Epidermal Growth Factor Receptor: Role in Human Cancer

Abstract

Cells are constantly exposed to various external stimuli which regulate the growth and survival of the cells. The signal transduction from the external environment to the interior of the cell is carried out by cell surface or transmembrane receptors. Epidermal growth factor receptor (EGFR) is a transmembrane receptor tyrosine kinase and along with its ligands, EGFR is involved in the regulation of multiple cellular pathways. EGFR and its signaling pathway have been studied extensively for the biological and pathophysiological role in health and disease. There is enough evidence to suggest that EGFR is involved in the pathogenesis and progression of various cancers. This review discusses the structural anatomy and physiology of EGFR and its ligands, the role of EGFR in cancer and EGFR-targeted therapy.

Keywords: Epidermal growth factor, epidermal growth factor receptor, ErbB family of receptors, EGFR-targeted therapy

Introduction

Cell signaling is a part of a complex system of communication that governs basic cellular activities and coordinates cell actions. The ability of the cell to perceive and correctly respond to their microenvironment is the basis of development, tissue repair, and immunity as well as normal tissue homeostasis. The cell surface and transmembrane receptors are involved in signal transduction and form an integral part of the signaling pathways. One large family of cell surface receptor is receptor tyrosine kinase (RTK). RTKs play an important role in the control of most fundamental cellular processes such as cell cycle, cell migration, cell metabolism and survival, as well as cell proliferation and differentiation.[1] Epidermal growth factor receptor (EGFR) is the inaugural member of erythroblastosis oncogene B (ErbB) family of RTK.

This review discusses the role of EGFR and its ligands in health and disease. It also focuses on the effectiveness and challenges of EGFR-targeted therapy in head and neck squamous cell carcinoma (HNSCC).

Structural Anatomy of Epidermal Growth Factor Receptor and Epidermal Growth Factor

EGFR is a 170-kDa monomeric glycoprotein. It is expressed in many adult tissues and involved in many cellular processes essential for survival and growth of cells.[2] EGFR is one of the members of the ErbB family of RTK, which also comprises three other structurally similar receptors:[3]
1. EGFR (ErbB1, HER1)
2. ErbB2 (neu, HER2)
3. ErbB3 (HER3)
4. ErbB4 (HER4).

ErbB is the name derived from the similarity of these receptors to viral oncogene, avian ErbB.[4] Human epidermal growth factor receptor (HER) is the other name for all the receptors of this group. In addition, ErbB2 is also called neu because it was derived from a rodent glioblastoma cell line, a type of neural tumor.[5] ErbB receptors are located in the basolateral membrane of the epithelial cells, where they interact with their ligands present in the stroma, thus mediating signaling between the epithelium and extracellular matrix.[6]

All members of the ErbB family have an extracellular domain, a hydrophobic transmembrane domain, and cytoplasmic tyrosine kinase-containing domain.[1,3,7] Extracellular domain (1–621 amino acids) consists of four subdomains, namely L1, CR1, L2, and CR2. L1 and L2 are responsible for binding to ligand, CR1 makes contact with CR1 of adjacent receptor.[7,8] The transmembrane domain extends from 622 to 644 amino acid residues. The α-helix of the transmembrane

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domain extends between 626 and 647 amino acid residues and thereby continues into the juxta-membrane domain. The juxta-membrane regions perform a number of regulatory functions such as downregulation and ligand-dependent internalization events, basolateral sorting of the EGFR in polarized cells and association with proteins such as eps8 and calmodulin.\[9] The intracellular domain contains tyrosine kinase and carboxy terminal region that contains autophosphorylation sites.\[9]

EGFR is the inaugural member of the ErbB family while the other members were discovered later. The ErbB-2 is an 185-kDa protein that was originally identified and cloned from a human breast and gastric carcinoma. The human gene is located on chromosome 17q11.2-q12. It is expressed at low levels in a number of human secretory epithelial tissues.\[2] The ErbB-3 was cloned from two groups, namely, human breast and epidermoid carcinoma cDNA libraries. The gene is located on chromosome 12q13 and microRNA (mRNA) transcript expressed in many adult tissues but not in stromal cells. The ErbB-4 is the last member of the EGFR family to be identified.\[2]

