Epidermal Growth Factor Receptor Inhibition in Squamous Cell Carcinoma of the Head and Neck

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KEYWORDS

• Epidermal growth factor receptor • Head and neck cancer
• Anti-EGFR monoclonal antibodies • Tyrosine kinase inhibitors • Pan-HER inhibitors

KEY POINTS

- Up to 90% of squamous cell carcinomas of the head and neck express high levels of epidermal growth factor receptor (EGFR).
- Overexpression and high *EGFR* gene copy number are associated with poor prognosis.
- Cetuximab improves overall survival either as curative treatment in combination with radiation therapy or as palliative treatment in combination with chemotherapy.
- A minority of patients derive long-term benefit of anti-EGFR treatment, outlining the importance of developing novel treatment strategies.
- Potentially more potent anti-EGFR compounds as well as combination strategies are under investigation to improve treatment efficacy.

THE EPIDERMAL GROWTH FACTOR RECEPTOR

The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein commonly expressed in many normal tissues. It is a member of the human epidermal receptor (HER) tyrosine kinase receptor family composed of 4 different receptors (EGFR/c-erbB-1, c-erbB-2/HER-2/neu, c-erbB-3/HER-3 and c-erbB4/HER-4), all of which are transmembrane proteins with tyrosine kinase activity (**Fig. 1**).

Conflicts of Interest: Dr J.P. Machiels is a member of the advisory board of Boerhinger-Ingelheim (without financial compensation).

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Hematol Oncol Clin N Am 29 (2015) 1011–1032
http://dx.doi.org/10.1016/j.hoc.2015.07.007 **hemonc.theclinics.com**
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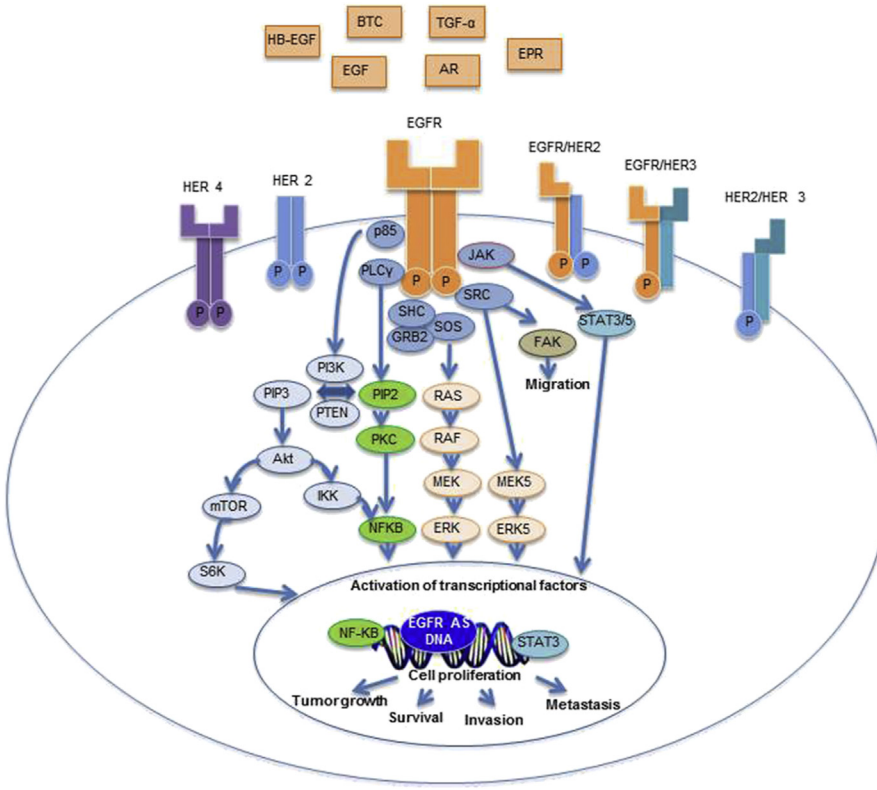

Fig. 1. Epidermal growth factor receptor (EGFR) is a member of the human epidermal receptor (HER) tyrosine kinase receptor family composed of 4 different receptors (EGFR/c-erbB-1, c-erbB-2/HER-2/neu, c-erbB-3/HER-3 and c-erbB4/HER-4), all of which are transmembrane proteins with tyrosine kinase activity. The EGFR has an extracellular domain, which provides a ligand-binding site for multiple ligands. Epidermal growth factor (EGF), transforming growth factor alpha (TGF-α) and amphiregulin (AR) are specific ligands of the EGFR, while β-cellulin (BTC), heparin-binding EGF (HB-EGF), and epiregulin (EPR) are less specific ligands that bind EGFR and ErbB4. Upon ligand fixation, EGFR homodimerization or heterodimerization with another HER receptor occurs, leading to the activation of the intracellular tyrosine kinase. This stimulates kinase signal transduction pathways involved in tumor proliferation, apoptosis, angiogenesis and cell migration/invasion. Downstream signaling through the Ras/Raf/Mek/Erk pathway controls gene transcription, cell proliferation, and cell-cycle progression, whereas the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (PI3K/Akt) pathway stimulates numerous antiapoptotic signals in the cell. Src tyrosine kinase, phospholipase-Cγ, protein kinase C (PKC), and signal transducer and activator of transcription (STAT) activation have also been documented.

The EGFR has an extracellular domain, which provides a ligand-binding site for multiple ligands. Upon ligand fixation, EGFR homodimerization or heterodimerization with another HER receptor occurs, leading to the activation of the intracellular tyrosine kinase. This leads to activation of molecular pathways involved in tumor proliferation, apoptosis, angiogenesis, and cell migration/invasion.[1] Downstream signaling through the Ras/Raf/Mek/Erk pathway controls gene transcription, cell proliferation, and cell-cycle progression, whereas the phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt)