1. Phylogeny  
   Epidermal growth factor receptor (EGFR), also known as ERBB1 or HER1, is a member of the ErbB family of receptor tyrosine kinases that comprises four closely related receptors: EGFR/ErbB1, ErbB2 (HER2), ErbB3 (HER3) and ErbB4 (HER4). Phylogenetic analyses indicate that the ErbB receptors derive from a common evolutionary ancestor and are highly conserved across vertebrate species, with orthologs present in all mammalian lineages as well as in other higher eukaryotes. Within the kinome, EGFR is grouped with other receptor tyrosine kinases that share similar extracellular modular organizations and intracellular catalytic domains. Its evolutionary conservation underscores the fundamental roles these receptors play in regulating growth, differentiation, and survival throughout metazoan evolution (kovacs2015astructuralperspective pages 1-3, yewale2013epidermalgrowthfactor pages 1-2).
2. Reaction Catalyzed  
   EGFR functions as a protein tyrosine kinase and catalyzes the transfer of a phosphate group from ATP to tyrosine residues on target proteins. The general reaction can be represented as follows: ATP + [protein]‑L‑tyrosine → ADP + [protein]‑L‑tyrosine‑phosphate + H⁺. This reaction, characteristic of tyrosine kinases, occurs both on downstream substrate proteins and via autophosphorylation on multiple tyrosine residues located in the receptor’s C-terminal tail. Consequently, this phosphorylation event creates docking sites for adaptor proteins essential for propagating intracellular signaling cascades (eck2010structuralandmechanistic pages 1-2).
3. Cofactor Requirements  
   The catalytic activity of EGFR depends on the presence of divalent cations. In particular, Mg²⁺ acts as a critical cofactor that facilitates ATP binding and proper orientation of the phosphate groups within the active site of the kinase domain. This requirement for Mg²⁺ is a common feature among protein kinases and ensures optimal phosphorylation kinetics during signal transduction (eck2010structuralandmechanistic pages 1-2).
4. Substrate Specificity  
   EGFR exhibits substrate specificity that is directed primarily toward tyrosine residues within protein substrates. In its activated state, EGFR autophosphorylates several tyrosine sites in its cytoplasmic tail, which then serve as binding motifs for proteins harboring Src homology 2 (SH2) and phosphotyrosine binding (PTB) domains. These sites include, for example, critical residues that facilitate interaction with adaptor proteins such as GRB2 and Shc. The structural configuration of the EGFR catalytic cleft supports a preference for substrates containing tyrosine within specific contexts, although a defined consensus motif beyond the requirement for a tyrosine side chain has not been universally established. Instead, substrate preference appears to be determined jointly by the primary amino acid sequence surrounding the tyrosine and the three-dimensional conformation of the substrate when bound to EGFR (purba2017activationofthe pages 1-3, sato2013cellularfunctionsregulated pages 1-3).
5. Structure  
   EGFR is characterized by a multi-domain architecture that underpins its dual role as a cell-surface receptor and a signaling enzyme. The extracellular region is comprised of four subdomains: domains I and III are involved primarily in ligand binding, exhibiting β‐helical structures that interact directly with EGF family ligands, while domains II and IV are cysteine-rich and contribute to receptor dimerization by acting as dimerization arms. In the inactive state, EGFR adopts a “tethered” conformation in which intramolecular interactions between domains II and IV limit dimerization; ligand binding induces a dramatic conformational change to an “extended” form that exposes the dimerization interface (yewale2013epidermalgrowthfactor pages 2-3, kovacs2015astructuralperspective pages 6-8).

Adjacent to the extracellular portion, a single transmembrane helix anchors the receptor within the plasma membrane. This helix not only provides membrane localization but also contributes to the stabilization of receptor dimers via helix–helix interactions. Immediately internal to the membrane, the juxtamembrane (JM) region plays a crucial regulatory role by participating in receptor dimerization and contributing to the formation of nuclear localization signals in certain contexts (purba2017activationofthe pages 5-7).

