# Epidermal growth factor receptor family and its role in cancer progression

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**Epidermal growth factor receptor (EGFR), a receptor tyrosine kinase has four members in its family. A set of specialized ligands have evolved which bind to and cause homodimerization or heterodimerization of the receptor and lead to activation of downstream signalling pathways. This receptor family has a critical role to play in normal development, and aberrant expression or activation of the receptor family has been associated with many diseases, including cancer. Here we attempt to compile the literature on the structure of the receptor, the activation of the receptor in a ligand-dependent or independent manner and signal transduction downstream. Finally we conclude by exploring therapeutic options and also by speculating where research in EGFR biology will be heading for in the future.**

EPIDERMAL growth factor receptor (EGFR, ErbB-1, HER-1) was the first receptor tyrosine kinase (RTK) to be discovered[1–3]. Most of the principles and paradigms of RTK activation were first established for EGFR[4,5]. Similarly, many of the mechanisms for activation and recruitment of intracellular signalling pathways following growth factor stimulation were discovered in studies of signalling via Epidermal Growth Factor (EGF) receptors. RTKs as well as cytoplasmic protein tyrosine kinases play a prominent role in the control of normal cellular processes during embryonic development and in the regulation of many metabolic and physiological processes in a variety of tissues and organs[5–7]. Dysfunctions in the action of protein tyrosine kinases or aberrations in the activities and cellular localization of key components of the signalling pathways that they activate will result in severe diseases like cancer, diabetes, immune deficiencies and cardiovascular diseases among many others[8].

Following the identification of EGFR (HER-1/ErbB1), three additional members of the same receptor family were identified, ErbB2 (HER-2/Neu), ErbB3 (HER-3) and ErbB4 (HER-4)[9]. The mammalian ligands that bind to EGFR include EGF, transforming growth factor-α (TGF-α), heparin-binding EGF-like growth factor (HB–EGF), amphiregulin (AR), betacellulin (BTC), epiregulin (EPR) and epigen[7]. In addition to HER-1, HB–EGF, BTC and EPR bind to and activate[10,11] HER4. The neuregulins (this family includes heregulin, acetylcholine receptor-inducing activity, neu differentiation factor, glial growth factor and sensory motor derived factor) bind both HER3 and HER4 (Figure 1). ErbB2 cannot be stimulated by any known ligand and ErbB3 is signalling, defective[5,12,13]. The ErbB2/ErbB3 heterodimer constitutes a novel adaptation in ErbB receptor evolution, demonstrating the capacity of evolution to form an extremely potent signalling module from a pair of singularly inactive receptors[11].

The ErbB receptor family plays a pivotal role in cell-lineage determination in various tissues, including mesenchymal–epithelial inductive processes in epithelial organs[6]. ErbB2, ErbB3 as well as ErbB1 are expressed in most epithelial cell layers, while mesenchymal cells are a rich source of ErbB ligands, both neuregulins and EGF-like ligands. Activating mutations and overexpression of members of this family of receptors are implicated in a variety of cancers including mammary carcinomas, squamous carcinomas, glioblastomas as well as other malignant diseases[14]. ErbB RTKs can promote multiple properties of neoplastic cells, including proliferation, migration, angiogenesis, stromal invasion, and resistance to apoptosis[4].

## Architecture of EGFR

EGFR is synthesized from a 1210 residue polypeptide precursor after cleavage of the N-terminal sequence; an 1186 residue protein is inserted into the cell membrane[15]. Over 20% of the receptor's 170 kDa mass is N-linked glycosylation and this is required for the translocation of EGFR to the cell surface and subsequent acquisition of function[16]. The sequence can be categorized into a number of domains, as shown in Figure 2. The sequence identity of the EGFR family varies from 37% (53% similarity) for EGFR and ErbB3 to 49% (64% similarity) for EGFR and ErbB2. The amino acid identity can also vary significantly among the domains, with the tyrosine kinase domains having the highest sequence identities (average 59–81% identity) and the carboxy terminal domains having the lowest (average 12–30% identity). The three-dimensional folds of the corresponding domains of the different EGFR homologues are expected to be similar, with the possible exception of the highly divergent C-terminal domains[17].

