EGFR (Epidermal Growth Factor Receptor)

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Abstract

ERBB family member epidermal receptor tyrosine kinase (EGFR) is composed of 28 exons and 27 introns. EGFR codes for 11 transcripts and 8 of them are protein coding. EGFR is a transmembrane glycoprotein that can be activated by several different ligands such as epidermal growth factor (EGF), transforming growth factor-alpha (TGFA), heparin-binding EGF-like growth factor (HBEGF), betacellulin (BTC), amphiregulin (AREG), epiregulin (EREG), and epigen (EPGN) (Singh, 2016). Ligand binding induces the dimerization of EGFR and autophosphorylation followed by a cascade of downstream phosphorylation events (Capuani et al., 2015). EGFR activation plays a key role in cell survival, proliferation, migration and differentiation ( Purba, 2017).

Keywords

Epidermal Growth Factor Receptor (EGFR), transmembrane receptor tyrosine kinase

Identity

Other names
ERBB (erb-b2 receptor tyrosin kinase); HER1 (human epidermal growth factor receptor 1)
mENA; ERBB1 (erb-b2 receptor tyrosin kinase 1); PIG61; NISBD2 (neonatal inflammatory skin and bowel disease-2); Erythroblastic leukemia viral (v-erb-b) oncogene homolog (avian)

HGNC (Hugo) EGFR

Location 7p11.2

Local order

Arrangement of genes on chromosome 7 from centromere to telomere: LOC100996654, LOC643168, LOC105375284, EGFR, EGFR-AS1, LOC100130121, ELDR, CALM1P2

DNA/RNA

Description

EGFR gene is 244589 bp long and resides on the positive strand of DNA

Transcription

EGFR gene codes for 11 transcripts which are splice variants; 8 of them are protein coding (9905 bp, 3844 bp, 5464 bp, 2239 bp, 2864 bp, 1570 bp, 4735 bp and 691 bp) and 3 of them are non-protein coding (561 bp, 452 bp and 665 bp)

Pseudogene

Not-reported

Figure 1. Local order of EGFR is shown together with proximal and distal genes on chromosome 7. The direction of arrows indicates transcriptional direction on the chromosome and arrow sizes approximate gene sizes.
Protein

Description
EGFR protein has four isoforms which are results of alternative splicing. Isoform 1 is the canonical one depicted above. Other isoforms are isoform 2 (p60, 405 aa, 44,664 Da), isoform 3 (p110, 705 aa, 77,312 Da) and isoform 4 (628 aa, 69,228 Da).

Localisation
Plasma membrane, Endosome, Endoplasmic Reticulum, Golgi apparatus, Nucleus

Function
EGFR is transmembrane receptor tyrosine kinase belonging to a cell surface receptor family. Other family members are HER2 (ERBB2), HER3 (ERBB3) and HER4 (ERBB4). Orthologs of EGFR in Drosophila melanogaster and Caenorhabditis elegans are DER (Lusk, 2017) and Let-23 (Bae, 2012), respectively. These monomeric proteins have intracellular C-terminal tyrosine kinase domain, membrane spanning domain and extracellular, cysteine rich N-terminal ligand binding domain from bottom to top of its structure. Without ligand binding, EGFR is in its monomeric form, once the ligand is bound, they form either homodimer or heterodimer resulting in autophosphorylation of their C-terminal domain (Ferguson, 2008).

In canonical EGFR signaling pathway, activation with ligand binding is a well characterized function of EGFR. With ligand binding, trans-autophosphorylation takes place between on tyrosine residues, which triggers the downstream signaling cascades (Maruyama, 2014). Conformational changes of C-terminal tail also trigger the components of endocytosis pathway and leads to EGFR internalization. EGFR, without ligand, can also be endocytosed with a rate 10-fold lower than the ligand induced ones (Sigismund, 2018).

When EGFR is induced with ligand binding on plasma membrane, it is not only phosphorylated, but also ubiquitinated at lysine residues on the cytoplasmic kinase domain by E3 ubiquitin ligase Cbl complex including GRB2 adaptor protein. Concentration of EGF is the regulator of EGFR ubiquitination.

At the beginning of internalization of EGFR, ubiquitination drives the non-clathrin endocytosis pathway, at later stages it steers EGFR to lysosomal degradation (Sigismund, 2013 and Sigismund, 2005).

