Molecular Pathways

The Epidermal Growth Factor Receptor Pathway: A Model for Targeted Therapy

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Abstract   The epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase receptor that is frequently expressed in epithelial tumors. The EGFR was the first receptor to be proposed as a target for cancer therapy, and after 2 decades of intensive research, there are several anti-EGFR agents available in the clinic. Recent advances in our understanding in the mechanisms of receptor activation and function, discovery of primary and secondary EGFR somatic mutations, as well as a new generation of anti-EGFR agents provide new leads on the clinical targeting of this receptor and may serve as a model for strategies aimed at targeting other receptors.

Background

The epidermal growth factor receptor (EGFR) belongs to a family of receptor tyrosine kinases that includes three other members (erbB2/HER-2, erbB3/HER-3, and erbB4/HER-4). These receptors are anchored in the cytoplasmic membrane and share a similar structure that is composed of an extracellular ligand-binding domain, a short hydrophobic transmembrane region, and an intracytoplasmic tyrosine kinase domain (reviewed in refs. 1, 2).

EGFR becomes activated by receptor overexpression (frequent in cancer) as well as ligand-dependent and ligand-independent mechanisms. There are six known ligands that bind to the EGFR, including EGF itself and transforming growth factor-α. Ligand binding to the receptor induces a conformational change of the receptor ectodomain that allows for receptor dimerization and autophosphorylation of several tyrosine residues within the COOH-terminal tail of the receptors (3, 4).

Ligand-independent receptor activation occurs in some tumors that display forms of the EGFR and HER that have a deletion of the extracellular domain that result in constitutive receptor activation (5, 6). Overexpression of the urokinase-type plasminogen activator receptor also results in ligand-independent activation of the EFGR via association $\alpha_5\beta_1$ integrin (7). Finally, ligand-independent receptor activation occurs as a result of cellular stresses, such as radiation, which silence phosphatases that antagonize the receptor kinase activity, thereby shifting the equilibrium of basal phosphorylation toward the activated state (8).

Activation of the receptor leads to the phosphorylation of key tyrosine residues within the COOH-terminal portion of EGFR and, as a result, provides specific docking sites for cytoplasmic proteins containing Src homology 2 and phosphotyrosine-binding domains (1). These proteins bind to specific phosphotyrosine residues and initiate intracellular signaling via several pathways (Fig. 1).

Ras/Raf/mitogen-activated protein kinase pathway. This is a critically important route that regulates cell proliferation and survival. Following EGFR phosphorylation, the complex formed by the adaptor proteins Grb2 and Sos binds directly, or through association with the adaptor molecule Shc, to specific docking sites on the receptor (9, 10). This interaction leads to a conformational modification of Sos, now able to recruit Ras-GDP, resulting in Ras activation (Ras-GTP). Ras-GTP activates Raf-1 that, through intermediate steps, phosphorylates the mitogen-activated protein kinases (MAPK) extracellular signal-regulated kinases 1 and 2 (11, 12). Activated MAPKs are imported into the nucleus where they phosphorylate specific transcription factors involved in cell proliferation (13, 14).

Phosphatidylinositol 3-kinase/Akt pathway. This pathway is involved in cell growth, apoptosis resistance, invasion, and migration (see refs. 15, 16 for review). Phosphatidylinositol 3-kinase (PI3K) is a dimeric enzyme composed of a regulatory p85 subunit, responsible of the anchorage to erbB receptor-specific docking sites, and a catalytic p110 subunit that generates the second messenger phosphatidylinositol 3,4,5-triphosphate, which is responsible for phosphorylation and activation of the protein serine/threonine kinase Akt (15). The principal mechanism that drives EGFR-dependent PI3K activation is the dimerization of the receptor with HER-3. In fact, docking sites for p85 are absent on EGFR, whereas, on the contrary, docking sites for p85 are abundant on HER-3 (17, 18). Alternatively, the p85 subunit can interact with EGFR through the docking protein Gab-1 (19).

Phospholipase Cγ. Phospholipase Cγ interacts directly with activated EGFR and hydrolyses phosphatidylinositol 4,5-diphosphate to give inositol 1,3,5-triphosphate, important for intracellular calcium release, and 1,2-diacylglycerol, cofactor in protein kinase C activation (20, 21). Protein kinase C activation can, in turn, result in MAPK and c-Jun NH_2-terminal kinase activation (22, 23).

