## Phylogeny

The epidermal growth factor receptor (EGFR) is a member of the ErbB/HER sub-family of receptor tyrosine kinases, which also includes ErbB2/HER2, ErbB3/HER3 and ErbB4/HER4 (Ferguson, 2008; Kumar et al., 2008; Wee & Wang, 2017). Phylogenetic placement within the larger RTK superfamily follows the classification of Manning et al. (Ferguson, 2008; Kovacs et al., 2015). Orthologs are present in diverse model organisms—e.g. mouse (Mus musculus), fruit fly (Drosophila melanogaster) and the nematode let-23 gene product in Caenorhabditis elegans—where core developmental roles are conserved (Kovacs et al., 2015; Wee & Wang, 2017).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-L-tyrosine phosphate (Ferguson, 2008; Mitchell et al., 2018).

## Cofactor Requirements

Mg²⁺ is routinely required in kinase assays; ATP serves as the phosphate donor (Yaron-Barir et al., 2024; Ferguson, 2008).

## Substrate Specificity

EGFR autophosphorylates multiple tyrosines on its C-terminal tail and phosphorylates cellular substrates that contain SH2/PTB docking motifs (Ferguson, 2008; Mitchell et al., 2018). Peptide-array profiling defines a consensus spanning positions –5 to +4 around the target tyrosine; a marked preference exists for a phosphorylated tyrosine at +1, a recognition aided by receptor residue Ala920 (Yaron-Barir et al., 2024).

## Structure

A single-pass, 1186-residue transmembrane glycoprotein (~170 kDa) comprising (i) an extracellular region of four sub-domains (I & III ligand-binding; II & IV cysteine-rich, with domain II harbouring the dimerization arm and 12 potential N-glycosylation sites), (ii) a 23-residue hydrophobic transmembrane helix, and (iii) an intracellular region containing a juxtamembrane segment, tyrosine-kinase domain (residues 690-953) and a C-terminal tail with multiple autophosphorylation sites (Ferguson, 2008; Wee & Wang, 2017; Bishayee, 2000; Chen et al., 2016).

## Regulation

• Ligand binding converts the ectodomain from a tethered to an untethered conformation, driving asymmetric kinase-domain dimerization and activation (Ferguson, 2008; Mitchell et al., 2018).  
• Trans-autophosphorylation occurs on Y703, Y920, Y992, Y1045, Y1068, Y1086, Y1148 and Y1173, creating adaptor docking sites (Wee & Wang, 2017).  
• Cbl-mediated ubiquitination of the C-terminal tail promotes endocytosis and degradation (Ferguson, 2008; Mitchell et al., 2018).  
• Negative regulation includes juxtamembrane interaction with acidic membrane lipids and inhibitory phosphorylation by Src (Y845) or PKC (T654) (Mitchell et al., 2018; Wee & Wang, 2017).

## Function

Highly expressed in most epithelial tissues (Wee & Wang, 2017). Essential for embryogenesis—mouse Egfr nulls are perinatally lethal (Wee & Wang, 2017). Upon activation, EGFR recruits adaptors such as GRB2 and Shc to stimulate the RAS-RAF-MEK-ERK, PI3K-AKT-mTOR, PLCγ-PKC and STAT pathways, driving proliferation, survival, migration and cell-cycle progression via Cyclin D induction (Ferguson, 2008; Mitchell et al., 2018; Wee & Wang, 2017). It forms homo-/hetero-dimers with other ErbB receptors and interacts with GRB2, SOS, GAB1, PI3K, PLC-γ1 and Src family kinases. Full-length EGFR can also translocate to the nucleus and co-activate transcription of genes such as cyclin D1 and c-MYC (Wee & Wang, 2017).

## Inhibitors

Clinically used ATP-competitive tyrosine-kinase inhibitors include first-generation (Gefitinib, Erlotinib), second-generation (Afatinib, Dacomitinib) and third-generation (Osimertinib) agents (Ferguson, 2008; Kumar et al., 2008; Zubair & Bandyopadhyay, 2023). Additional strategies employ monoclonal antibodies, affibodies targeting the ectodomain and peptides that disrupt transmembrane dimerization (Mitchell et al., 2018).

## Other Comments

Oncogenic EGFR alterations—overexpression, gene amplification or activating mutations (e.g., L858R or exon 19 deletions)—drive numerous cancers, notably non-small-cell lung cancer, glioblastoma, and carcinomas of breast, colon and head-and-neck (Ferguson, 2008; Kumar et al., 2008). Resistance to early TKIs often arises from the T790M gatekeeper mutation, whereas the extracellular deletion mutant EGFRvIII confers ligand-independent signaling in glioblastoma (Wee & Wang, 2017; Bishayee, 2000).

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