After internalization, some of its ligands, like TGFA and EREG (epiregulin), dissociates from EGFR in the milder acidic environment of endosome and drives recycling of EGF to plasma membrane. In contrast, ligands (like EGF) which are not affected from the acidity of endosome, favors the passage of majority of EGFR from early to late endosomes to be degraded by the lysosome (Ebner, 1991).

Fate of EGFR depends also on the type of ligand. Additionally, HBEGF (heparin-binding EGF-like
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growth factor) and BTC (betacellulin) drives all EGF receptors to lysosomal degradation (Sigismund, 2018; Roepstorff et al., 2009; Ebner and Derync, 1991).

Ligand induced EGFR activation in turn activates downstream signaling pathways, named as, RAS/MAPK pathway, PI3K/AKT pathway and PLC/Protein kinase C cascade. Activation of these pathways with canonical EGFR signaling controls the crucial functions of cells such as survival, proliferation, differentiation and migration (Scaltriti and Baselga, 2006). In addition, activation of EGFR regulates other important metabolic functions such as autophagy in response to cellular or environmental stress via non-canonical signaling. Dealing with stress conditions with the action of non-canonical EGFR signal is preferred in cancer cells to provide advantage for survival and drug resistance (Tan et al., 2015; Henson, Chen and Gibson, 2017).

EGFR is expressed in many organs is involved in diverse roles including proliferation (Buchon et al., 2010), survival (Crossman, Streichan and Vincent, 2018), embryogenesis (Lusk, Lam and Tolwinski, 2017) differentiation during development and maintenance of cellular physiology (Dumstrei et al., 1998).

During lung development, EGFR is critical in type II pneumocyte maturity. Inhibition of EGFR gives rise to immature type II pneumocytes and alveolar deficiency (Inamura, 2018; Kothe et al., 2018)
In heart development, EGFR takes role in differentiation of cardiac valves (Barrick et al., 2009; Qi, 2015)

Surviving mice among the EGFR deficient group showed valvular deficiency and further survived mice experienced aortic valve thickening, aortic stenosis and heart deficit (Makki et al., 2013)

Expression of EGFR also correlates with the level of neurogenesis in rodents and EGFR activity controls the proliferation and survival of neuronal cells and their proper migration (Puehringer et al., 2014). Moreover, EGFR mutant mice showed substantial neurodegenerative damage in the frontal cortex, olfactory bulb, thalamus and irregular migration in mutant mice brains (Sibilia et al., 1998)

EGFR null mice have abnormal primary endochondral ossification and malformation of osteoclasts (Wang et al., 2009).

EGFR+ mice models show massive abnormality in epithelial development in which newborns had open eyes, whiskers were curly, and they died within 8 days after birth due to the epithelial disorder in skin, lung and gastrointestinal tract (Miettinen et al., 1995).

EGFR is expressed normally in the outer sheath of the root and its expression decreases when follicular growth is completed. Impaired downregulation of EGFR in hair growth arrest the hair growing cycle at anagen phase and prevent beginning of catagen phase (Mak and Chan, 2003). The importance of EGFR signaling in fur development and maintenance of hair follicle integrity and differentiation were shown in EGFR null mice models. Deregulation of keratin synthesis, dysregulated differentiation of follicle bulb, cuticle disorder and improper integration of hair fibers were observed in EGFR null mice (Hansen et al., 1997) EGFR signaling and its downstream pathways are also important in skin homeostasis. Activation of EGFR-ERK pathway has a critical role in healing of skin damages, while EGFR-PI3K/AKT pathway is critical to inhibits initiation of apoptosis under UV stress (Peus et al., 2000). Additionally, for keratinocyte migration during healing of skin wounds, necessary amount of collagenase-1 production is provided by the activation of EGFR by autocrine manner (Pilcher et al., 1999). In case of skin lesion, released cytokines from leucocytes activates keratinocytes, which in turn release several chemokines like CXCLs, and ILs. EGFR is responsible from the regulation of chemokine release from keratinocytes, which sets a crosstalk between skin inflammation and EGFR signaling (Pastore et al., 2008).

Even though the mechanism of transport of EGFR to nucleus is still not clear, EGFR also functions in nucleus as transcriptional co-activator of cell cycle related genes like CCND1 (cyclin D1) and MYC. Additionally; EGFR nuclear signaling is stimulated by EGF and stress factors like H2O2, UV, ionizing radiation and drugs (Wee and Wang, 2017).