The EGFR extracellular portion (or ectodomain) consists of four domains that are referred to as the L1, CR1, L2 and CR2 domain (Figure 2). The LI and L2 domains resemble the corresponding domains of the IGF-1 receptor[15]. In EGFR,

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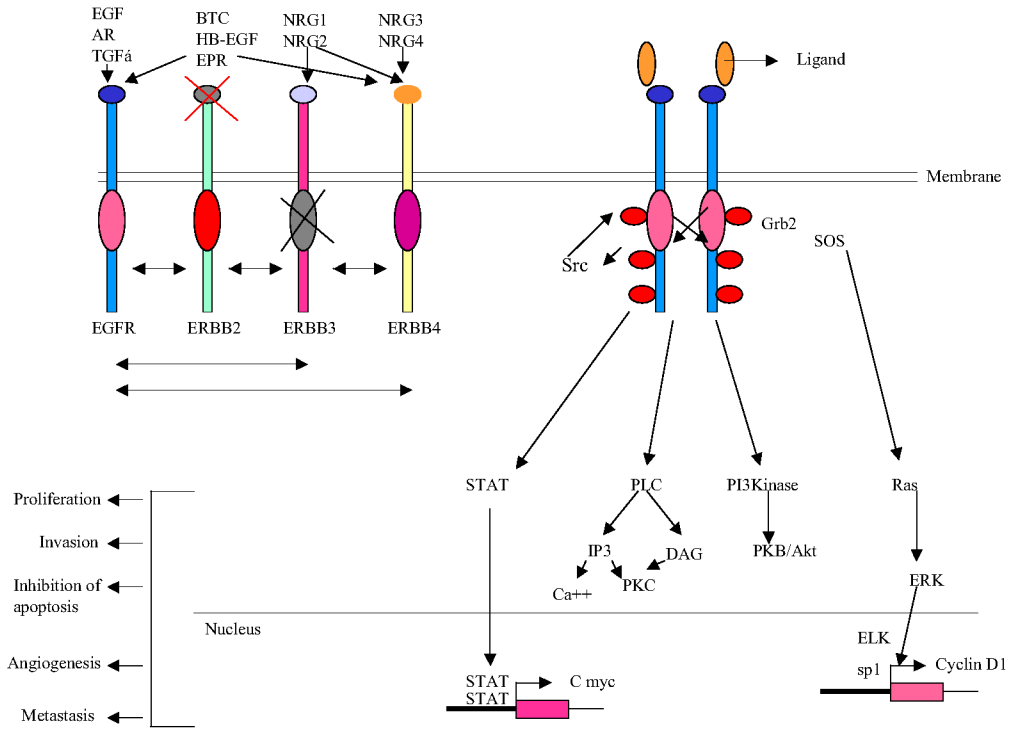


**Figure 1.** EGFR (blue), ERBB2 (green), ERBB3 (red) and ERBB4 (yellow) are shown. ERBB2 cannot bind to a ligand, while ERBB3 is tyrosine kinase-defective. Ten ligands to the EGFR family are shown. EGF (Epidermal Growth Factor), amphiregulin (AR) and TGF-α bind preferentially to EGFR, while betacellulin (BTC), HB–EGF (heparin-binding EGF) and EPR (epiregulin) bind both to EGFR and ERBB4. Neuregulins (NRG) 1 and 2 bind preferentially to ERBB3 and ERBB4, while neuregulin 3 and 4 bind to ERBB4. Upon ligand-binding, the receptors homodimerize or heterodimerize (possible heterodimerization combinations are shown as double arrows) and cause tyrosine phosphorylation by cross-phosphorylation using the tyrosine kinase domain present on the cytoplasmic side of each receptor. Here a EGFR homodimer is shown and the phosphorylated tyrosine domains are shown in red (not all the residues phosphorylated are shown here). The homodimerized or heterodimerized receptor then activates downstream-signalling pathways which include STAT, phospholipase C, PI3 kinase, and the ras, ERK pathway and also Src kinase. This leads to oncogenesis by causing the cells to proliferate, invade, induce resistance to apoptosis, initiate angiogenesis and metastasis.

