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Current and Potential Inflammation Targeted Therapies in Head and Neck Cancer

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Abstract

Inflammation often exists in the tumor microenvironment and is induced by inflammatory mediators (cytokines, chemokines, and growth factors) produced by the tumor, stroma, and infiltrating cells. These factors modulate tissue remodeling and angiogenesis and actively promote tumor cell survival and chemoresistance through autocrine and paracrine mechanisms. Head and neck squamous cell carcinomas (HNSCCs) are highly inflammatory and aggressive in nature, and they express a number of cytokines and growth factors involved in inflammation. These cytokines and growth factors activate important signal transduction pathways, including NF-κB, JAK/STAT, and PI3K/Akt/mTOR, which regulate the expression of genes controlling growth, survival, and chemosensitivity. This review provides an update on recent advances in the understanding of the mechanisms driving cancer-related inflammation in HNSCC and on molecular targeted therapies under pre-clinical and clinical investigation.

Keywords

Inflammation; cytokines; signal pathways; targeted therapies; head and neck cancer

Background

Introduction

Head and neck squamous cell carcinoma (HNSCC) ranks among the 8 most common cancers in the world and is a significant cause of cancer morbidity and mortality. Approximately 35,000 new cases are diagnosed and 7,600 deaths occur annually in the United States alone [1]. Despite advances in treatment, the overall five-year survival rate has improved marginally over the past 40 years and remains relatively low at approximately 60% [1]. Tobacco and alcohol consumption, betel nut chewing, and human papillomavirus (HPV) infection are the most

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commonly cited risk factors for the development of HNSCC, and while our knowledge of the mechanisms driving transformation is incomplete, these conditions contribute to increased pro-inflammatory cytokine expression and aberrant signaling through inflammatory pathways [2, 3]. Here, we briefly review the cytokines and inflammatory signal pathways that have been implicated in the development of HNSCC and discuss molecular therapeutics that have been used to target these pathways in the pre-clinical and clinical setting.

Aberrant expression of inflammatory cytokines and activation of signaling pathways in HNSCC

Cytokines regulate immunity, inflammation, and hematopoiesis, and this family of proteins includes interleukins (ILs), interferons (IFNs), tumor necrosis factors (TNFs), and growth factors [4]. They are typically divided into two categories: pro-inflammatory (e.g. IL-1, IL-6, IL-8, TNF-α, IFN-γ) and anti-inflammatory (e.g. IL-4, IL-10, TGF-β, and VEGF) [4]. They bind to receptors and transduce signals via second messengers to control growth, differentiation, and activation of cells [4].

Altered expression of cytokines and growth factors plays a major role in the malignant transformation of many cancers including HNSCC [5,6]. A number of such factors are found in HNSCC cell lines in vitro as well as in patients' tumor specimens and serum. These include IL-1α, IL-6, IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF), GRO1, vascular endothelial growth factor (VEGF) [7–9], and hepatocyte growth factor (HGF) [10]. Decreasing cytokine and growth factor levels are associated with response to therapy, while increasing levels are related to cancer progression and recurrence [9]. A longitudinal increase in serum levels of these factors is significantly associated with decreased survival in patients who had local-regionally advanced oropharyngeal HNSCC undergoing chemotherapy and radiation [9]. IL-6 increases VEGF expression and the invasive potential in cell lines [11], and its expression correlates with poor prognosis in HNSCC patients [12]. IL-8 and GRO1 serve as chemoattractants for neutrophils, monocytes, and endothelial cells, which are all major constituents of the inflammatory and angiogenesis response, and their expression promotes aggressive growth and metastasis [13]. In addition, IL-1 and IL-6 are potent inducers of HGF production by stromal cells, such as fibroblasts, and HGF is capable of further enhancing IL-8 and VEGF expression [10]. Several cytokines and growth factors also activate signal pathways that promote the malignant phenotype. TNF-α, IL-1, HGF, and their receptors promote activation of the mitogen activated protein kinase-activator protein-1 (MAPK-AP-1), nuclear factor-kappa B (NF-κB), and phosphotidylinositol-3 kinase (PI3K)/Akt pathways [13]. Epidermal growth factor (EGF) and IL-6 activate signal transducer and activating transcription factor-3 (STAT3) in HNSCC cells (Fig. 1) [7,14,15].