Homology

Human EGFR has homologs in chimpanzee (Pan troglodytes), Rhesus monkey (Macaca mulatta), dog (Canis lupus familiaris), cattle (Bos taurus), mouse (Mus musculus), rat (Rattus norvegicus), chicken (Gallus gallus), zebrafish (Danio rerio) and frog (Xenopus tropicalis). Human EGFR has orthologs with 259 organisms.

Mutations

Somatic

According to current information in cbioportal database, somatic mutation frequency is 3.8% in 10967 samples obtained from 10953 patients.

Distribution of totally 512 mutations: 412 missense mutations, 42 truncating mutations (including nonsense, nonstop, frameshift deletion, frameshift insertion, splice site mutations), 33 in-frame mutations (in-frame deletions and in-frame insertions) and 30 other mutations.

Non-small cell lung cancer (NSCLC): Very common (85-90%) and classical mutations frequently seen in NSCLC are L858R point mutation in exon 21 and residual deletions of exon 19.
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Additionally, insertions in exon 20 is related with the resistance against therapeutic EGFR inhibitors like Afatinib, Erlotinib and Gefitinib. H773-V774insX, D770-N771insX and V769-D770insX are the insertions of exon 20 with higher incidence (Vsy and Huang, 2019). T790M point mutation on tyrosine kinase domain of EGFR is accepted as a drug resistance marker of NSCLC and this mutation typically coexist with L858R mutation (Denis et al., 2015; Li et al., 2018). In general, substitution in leucine to arginine at position 858 in tyrosine kinase domain of EGFR is well known activating mutation. With this mutation, autoinhibitory conformation of EGFR is suppressed and the receptor becomes active even without ligand binding (Wee and Wang, 2017).

Glioblastoma (GBM): Point mutations of EGFR are common in GBM. Deletions observed in GBM are N-terminal deletion of EGFR (EGFRvI), exon 14-15 deletion (EGFRvII that is oncogenic), exon 2-4 deletion (EGFRvIV, which is oncogenic), exon 25-27 deletion (EGFRvIV), exon 25-28 deletion (EGFRvV), R108K, A289V, A289D, A289T and G598D are point mutations in EGFR seen in 24% of GBM cases (Larysz, 2011; An et al., 2018).

Breast cancer: 11.4% of 70 paraffin tumor samples randomly selected from among 653 triple negative breast cancer (TNBC) patients showed EGFR mutations. These mutations were deletions in exon 19, missense substitutions of exon 21 and inversions in EGFR sequence (Teng et al., 2011). Another study showed 28.3% of 180 patients had EGFR mutations. Thirty patients had exon 19 deletions, 21 of them showed exon 21 mutations (Ma et al., 2017). Additionally, 50% of TNBC cases were characterized by EGFR overexpression, which is correlated with poor prognosis, less differentiation and increased tumor size. Percentage of EGFR overexpression in TNBC is quite high when compared to other subtypes of breast cancer (Masuda et al., 2012).

Esophageal cancer: Although it is rare, G to A substitution was observed in esophageal cancer. 40-70% of esophageal squamous cell carcinoma shows overexpression and increased gene copy number of EGFR (Anvari, Anvari and Toosi, 2014)

Head and Neck squamous cell carcinoma (HNSCC): Among 47 HNSCC cases, 21% of EGFR mutations is L876Q point mutation in exon 21, 19% of them is insertion in exon 20 and 17% of them included exon 19 deletions (Vatte et al., 2017). Additionally, with 41.5, exon 19 had the highest percentage of tyrosine kinase domain (TKD) mutations. 32.1 %, 17 % and 9.4 % are distribution of TKD mutations in exon 20, exon 21 and exon 18, respectively. Among all EGFR mutations, 73% of them was exon 18-21 missense mutations, 22% was exon 19 deletions and 5% was exon 20 insertion mutations (Perisanidis, 2017)

Gastric cancer: Exon 19 and exon 21 EGFR mutations were identified in gastric cancer in addition to single nucleotide polymorphisms Q787Q (37.9%). In addition, Y801C, L858R and G863D point mutations were revealed for the first time in gastric cancer samples (Liu et al., 2011).

Endometrial cancer: Samples taken from 28 woman with endometrial cancer showed three different mutations in separate patients. L688F and E909K in exon 18 and K754E in exon 19, which is in contrast to others responsive to lapatinib treatment (Leslie et al., 2013; Reyes et al., 2014).

Colorectal cancer: EGFR mutation status of 13 patients among 35 male and 23 female patients at different stages of colorectal cancer showed exon 20 mutation but not exons 18,19 and 21 mutations (Oh et al., 2011). S492R EGFR ectodomain mutation also increases the mutation rate and mABCH12 was suggested to prevent the effect of mutated EGFR (Dong et al., 2019).