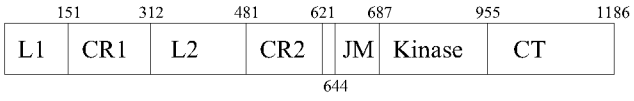


**Figure 2.** Distribution of domains on the EGFR receptor. L1 is at the amino terminus, while CT is the carboxy terminus. Number shows the amino acid position between the domains.

the ligand binds between the L1 and L2 domains of the receptor[18]. In ErbB2, there is a strong interaction between the L1 and L2 domains, rendering ErbB2 incapable of binding to ligands[11]. Therefore, ErbB2 has to heterodimerize with other members of the ErbB family to be normally functional. The CR1 and CR2 domains consist of a number of small molecules, each appearing to be held together by one or two disulphide bonds. When the receptor dimerizes, loops from CR1 make contact with each other. The recent literature also suggests that receptor dimerization is an unique property of the receptor themselves, although the ligand may cause dimerization through some conformational changes in the receptor[19,20]. The CR2 domain is involved in targetting EGFR to the caveolae/raft component prior to ligand-binding[21]. Residues 626–647 of EGFR constitute the transmembrane domain and are α-helical[22]. The juxtamembrane region appears to have a number of regulatory functions like down-regulation and ligand-dependent internalization events[23], basolateral sorting of the EGFR in polarized cells[24], and association with proteins such as[25] eps 8 and calmodulin (which is competitive with protein kinase C association)[22]. The experimental three-dimensional structure of the EGFR kinase domain is similar to other tyrosine kinases[26]. It has been shown that the ATP sits between the N-terminal (dominated by a β-sheet) and the larger C-terminal lobe (mainly α-helical), with the γ-phosphate group of ATP positioned to be transferred to the acceptor tyrosine residue of the substrate[27]. The carboxyl terminal (CT) domain of EGFR contains tyrosine residues which upon phosphorylation modulate EGFR-mediated signal transduction. There are also several threonine serine residues, where phosphorylation

has been inferred to be important for the receptor downregulation processes and sequences thought to be necessary for endocytosis[28]. A number of mutations in EGFR have been observed in tumours where gene amplification has occurred[15,26]. The best characterized EGFR mutation is the Δ2–7 truncation in which exons 2–7 are lost. This receptor mutation is constitutively active and has defective downregulative behaviour[15,29]. Other mutations have deletions, regions of sequence duplication or defective kinase regulatory signals.

## Activation of receptor signalling

It is now well established that growth factor-induced receptor oligomerization is mainly responsible for the activation of the RTKs and other receptors that contain a single transmembrane domain[30]. Growth factor-induced receptor dimerization is followed by intramolecular autophosphorylation of key tyrosine residues in the activation loop of the catalytic PTK domain, resulting in stimulation of PTK activity (Figure 1). Tyrosine autophosphorylation sites in other parts of the cytoplasmic domain then serve as docking sites for SH2 (Src homology 2) and PTB (phospho tyrosine binding) domains of signalling proteins that are recruited and activated upon growth-factor stimulation[8]. Recent studies have shown that a ligand (EGF or TGF-α) molecule is bound exclusively to a single EGFR molecule and dimerization is mediated entirely by receptor–receptor interactions[20].

### *Ligands to the EGFR family*

EGF is a 53 amino acid (aa) polypeptide with a molecular weight of 6045, that is derived by proteolytic processing (by an as yet unidentified metalloproteinase) from the transmembrane precursor (prepro EGF) of 1207 aa in humans and 1217 aa in rodents[1,10,31,32]. EGF was originally detected and isolated by Stanley Cohen, because of its abilities to stimulate precocious tooth eruption and eyelid opening in newborn mice[4,33]. EGF binds to both low affinity ($K_D$ = 1–2 nM) and high affinity ($K_D$ = 10–50 pM) sites on the cells that express EGFR. Studies have shown that this may be on account of the presence of the receptor dimers[20].

TGF-α derives from a shorter 160 aa precursor and it exhibits 33–44% sequence homology with mouse or human EGF (12 residues are strictly conserved). Of interest, its discovery in the culture medium of established cell lines contributed to elaborate the autocrine hypothesis of cell growth control[34]. TGF-α is sorted to the basolateral surface of polarized epithelial cells, where it is cleaved by TNF-α converting enzyme/disintegrin and metalloproteinase 17 (TACE/ADAM 17), whereupon mature soluble growth factor is avidly bound to basolaterally restricted EGFRs[35]. TGF-α has been shown to be rapidly consumed by the receptor[10].