Aberrant activation of NF-κB and related pathways

NF-κB, an injury signal transcription factor, is activated in many cancers and contributes to cell survival, proliferation, invasion, inflammation, and angiogenesis (Fig. 1) [13,16]. NF-κB1 (p105/p50), NF-κB2 (p100/p52), RelA (p65), c-Rel, and RelB comprise the NF-κB family. These proteins form dimers and in the absence of signal are bound to inhibitor-κBs (IκBs), which sequester these proteins in an inactive form within the cytoplasm. Upon activation by pro-inflammatory cytokines, such as IL-1 and TNF-α, IκB kinases (IKKs) and Casein kinase 2 (CK2) can phosphorylate IκBs, which leads to ubiquitination and degradation of the IκBs by the 26S proteasome. This releases the bound NF-κB1/RelA and allows for its processing and translocation to the nucleus, resulting in the activation of multiple target genes [16].

Constitutive activation of NF-κB dysregulates genes that regulate cell proliferation (cyclin D1), apoptosis and resistance to chemotherapeutics and radiation (IL-6, IL-8, cIAP1, Bcl-xL, YAP1), angiogenesis, immune, and proinflammatory responses (IL-6, IL-8, VEGF, HGF), and

metastasis (IL-8, HGF, MMP9) [3,7,8,10,15,17,18]. Nuclear staining of the phospho-activated form of p65 increases with the stage of HNSCC, and upregulation of phosphorylated p65 correlates with decreased survival [13].

Blocking NF-κB function in HNSCC greatly reduces tumor growth and decreases the expression of IL-6 and IL-8 along with many other cytokines and chemokines associated with the pro-inflammatory state [7,8,13,15]. Experiments demonstrating this phenomenon include overexpression of an IκBα with S32/S36 phosphorylation site mutations (IκBαM) unresponsive to IKK phosphorylation, expression of kinase-dead mutants of IKK1 and IKK2 subunits [19,20], and inhibition of CK2 kinase activity with apigenin and siRNA targeting CK2β [20]. Knockdown of p65 inhibits the expression of downstream NF-κB target genes, such as IL-6, IL-8 and YAP1, and results in the induction of cell death [8].

Recently, evidence for cross-talk between NF-κB and p53 in HNSCC has been obtained. Using genome-wide cDNA microarray profiling in a panel of HNSCC cell lines, unique gene signatures that distinguish subsets based on the mutation status of p53 were found [8]. Cell lines with minimal or weak TP53 expression exhibited strong expression of NF-κB target genes (IL-6, IL-8, cIAP1), and nuclear staining of activated p65 (phosphorylated at Ser^{536}) was inversely related to p53 staining [8]. In addition, ΔNp63, a p53 family member, was found to form a novel complex with NF-κB subunit cRel to down-modulate p21 and promote growth [21]. Agents that inhibit NF-κB and promote re-expression of inactivated p53 have been identified, including aminoacridines, such as quinacrine [22,23], but their mechanism of action and suitability as oral or intravenous clinical agents remain unclear.

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) may also play a role in the pathogenesis of HNSCC [24]. Loss of functional p53 has been implicated in the generation of ROS that may drive inflammatory gene expression mediated by NF-κB and propagation of genomic instability. Sablina et al. demonstrated that p53 maintains an important antioxidant function [25]. In addition, a variety of cell types from TP53 knockout mice, which are prone to tumor formation, have an increase in ROS, DNA damage, and mutagenesis. Antioxidants, such as tempol, have demonstrated potential in delaying onset of malignancy and prolonging survival in such tumor prone mice [26] but have yet to be developed and tested clinically.