Prostate cancer: Studies revealed the overexpression, amplification and mutation of EGFR in prostate cancer (Guerin et al., 2010).

Testicular cancer: From 110 testicular germ cell tumors 209 distinct components were obtained and analyzed for EGFR expression. Among those components, 28% of 83 seminomas, 11% of 27 embryonal carcinomas, 88% of 8 choriocarcinomas and 44% of 18 yolk sac tumors showed EGFR overexpression. Additionally, among them, some of the samples showed amplification and high copy number of EGFR, which is also in correlation with overexpression of EGFR according to IHC studies (Miyai et al., 2010).

Implicated in

Non-Small Cell Lung Cancer

Approximately 70% of lung cancers is non-small cell lung cancer (NSCLC) and 43-89% of NSCLC is caused by EGFR overexpression. Other mutations are short in frame deletions in exon 19 which includes leucine-747 to glutamic acid-749 (ΔLRE) deletion or point mutations in exon 21 (L858R). These two mutations constitute around 90% of EGFR activating mutations and lead to cell proliferation, anti-apoptotic signaling by constitutively activating the downstream signaling pathways (Bethune et al., 2010). Bases insertions to exon 20 of EGFR is related with de novo resistance against EGFR inhibitors and poor patient prognosis (Vsy and Huang, 2019). Additionally, point mutation at exon 20; threonine to methionine transition (T790M) is strongly linked to acquired resistance especially against very commonly used EGFR inhibitors, namely, erlotinib and gefitinib (Gazdar, 2009). Higher methylation pattern at promoter region of EGFR is related with insensitivity against EGFR targeted treatments in...
NSCLC with low expression of EGFR (Pan, 2015). Moreover, higher DNA methylation level of EGFR indicates the stage of malignancy in these patients (Li, 2015).

**Breast Cancer**

In triple negative breast cancer (TNBC), EGFR is frequently overexpressed and EGFR inhibition in these patients is mostly ineffective. EGFR methylation by PRMT1 at arginine 198/200 of extracellular domain is related to resistance to EGFR monoclonal antibody therapies (Nakai et al., 2018). CAMA1, MDA-MB-435 and MDA-MB-435 were also shown to be methylated at EGFR CpG island in exon 1 as a reason for transcriptional downregulation of EGFR (Montero et al., 2006).

**Head and Neck Cancer**

Mono methylation of lysine 721 in the tyrosine kinase domain of EGFR by NSD3 (WHSC1L1) results in enhanced downstream signaling (ERK) in the squamous cell carcinoma of head and neck cells even in the absence of EGF (Saloura et al., 2017).

**Cutaneous Melanoma**

EGFR promoter and regulatory elements hypomethylation increases EGFR expression and enhances PI3K/AKT pathway in cutaneous melanoma. Activation of PI3K/AKT pathway leads to BRAF inhibitor resistance (Wang et al., 2015).

**Glioma**

In gliomas and development of neurons, H3K27ac and H3K4me3 were found at promoter region of EGFR. Additionally, during development of germinal matrix, both EGFR-positive and EGFR-negative germinal matrix cells show DNA hypomethylation at promoter region but H3K27ac and H2K4me3 marks the EGFR-expressing, activated germinal matrix cells (Erfani et al., 2015).

**Prostate Cancer**

18% of tissue samples obtained from 2497 prostate tumors showed DNA level amplification or overexpression at protein level, high EGFR levels correlate with grade and stages of prostate cancer (Guerin et al., 2010). Interestingly, in prostate cancer patients, EGFR was detected in secreted exosomes, also in serum of mouse models, and these secreted exosomes could be related with the resistance against EGFR targeted therapies (Kharmate et al., 2016).

**Gastric Cancer**

Analysis of 683 T3 stage gastric adenocarcinoma samples revealed that low EGFR expressing 406 patients showed longer overall (39 months) and recurrence free survival times, 18 and 13 months respectively. Including anti-EGFR agents in combination with chemotherapy in esophago-gastric adenocarcinoma provided no advantage in terms of overall and relapse-free survival of patients (from meta-analysis of 1817 patients of six studies) (Kim et al., 2017; Wang et al., 2017). Hypermethylation of EGFR promoter region in analyzed tumor samples indicates the possible use of this methylation status as a maker for gastric cancer (Weng et al., 2015).