The intracellular region contains a bilobal tyrosine kinase domain that is nearly canonical in its organization. The N-lobe contains a conserved β-sheet and an important C-helix, while the larger C-lobe houses the catalytic core with signatures such as the DFG motif, essential catalytic aspartate, and hydrophobic spines required for allosteric regulation. Key residues, including the gatekeeper residue Thr790 and a critical cysteine (Cys797), are instrumental in ATP binding and are also targets for inhibitor binding. Following the kinase domain is a C-terminal tail, which harbors multiple tyrosine residues that become autophosphorylated upon EGFR activation, thus functioning as docking sites for downstream signaling effectors (eck2010structuralandmechanistic pages 1-2, kovacs2015astructuralperspective pages 3-4, yewale2013epidermalgrowthfactor pages 2-3).

1. Regulation  
   Regulation of EGFR activity is multifaceted and involves a series of post-translational modifications and protein–protein interactions that fine-tune its signaling output. Ligand binding to the extracellular domain triggers a conformational shift from the tethered to the extended dimerization-competent structure, thereby initiating receptor dimerization. This ligand-induced dimerization is the critical event that facilitates trans-autophosphorylation on several tyrosine residues within the cytoplasmic tail. Specific autophosphorylation sites, once phosphorylated, serve as binding platforms for SH2- and PTB-domain containing adaptor proteins, which in turn relay signals downstream through the RAS-RAF-MEK-ERK, PI3K-AKT, PLCγ-PKC, and STAT pathways (purba2017activationofthe pages 1-3, sigismund2018emergingfunctionsof pages 1-5).

Additional regulation is exerted by the phosphorylation of EGFR by non-receptor kinases. For instance, Src family kinases phosphorylate EGFR at Tyr845, a modification that modulates receptor activation and is associated with enhanced mitogenic signaling in cancer cells (sato2013cellularfunctionsregulated pages 16-19). Ubiquitination of EGFR also plays a major role in controlling receptor internalization and degradation. Post-ligand binding, EGFR undergoes clathrin-mediated endocytosis and is either recycled back to the plasma membrane or targeted for lysosomal degradation, effectively attenuating the signal (sigismund2018emergingfunctionsof pages 35-39).

Furthermore, extensive N-linked glycosylation in the extracellular domain is crucial not only for proper protein folding and stability but also for modulating ligand affinity and receptor dimerization. Negative regulatory proteins, such as MIG6, bind directly to the kinase domain and hinder receptor dimerization, thus providing an inhibitory feedback loop that limits EGFR activity. MIG6 binding has been characterized by high-resolution structural studies, which illustrate how it occupies key dimerization surfaces of the kinase domain, thereby precluding activation (park2015structureandmechanism pages 1-3).

EGFR is also subject to a dynamic balance between its membrane-associated and nuclear forms. Nuclear translocation of EGFR, which involves specific nuclear localization signals within the JM region and interactions with importins, confers additional layers of regulation by enabling EGFR to function as a transcriptional co-activator for genes involved in cell cycle progression and DNA repair. This nuclear function of EGFR is associated with increased resistance to certain chemotherapeutic agents and radiation therapy (brand2013nuclearegfras pages 7-9, ali2017theparadoxicalfunctions pages 3-4, wee2017epidermalgrowthfactor pages 15-17).

1. Function  
   EGFR is a central mediator of cell signaling pathways that translate extracellular cues into diverse cellular responses. Upon binding its ligands – which include epidermal growth factor (EGF), transforming growth factor-alpha (TGF-α), amphiregulin (AREG), epigen, betacellulin (BTC), epiregulin (EREG), and heparin-binding EGF-like growth factor (HBEGF) – EGFR undergoes homo- or hetero-dimerization with other ErbB family members. This dimerization event catalyzes autophosphorylation on multiple tyrosine residues in the receptor’s C-terminal tail, thus generating binding sites for adaptor and scaffold proteins such as GRB2 and Shc. These interactions then trigger the activation of several downstream signaling cascades, including the RAS-RAF-MEK-ERK pathway that promotes cell proliferation, the PI3K-AKT pathway that supports cell survival and metabolism, and the PLCγ-PKC and STAT pathways that regulate diverse processes from migration to gene expression (brand2013nuclearegfras pages 1-2, eck2010structuralandmechanistic pages 1-2, sigismund2018emergingfunctionsof pages 39-42).