Epidermal growth factor (EGF)-peptides are a family of growth factors that share the ability to bind to the same receptor, i.e., the ErbB receptor family. The ligands that bind to ErbB family of receptors can be divided into three groups as follows:

1. Group I: EGF, transforming growth factor-α (TGF-α), and amphiuregulin (AR) bind to EGFR
2. Group II: Betacellulin (BTC), heparin-binding EGF (HB-EGF), and epiuregulin (EPR) bind both to EGFR and ErbB-4
3. Group III: Contains neuregulins (NRG) which can be further subgrouped into
   a. NRG-1 and NRG-2 which bind to ErbB-3 and ErbB-4
   b. NRG-3 and NRG-4 which bind to ErbB-4.

No ligands bind to ErbB2.\[7] Erb2 is considered to be an “orphan receptor” since no specific direct ligand has been identified yet. It acts as a co-receptor and increases the affinity of ligand binding to the dimeric receptor complex.\[10] Other ligands such as heregulin α and β, crypto-1 and a series of DNA pox virus-derived peptides are also known to bind to ErbB family of receptors.\[3]

EGF or urogastrone was discovered by Dr. Stanley Cohen in 1962.\[11,12] EGF has been detected in a variety of body tissues such as milk, saliva, urine, plasma, intestinal fluid, amniotic fluid, exocrine glands of the gastrointestinal tract (GIT), and serous acini of the nasal cavity.\[4] In humans, kidney, Brunner glands in the small intestine, and submandibular glands are the predominant sources for EGF production.\[3]

TGF-α can be produced in macrophages, brain cells, and keratinocytes. In females, TGF-α is restricted to mammary tissue. In males, TGF-α may be detected in testis, seminal vesicles, salivary glands, and lungs.\[4] It induces epithelial development and has biological actions similar to EGF. It can initiate multiple cell proliferation events for wound healing and embryogenesis.\[13] TGF-α is also involved in tumorigenesis and believed to promote angiogenesis. Amphiuregulin (AR) is an autocrine growth factor as well as a mitogen for astrocytes, schwann cells, and fibroblasts. It is found to be essential for mammary ductal development.\[10,14]

HB-EGF is produced by the uteri of pigs, mice, rats, and humans. It is expressed in human uterus during the earliest stage of pregnancy.\[15] It is required for cardiac development, vulvogenesis, and epidermal wound healing. It is a potent mitogen for epithelial, endothelial, and smooth muscle cells and is induced in response to injury of these tissues.\[4] EPR is produced by keratinocytes and stimulates keratinocyte growth. It is also expressed in small quantities in epidermis.\[16] BTC is detected in higher quantity in pancreas where it may play a role in β-cell differentiation.\[4]

**Physiology of Epidermal Growth Factor and Epidermal Growth Factor Receptor**

EGF is a mitogenic growth factor and plays an important role in the development of embryo from the preimplantation stage and also in the placental developmental. The biological effects of EGF were determined by Cohen. He noted that daily subcutaneous injection of small quantities of EGF into mice resulted in precocious opening of eyelid and eruption of incisor. At higher doses, there was a distinct growth inhibition of animals and liver had large accumulations of fat.\[8,17] EGF alone or along with other growth factors induces a number of biological responses such as cell proliferation, differentiation, and migration. It also participates in pathophysiological process such as tissue repair. Antiapoptotic and antioxidant actions of EGF are noticed when it is administered exogenously. EGF has also been identified as one of the potent microenvironmental growth factor for stem cells in a variety of tissues.\[11]

EGF and TGF-α are necessary for normal development of prostate glands. EGF, HB-EGF, and TGFα are expressed throughout the central and peripheral nervous system and regulate cellular activities such as proliferation, migration, and differentiation.\[7]

The prepro-EGF, EGF, and other related growth factors are biologically active on binding to its receptor, EGFR. All above-mentioned biological activities of EGF-related peptides are brought about only after their binding to EGFR. When the ligand binds to EGFR, the receptors undergo a transition from an inactive monomer to active homodimer with another EGF or heterodimer with other ErbB family members. This dimerization stimulates its intracellular protein tyrosine kinase activity, leading to auto phosphorylation of several tyrosine residues in the C-terminal domain of EGFR.\[9] Phosphorylation of
the C-terminus of EGFR provides docking sites for the SH2 and PTB domains and thus activating a network of signaling pathways. The important signaling pathways initiated include mitogen-activated protein kinase pathway, phosphatidylinositol 3 kinase pathway (PI3K)/Akt pathway, and phospholipase Cγ pathways.

EGFR is a versatile signal transducer and plays a significant role in a number of cellular processes such as cellular proliferation, survival, differentiation, migration, inflammation, and matrix homeostasis. It has been well documented that EGFR signaling is essential for cell movement as in embryonic development. Genetically engineered mice with mutations in genes that encode ErbB receptors develop multiorgan failure leading to embryonic or perinatal death. Null mutations of EGFR cause developmental defects in the epithelial structures of the skin, lung, pancreas, GIT, and central nervous system. ErbB deficient mice show altered motor and behavioral activities, neural and cardiac defects, and defects in mammary ductal glands. EGFR-knockout mice are severely affected, the most severe being peri-implantation and mid-gestational death. The mice that survived up to 3 weeks postbirth showed severe abnormalities in skin, lungs, GIT, brain and liver, confirming the importance of EGF/EGFR system in epithelial cell regulation.

Epidermal Growth Factor Receptor System and Cancer

EGFR is known to contribute both to normal and neoplastic growth processes in humans. A number of tumors, namely, glioblastomas, nonsmall cell lung cancer, head and neck, breast, colorectal, ovarian, prostatic, pancreatic cancers, etc., are known to exhibit increased EGFR activity. This may be due to increased EGF synthesis, overexpression, or mutation of EGFR. A number of physical stimuli can transactivate EGFR without the need for ligand binding. These stimuli include osmotic stress, ultraviolet radiation, and shear stress. EGFR transactivation in cancer cells can confer properties such as growth, survival, and angiogenesis to the cancer cells. TGF-α is the only EGF-like growth factor that can induce neoplastic transformation in different tissues. TGF dysregulation plays a crucial role in various epithelial cancers such as colon, breast, and gastric cancers.

ErbB2 is the receptor that has highest transforming power. ErbB receptors induce tumors more efficiently in the mammary glands although other factors such as pregnancy and hormonal variations influence the induction of tumors. Coexpression of different ErbB receptors is necessary to bring about full transformation in vivo and in vitro. Fifty to seventy percent of lung, colon, and breast carcinomas have been found to express EGFR or erbB3. EGFR and ErbB2 expression are associated with worse prognosis. Overexpression of EGFR is associated with decreased survival of cancer of head and neck, bladder, cervix, esophagus, and ovary.

EGF and EGFR are associated with progressive tumor growth and metastasis through a number of ways:
1. Increasing tumor cell proliferation and migration through EGFR-Ras/Raf/MEK/ERK and EGFR-PI3K/Akt pathways
2. Localization of EGFR to the nucleus to promote cell proliferation
3. Dysregulation of autophagy activity
4. Stimulation of several matrix metalloproteinases that facilitate cancer invasion and metastasis
5. EGF-mediated decrease in the abundance of mRNAs that restrain oncogenic transcription factors

EGFR is frequently overexpressed or mutated in human cancers. About 30% of solid tumors show gain-of-function genetic alteration of EGFR. Some tumors cells exhibit “oncogene addiction,” a concept introduced by Weinstein in 2002, as they are dependent on EGFR signaling for survival and growth. EGFR-mediated activation of PI3K/Akt pathway promotes cell growth, survival, migration as well as resistance to apoptosis. Mutations of EGFR are specific to tumor types, i.e., certain mutations of EGFR are a common finding in some tumors but rare in others. Overexpression of ErbB2, which occurs in 25%–30% of breast cancers, is associated with poor prognosis and shorter survival. In normal cells, the expression of EGFR ranges from 40,000 to 100,000 receptors per cell. Up to 2 × 10⁶ EGFR molecules per cell have been expressed in some breast cancers.