Overexpression and autocrine activation of EGF receptor (EGFR) are detected in 90% of HNSCC. EGFR can activate the PI3K/Akt and mitogen-activated/extracellular signal-regulated kinase (MEK) pathways, which modulate activation of NF-κB and AP-1 and induce proinflammatory and proangiogenic IL-8 and VEGF expression [7,27]. Akt kinase contributes to NF-κB activation and also activates mammalian target of rapamycin (mTOR), a kinase important in initiating synthesis of inflammatory and angiogenic proteins induced by NF-κB, hypoxia inducible factor (HIF-1α), and VEGF (Fig. 1) [28]. Rapamycin and synthetic mTOR inhibitors have demonstrated significant antitumor activity in vivo in preclinical animal models [29,30]. EGFR and IL-6 have both been shown to activate STAT3 (Fig. 1), and the relative role of these ligands and their receptors may depend on epigenetic inactivation of SOCS-1, a gene involved in negative feedback of IL-6R-janus kinase-mediated STAT3 activation [7, 15]. Both promote expression of genes important in proliferation and cell survival via STAT3 in coordination with AP-1 and NF-κB. Thus, it may not be surprising that using EGFR inhibitors alone have shown limited activity in only ~10% of patients with HNSCC [27,31].

Prostaglandins and COX2 in HNSCC

Prostaglandins have been found to be increased in HNSCC, and one of the most important members, prostaglandin E_2 (PGE_2), promotes growth, inhibits apoptosis by upregulating Bcl-2 expression, increases the production of angiogenic factors, and promotes invasiveness and metastatic growth [32]. The cyclooxygenase (COX) enzymes facilitate the synthesis of

prostaglandins. COX-1 and COX-2 are the two isoforms found in humans. COX-1 is present in most tissues, but COX-2 is usually over-expressed in inflammation and in pre-neoplastic lesions and tumors, consistent with its regulation as another target gene of NF-κB (Fig. 1). Higher expression of COX-2 in tumor cells is seen in conjunction with increased PGE_2 levels in HNSCC, suggesting that COX-2 may be a rate-limiting step in the formation of PGE_2. The level of COX-2 expression in HNSCC has prognostic value, and selective inhibitors of COX-2 inhibit HNSCC and increase the effectiveness of radiotherapy in vitro [32].

Therapeutics Targeting Inflammation in HNSCC

The increased expression of inflammatory mediators in HNSCC suggests that blocking these pathways could play an important role in treating these cancers in conjunction with drugs that target other pathways that contribute to the global phenotype of HNSCC (Fig. 1, Table 1).

Immunological blockade of cytokines

Preclinical studies indicate that TNF-α and IL-1, pro-inflammatory cytokines that potentiates the activation of NF-κB, contribute to tumorigenesis. Anakinra is an IL-1RA that has been studied clinically. IL-1 receptor antagonist (IL-1RA) expressed intracellularly can block IL-1 mediated signal activation of NF-κB, although a recombinant IL-1RA did not have significant activity [13]. Anti-TNF-α antibodies infliximab and etanercept demonstrated antitumor effects in pancreatic cell lines in vitro and significantly reduced primary tumor burden and number of liver metastases in mouse models in vivo (Fig. 1) [33,34]. While monoclonal antibodies against TNF-α have been studied in clinical trials as therapeutic agents in a number of chronic inflammatory disorders, their study in cancer has been limited. Tocilizumab, a monoclonal antibody against IL-6, is currently under evaluation in chronic inflammatory diseases and may be of interest for studies in HNSCC as well [35].

