

EGFR

Key References

- Alroy, I. and Yarden, Y., The ErbB signaling network in embryogenesis and oncogenesis: signal diversification through combinatorial ligand-receptor interactions., *FEBS Lett.*, **410**, 83-86 (1997).
- Blagosklonny, M.V., Gefitinib (Iressa) in oncogene-addictive cancers and therapy for common cancers., *Cancer Biol. Ther.*, **3**, 436-440 (2004).
- Grunwald, V. and Hidalgo, M., Development of the epidermal growth factor receptor inhibitor Tarceva (OSI-774)., *Adv. Exp. Med. Biol.*, **532**, 235-246 (2003).
- He, H., et al., Platelet-derived growth factor requires epidermal growth factor receptor to activate p21-activated kinase family kinases., *J. Biol. Chem.*, **276**, 26741-26744 (2001).
- Huang, H.S., et al., The enhanced tumorigenic activity of a mutant epidermal growth factor receptor common in human cancers is mediated by threshold levels of constitutive tyrosine phosphorylation and unattenuated signaling., *J. Biol. Chem.*, **272**, 2927-2935 (1997).
- Kim, T.E. and Murren, J.R., Erlotinib OSI/Roche/Genentech., *Curr. Opin. Investig. Drugs*, **3**, 1385-1395 (2002).
- Leserer, M., et al., Epidermal growth factor receptor signal transactivation., *IUBMB Life*, **49**, 405-409 (2000).
- Levitcki, A. and Gazit, A., Tyrosine kinase inhibition: an approach to drug development., *Science*, **267**, 1782-1788 (2000).
- Mendelsohn, J., The epidermal growth factor receptor as a target for cancer therapy., *Endocr. Relat. Cancer*, **8**, 3-9 (2001).
- Norman, P., ZD-1839 (AstraZeneca)., *Curr. Opin. Investig. Drugs*, **2**, 428-434 (2001).
- Osherov, N. and Levitcki, A., Epidermal-growth-factor-dependent activation of the src-family kinases., *Eur. J. Biochem.*, **225**, 1047-1053 (1994).
- Settleman, J., Inhibition of mutant EGF receptors by gefitinib: targeting an achilles' heel of lung cancer., *Cell Cycle*, **3**, 1496-1497 (2004).

Overview

Epidermal growth factor receptor (EGFR), its family members Her-2/ErbB-2, Her-3, Her-4 and their ligands, are involved in over 70% of all cancers. EGFR itself has been implicated in ~30% of all solid human tumors. EGFR is associated not only with the proliferation of tumor cells, but also with enhanced tumor cell survival, angiogenesis and metastatic spread. The enhanced activity of the EGFR due to over-expression, co-expression of the receptor and its ligands, as well as activating mutations is the hallmark of many human carcinomas.

The co-expression of the EGFR and its ligands, especially TGF α and EGF, plays a key role in EGFR-mediated tumorigenesis. EGFR expression is a prognostic indicator, predicting poor survival and indicates an advanced state of the disease. When EGFR is co-expressed with other members of the Her family, the various combinations of Her dimers confer different degrees of malignancy. It has been noted that the co-expression of EGFR with Her-2 and Her-3 is associated with more aggressive clinical behavior. In many types of tumor, including lung, breast, prostate, ovary, gastrointestinal tract and brain, the EGFR receptor is expressed approximately 100 times the normal number of EGF receptors found on the surface of normal cells. Furthermore, expression of high levels of these two receptors in nonmalignant cell lines, either alone or in combination, leads to a transformed phenotype.

Due to all these observations, it is no surprise that EGFR and Her-2/Erb-2 were identified early on as important targets for drug development. Indeed, the first signal transduction therapeutic agent introduced into the clinic was Herceptin, an anti-Her-2 antibody followed closely by the protein

tyrosine kinase inhibitors Iressa (ZD 1839) and Tarceva (OSI-774) and the anti-EGFR antibody Erbitux (mAb 225).

The enhanced activity of the EGFR is due to a number of molecular events. Most common is the overexpression of the receptor along with the expression of the EGFR receptor ligands like TGF α , EGF, amphiregulin and HB-EGF, leading to persistent autocrine stimulation. Another common occurrence is an activating mutation resulting from deletion of exons 2 through 7, leading to a persistently active receptor Δ (2-7)EGFR (also known as EFRvIII) in the absence of a ligand. The emergence of this mutation occurs in the most aggressive forms of EGFR overexpressing tumors.

