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Targeting the epidermal growth factor receptor for head and neck cancer chemoprevention

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SUMMARY

The epidermal growth factor receptor (EGFR) has been implicated in head and neck squamous cell carcinoma (HNSCC) carcinogenesis. It is currently the only molecular target in head and neck cancers for which there are pharmacologic therapeutic interventions approved by regulatory agencies worldwide to treat advanced disease. Oral pre-malignant lesions have increased EGFR protein expression and increased *egfr* gene copy number compared to normal mucosa. Oral pre-malignant lesions with overexpression of EGFR or *egfr* gene copy number gain are at higher risk for malignant transformation. Inhibition of EGFR in pre-clinical models of oral pre-malignancies validates this approach as an effective way to reduce the incidence of oral cancer, and supports investigation of this strategy in the clinic. Clinical trials with EGFR targeted agents, including cetuximab, erlotinib, and vandetanib, are currently under way, some with promising preliminary results. If ultimately shown to reduce the risk of oral cancer, chemoprevention with EGFR inhibitors may significantly reduce morbidity and possibly mortality from HNSCC.

Introduction

The epidermal growth factor receptor (EGFR) is a cytoplasmic transmembrane protein belonging to the HER (ErbB) family of receptor tyrosine kinases and encoded by the *egfr* gene located on chromosome 7p12-13. The HER family is comprised of four distinct receptors: EGFR (also known as HER1 or ErbB-1), HER2 (ErbB-2, Neu), HER3 (ErbB-3) and HER4 (ErbB-4). The EGFR is a 170-kd protein encoded by a 110-kb-long gene localized in the short arm of chromosome 7. Its structure consists of an extracellular ligand-binding domain, a single transmembrane hydrophobic helix, and a cytoplasmic carboxy-terminal domain, to which tyrosine kinase activity is confined [1].

HER receptors are usually located in the basolateral membrane of the epithelial cells, where they can interact with their ligands present in the stroma, thus mediating signaling between the epithelium and the extra-cellular matrix. The ligands to HER receptors (also known as epidermal growth factor [EGF] family of growth factors) are characterized by the presence of an EGF-like domain (composed of three disulfide-bonded intramolecular groups, which confer binding specificity) and additional structural motifs (such as immunoglobulin-like domains, heparin-binding sites and glycosilation sites). They are produced as transmembrane precursors and may be subdivided into three groups according to their affinity for one or more HER receptors: the first group includes ligands that bind exclusively to EGFR (e.g. EGF, transforming growth factor-alpha [TGF-alpha], amphiregulin, CRIPTO); the second group includes ligands to both EGFR and HER4 (e.g. betacellulin, heparin-binding epidermal growth factor, epiregulin); the third group includes ligands to HER3 and HER4 (tomoregulin, neuregulins/heregulins, neu differentiation factor). HER2 has no identified ligand, a fact explained by the structure of the extracellular region of the receptor, which is already in an activated conformation and does not allow ligand docking. Once the ligand binds to the extracellular domain, the receptor undergoes a conformational change of this region, which allows homodimerization or heterodimerization with another activated receptor of the HER family. Following dimerization, there is increased intracellular kinase activity of the receptor through a proximity effect, resulting in phosphorylation of critical tyrosine residues on the cytoplasmic domain, which then triggers the signal transduction cascade. Three major intracellular signaling pathways linked to EGFR activation have been identified: the Ras–Raf–mitogen-activated protein (MAP) kinase pathway, the phosphatidylinositol 3-kinase (PI-3 K)/Akt pathway and the Janus-kinase/signal transducer and activator of transcription (Jak2/STAT3) pathway. Once activated, these pathways contribute to the development of a malignant cellular phenotype, including resistance to apoptosis, increased proliferation, invasion, metastasis, and stimulation of angiogenesis (Fig. 1) [1].

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The EGFR has been implicated in head and neck squamous cell carcinoma (HNSCC) carcinogenesis. It is currently the only molecular target in head and neck cancers for which there are pharmacologic therapeutic interventions approved by regulatory agencies worldwide to treat advanced disease. The purpose of this review is to discuss the importance of EGFR in oral pre-malignant lesions and the possible role of EGFR-targeted therapies for head and neck cancer chemoprevention.

EGFR-targeted agents for treatment of HNSCC

Pharmacologic strategies targeting the EGFR that have been approved for cancer therapy include the use of antibodies and small molecule receptor tyrosine kinase inhibitors (TKIs).

The monoclonal antibody cetuximab has been demonstrated to improve overall survival when added to radiation therapy for treatment of locally advanced disease [2] and when added to chemotherapy for recurrent/metastatic disease [3]. As a single agent, cetuximab elicited a response rate of 13% in patients with platinum-refractory HNSCC [4]. The humanized monoclonal antibody panitumumab has also been studied for management of patients with recurrent/metastatic HNSCC in a large phase 3 trial. The primary endpoint of overall survival was not met, but the panitumumab plus chemotherapy arm had improved progression-free survival and response rates compared to the chemotherapy only arm [5]. The third EGFR antibody studied in the phase 3 setting was zalutumumab. In patients with recurrent/metastatic disease, the drug failed to improve survival over best supportive care, although progression-free survival and response rates were higher in the zalutumumab-treated patients [6].