**Alzheimer’s Disease**

Analysis of Genome wide linkage (GWL), genome-wide associations (GWA) and genome-wide expression (GWE) datasets for Alzheimer’s disease (AD) revealed EGFR to be a significant AD specific biomarker. Dataset analysis revealed 108 AD related genes including EGFR and ACTB. Since, these two biochemical markers were found overlapping with proteins of cerebrospinal fluid and plasma proteins, they were characterized as the most significant risk genes in AD (Talwar et al., 2014). Mutations in Presenilin (PS) proteins PSEN1 and PSEN2 cause dramatic severity in early-onset of AD. PSEN1 controls the cell-specific transcription of EGFR in neural cells. PSEN1 null (PS1(-/-)) cortical neurons showed decreased level of EGFR related survival signaling, until exogenous EGFR rescues the signaling phenotype. Interestingly, while overexpression of PSEN1 upregulates the transcriptional level of EGFR, downregulation of it reduces the EGFR mRNA level (Bruban et al., 2015).

EGFR has critical role in APBA2 (amyloid β42) induced memory loss in AD. Studies on APP/PSEN1 double transgenic mice had high levels of active EGFR level. Inhibition of EGFR activity reversed the action of APP/PSEN1 related impairment of memory in mice. Similarly, in fruit flies, upregulation of EGFR elevated the memory loss while pharmaceutical inhibition of EGFR rescued memory loss in Aβ42 expressing fruit flies (Wang et al., 2012). Immunoperoxidase staining showed higher level of EGFR immune reactivity in both pathologically confirmed AD brain samples and in normal aging brain samples with neuritic plaques (Birecree et al., 1988).

**Rapidly Progressive Glomerulonephritis (RPGN)**

EGFR pathway is implicated in RPGN and other glomerular diseases. RPGN is mainly characterized by proliferation of epithelial cells and inflammatory cell infiltration (Harskamp et al., 2016). HBEGF (Heparin Binding EGF) is increased in RPGN and other glomerular diseases such as puromycin-aminonucleoside-induced focal segmental
glomerulosclerosis and membranous nephropathy (passive Heymann nephritis) (Paizis et al., 1999).
there is de novo expression of heparin-binding growth factor-like growth factor (HBEGF) in glomerular epithelial cells specifically in human glomerulonephritis (Flamant et al., 2012).

**Diabetic Nephropathy**
Phosphorylated EGFR and EGF upregulation were shown in high glucose treated renal cells (Saad et al., 2005). Activation of EGFR causes upregulation of SGK1 (serum glucocorticoid-regulated kinase 1), which is important in regulating ion transport protein ENaC, important in sodium reabsorption (Saad et al., 2005). Also, Ang II mediated EGFR transactivation regulates gene expression of glucose transporter 1 (Nose et al., 2003). Finally, EGFR activation in diabetic animals, mediates deviated activation of TGFβ1 (Uttarwar et al., 2011).

**Chronic Allograft Nephropathy**
Increased levels of renal EGF and EGFR was shown in rats and EGFR expression was demonstrated in human renal allograft biopsy samples (Sis et al., 2004). Erlotinib (a tyrosine kinase inhibitor) prevent chronic allograft rejection (Rintala et al., 2014).

**Polycystic Kidney Disease**
EGFR expression is increased in PKD and EGFR activation via its ligands (EGF, TGFα, HBEGF and AREG26) leads to cyst formation (Harskamp et al., 2016). Cellular localization alteration of EGFR is also found in PKD. Normally, EGFR is localized on the basolateral membrane of tubular cells, but in PKD, receptor is found on the apical surface of the cyst epithelium (Du and Wilson, 1995).

**Kidney Fibrosis**
Ang II-induced renal fibrosis is associated with EGFR pathway. EGFR inhibition attenuates renal fibrosis and kidney dysfunction in Ang II infused mouse models, indicating that EGFR may be a therapeutic target in chronic renal diseases (Qian et al., 2016).

**Hypertension**
Kidney is known to express four members of ErbB receptor family (Staruschenko et al., 2013). EGFR pathway may regulate sodium transport and development of hypertension because EGFR pathway determines renal lesions and regulates sodium reabsorption in collecting ducts (Staruschenko et al., 2013).

**Congenital Hydronephrosis**
Children with pelviureteral junction obstruction (PUJO) had a significant increase in TGF-β1 and decrease in EGF expression which may play a role in the development of obstructive nephropathy (Yang et al., 2006).

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