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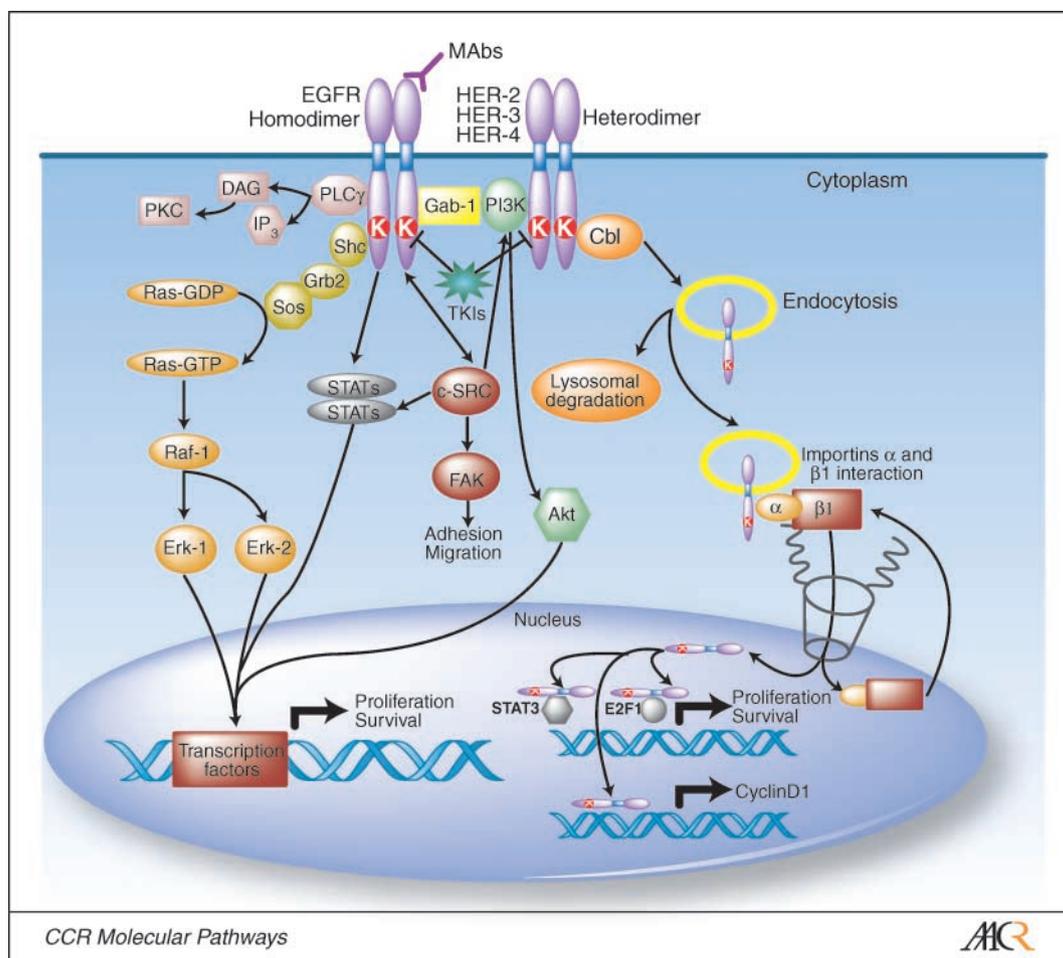
Fig. 1. Signaling pathways and inhibitors of EGFR. Activation of EGFR leads to homodimerization/heterodimerization, phosphorylation of specific tyrosine residues, and recruitment of several proteins at the intracellular portion of the receptors. Phospholipase Cγ (*pink*) and STAT transcription factors (*blue*) bind directly to the receptor, whereas Ras/Raf/MAPK pathway (*orange*) and PI3K pathway (*green*) need several specific adaptor molecules (*yellow*). PI3K can also bind directly any of the erbB partners of EGFR heterodimers. Concomitantly, the activated receptors undergo endocytosis and follow two possible routes: lysosomal degradation or importin-mediated nuclear translocation. Once in the nucleus, EGFR can either behave as a proper transcription factor (for *cyclin D1* up-regulation) or as coregulator of other gene transactivators. Both pathways result in nuclear activation of genes related with cell proliferation, survival, invasion, and metastasis. Two main strategies are available for EGFR kinase inhibition: mAb and small-molecule TKIs. mAbs act extracellularly, avoiding EGFR ligands binding, whereas TKIs compete with the ATP binding to the kinase domain of the receptor. DAG, 1,2-diacylglycerol; IP_3, inositol 1,3,5-triphosphate; PLCγ, phospholipase Cγ; Erk-1, extracellular signal-regulated kinase-1; Erk-2, extracellular signal-regulated kinase-2; FAK, focal adhesion kinase; PKC, protein kinase C.