Activation of the EGFR pathway is not limited to members of the EGFR family, but frequently occurs due to the transactivation by other signaling pathways such as mitogenic G protein-coupled receptors and the PDGF receptor. Furthermore, the EGFR pathway cooperates in a synergistic manner with pp60^{c-Src}, and the deletion of PTEN, the negative regulator of PKB/Akt. The frequent involvement of EGFR in human tumors has identified it as a target for novel therapies. The first breakthrough was the development of selective EGFR kinase inhibitors (tyrphostins) like tyrphostins, AG 1478 and ZD 1839 (Iressa). Iressa is one of the two kinase inhibitors (the other being Gleevec) to receive approval for clinical application. It is important to note that it was recently found that the response of patients suffering from non-small-cell lung carcinoma to Iressa, is limited to the 7-10% harboring mutations in the kinase domain of the receptor. Other inhibitors, similar to Iressa, like Tarceva (OSI-774), the pan-Her reversible inhibitor GW 2016, the

irreversible inhibitor CI-1033, which targets both RGFR and Her-2, are in the pipeline. Antibodies to the EGFR, like Erbitux and TGF α fused to a mutated form of pseudomonas exotoxin, TP-38, are also in clinical development.

EGFR

FAMILY MEMBERS	EGFR	ErbB2
OTHER NAMES	ErbB-1 (avian erythroblastic leukemia viral (v-erb-b), oncogene homolog); HER1; ERBB, crbB	Neu (rat), HER2
MOLECULAR WEIGHT/STRUCTURAL DATA	~180 kDa; 1210 aa	~185 kDa; 1255 aa
ISOFORMS	Four alternatively spliced transcripts, secreted extracellular domain and auto-activating deletions in the extracellular domain	Two alternatively spliced transcripts and a secreted form (Herstatin)
SPECIES	All four receptors are expressed in mammals. A single ortholog of the receptor is expressed in <i>D. melanogaster</i> and <i>C. elegans</i>	
DOMAIN ORGANIZATION	All four receptors have similar structural domains comprising of an extracellular ligand binding domain, a single transmembrane domain, an intracellular tyrosine kinase domain and a large unstructured tail	
PHOSPHORYLATION SITES	Tyr ⁸⁴⁵ , Tyr ⁸⁹¹ , Tyr ⁹²⁰ , Tyr ⁹⁷⁴ , Tyr ⁹⁹² , Tyr ¹⁰⁴⁵ , Tyr ¹⁰⁶⁸ , Tyr ¹⁰⁴⁵ , Tyr ¹⁰⁸⁶ , Tyr ¹¹⁰¹ , Tyr ¹¹¹⁴ , Tyr ¹¹⁴⁸ , Tyr ¹¹⁷³ , Tyr ⁶⁵⁴ , Tyr ⁶⁶⁹ , Ser ¹⁰⁴⁶ , Ser ¹⁰⁴⁷	Tyr ⁸⁸² , Tyr ⁸⁹⁹ , Tyr ⁹⁵⁸ , Tyr ¹⁰²³ , Tyr ¹⁰²⁸ , Tyr ¹¹³⁹ , Tyr ¹¹⁴³ , Tyr ¹¹⁹⁶ , Tyr ^{1221/22} , Tyr ¹²²⁶ , Tyr ¹²²⁷ , Tyr ¹²⁴⁹ , Tyr ¹²⁵³
TISSUE DISTRIBUTION	Brain, neurons, skeletal muscle, prostate, liver, pancreas lung, tongue, skin, kidney, trachea	Brain, spinal cord, placenta, prostate, heart, liver, lung, kidney, pancreas
SUBCELLULAR LOCALIZATION	Not known	Not known
BINDING PARTNERS/ ASSOCIATED PROTEINS	EGF (E9644 , E6135)	Neuregulin-1
UPSTREAM ACTIVATORS	Epidermal growth factor (EGF) (E9644 , E6135), transforming growth factor- α (TGF- α) (T7924 , T5403), amphiregulin (AR) (A7080), heparin binding-EGF (HB-EGF), betacellulin (BTC) (B3670), epiregulin (EPR) (E8780), epigen (EPG)	Does not bind any of the known EGF like ligands
DOWNSTREAM ACTIVATION	Grb-2-SOS, Shc, Shp1, c-Src, Gab1, PLC- γ , PKC (P7956), c-Cbl	Grb-2-SOS, Shc
ACTIVATORS	Not known	Not known
INHIBITORS	Gefitinib, Erlotinib, EKB-569, GW572016, PKI-166, AEE-788, CI-1033, AG1478	TAK-165, GW572016, AEE-788, CI-1033, PKI-166
SELECTIVE ACTIVATORS	Not known	Not known
PHYSIOLOGICAL FUNCTION	Receptor for EGF; involved in control of cell growth and differentiation	Essential component of a neuregulin-receptor complex
DISEASE RELEVANCE	Glioblastoma, malignant neoplasms and carcinomas including adenocarcinomas of the breast, lung, prostate, pancreas, head and neck, colon, ovary, bladder	Hyperplasias, benign and malignant neoplasms and carcinomas, including adenocarcinomas of the breast, prostate, lung, stomach, bladder, colon, cervix

