## Phylogeny

• Orthologous ERBB3 genes are reported in Homo sapiens, Pan troglodytes, Macaca mulatta, Bos taurus, Canis familiaris, Mus musculus, Rattus norvegicus, Gallus gallus, Xenopus tropicalis, Danio rerio and Takifugu rubripes (Stein 2006).  
• Additional ERBB-related sequences occur in non-vertebrate deuterostomes including Ciona intestinalis, Branchiostoma floridae and Saccoglossus kowalevskii (Brunet 2016).  
• Phylogenetic analyses place ERBB3 and ERBB4 in one clade that diverged from the EGFR/ERBB2 lineage after an ancestral duplication; subsequent whole-genome duplications generated the four vertebrate paralogs (Stein 2000).  
• Kinome assignment: Receptor Tyrosine Kinase (RTK) superfamily, ERBB subfamily (Manning 2002 Science, Manning 2002 TIBS).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-O-phospho-L-tyrosine (Roskoski 2004).

## Cofactor Requirements

• Autophosphorylation of the purified intracellular domain requires Mg²⁺ or Mn²⁺ ions in vitro (Shi 2010).  
• Recombinant kinase domain displays extremely weak intrinsic activity even at 10 mM Mg²⁺/Mn²⁺ (Sierke 1997).

## Substrate Specificity

• Not established; high-throughput peptide-array profiling detected no dominant intrinsic consensus motif for ERBB3 (Yaron-Barir 2024).  
• EGFR efficiently phosphorylates multiple ERBB3 cytoplasmic-tail tyrosines, indicating ERBB3 acts primarily as a substrate within ERBB heterodimers (Fan 2005).

## Structure

• Modular architecture: ectodomain (aa 20–630), single transmembrane helix (642–666), juxtamembrane region (667–709), pseudokinase domain (709–965; activation loop 830–890) and C-terminal signaling tail (990–1342) (Black 2019).  
• Crystal structure of the isolated kinase domain (PDB 3KEX) adopts a Src/CDK-like inactive conformation; helix αC is rotated outward and the catalytic HRD Asp is replaced by Asn815 (Jura 2009).  
• N-lobe homodimerization and reciprocal C-terminal tail exchange stabilize this inactive state (Jura 2009).  
• Heterodimeric structure with EGFR (PDB 4RIW) shows ERBB3 as the allosteric activator in an asymmetric kinase dimer; the EGFR juxtamembrane latch extends the interface (Littlefield 2014).  
• Helix αC is shortened and capped by Thr738, disrupting the regulatory spine; the activation loop remains folded over the active site (Jura 2009).

## Regulation

• Ligand binding by neuregulin-1 or neuregulin-2 untethers the ectodomain and promotes heterodimerization with kinase-active partners (Roskoski 2004).  
• NRG1 stimulation induces >10-fold phosphorylation of Tyr1328 and additional tail sites, enabling SHC and PI3K-p85 recruitment (Wandinger 2016).  
• The RING E3 ligase Nrdp1 and the transmembrane adaptor LRIG1 ubiquitinate ERBB3, targeting it for degradation; HRG-induced signaling stabilizes Nrdp1 as feedback control (Hamburger 2008).  
• Divergent JM-B segment prevents ERBB3 from acting as the receiver kinase, confining it to the activator position in asymmetric dimers (Jura 2009).

## Function

• Expressed in neuronal, epithelial and mesenchymal tissues; frequently overexpressed in HER2-amplified breast cancers (Black 2019).  
• Principal ligands: neuregulin-1 and neuregulin-2 (Black 2019).  
• Preferentially forms heterodimers with ERBB2; also partners with EGFR and ERBB4 (Black 2019).  
• Phosphorylated YXXM motifs bind PI3K-p85, activating the PI3K–Akt pathway; SHC binding connects to the Ras–MAPK cascade (Wandinger 2016).  
• Co-expression with ERBB4 amplifies NRG1-driven proliferation and Akt phosphorylation (Wandinger 2016).  
• Transcriptional and post-translational up-regulation of ERBB3 compensates for HER2 inhibition, sustaining PI3K–Akt signaling (Garrett 2011).  
• Genetic ablation causes severe neural crest and cardiac defects, demonstrating essential developmental roles (Black 2019).

## Inhibitors

• The dual EGFR/HER2 kinase inhibitor lapatinib lowers ERBB3 phosphorylation by blocking its kinase-active partners (Garrett 2011).  
• NRG1-blocking antibodies attenuate ligand-dependent ERBB3/ERBB4 signaling in tumour models (Wandinger 2016).

## Other Comments

• Cancer-associated kinase-domain mutations Q790R, S827I and E909G enhance the activator interface in EGFR/ERBB3 heterodimers without restoring catalytic activity (Littlefield 2014).  
• ERBB3 hyperactivation drives resistance to EGFR/HER2 inhibitors and to hormone therapy in breast cancer (Hamburger 2008).  
• ERBB3 forms an indispensable oncogenic unit with ERBB2 in HER2-amplified tumours (Garrett 2011).