The biological roles of EGFR extend beyond classical membrane signaling. In many cancer types, aberrant EGFR signaling drives oncogenic processes such as uncontrolled proliferation, enhanced survival, and increased invasion and metastasis. Overexpression of EGFR or mutations within its kinase domain (for example, substitutions or deletions known to activate the receptor constitutively) have been strongly correlated with poor prognosis in non-small cell lung cancer (NSCLC), colorectal cancer, head and neck cancers, breast cancer, glioblastoma, and other malignancies (purba2017activationofthe pages 17-19, yewale2013epidermalgrowthfactor pages 1-2).

In addition, EGFR has non-canonical roles in the nucleus, where it functions as a transcriptional co-activator. Nuclear EGFR can interact with transcription factors such as STAT3 to induce the expression of genes including cyclin D1, thereby linking EGFR activity to cell cycle progression. This nuclear function is particularly prominent in certain aggressive tumors and is associated with therapeutic resistance (brand2013nuclearegfras pages 7-9, ali2017theparadoxicalfunctions pages 3-4, wee2017epidermalgrowthfactor pages 17-18).

EGFR also contributes to the modulation of cell metabolism, for instance by influencing glucose uptake and glycolytic flux, which further underscores its pivotal role in cancer cell biology. Moreover, in the nervous system, EGFR regulates processes such as neural stem cell maintenance, oligodendrogenesis, and neurite outgrowth, underscoring its versatile roles in both normal physiology and disease states (romano2020roleofegfr pages 17-19).

Collectively, the multifunctional roles of EGFR demonstrate its capacity to integrate extracellular signals with intracellular responses, thereby regulating critical aspects of cell fate, proliferation, differentiation, and survival.

1. Other Comments  
   EGFR is one of the most intensively studied molecular targets in oncology and has been the focus of extensive therapeutic development. Clinically approved inhibitors of EGFR include small molecule tyrosine kinase inhibitors (TKIs) such as gefitinib, erlotinib, lapatinib, and afatinib, which target the ATP-binding pocket of the kinase domain to block autophosphorylation and downstream signaling (park2015structureandmechanism pages 14-16, wee2017epidermalgrowthfactor pages 17-18). In addition, monoclonal antibodies, such as cetuximab and panitumumab, target the extracellular domain of EGFR to prevent ligand binding and subsequent receptor activation (yewale2013epidermalgrowthfactor pages 13-14).

Notable disease-associated mutations in EGFR include activating mutations such as L858R and exon 19 deletions, which increase kinase activity and render tumors more sensitive to TKIs, as well as resistance-associated mutations such as T790M, which hinder inhibitor binding. Moreover, rearrangements such as tandem duplications within the kinase domain have been observed in gliomas and influence drug sensitivity, specifically to irreversible inhibitors like afatinib (purba2017activationofthe pages 17-19, sato2013cellularfunctionsregulated pages 16-19).

Overexpression of EGFR is another common feature in various epithelial cancers, where it is associated with enhanced proliferation, invasion, and lower overall survival rates. Furthermore, nuclear localization of EGFR has been documented and is proposed to serve as both a prognostic marker and a mechanism contributing to resistance against conventional therapies (brand2013nuclearegfras pages 7-9, ali2017theparadoxicalfunctions pages 3-4).

The receptor’s regulation by negative feedback mechanisms is equally critical. Proteins such as MIG6 bind to the intracellular kinase domain of EGFR, impeding dimerization and attenuating kinase activity. In many tumors, loss or reduced expression of negative regulators like MIG6 leads to sustained EGFR signaling. In the context of targeted therapy, several combination strategies are under investigation to overcome resistance mechanisms that arise from EGFR mutations, gene amplification, or compensatory signaling from other ErbB family members (park2015structureandmechanism pages 1-3, sigismund2018emergingfunctionsof pages 42-46).

Additionally, EGFR undergoes extensive post-translational modifications beyond phosphorylation, including glycosylation and ubiquitination, which not only influence receptor folding and trafficking but also modulate its interaction with ligands and inhibitors. Computational analyses of predicted post-translational modification sites have further expanded the understanding of EGFR’s regulatory network and its integration into complex signaling cascades (malik2019networkingofpredicted pages 1-5, malik2019networkingofpredicted pages 5-6).

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