Amphiregulin is detected in moderate level in normal colonic mucosa but overexpressed in colon cancer and colorectal cancer cell lines Caco-2 and HCA-7. EPR is overexpressed in many cancers and cancer cell lines. EPR is the most common overexpressed gene in MDA-MB-231 breast cancer cells which resulted in metastasis to lung. HB-EGF is involved in breast cancer metastasis to the brain.

Epidermal Growth Factor Receptor-targeted Therapy

EGFR is known to be overexpressed or mutated in most malignancies. Hence, targeting EGFR may be a better treatment modality with better results.

The three most common agents that target EGFR are as follows:
1. Monoclonal anti-EGFR antibodies (mAbs) – cetuximab and panitumumab
2. Small molecule receptor tyrosine kinase inhibitors (TKIs) such as gefitinib, erlotinib, and lapatinib
3. Anti-EGFR vaccines that elicit an immune response against EGFR-expressing tumor cells

Cetuximab (IMC-C225), a chimeric monoclonal mouse-human immunoglobulin G1 (IgG1) antibody and
panitumumab, a fully humanized IgG2 antibody, are both Food and Drug Administration (FDA)-approved for the treatment of colorectal cancer. Cetuximab and panitumumab block ligand binding to the extracellular domain of EGFR, promote receptor internalization, and mediate antibody- and complement-mediated cytotoxicity. Antibody- and complement-mediated cytotoxicity/killing may be more effective with cetuximab when compared to panitumumab as the IgG1 subclass is more effective than IgG2 at activating complement and Fc receptor on immune effector cells. Cetuximab has undergone extensive preclinical and clinical evaluation. Cetuximab has shown anti-tumor, antiproliferative, and cytotoxicity in vitro on a number of cell lines. A study done by Bonner et al. in 2000 showed that cetuximab when combined with radiotherapy caused by greater decrease in cell proliferation. A multicenter study done to compare the improvement of HNSCC between radiotherapy alone with radiotherapy and cetuximab showed that there was 10% improvement in 3-year survival when cetuximab was used. Cetuximab has been demonstrated to improve overall survival when added to radiation therapy for locally advanced disease and when added to chemotherapy for recurrent/metastatic disease.

Nimotuzumab, another humanized antibody, is used clinically for the treatment of HNSCC and glioblastoma. Another chimeric antibody, ch806, binds specifically to the activated form of wild-type EGFR and with even greater affinity to mutated EGFR and is thus selective for tumors and has no effect on normal tissues. The monoclonal antibodies against ErbB2 are Herceptin and Gleevec. Herceptin (Trastuzumab) represents the only biological-targeted therapy for breast cancer in routine clinical practice. Gleevec has been used for the treatment of chronic myeloid leukemia. Trastuzumab is a humanized antibody composed of an antigen-binding component combined with human IgG.

ABX-EGF is a fully humanized monoclonal antibody with very high affinity for EGFR. It has shown to prevent solid tumor formation as well as to eradicate large, established tumors in nude mice. ICR-62 and EMD-72000 are rat and murine monoclonal antibodies, respectively, and both have shown antiproliferative activity on HNSCC.

EGFR TKIs are classified as follows:

1. First-generation reversible inhibitors which target EGFR and its coreceptors ErbB2 and include gefitinib, erlotinib, and lapatinib
2. Second-generation irreversible inhibitors include afatinib, dacomitinib, and neratinib
3. Third-generation inhibitors target T790 mutation associated with acquired resistance to first-generation EGFR TKIs in NSCLC and include AZD9291, CLO-1686.