Targeting NF-κB and related pathways

Several agents have been studied that inhibit the activation of NF-κB. Bortezomib, a boronic dipeptide that inhibits the catalytic site of the 26S proteasome, inhibits the degradation of IκBα and the nuclear translocation and activation of canonical subunits of NF-κB, p65 and p50, and induces cell death in HNSCC cell lines and murine xenograft models (Fig. 1) [36]. Clinical trials in patients with HNSCC using this drug show inhibition of nuclear p65 and enhanced apoptosis, but its use in combination with re-irradiation has demonstrated limited clinical responses (Table 1) [18]. It is currently undergoing clinical trials in combination with other chemotherapeutics, including cetuximab, cisplatin, docetaxel, doxorubicin, gemcitabine, irinotecan, and with radiation [37]. IKKβ inhibitors have been a major subject for more specific targeting of NF-κB activation, but evidence that IKKα and IKKβ both contribute to NF-κβ activation may explain the limited activity of IKKβ agents found in HNSCC in pre-clinical studies [19,20].

Geldanomycins are natural inhibitors of heat shock protein 90kD (HSP90), a chaperone of IKK and Akt involved in NF-κB and mTOR activation (Fig. 1) [38]. They exhibit cytotoxic activity in a number of cancers but have demonstrated significant toxicity in clinical trials [38]. Synthetic HSP90 inhibitors with wider therapeutic window in preclinical studies (e.g. SNX-5422, IPI-504) are under clinical investigation.

Curcumin, a naturally occurring polyphenol, inhibited NF-κB as demonstrated by impairment of IKK activation and nuclear translocation and DNA binding (Fig. 1) [39]. Phase I studies using this drug have highlighted the lack of toxicity even when given in large doses and showed potent anti-inflammatory effects demonstrated by reduced inducible PGE_2 levels in the blood [40]. Phase II trials in pancreatic cancer documented poor bioavailability with oral

administration but reported reduction in tumor burden in two out of 21 patients. Even with low serum levels of curcumin, expression levels of NF-κB, COX-2, and STAT-3 in peripheral blood mononuclear cells were found to be downregulated, indicating that facilitation of bioavailability could potentially improve outcomes [41]. Early results from a clinical trial studying the effects of oral administration of curcumin in oral premalignant lesions have shown histologic improvement in 29% of patients within 3 months of treatment [42].

mTOR inhibitors

mTOR has been classically described as a downstream target of oncogenic Akt signaling. Akt-independent activation of mTOR also occurs in response to treatment with inflammatory cytokines like TNF-α, which is mediated through IKKα [43]. Preclinical studies using rapamycin to inhibit mTOR signaling (Fig. 1) have been promising. The drug, administered to mice with cancerous and pre-cancerous oral lesions induced with 4-Nitroquinoline 1-oxide (4NQ), prevented premalignant lesions from progressing to squamous carcinoma and reduced the size of cancerous lesions [44]. Success with mTOR inhibition strategies in cancer cell types from diverse sites is reflected in a number of ongoing trials using mTOR inhibitors, both alone and as adjuvant treatment, for advanced cancers.

EGFR and STAT3 inhibitors

Cetuximab, a monoclonal antibody against EGFR, and gefitinib, an inhibitor of EGFR tyrosine kinase, have been used clinically to block downstream EGFR signaling in HNSCC. Used as a single agent or in combination with chemotherapy or radiation, gefitinib has shown limited efficacy with a response rate of ~10–15% in clinical trials in HNSCC [45]. In a phase I trial of gefitinib combined with paclitaxel and radiation for patients with locoregionally advanced HNSCC, resistance to gefitinib was associated with STAT3 overexpression and activation but not with EGFR phosphorylation or mutation [27,31]. In addition, STAT3 decoy oligonucleotides have demonstrated inhibition of STAT3, angiogenesis, and tumor activity in preclinical models, and a STAT3 decoy phase I trial is underway [14]. Since STAT3 is activated by EGFR and IL-6R, EGFR inhibition in combination with IL-6 antagonists [7] or STAT decoy oligonucleotides [46] holds potential for synergistic activity.