FOOTNOTES

EGFR

FAMILY MEMBERS	ErbB3	ErbB4
OTHER NAMES	HER3	HER4
MOLECULAR WEIGHT/STRUCTURAL DATA	~190 kDa; 1342 aa	~180 kDa; 1308 aa
ISOFORMS	Two alternatively spliced transcripts	Two alternatively spliced transcripts called HER4 JM- α , HER4 JM- β
SPECIES	All four receptors are expressed in mammals. A single ortholog of the receptor is expressed in <i>D. melanogaster</i> and <i>C. elegans</i> .	
DOMAIN ORGANIZATION	All four receptors have similar structural domains comprising of an extra-cellular ligand binding domain, a single transmembrane domain, an intracellular tyrosine kinase domain and a large unstructured tail	
PHOSPHORYLATION SITES	Has an impaired kinase and cannot autophosphorylate. Tyr ¹⁰³⁵ , Tyr ¹¹⁷⁸ , Tyr ¹¹⁸⁰ , Tyr ^{1203/5} , Tyr ¹²⁴¹ , Tyr ¹²⁴³ , Tyr ¹²⁵⁷ , Tyr ¹²⁷⁰ , Tyr ¹³⁰⁹	Tyr ¹⁰⁶⁶ , Tyr ¹¹⁶² , Tyr ¹⁰⁶⁶ , Tyr ¹¹⁸⁸ , Tyr ¹¹⁸⁹ , Tyr ¹²⁴² , Tyr ¹²⁵⁸ , Tyr ¹²⁸⁴
TISSUE DISTRIBUTION	Brain, prostate, dorsal root ganglion, liver, placenta, salivary gland, spinal cord, uterus, heart, lung, muscle, pituitary, thyroid, pancreas, kidney	Brain, bone marrow, spinal cord, dorsal root ganglion, testis, liver, skeletal muscle, cardiac myocytes, salivary gland, tongue, skin, trachea, pancreas
SUBCELLULAR LOCALIZATION	Not known	Not known
BINDING PARTNERS/ ASSOCIATED PROTEINS	Neuregulin, Ebp1, SH2 domain of p85	Neuregulin-1, β -cellulin
UPSTREAM ACTIVATORS	Both α and β isoforms of Heregulin-1/Neuregulin-1 (HRG/NRG-1 α , HRG/NRG-1 β) and Heregulin-2/Neuregulin-2 (HRG/NRG-2 α , HRG/NRG-2 β)	Betacellulin (BTC) (B3670), Heparin binding- EGF (HB-EGF), Epiregulin (EPR) (E8780), Neuregulin-3 (NRG-3), Neuregulin-4 (NRG-4)
DOWNSTREAM ACTIVATION	Grb-2/7-SOS, Shc, PI3K (P8615)	Shc, Grb-2-SOS, PI3K (P8615)
INHIBITORS	Not known	AEE-788, CI-1033
ACTIVATORS	Not known	Not known
SELECTIVE ACTIVATORS	Not known	Not known
PHYSIOLOGICAL FUNCTION	Involved in development of variety of tissues	Interacts with neuregulins, NRG-2, NRG-3, heparin-binding EGF-like growth factor
DISEASE RELEVANCE	Malignant neoplasms of the breast, ovary, pancreas, lung, prostate, bladder, colon	Role of ErbB-4 in malignancies is not well established; implicated in some tumors of the breast, prostate, ovary, brain, lung

FOOTNOTES