Phylogeny  
ErbB4 is a tyrosine-protein kinase belonging to the ErbB (EGFR/HER) sub-family within the Tyrosine Kinase group. Its cytoplasmic domain shares ~79 % amino-acid identity with EGFR/HER1 (El-Gamal et al., 2021). Vertebrate orthologues are conserved; genetic ablation of Mus musculus Erbb4 causes embryonic cardiac and neural defects (Monsey et al., 2010).

Reaction Catalyzed  
ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine-phosphate (Qiu et al., 2008).

Cofactor Requirements  
Catalytic activity is divalent-cation dependent; in vitro assays are typically carried out with 10 mM Mn²⁺ (Qiu et al., 2008).

Substrate Specificity  
Phosphorylates generic tyrosine-containing peptides; biochemical assays have not identified a strict consensus motif (Qiu et al., 2008).

Structure  
ErbB4 comprises an ectodomain of four β-hairpin subdomains linked to a JM-a stalk, a single transmembrane helix, an intracellular juxtamembrane segment, a bilobed kinase domain, and a C-terminal tail containing multiple autophosphorylation sites (El-Gamal et al., 2021; Río et al., 2000). Crystal structures of the isolated kinase bound to AMP-PNP or lapatinib display canonical N- and C-lobes with an activation loop that toggles between active and inactive conformations; lapatinib occupies the ATP-binding pocket (Qiu et al., 2008). Catalytic features include Lys726 (β3) for ATP anchoring, Asp836/Phe837 (HRD motif) for catalysis and spine assembly, and Thr771/Met774 lining the adenine pocket (Sahu et al., 2017). Signal activation requires formation of asymmetric C-lobe/N-lobe dimers analogous to EGFR, a cooperative and concentration-dependent process (Monsey et al., 2010). The JM-a sequence confers unique susceptibility to TACE cleavage, absent in other ErbBs (Río et al., 2000).

Regulation  
Ligand binding by neuregulins 1–4, betacellulin, epiregulin or HB-EGF triggers homo- or heterodimerization followed by trans-autophosphorylation (El-Gamal et al., 2021). Principal autophosphorylation sites are Y984, Y1056 and Y1188 (Ojala et al., 2024). Feedback phosphorylation by ERK attenuates signalling (El-Gamal et al., 2021). The JM-a isoform undergoes sequential cleavage by TACE and γ-secretase, generating a nuclear intracellular domain (ICD) that associates with STAT5A (Río et al., 2000; Määttä et al., 2006). Heterodimerization with HER2 augments kinase activity, while co-expression with HER3 amplifies downstream Akt and ERK phosphorylation (Monsey et al., 2010; Wandinger et al., 2016). Cancer-associated mutations (e.g., K935I, Y285C, D595V) enhance dimerization, autophosphorylation and ICD release (El-Gamal et al., 2021).

Function  
ErbB4 is widely expressed in fetal heart, nervous system, basal epidermis, skeletal muscle neuromuscular junctions, adult cardiomyocytes and mammary epithelium (El-Gamal et al., 2021). It is essential for cardiac trabeculation, neural crest migration, axon guidance, and mammary gland differentiation/lactation (El-Gamal et al., 2021). Upon activation it engages PI3K/AKT and MAPK cascades; neuregulin-stimulated homodimers induce BRCA1 expression and G2/M checkpoint activation, slowing proliferation in breast cancer cells (El-Gamal et al., 2021). Co-expression with HER3 strengthens Akt-Ser474 and MEK/ERK phosphorylation after neuregulin stimulation (Wandinger et al., 2016). The cleaved nuclear ICD partners with STAT5A to regulate transcription (Määttä et al., 2006).

Inhibitors  
Reversible ATP-competitive inhibitors: lapatinib (Ki = 347 nM), gefitinib (Ki = 1.1 µM), erlotinib (Ki = 1.5 µM) and AC-480/BMS-599626 (IC₅₀ = 190 nM) (Bose & Zhang, 2009; El-Gamal et al., 2021).  
Irreversible inhibitors: canertinib (IC₅₀ = 14 nM), ibrutinib (covalent), pyrotinib (pan-HER) and imidazo[2,1-b]thiazole derivatives (Compound I IC₅₀ = 15.24 nM; Compound II IC₅₀ = 17.70 nM) showing >60-fold kinome selectivity (El-Gamal et al., 2021; Sahu et al., 2017).

Other Comments  
Phosphorylated ErbB4 correlates with poor prognosis in glioblastoma, melanoma and gastric cancer, whereas high total ErbB4 expression predicts favourable outcomes in bladder and hormone-sensitive prostate cancers (El-Gamal et al., 2021). Recurrent activating mutations can confer resistance to targeted therapies (Ojala et al., 2024).

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