HB–EGF is expressed in a wide variety of hematopoetic cells, endothelial cells, vascular smooth muscles and epithelial cells[36–38]. HB–EGF has been implicated in wound-healing, blastocyst implantation, atherosclerosis and tumour growth[39]. The precursor for HB–EGF is a 206 aa peptide, which after a metalloprotease-dependent cleavage yields an 86 aa secretory protein[10]. The identity of the metalloproteinase involved in cleaving of HB–EGF is an area of current interest. Although matrix metalloproteases were suspected to be involved[40], the recent literature suggests another class of metalloproteinases, the ADAMs (a disintegrin and metalloproteinase). ADAM 9, 10, 12 and 17 have been implicated in HB–EGF shedding[41]. ADAM 10 has also been implicated in Delta Notch signalling[42,43]. Hence these results indicate that multiple ADAMs possess the capability of processing proHB–EGF and the specific metalloprotease involved may be dependent upon cellular/tissue specificity in ADAM distribution. Mechanisms of ADAM activation are still under investigation.

Amphiregulin (AR) was originally identified as an EGFR ligand from a phorbol ester-treated human breast adenocarcinoma cell line[44–46], MCF 7. Although the growth inhibitory properties of AR have not subsequently been validated, Shoyab and colleagues[45] named it amphi because of its growth inhibitory properties in A431 cells and several other cancer cell lines and growth stimulatory properties of many other cell lines normal as well as transformed. A 252 aa transmembrane precursor is cleaved on the baso-lateral side by TACE/ADAM 17, metalloprotease to a 78–84 aa peptide[10].

Betacellulin (BTC) was originally identified in conditioned media from a pancreatic cancer cell line, but since has been shown to be expressed in adults in pancreas, liver, kidney and small intestine[47]. BTC has also been detected in a variety of tumour cell lines and tumours *in situ* with high expression, especially in pancreatic cancer[31,48].

Epiregulin (EPR) was purified from conditioned media of the mouse fibroblast-derived cell line NIH3T3/clone T7 as a 46 aa peptide cleaved form a 162 aa transmembrane peptide. Structurally, it resembles TGF-α and is expressed predominantly in the placenta and peripheral blood leucocytes of normal adults as well as bladder, lungs, kidney and colon[49,50].

G-protein coupled receptor (GPCR) transactivation of EGFR was thought initially to be an intracellular ligand-independent process due to the rapid onset (within minutes) of EGFR activation and the absence of detectable EGFR ligands in conditioned medium. However, Prenzel *et al.*[51] provided convincing evidence for a metalloprotease-dependent cleavage of HB–EGF upon GPCR activation, with soluble HB–EGF then activating EGFR.

### *Ligand–receptor interaction*

Apart from *in vitro* data suggesting a role of EGF/EGFR in cell proliferation, evidence has been accumulating that overexpression of the ligands and/or receptors as well as ligand-independent receptor activation occurs in many epithelial cancers, most notably gliomas and breast, pancreas and

liver carcinoma. What, however, is not clear is whether overexpression/activation is indeed causative for the formation of tumours or occurs during tumour progression. Using transgenic animals, overexpression of especially the TGF-α ligand has been well studied. Targetting of TGF-α to the skin by means of keratin promoters results in hypertrophy and hyperkeratosis accompanied by alopecia, stunted hair growth and psoriasis-like lesions[52–57]. TGF-α is also linked to the appearance of papillomas following irritation or wounding, without progression to carcinomas. In all studies it appears therefore that the activation of TGF-α is linked to hyperproliferative responses, but does not generally lead to tumours in rodents. In breast carcinomas, apart from the ras oncogene components of the EGF/EGFR family of ligands and receptors, the most commonly activated oncogene is c-Myc. Transgenic mice which overexpress both TGF-α and c-Myc develop mammary tumours in both sexes, while overexpresion of c-Myc alone resulted in tumour formation in females with reduced frequency and long latency periods. This combination also leads to formation of hepatocellular carcinomas[57–63].