The EGFR TKI gefitinib 250 or 500 mg/day was evaluated as monotherapy in phase 2 and 3 studies in recurrent/metastatic disease. Response rates ranged from 1.4% to 10.6% [7–9], but in the larger phase 3 trial, gefitinib failed to improve the primary endpoint of overall survival when compared to methotrexate [9]. In a phase 2 study involving 115 patients with recurrent/metastatic HNSCC, treatment with erlotinib was associated with a response rate of 4.3%, with disease stabilization in 38.3% of patients, maintained for a median of 16.1 weeks [10]. Newer generation of EGFR TKIs are being evaluated, including for example, the irreversible dual EGFR/HER2 inhibitor afatinib – preliminary results of a randomized phase II study demonstrated comparable efficacy with cetuximab in terms of response rates in previously treated patients with incurable HNSCC [11].

Taken together, the clinical trials completed to date demonstrate that targeting the EGFR for head and neck cancer therapy may improve survival, particularly with strategies using the monoclonal antibody cetuximab. EGFR TKIs also have activity against HNSCCs, but the majority of studies were performed in heavily pre-treated patients with recurrent/metastatic disease; in this setting, response rates were modest and regulatory approval of EGFR TKIs for HNSCC therapy has not been granted.

EGFR-targeted agents are, in general, well tolerated. Low grade skin toxicities (including acneiform rash, pruritus, dry skin) and diarrhea are the most common adverse events associated with EGFR TKIs. EGFR antibodies are also associated with similar skin toxicities, in addition to hypomagnesemia and risk for uncommon, albeit potentially severe, hypersensitivity reactions (especially with the non-humanized antibody cetuximab) [2,3,9]. The favorable toxicity profile and activity in advanced disease allow EGFR-targeted drugs

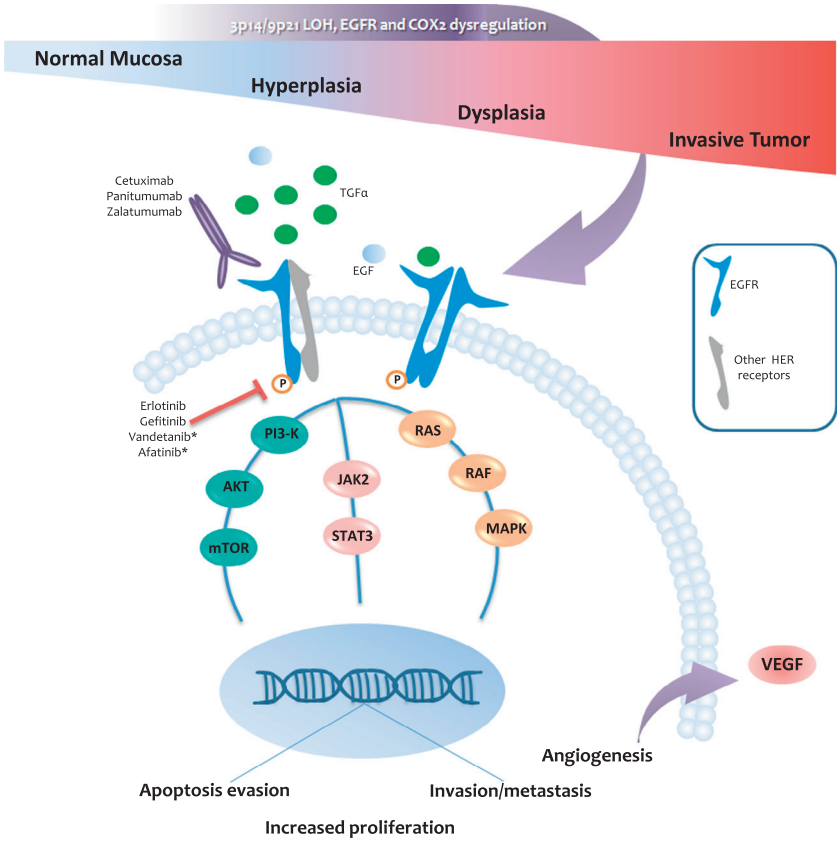

Figure 1. Epidermal growth factor receptor (EGFR) pathway activation during HNSCC carcinogenic process. Loss of heterozigosity (LOH), EGFR overexpression/amplification and cyclooxygenase-2 (COX2) dysregulation in pre-malignant lesions have been associated with invasive cancer risk. EGFR activation contributes to acquisition of cancer hallmarks represented in the figure. EGFR can be inhibited by the use of monoclonal antibodies (cetuximab, panitumumab, zalatumumab) and tyrosine kinase inhibitors (erlotinib, gefitinib, vandetanib and afatinib). Vandetanib and afatinib exhibit multikinase activity against other targets such as the vascular endothelial growth factor (VEGF) receptor (vandetanib) and HER-2 (afatinib).