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A Model for Targeted Therapy Using Epidermal Growth Factor Receptors

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Introduction

The Epidermal Growth Factor Receptor (EGFR) is one of three tyrosine kinase receptors (erbB2/HER-2, erbB3/HER-3, and erbB4/HER-4) that make up the EGFR family. The extracellular ligand-binding domain, a brief hydrophobic membrane region, and an intracytoplasmic protein tyrosine domain are all found in these receptors, which are all anchored in the cellular membranes. Overexpression of the receptor (which is common in cancer) as well as ligand-dependent and ligand-independent pathways activates EGFR. EGF and transforming growth factor-a are two of the six known ligands that bind to the EGFR. When a ligand binds to a receptor, the ecto domain undergoes a conformational shift, allowing for receptor dimerization and autophosphorylation of multiple tyrosine residues in the receptor's COOH-terminal tail. Some malignancies include versions of the EGFR and HER that have a loss of the extracellular domain, resulting in continuous receptor activation, which results in ligand-independent receptor activation. Through interaction with the a5h1 integrin, overexpression of the urokinase type plasminogen activator receptor activates the EFGR without the need for a ligand. Finally, ligand-independent receptor activation is caused by cellular stressors such as radiation, which quiet phosphatases that oppose receptor kinase activity, moving the basal phosphorylation equilibrium toward the activated state [1].

Pathway involving Ras/Raf/mitogen-activated protein kinase

This is an essential pathway that controls cell growth and survival. Following EGFR phosphorylation, the adaptor proteins Grb2 and Sos create a complex that binds to particular docking sites on the receptor either directly or by connection with the adaptor molecule Shc. This contact causes a conformational change in Sos, allowing it to attract Ras-GDP and activate Ras (Ras-GTP). Ras-GTP stimulates Raf-1, which phosphorylates the mitogen-activated protein kinases (MAPK) extracellular signal-regulated kinases 1 and 2 through intermediary stages. MAPKs that have been activated are transported to the nucleus and phosphorylate certain transcription factors involved in cell growth [2].

Transcription pathway signal transducers and activators

STAT proteins bind with phosphotyrosine residues via their Src homology 2 domains, then dimerize and translocate to the nucleus, driving the expression of certain target genes. In many primary malignancies and tumour-derived cell lines, constitutive activation of STAT proteins, particularly STAT3, has been observed. STAT3 persistent activation is promoted by increased activity of membrane-associated tyrosine kinases such EGFR, HER-2, and platelet-derived growth factor receptor, which contributes to oncogenesis and tumour development [3].

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Secondary mutations have resulted in acquired resistance to anti-EGFR therapies

Individuals who react to gefitinib or erlotinib initially may develop secondary EGFR mutations, particularly the T790M mutation. Interestingly, a number of irreversible EGFR inhibitors have been found to disrupt receptor activation and reduce tumour cell proliferation in tumour cells with the T790M mutation. Patients with lung cancer who have progressed to erlotinib are now undergoing clinical trials with these medicines.

Recent Advances

The initial rationale for targeting the EGFR in cancer stemmed mostly from the discovery that the receptor was commonly overexpressed in epithelial malignancies and the preclinical effectiveness of anti-EGFR monoclonal antibodies. The oncogenic role of the EGFR has been finely characterized in recent years as a result of enhanced understanding of receptor activation mechanisms, the discovery of somatic mutations in the receptor as well as mutations in components of the receptor's signalling pathway, and, in large part, the clinical success of anti-EGFR therapies [4].

Clinical-Translational Advances

There are two types of anti-EGFR medicines that have proven clinical efficacy and have been approved by the FDA for cancer therapy. These are mAbs aimed targeting the receptor's extracellular domain as well as low molecular weight, ATP-competitive inhibitors of the receptor's tyrosine kinase (TKIs; reviewed in ref. 55). Anti-EGFR mAbs and EGFR TKIs have both been authorized for the treatment of advanced colorectal and head and neck cancers, as well as advanced non–small cell lung cancer and pancreatic carcinoma. EGFR TKIs have also been shown to be effective in head and neck cancers including glioblastoma. Finally, the majority of EGFR-expressing cancers have a complicated genetic background, and there is a large amount of compensatory 'cross-talk' across receptors within a signalling network, as well as with other pathways that regulate cell proliferation, trafficking, and survival. As with traditional chemotherapeutic treatments, rationally created biologically and molecularly targeted combinations are anticipated to improve these drugs' contribution to cancer treatment [5].

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