Given the pleiotropic effects of TGF-α, the phenotype of the TGF-α null mice is mild. In skin, wavy fur and whiskers were observed and the eyes of the TGF-α, null mice were open, opaque and also a significant reduction in dopaminergic neurons was observed[52,54–56]. EGF null or AR null mice do not show any obvious phenotype and this may be partly explained by compensatory mechanism present, such as upregulation of other EGF family of ligands[53–57]. Double and triple null mice generated by crosses showed increased penetrance of eye defects, dermatitis and skin ulcers with aging[56]. However, only the absence of AR combined with either EGF or TGF-α results in impaired mammary gland development attributed not to abnormal cell proliferation, but to abnormal epithelial cell migration[44]. These experiments show that ligand mutations only lead to remarkably mild phenotypes, possible due to the compensatory mechanisms present. However, EGFR knockout mice were severely affected showing peri implantation and mid gestational deaths[44]. In some strains, the mice survive up to three weeks after birth and these animals also show severe abnormalities of the skin, lungs, gastrointestinal tract, brain and liver[64]. Also, waviness of fur and whiskers characteristic of the TGF-α null mice were observed. ErbB 2, 3 and 4 also showed severe cardiac and cranial ganglia defects and consequent embryonic lethality[26,65,66]. Table 1 summarizes the phenotypes and references for ligand overexpression, ligand null and receptor knockout studies in mice.

In the past year, major advances in understanding EGF action have come from crystallographic studies of extracellular regions from three members of the EGF receptor (EGFR) or ErbB family, namely EGFR itself, ErbB2 (HER2/Neu), and ErbB3 (HER3). The structures revealed a dramatic conformational transition occurring upon ligand binding an unprecedented (entirely receptor-mediated) mode of dimerization was identified; and an unexpected apparently 'preactivated' state was defined for the ErbB2 monomer[18,67].

However, the inability of the ligand null mutations to mimic the severity of function to the receptor null mutation could also suggest ligand-independent activation of the

**Table 1.** Summary of phenotypes for ligand overexpression, ligand null and receptor knockout studies in mice

| | Phenotype | Reference |
|---|---|---|
| Ligand overexpression | | |
| TGF-α overexpression in mice by keratin promoter | Hypertrophy and hyperkerotosis with alopecia, stunted hair growth, psoriasis-like lesions. However, no tumours. | 52 |
| TGF-α and c-Myc overexpressing transgenic mice | Mouse mammary tumours in both sexes and also hepatocellular carcinomas. | 57, 60–63 |
| Ligand null | | |
| TGF-α null mice | Very mild phenotype like wavy fur and whiskers in skin, eyes open and opaque, and reduction in dopaminergic neurons. | 44, 54 |
| EGF/AR null mice | No obvious phenotype. | 44 |
| Absence of AR + EGF + TGF-α | Impaired mammary development. | 44 |
| Receptor knockout | | |
| EGFR knockout | Peri-implantation and mid-gestational death. Some strains of mice survive up to three weeks after birth and show abnormalities of skin, lungs, gastrointestinal tract, brain, liver, waviness of fur and whiskers. | 44, 64 |
| ErbB 2, 3, 4 | Severe cardiac and cranial ganglia defects and consequent embryonic lethality. | 26, 65, 66 |

receptor. Recent studies have shown that Src, which was the first oncogene to be discovered and the first protein tyrosine kinase[68], could activate the RTK in a ligand-dependent/independent fashion[69]. Integrins were also shown to associate with the EGFR receptor in a macromolecular complex along with p130Cas and c-Src kinase and induce phosphorylation of EGF receptor at tyrosine residues 845, 1068, 1086 and 1173, but not on residue 1148 which is a major residue phoshorylated in response to EGF[70,71]. Another study showed that c-Src up-regulates EGFR by inhibiting receptor ubiquitylation and endocytosis, and both effects are attributable to accelerated destruction of c-Cbl[72]. Src has also been shown to potentiate EGFR-mediated oncogenesis[73]. Src has also been positioned downstream to RTK activation, especially in cells which overexpress EGFR[74]. Therefore, it should be understood that both the signalling possibilities exist, i.e. Src could activate EGFR and vice versa, simultaneously (Figure 1). The physiological consequence of such signalling will have to be studied further.

Several modes of indirect EGFR activation have been described. Stimulation of EGFR phosphorylation occurs after treatment with unphysiological stimuli, including hyperosmolarity, oxidative stress, mechanical stress, UV light and γ-irradiation[75]. This effect has been predominantly attributed to the inactivation of phosphatases that antagonize the intrinsic receptor kinase activity, thereby shifting the equilibrium of basal autophosphorylation and dephosphorylation towards the activated state[76,77]. Apart from unphysiological stimuli, receptor activation can also be induced by chemokines, cell-adhesion molecules and GPCRs.