Signal transducers and activators of transcription pathway. Signal transducers and activators of transcription (STAT) proteins interact with phosphotyrosine residues via their Src homology 2 domains and, on dimerization, translocate to the nucleus and drive the expression of specific target genes (24). Constitutive activation of STAT proteins and especially STAT3 has been found in numerous primary cancers and tumor-derived cell lines (25). Augmented activity of membrane-associated tyrosine kinases, such as EGFR, HER-2, and platelet-derived growth factor receptor, promotes STAT3 persistent activation, which contribute to oncogenesis or tumor progression (25).

Src kinase pathways. Src is the archetypal member of a nine-gene family of nonreceptor tyrosine kinases that plays a critical role in the regulation in cell proliferation, migration, adhesion, angiogenesis, and immune function (26, 27). Src, which is located in the cytosol, activates a series of substrates, including focal adhesion kinase, PI3K, and STAT proteins (26, 27). Although Src functions independently, it also cooperates with other receptor tyrosine kinases signaling. The interaction between EGFR and Src is complex. On one hand, Src serves as a signal transducer and an enhancer of EGFR activation (28, 29). On the other, it may be involved in resistance to EGFR therapies via independent activation or association with other receptors.

Recent Advances

The initial proposal for targeting the EGFR in cancer was mostly based on the observation that the receptor was frequently overexpressed in epithelial tumors and on the preclinical activity of anti-EGFR monoclonal antibodies (mAb; ref. 30). In the last few years, the oncogenic role of the EGFR has been more finely characterized due to an improved understanding of the mechanisms of receptor activation, the finding of somatic mutations of the receptor as well as mutations in components of the signaling pathway of the receptor, and in great measure due to the clinical success of anti-EGFR therapies in the clinic.

New insights into mechanisms of receptor activation and function. Over the last few years, a substantial amount of structural data has illuminated the mechanisms governing ligand-mediated activation of the EGFR. Ligand binding to the receptor ectodomain creates an extended and stabilized conformation of the entire ectodomain, which promotes homodimerization and heterodimerization (see refs. 3, 4 for reviews). mAbs prevent the receptor from adopting this extended and stabilized conformation required for dimerization due to steric clashes between the Fab domain of the antibody and one of the domains of the extracellular portion of the receptor. This mechanism of action could be important in situations in which activation of the receptor occurs via stabilization of the extended configuration in the absence of ligand binding, which is felt to occur under conditions of high receptor expression. Although ligand-induced conformational changes of the receptor explain ligand-induced dimerization, the mechanism by which the EGFR is activated on dimerization has not been well understood. In an important recent contribution, it has been shown that, in basal conditions, the EGFR kinase domain remains in an autoinhibited conformation similar to that of Src and cyclin-dependent kinases (31). EGFR activation results from the formation of an asymmetrical dimer in which the COOH-terminal lobe of one kinase domain plays a role analogous to that of cyclin in activated cyclin-dependent kinase/cyclin complexes (31).

There is also increasing evidence that the EGFR family of receptors has the ability to translocate to the nucleus where it may exert a variety of biological actions. Members of this receptor family that have been found in the nucleus include HER-2 (32), HER-3 (33, 34), the truncated COOH-terminal portion of HER-4 (35), and, more recently, a truncated constitutively active form of HER-2 (6). For EGFR, part of the receptors may escape the internalization and lysosomal degradation route and translocate in the nucleus, where it functions as a transcription factor of the *cyclin D1* gene (36) or behaves like a cofactor of STAT3 and E2F1 transcription factors (37, 38). The functional implications of EGFR localization in the nucleus are unknown but nuclear EGFR may correlate with a decreased overall survival in patients with breast cancer (39). The therapeutic implications of localization of the receptor in the nucleus are that it may result in resistance to the growth-inhibitory effects of mAbs (6).

Somatic mutations of the EGFR and downstream signaling molecules. Recently, several somatic mutations in the *EGFR* gene have been found to be closely linked with favorable response to the anti-EGFR tyrosine kinase inhibitors (TKI) gefitinib and erlotinib in non–small cell lung cancer patients (40, 41). The mutations arise in four exons within the kinase domain of the receptor: point mutation of G719 in the exon 18, deletion of the amino acids 747 to 750 in the exon 19, in-frame insertions in the exon 20, and point mutations of L858 and L861 in the exon 21. These mutations arise more frequently in a subpopulation of non–small cell lung cancer patients: women, Japanese, and nonsmokers with bronchioalveolar adenocarcinoma histology (42).