The TKIs used in the treatment of breast cancer include TAK-165, curcumin, and emodin inhibit tyrosine kinase activity of ErbB2. Adenoviral 5E1A gene product has shown to downregulate the ErbB2 promoter, repress the ErbB2 gene, and reverse the transformed phenotype in preclinical studies. Gefitinib (Iressa) and erlotinib (Tarceva) are Type I ATP-competitive TKIs. FDA of the United States has restricted the use of gefitinib to patients who had previously benefitted or continue to benefit from it based on a 2005 Phase III trial which showed that gefitinib was no better than placebo but is used as first-line therapy in many countries. Erlotinib is a FDA-approved therapy for the treatment of patients with locally advanced or metastatic NSCLC, either following failure of at least one prior chemotherapy or as a maintenance therapy. Lapatinib is a dual EGFR/ErbB-2 inhibitor is used clinically to treat HER-2 positive breast cancer patients. Irreversible small molecule such as HKI-272 and BIBW 2992, which covalently bind to cystein in EGFR kinase domain are being tested in various malignancies.

**Epidermal Growth Factor Receptor-targeted Therapy in Head and Neck Cancers**

The rationale for the development of EGFR-targeted therapies for the treatment of HNSCC includes the following:

1. EGFR is highly expressed in many HNSCC
2. EGFR overexpression in HNSCC is associated with reduced survival
3. EGFR-targeting in HNSCC preclinical models demonstrated antitumor efficacy

More than 80% of invasive squamous cell carcinoma cases of head and neck overexpressed EGFR and excess of EGFR in often linked to unfavorable clinical outcome, decreased chemosensitivity, high recurrence, and low survival rates. The normal mucosa, several centimeters from the primary tumor site demonstrate elevated levels of EGFR mRNA, and TGF-α. EGFR expression remains elevated as the tissue progresses from normal mucosa to hyperplasia to dysplasia, once the tissue changes to squamous cell carcinoma, there is dramatic increase in EGFR expression.

A study done in 2010 by Brenchekroun et al., to determine the prognostic significance of EGFR protein expression in oral premalignant lesions, showed that high EGFR protein expression scores were associated with higher oral cancer risk and shorter time to oral cancer progression. Few clinical trials have been undertaken for evaluating the efficacy of EGFR inhibitors for oral cancer chemoprevention. Phase 2 trial of cetuximab by Califano et al. in 2012 observed the response of premalignant lesions to cetuximab. Twenty-five percent of patients showed complete resolution of dysplasia while none of the patients under observation without active treatment showed resolution of dysplastic changes.

Erlotinib prevention of oral cancer study is the largest EGFR-targeted chemoprevention trial in HNSCC. The
objective of the study was to determine whether erlotinib can reduce oral cancer development in patients with high-risk oral premalignant lesions. The study was undertaken between 2006 and 2012. Patients who enrolled for the study were classified into high- and low-risk patients based on their loss of heterozygosity and oral cancer history. Oral erlotinib (150 mg/day) or placebo was given for 12 months. They concluded that erlotinib did not improve cancer-free survival in high-risk patients.[30]

Targeting HER1/EGFR as a therapeutic strategy against HNSCC is a rational approach substantiated by multiple lines of evidence.[28] Current strategies include mAbs and TKIs, both of which have demonstrated efficacy in HNSCC lines in preclinical models.[29] Cetuximab was approved by the FDA in March 2006, for the treatment of unresectable HNSCC in combination with radiation therapy following in Phase III HNSCC clinical trial with 424 subjects that demonstrated a significant survival benefit for HNSCC patients receiving cetuximab plus radiation therapy compared to HNSCC patients receiving radiotherapy alone.[26,31] Extensive clinical testing of cetuximab has shown this agent to be particularly useful as an adjunct to primary radiotherapy, with improvements in overall survival, progression-free survival, and duration of locoregional control versus radiation alone in the treatment of HNSCC.[20] Cetuximab has shown to sensitize HNSCC to external beam radiation, and this can lead to decreased clonogenic survival of tumor cells in vitro assays and decreased tumor growth in vivo models.[32]

Vermorken et al. in 2008 reported that when cetuximab was combined with platinum-based chemotherapy in recurrent or metastatic HNSCC, cetuximab prolonged the median progression-free survival from 3.3 to 5.6 months.[33] As a single agent, cetuximab has elicited a response rate of 13% in patients with platinum-resistant HNSCC. Panitumumab is in phase III clinical trial for the management of patients with recurrent/metastatic HNSCC. When panitumumab is combined with chemotherapy, there has been improved progression-free survival and response rate when compared to chemotherapy alone. Zalutumumab, another EGFR antibody, demonstrated better progression-free survival and response rate in recurrent/metastatic HNSCC.