Targeting the COX-2/PGE2 pathway

COX-2 is overexpressed in oral premalignant lesions (OPL) and in HNSCC, and this is correlated with decreased apoptosis and increased angiogenesis and invasiveness [47]. However, clinical trials using non-steroidal anti-inflammatory drugs (NSAIDs) to inhibit COX-2 have not been very successful in chemoprevention of OPL and HNSCC. Ketorolac, a COX-1 and COX-2 inhibitor, failed to demonstrate any significant reduction in oral leukoplakia compared to placebo when administered as an oral rinse [48]. Celecoxib, a specific inhibitor of COX-2, was ineffective in controlling oral premalignant lesions, and accumulating evidence of cardiotoxicity in these drugs has limited the investigation of these drugs as primary chemoprevention agents [49]. There are several trials in progress that are studying the benefit of celecoxib for prevention of recurrence in high-risk patients with head and neck cancer [50].

Conclusion

The role of inflammation in head and neck cancer has been studied quite extensively at the molecular level, but there are still many questions left to be answered. Dysregulation of inflammatory responses in cancer perpetuates the malignant phenotype, and many pharmacological interventions have been developed to target inflammatory mediators and signal pathways. However, only a few of these promising pharmacologic interventions have been tested or proven to be efficacious in treating patients with HNSCC in clinical trials. Most

researchers are now studying therapies that act in combination with other targeted agents or conventional chemotherapy and radiation treatments with the hope that attacking multiple pathways in these tumors will disrupt the malignant programming of the cells and inhibit the pro-survival signals, resulting in significant clinical activity. Based on evidence for co-activation of MAPK-AP-1, IKK-NF-κB, and JAK-STAT3 pathways, small molecule inhibitors targeting these kinases or upstream ligands and receptors would seem to merit investigation for combined therapy. Also of interest are several natural or synthetic products that act concurrently on IKK, Akt, NF-κB, and p53, but the efficacy of these drugs has yet to be developed fully for clinical use in HNSCC.

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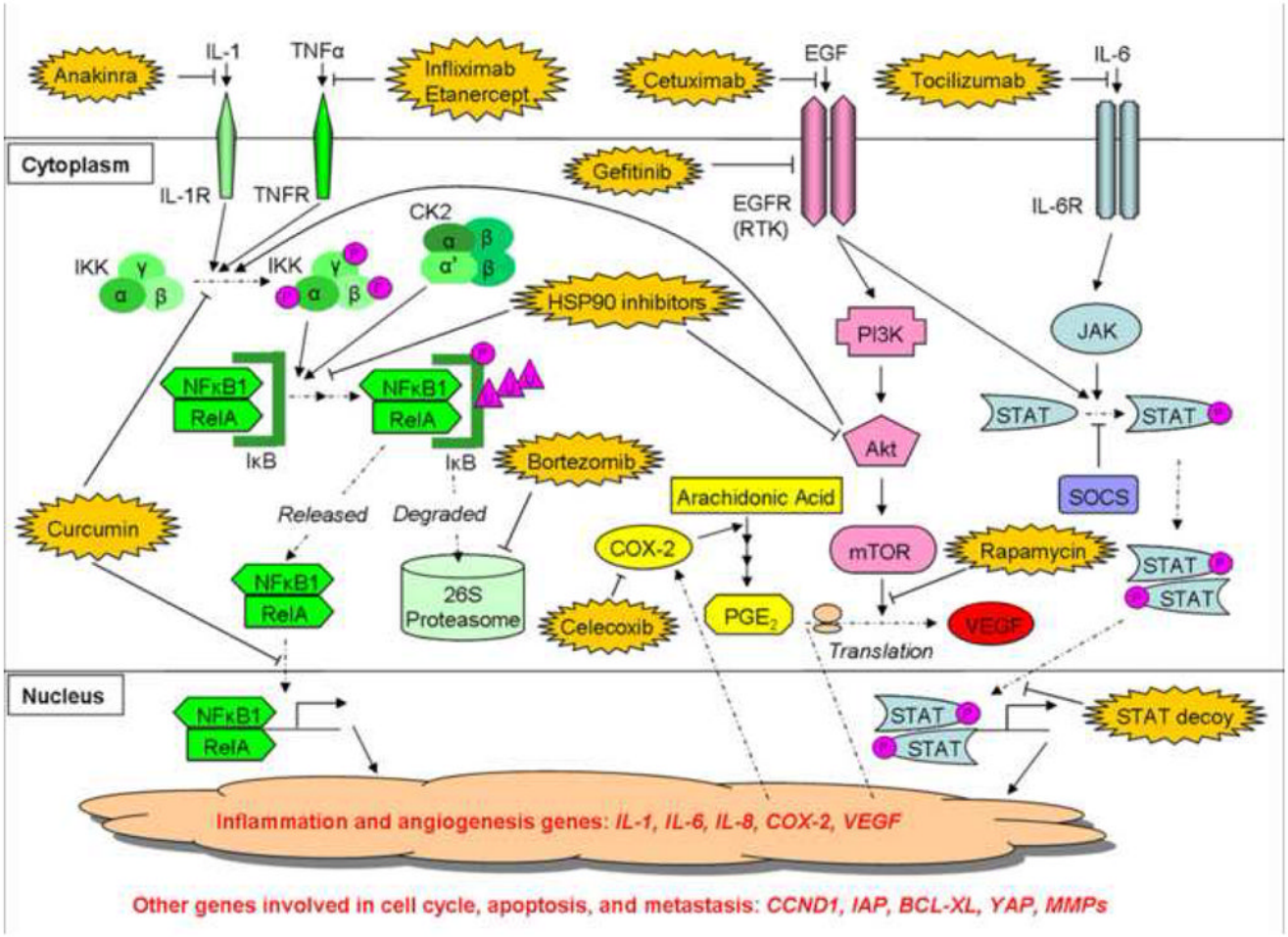