## EGFR family and cancer

The ErbB proteins are homologous to the avian viral oncogene v-ErbB[78]. The impact of the EGFR signalling system on human neoplasia is underscored by the following: (i) EGFR is overexpressed or activated by autocrine or paracrine growth factor loops in at least 50% of epithelial malignancies. (ii) HER2 is amplified and dramatically overexpressed in approximately 20–30% of breast cancers and also cervical cancers. (iii) HER3 is variably expressed in breast and colon, prostate, and stomach malignancies. (iv) ErbB4 is overexpressed in breast cancer and granulosa cell tumours of the ovary[79].

EGFR and ErbB2 have been showed to be overexpressed in a large proportion of breast and ovarian tumours, primarily by gene amplification[79–81]. In cervical cancers, HPV E5 is known to cause overexpression of EGFR[82]. Recently, ErbB2 was shown to cooperate with HPV viral oncoproteins E6 and E7 to cause transformation[83,84]. The transmembrane receptor Notch1 protein has been shown to overexpress ErbB2[42] and this along with the ability of Notch1 to activate the PI3kinase PKB/Akt pathway[85] and protect cells from anoikis[85] and also to protect cells from p53-induced cell death[86] could play a major role in the progression of many cancers like the cancer of the uterine cervix where Notch is known to be overexpressed[85]. It would be interesting to see whether Notch drives PI3kinase through overexpression of ErbB2 in cervical cancers.

The second member of the ErbB family to be identified, ErbB2, has several unique properties. First, it has no known ligand, suggesting that it may function as a coreceptor (or heterodimerization) partner for other ErbB receptors that do not have ligands[5]. Second, unlike other ErbB receptors, ErbB2 overexpression by itself can cause cellular transformation even in the absence of added ligand[19]. The rodent ErbB2 named neu, was shown to be a potent transforming oncogene[19]. The unaltered wild-type human ErbB2 is amplified or overexpressed in a subset of breast cancers and this correlates with an aggressive tumour phenotype, including tumour size, lymph node involvement, high percentage of S-phase cells, aneuploidy and lack of steroid hormone receptors[13,26,80]. Recently, ErbB2 overexpression was observed in cervical cancer cell lines derived from various biopsies, and they were shown to have a positive selection over ErbB2-negative cells[87]. ErbB2 has been shown to be overexpressed in some ovarian, gastric and salivary cancers. Details[79,88–91] of expression of ErbB family members in different tumours are given in Table 2. The overexpression of ErbB2 in breast cancers has made it a key target for breast and ovarian cancer therapies, such as humanized ErbB2 herceptin antibody. While herceptin alone showed a median overall response rate of 16%, with chemotherapy, the median time of disease progression was found to have increased[92] by 65%.

## Signal transduction through EGFR

EGFR–TK (tyrosine kinase) plays a key role in numerous processes that affect tumour growth and progression, including proliferation, dedifferentiation, inhibition of apoptosis, invasiveness and lack of adhesion dependence[7]. Phosphorylated tyrosine residues in EGFR serve as binding domains for the Grb2/Sos complex, thus activating the Ras/Raf/mitogen activated protein kinase (MAPK) signalling cascade,

**Table 2.** Summary of expression in percentage of different receptors in different cancers

| Tissue | EGFR% | ErbB2% | ErbB3% | ErbB4% |
|---|---|---|---|---|
| Bladder | 31–72 | 9–36 | 30–56 | 30 |
| Gastric | 41–83 | 38–45 | 20–35 | |
| Breast | 14–91 | 25–30 | 22–52 | |
| Colon | 50–80 | 26–90 | 89 | |
| Stomach | 40–81 | 26–55 | 35 | |
| Head and neck | 80–100 | | | |
| NSCLC | 40–80 | 18–37 | | |
| Ovary | 35–70 | 10–15 | | 90 |
| Pancreas | 30–50 | | | |
| Cervix | 40–80 | 30–60 | 0–90 | 0–60 |
| Gliomas | 40–80 | 20–54 | | 30–70 |

which in turn influences cell proliferation migration and differentiation[76]. Recruitment of the second signalling pathway, the phosphatidylinositol 3 kinase pathway (PI3K), results in inhibition of apoptosis mechanisms in tumour cells[93] (Figure 1). Other key downstream signalling molecules that are influenced by EGFR–TK activity include phospholipase C, $Ca^{2+}$/calmodulin-dependent kinases and the Janus kinase signal transducer and activator of transcription pathway[15,80]. Activity of EGFR–TK also influences tumour angiogenesis by upregulating[77,94,95] expression of VEGF and interleukin 8.

