone invasion and metastasis in several types of malignancies [15]. Therefore, to prevent bone invasion by OSCC cells, it is absolutely necessary to understand the molecular mechanisms by which OSCC regulates osteoclastogenesis. Three proteins are crucial for osteoclastogenesis, including the receptor activator of NF-κB ligand (RANKL), its receptor RANK, and its decoy receptor osteoprotegerin (OPG). The RANKL/RANK interaction induces osteoclastogenesis, while OPG prevents this process in vitro and in vivo [16,17]. Although these proteins are known to be involved in normal bone development, they have also been shown to contribute to pathological bone metabolic processes, such as osteolysis, which is associated with the progression of malignant tumors at the bone site [18,19]. Binding of RANKL to RANK activates several intracellular signaling pathways, and activation of NF-κB is an important step for RANKL-induced osteoclastogenesis. Inhibition of NF-κB by selective NF-κB inhibitors prevents RANKL-induced osteoclastogenesis in vitro and inflammatory bone loss in vivo [20–22]. Therefore, the inhibition of NF-κB activity may constitute a promising approach for the treatment of bone invasion by OSCC.

In this review, we first summarize the NF-κB signaling pathway and describe recent findings from our laboratory and others that highlight a role for NF-κB signaling in OSCC development and osteoclastogenesis. Finally, we discuss the possibility that inhibition of NF-κB signaling might successfully prevent bone invasion by OSCC.

2. Regulatory mechanisms of NF-κB signaling pathway

2.1. Structures of NF-κB/Rel family, IκB family, and IKK complex

NF-κB was originally identified as a transcription factor that bound to the enhancer region of the immunoglobulin κ light chain promoter in B cells [23]. The NF-κB family of transcription factors consists of five ubiquitously expressed proteins in mammals, including p65 (RelA), c-Rel, RelB, NF-κB1 (p105/p50), and NF-κB2 (p100/p52), which form various homo- and heterodimers (Fig. 1) [8,24]. All five members share an N-terminal domain of 300 amino acids, designated as the Rel homology domain (RHD), which is derived from the retroviral oncoprotein v-Rel and is responsible for DNA binding, dimerization, and the interaction with IκB (inhibitor of κB) proteins. Three members, p65, c-Rel and RelB, contain C-terminal transcriptional activation domains (TAD) that are crucial for their ability to induce target gene expression. p65, c-Rel, and RelB are synthesized as mature proteins, whereas NF-κB1 and NF-κB2 are synthesized as the large precursor proteins p105 and p100, which undergo processing to generate the mature NF-κB subunits p50 and p52, respectively. The C-terminal regions of p105 and p100 contain ankyrin repeats that are selectively degraded by the ubiquitin/proteasome pathway. Thus, the homodimers of p50 and p52 lack TADs, and therefore have no intrinsic ability to drive transcription as transcriptional repressors. However, the p65:p50, c-Rel:p50, and RelB:p52 heterodimers function as transcriptional activators [8,24].

The activation of NF-κB signaling is regulated by IκB proteins, such as IκBα, IκBβ, and IκBε, and the precursors p105 (NF-κB1) and p100 (NF-κB2), which are characterized by multiple ankyrin repeat domains and the ability to bind NF-κB dimers. In unstimulated cells, NF-κB dimers are maintained in the cytosol complex with IκB proteins (Fig. 1) [24,25]. Activation of NF-κB is achieved through phosphorylation of IκBs at conserved "destruction box" serine residues (D$\underline{S}$GXX$\underline{S}$), which leads to recognition by βTrCP proteins [24,25].

The IκB kinase (IKK) is an enzyme complex that is involved in modulating the cellular response [8,24,25]. The IKK complex consists of three subunits that are each encoded by a separate gene, *IKKα* (also known as *IKK1*), *IKKβ* (also known as *IKK2*), and NF-κB essential modulator (NEMO) (also known as *IKKγ*) (Fig. 1). Together, the α- and β-subunits are catalytically active, whereas NEMO serves a regulatory function. IKKα and IKKβ, 85 and 87 kDa, respectively, have high sequence homology and contain an N-terminal kinase domain, a dimerization domain, and a C-terminal NEMO-binding domain (NBD) [26]. Despite the structural similarity of IKKα and IKKβ, biological and genetic studies indicate that IKKβ is the dominant kinase involved in IκB phosphorylation [27–31]. IKKβ-deficient mice present a phenotype similar to that of p65-deficient mice, which die at E13.5 from severe liver damage due to massive apoptosis, reinforcing the importance of IKKβ in IκB phosphorylation. By contrast, IKKα-deficient mice die perinatally with multiple morphological defects [32,33]. Recent studies have shown that IKKα is involved in an alternative NF-κB pathway that regulates the RelB/p52 dimer [34]. Mice deficient in the third component, NEMO, die at E12.5-E13.0 from severe liver damage due to massive apoptosis, suggesting that NEMO is indispensable for activation of NF-κB signaling [35].

2.2. Regulatory mechanisms of NF-κB signaling

NF-κB is activated by two distinct pathways, referred to as the "classical or canonical" or "alternative or non-canonical" NF-κB

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