Figure 1.

Pharmacological inhibition of inflammatory signal pathways. Dysregulation of NF-κB (green), PI3K/Akt/mTOR (pink), and JAK/STAT (blue) signaling as well as PGE_2 synthesis (yellow) contribute to inflammation seen in HNSCC as described in this review. Signal cascades activate (solid arrows) downstream targets and changes (dashed arrows) in target phosphorylation (circles), ubiquitination (triangles), association, or localization. Drugs (orange) have been developed to inhibit these pathways (blocking arrows), and several are depicted with their currently understood targets of activity.

Table 1

Summary of drugs targeting inflammation and their clinical status.

Drug	Target Site(s)	Stage of Development	Reference
EGFR antibodies (Cetuximab)	EGFR	FDA-approved for head and neck cancer.	[45]
EGFR tyrosine kinase inhibitors (Gefitinib)		Phase II clinical trials	
Curcumin	NFkB COX-2 Cytokines EGFR	Phase II/III clinical trials in head and neck cancer.	[42]
COX Inhibitors (Ketorolac, Sulindac, Celecoxib, etc.)	COX-2	Phase II chemoprevention trials in head and neck cancer.	[49,50]
Bortezomib	26S Proteasome	Phase I/II in head and neck cancer.	[18,37]
STAT3 decoy oligonucleotide	STAT3	Phase I clinical trial in HNSCC.	[46]
mTOR Inhibitors (Rapamycin, etc.)	mTOR	Animal models in head and neck cancers, Phase I trials.	[44]
Anti-TNF-α monoclonal antibodies (Infliximab, Etanercept)	TNF-α	Phase III clinical trials in lung cancer.	[34]
Thalidomide and analogues		Phase II clinical trials in prostate and colorectal cancers.	
Anakinra	IL-1	Phase I clinical trials in solid tumors.	[13]
Hsp-90 Inhibitors (Geldanamycins, etc.)	IKK Akt Other kinases	Phase I in solid tumors, phase II in breast cancer	[38]
Tocilizumab	IL-6	Phase III clinical trials in chronic inflammatory conditions.	[35]