The current investigation of TKIs in head and neck cancer is limited to Phase I and Phase II trials. The best studied TKIs, erlotinib and gefitinib, demonstrate modest increases in overall survival and progression-free survival in the treatment of HNSCC.[20] In a Phase II study undertaken by Soulieres et al., in patients with recurrent or metastatic HNSCC, erlotinib treatment as a single agent was associated with an objective response rate of 4.3% with a median progression-free survival of 9.6 weeks.[20] A median progression-free survival of 3.3 months was reported by Siu et al., when erlotinib was combined with cisplatin for the treatment of recurrent or metastatic HNSCC.[34] Erlotinib has a response rate of 4.3%. These cumulative results demonstrate that erlotinib has antitumor activity in HNSCC comparable to standard chemotherapy regimens.

Gefitinib, a small molecule EGFR TKI, can inhibit the proliferation of oral squamous cell carcinoma cell lines in a dose- and time-dependent manner and lead to cell-cycle arrest with accumulation of cells in the G1 phase, and a decrease of cells in the S phase.[35] Gefitinib 250 or 500 mg/day, when used as monotherapy in the recurrent/metastatic HNSCC, demonstrated a response rate of 1.4%–10.6%. Phase III trial comparing gefitinib with methotrexate reported that there was no improved survival with gefitinib. The efficacy of afatinib is comparable to cetuximab. The completed trials of EGFR-targeted therapy in HNSCC demonstrate better survival rate specially so with cetuximab.[6]

Antisense oligonucleotides, mRNA, siRNA, 2 affibodies, and nanobodies have begun to show efficacy in targeting and inhibiting EGFR. Antisense oligonucleotides consist of a stretch of a single-stranded DNA molecule of ~20 nucleotides in length. They exert their antitumor effect through binding of mRNA, sterically hindering ribosomes, and preventing translation. The ability of antisense therapy to reduce translation is illustrated by preclinical studies downregulating EGFR in HNSCC. HNSCC xenografts treated with TGF-α antisense DNA plus liposomes showed an inhibition of tumor growth when compared to controls.[36] Small interfering RNA (siRNA) strategies are emerging as potential approaches to target gene expression. siRNA consists of double-stranded RNA, containing a sequence necessary to silence the translation of a target protein. Preclinical studies using siRNA have shown that it can significantly decrease EGFR expression compared to scrambled siRNA-transfected controls, as evaluated by flow cytometry. HNSCC xenografts treated with EGFR siRNA and cisplatin revealed a significant decrease in tumor burden when compared to controls.[37] However, preclinical studies using siRNA to downregulate EGFR expression in HNSCC are limited.

Response to Targeted Therapy

Although EGFR signaling plays a critical role in tumorigenesis in a variety of tissues of origin, agents targeting EGFR are variably effective in different cancers. This presumably reflects the developmental origins of different tissues, environmental factors, and host genetic background.[38]

The outcome of targeted therapy can be any of the three as follows: dramatic response, initial response, and no response. In some other cases, an initial response is achieved with the reduction of tumor burden followed by rapid tumor relapse as a result of acquired resistance. No response to EGFR inhibition implies inherent resistance to therapy. Inherent resistance may be due to poor penetration...
of the drug to the tumor cells or due to non-dependence of tumor cells on EGFR for proliferation and survival.[31]

Despite ubiquitous EGFR expression in HNSCC tumors, only a subset of patients will respond to the EGFR-targeted therapy owing to various resistance mechanisms.[36] The mechanisms involved in acquiring resistance to therapy include as follows:
1. Overexpression of ErbB2 and ErbB3
2. Presence or activation of compensatory tumor survival cell signaling pathway
3. Mutation of EGFR.