It is important to realize that the clinical benefit observed with anti-EGFR TKIs is not restricted to those patients harboring *EGFR* gene mutations. There is also a strong correlation between *EGFR* gene amplification and a high response to

EGFR TKIs and tumors that, with EGFR amplification, have frequently coexisting EGFR mutations (43). On the other hand, the presence of *K-RAS* mutations, frequent in smokers, correlates with resistance to EGFR inhibitors (44). In a similar fashion as with EGFR, *HER-2* mutations have been observed in lung adenocarcinomas (45). Another potential molecular predictor of response to EGFR TKIs is expression of erbB3, expressed in high levels in gefitinib-sensitive non–small cell lung cancer cell lines and in patients that achieve clinical benefit from gefitinib (46).

Genome sequencing approaches have identified additional activating mutations in components of the EGFR receptor signaling pathway. These include, in addition to the *RAS* mutations mentioned above, *B-Raf* mutations in melanoma (47) and somatic mutations in the *PI3KCA* gene, which encodes the p110α catalytic subunit of PI3K, in a variable cohort of colon, brain, gastric, breast, and lung cancers (48). These findings are of considerable importance, as *B-Raf* mutant tumors are exquisitely sensitive to small-molecule MAPK/extracellular signal-regulated kinase kinase inhibitors (49). Loss of function of *PTEN*, a tumor suppressor phosphatase gene that selectively dephosphorylates phosphatidylinositol 3,4,5-triphosphate, has been found in a wide group of cancers (50) and results in increased PI3K activity and overdependence on this pathway, as PTEN-null cells exhibit supersensitivity to mammalian target of rapamycin (downstream of Akt) and PI3K inhibitors (51). The potential therapeutic implications of these mutations are substantial, and clinical trials with MAPK/extracellular signal-regulated kinase kinase and PI3K inhibitors are under way.

Acquired resistance to anti-EGFR agents due to secondary mutations. Patients who initially respond to gefitinib or erlotinib may acquire secondary *EGFR* mutations, specifically the T790M mutation (52, 53). Interestingly, a series of irreversible EGFR inhibitors have shown to be active at blocking receptor signaling and inhibiting growth in tumor cells harboring the T790M mutation (54). Clinical studies with these agents are ongoing in patients with lung cancer that have progressed to erlotinib.

Clinical-Translational Advances

There are two classes of anti-EGFR agents that have shown clinical activity and achieved regulatory approval for the treatment of cancer. These are mAbs directed at the extracellular domain of the receptor and low molecular weight, ATP-competitive inhibitors of the tyrosine kinase of the receptor (TKIs; reviewed in ref. 55). Anti-EGFR mAbs have now been approved for the treatment of advanced colorectal and head and neck tumors, and EGFR TKIs have been approved for the treatment of advanced non–small cell lung cancer and pancreatic carcinoma. Of note, EGFR TKIs have also activity in head and neck tumors and in glioblastoma.

An important challenge is the identification of EGFR-dependent tumors that may therefore be sensitive to EGFR inhibitors. Several tumor biopsy-driven clinical trials have shown that, at EGFR, inhibitors given at full doses successfully prevent receptor activation in the vast majority of cases and that receptor inhibition does not correlate with clinical benefit

(56, 57). Hence, inhibition of receptor activation may be required but is not enough to achieve clinical benefit with anti-EGFR. As mentioned above, in non–small cell lung cancer, the presence of somatic EGFR mutations and/or EGFR gene amplification predicts for a higher response rate but mutations have not been identified in other tumor types that benefit from EGFR therapies (58). Therefore, in addition to looking at specific EGFR gene mutations, alternative approaches, such as gene expression signatures, could also reflect the activation status of several oncogenic pathways (59) and there are several ongoing studies that are incorporating this approach.

It would also be most useful to incorporate on-study assessments of biomarkers of drug sensitivity in tumors. For example, in transgenic mice expressing a mutant EGFR under transcriptional control develop lung carcinomas. On reduced expression of the transgene or, as a result, treatment with EGFR inhibitors, tumor regression was observed due to enhanced apoptosis (60). Enhanced apoptosis has also been in patients with lung cancer treated with EGFR inhibitors (61). Therefore, window trials before surgery could establish if apoptosis would be a marker of EGFR dependency.

Finally, the majority of EGFR-expressing tumors have a complex genetic background and there is a significant level of compensatory 'cross-talk' among receptors within a signaling network as well as with other pathways regulating cell proliferation, trafficking, and survival. As with conventional chemotherapeutic agents, rationally developed biologically and molecularly targeted combinations are going to be likely to enhance the contribution of these agents to the treatment of cancer.

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