Recent reports also suggest that following EGF stimulation at the cell surface, the full-length EGF receptors also migrate to the nucleus, where they bind an AT-rich consensus sequence (ATRS) via an undefined domain and enhance transcription via proline-rich region near their carboxy terminal domain[96–98]. They also show that EGFRs associate with the promoter region of cyclin D1, a protein that can play a key role in mitogenesis[96]. These results challenge the dogma that receptor kinases stimulate mitogenic pathways only through sustained second messenger signalling at the plasma membranes or in the endosomes[99]. RTKs are predominantly found in the nucleus in two forms, either as the intact molecule or its cytoplasmic domain fragment. While the means by which an intact receptor is translocated from the plasma membrane to the nucleus is not currently understood, the mechanism for fragment formation and translocation is in general known and supported by other cell surface transmembrane molecules like Notch[100]. The Notch receptor, the Alzheimer's precursor protein and ErbB4 show similar sequential cleavage and nuclear translocation[43,101]. The recent literature also suggests a role for the EGFR holoreceptor in the nucleus[99]. Apart from ErbB1, ErbB3 which binds to the growth factor heregulin, was reported to be present in its uncleaved state in the nucleus[102]. Recently, FGFR (fibroblast growth factor receptor 1), insulin growth factor, nerve growth factor fibroblast growth factor, platelet-derived growth factor among others, have been shown to have nuclear localization[99]. HER2/neu have also been shown by Xie *et al.*[103] to have similar transactivation function as EGFR. RTKs may also carry other molecules like STAT 1 into the nucleus and these receptor-associated molecules are functional in the nucleus[104].

## Conclusion

EGFR was the first cell-surface receptor to be linked directly to cancer when Stanley Cohen and colleagues[105] described the downregulation of EGFR in fibroblasts infected with oncogenic viruses. EGFR overexpression is known to cause mislocalization and aberrant signalling. For example, EGFRs are normally confined to the basolateral surface of polarized epithelial cells, but when they are overexpressed receptors also appear at the apical surface[24,35,106]. EGFRs that are misdirected through overexpression to the apical surface undergo prolonged activation, giving rise to augumented phosphorylation of focal adhesion kinase and β-catenin[107]. Similarly, nuclear EGFR signalling may also only be observed as a consequence of deregulated EGFR signalling in disease condition. This could then be exploited for therapeutic purposes (using radiolabelled EGF) in pathologies involving overexpression of EGFR[108].

### *Therapeutic options*

The recent literature on the mechanism of action of ErbB receptors and their relevance in tumourigensis opens windows for therapeutic opportunities. The reasonable successes of clinical trials of herceptin in breast cancers[92] and an inhibitor, Gefitinib in non-small cell lung cancer (NSCLC) are pointers in this direction. The recently resolved structures of the ErbB receptors will be instructive not only for understanding how ligands promote receptor dimers, but also help in the development of peptidergic and other ErbB blockers. Thus in terms of cancer therapy, understanding of the basic mechanisms underlying ErbB-dependent tumourigenesis have led to a major focus on the receptors as targets for therapeutics. However, to achieve increased clinical successes in the future, targets designed against the additional components of the ErbB network would be necessary. This can be seen from recent studies where Gefitinib (Iressa), a tyrosine kinase inhibitor, that targets the EGFR, and induces dramatic clinical responses in NSCLCs (10–20% patients) with activating mutations within the EGFR kinase domain[109], was shown to selectively activate Akt and STAT signalling pathways, which promote cell survival, but have no effect on Erk/MAPK signalling that induces proliferation[110].

Apart from drug designing, future research would also be directed to the study of the spatio-temporal regulation of the ligands, receptors and downstream effectors. The future would also involve understanding further, mechanisms of ligand mediated or constitutive receptor dimerization, activation of the receptor by focusing on amino acid modifications and the signalling pathways activated downstream to this.

Thus EGFR and its family members are potential drug targets. Recent studies suggest that these signalling pathways are not discreet entities, but involve a lot of crosstalk with other RTKs and also signalling events downstream to them. Elucidating these pathways in different cancers would enable better drug designing and therapeutics.

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