Wheeler and colleagues generated a cetuximab-resistant HNSCC cell line in vitro and found that these cells expressed higher levels of HER2 and HER3 with EGFR.[40]

At the preclinical investigation level, ErbB2 is the most well studied in HNSCC. Overexpression of ErbB2 has also been linked to resistance to gefitinib.[37] HNSCC patient responses to EGFR-targeted monotherapies in clinical trials though significant have been limited. This is likely due to the presence or activation of compensatory tumor-survival cell signaling pathways.[20] Translocation of EGFR to the nucleus confers acquired resistance to these drugs and can be due to increase in Src family kinase (SFK) activity.[41]

A number of studies reported that the incidence of EGFR mutations in HNSCC differs between ethnic groups, ranging from 0% to 4% in whites to 7% in Asians.[20] EGFRvIII, the most frequently detected genomic variant in human malignancies, is expressed in 42% of oral tumors. EGFRvIII is formed due to the deletion of exons 2–7 from the extracellular region.[7] It is a 145-kDa protein and the amino acids 6–273 are deleted from the extracellular domain.[20] EGFRvIII is co-exhibited along with wild-type EGFR. This combination may enhance tumor growth and resistance to wild-type EGFR-targeted pharmacotherapy. EGFRvIII expression is associated with increased ability of malignant cells to migrate and invade the tissues, thus contributing to metastasis.[20] EGFRvIII can be detected in 19% of glioblastoma multiforme. The presence of EGFRvIII is a useful tumor-specific marker that is fairly specific to glioblastoma multiforme, as it has only rarely been identified in other cancers.[21,42] Missense mutations of the ATP binding cleft (p. K745R) and the tyrosine kinase domain (p. G796S) were identified in white HNSCC patients by Loeffler-Ragg and Schwentner, respectively.

Since EGFRvIII is expressed exclusively by tumor cells, targeting of EGFRvIII may offer the opportunity of tissue specificity in the treatment of HNSCC. The immunotoxin, MR-1 binds to EGFRvIII and has shown to have high specificity, potency, and no resistance in preclinical testing. A phase I trial is underway in glioma patients.[20] EGFRvIII expressing tumors have shown decreased in vitro response to cetuximab and EGFRvIII may be one of the mechanisms for resistance to EGFR-targeted therapy.

Drugs/Methods to Combat to Resistance to Targeted Therapy

Afatinib and dacomitinib, irreversible inhibitors of EGFR are currently under development. Co-1686 specifically targets EGFR T790M. AZD9291, another EGFR T790M-inhibitor, has shown promising activity in phase I trials of patients with acquired resistance through this mechanism. Midostaurin, FLT, and KIT are currently in clinical development in acute myelogenous leukemia, selectively target EGFR T790M with greater selectivity than wild-type EGFR.[22]

The combination of drugs can be used to combat resistance of cells and have been effective clinically.
1. Afatinib and cetuximab in lung cancer
2. Cetuximab and erlotinib in metastatic chemotherapy-refractory colorectal cancer.

A combination of the ErbB2-targeting agent perezumab with gefitinib increased growth inhibition in resistant HNSCC.[43] A gefitinib-trastuzumab combination was effective in increasing growth inhibition of ErbB2 positive HNSCC cell lines.[37] Trials of pan-HER inhibitors are underway in HNSCC.[39] Treatment of resistant cells with dasatinib, an inhibitor of SFK, resensitize them to cetuximab.[41]

A novel monoclonal antibody, mAb806, is active against wild-type EGFR as well as the EGFRvIII variant. mAb806 recognizes an epitope that is present in cells that overexpress wild-type EGFR and EGFRvIII.[39] However, combination strategies are associated with hurdles such as increased toxicity of drugs due to overlapping side effects and lack of efficacy in certain cancers.[22] Preventing drug resistance is better than treating drug resistance. Prevention of drug resistance can be brought about by altering the dose and schedule of the drugs. The previous studies have reported that patients responded better to TKIs after a “treatment holiday.”[44]

Conclusion

EGFR signaling pathway is part of the large signaling network involved in many oncogenic pathways. EGFR is not only essential for normal physiological activities, but it is also implicated in various cancers. EGFR is either overexpressed or mutated in most human cancers including HNSCC. Targeting EGFR has been proven to be an effective anticancer therapy, but many challenges still remain. Future studies might lead to better treatment outcomes from EGFR-targeted therapy in HNSCC.

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