Review Article

The epidermal growth factor receptor as target for cancer therapy

M. Indhumathi[1], M. P. Brundha[1], Hemavathy O. R[2*]

ABSTRACT

Human carcinomas express high levels of receptors in the epidermal growth factor (EGF) receptor family, it includes two important EGF receptors; they are EGF receptor (EGFR) and ErbB2. Function of these receptors is more useful for anticancer treatments. The monoclonal antibodies (MAbs) block the activation of EGFR and ErbB2. A humanized anti-ErbB2 is active and recently approved in combination with paclitaxel for the therapy of patients with metastatic ErbB2 over aggressive breast cancer, a chimeric anti-EGFR MAb is active in combination with radiation therapy and reverses resistance to chemotherapy.

KEY WORDS: Anticancer treatment, Carcinoma, Chemotherapy, Epidermal growth factor receptor, Monoclonal antibodies

INTRODUCTION

Epidermal growth factor (EGF) receptors are expressed about one-third of epithelial cancers, and the autocrine activation may result in various tumors. We hypothesized that blockade of the binding sites for EGF and transforming growth factor-alpha on EGF receptors (EGFR) with an antireceptor monoclonal antibody (MAb) might be an effective anticancer therapy. The most common form of EGFR were EGFRvIII, it is one in which amino acids 6–273 of the extracellular domain are deleted. This specific mutation is common in glioblastoma and several other types of cancer and has been shown to promote aggressive growth of tumors *in vivo*. The loss of part of the extracellular domain results in a receptor that has constitutive tyrosine kinase (TK) activity. The current evidence suggests that EGFRvIII has altered signaling properties compared to normal EGFR. The mutation in EGFRvIII also creates a new, cancer cell-specific epitope.[1-3] This epitope is extracellular and, therefore, represents a very promising target for antibody-directed therapeutics.[4] This review covers our current understanding of the properties of EGFRvIII, and recent developments in the characterization and therapeutic application of EGFRvIII-specific antibodies. Drugs for which this has been demonstrated include doxorubicin, paclitaxel, cisplatin, and topotecan. Antibody treatment also potentiated the responsiveness of human tumor xenografts to radiation therapy.[5]

Access this article online	
Website: jprsolutions.info	ISSN: 0975-7619

Therapeutic Inhibitors for Cancer Therapy

The cancer therapeutics field has taken several innovative approaches in an effort to develop effective EGFR inhibitors for cancer treatment. Recognizing a central role of EGFR intracellular proliferation and differentiation, Mendelsohn and colleagues (MoAbs) purified a series of MAbs against the EGFR in the early 1980s to test these agents as inhibitors of tumor growth (Sato *et al*., 1983). This dominant approach has been adopted by the pharmaceutical industry and has since prompted clinical development of a broad spectrum of EGFR inhibitors for testing in cancer therapy. Different approaches to inhibit EGFR have resulted in a number of EGFR-targeted agents in clinical development including small-molecule EGFR-TK inhibitors (TKIs), mAbs, vaccines, immune toxins, antisense oligonucleotides, and recombinant ligand-toxin fusion proteins. MoAbs block ligand from binding to the extracellular domain of the receptor, whereas TKIs target the ATP-binding

[1]Department of General Pathology, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India, [2]Department of Oral and Maxillofacial Surgery, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India

***Corresponding author:** O.R. Hemavathy, Department of Oral and Maxillofacial Surgery, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, 162, Poonamallee High Road, Chennai - 600077, Tamil Nadu, India. Phone: +91-9626033600. E-mail: hemadocmd@gmail.com

Received on: 21-07-2018; Revised on: 23-08-2018; Accepted on: 29-09-2018

pocket of the cytoplasmic domain to inhibit receptor phosphorylation.[6] To date, the FDA has approved only two MoAbs for clinical use, cetuximab and panitumumab and two TKIs, erlotinib and gefitinib (Sato *et al*., 1983). Most of the EGFR inhibitors that are in clinical trials are based on a quinazoline-type scaffold. The first EGFR-TKI to be approved in the United States in 2003 was gefitinib (Iressa). It was approved for use in metastatic non-small-cell lung cancer (NSCLC) after the failure of a platinum-based regimen of chemotherapy, based on Phase II data showing some good responses. However, gefitinib was removed from the market in 2004 based on Phase III data that showed that gefitinib did not show a statistically significant survival over placebo in all-comers with NSCLC. The drug can now only be used in patients who have shown clinical or radiographic benefit from the drug in the past.[7] Erlotinib (Tarceva) is also an EGFR-TKI approved for the second- or third-line use after the failure of a platinum-based chemotherapy regimen in metastatic NSCLC. This received approval in 2004 based on the BR21 trial, showing a modest benefit when used in patients with NSCLC. Patients on erlotinib had a 6.7-month average survival, while only 4.7 months on placebo. At the initiation of the BR21 trial, there was no FDA approved standard treatment for the second- or third-line treatment of NSCLC, and therefore, a placebo control arm was necessary and ethical. The study was randomized at a 2:1 ratio, in favor of receiving the drug based on the idea that the drug did show responses in Phase II studies. Furthermore, notable about the BR21 trial is that it allowed for patients with an ECOG (Lichtner *et al*., 2001). A variety of different approaches are currently being used to target the EGFR. The most promising strategies in clinical development include MAbs to prevent ligand binding and small-molecule inhibitors of the TK enzymatic activity to inhibit autophosphorylation and downstream intracellular signaling.[8] At least five blocking MAbs have been developed against the EGFR. The receptor IMC-225 is a chimeric human-mouse monoclonal IgG1 antibody was the first anti-EGFR targeted therapy to enter clinical evaluation incancer patients in Phase II and III studies, alone or incombination with conventional therapies, such as radiotherapyand chemotherapy. A number of small-molecule inhibitors of EGFR tyrosine kinase enzymatic activity were also in development. OSI-774 and ZD1839 (Iressa) are currently in Phase II and III development, respectively. ZD1839, a p.o. active, selective quinazoline derivative has demonstrated promising *in vitro* and *in vivo* antitumor activity.[9] Preliminary results from Phase I and II trials in patients with advanced disease demonstrate that ZD1839 and OSI-774 have an acceptable tolerability profile and promising clinical efficacy in patients with a variety of tumor types (Lichtner *et al*., 2001).

Strategies Targeting EGFR Pathway

Four strategies for targeting the EGFR are at different stages of development. These include (1) MAbs against the EGFR (Sato *et al*., 1983), (2) inhibition of the receptor tyrosine kinase (RTK) domain (Lichtner *et al*., 2001), (3) inhibition of receptor trafficking to the cell membrane (Yamazaki *et al*., 1998), and (4) inhibition of EGFR synthesis through antisense oligonucleotides (Ciardiello *et al*., 2001b). Only the MAb and RTK inhibitor class of agents have been evaluated through Phase III trials.

MAbs

MAbs bind to the extracellular domain of the EGFR and inhibit ligand binding to the receptor (Sato *et al*., 1983).[10] After binding to the EGFR, the MAbs induce receptor dimerization and downregulation. Cetuximab (IMC-C225, Erbitux Im Clone Systems Inc., New York, NY, USA), ABX-EGF (Abgenics, San Francisco, CA, USA), and EMD 72000 are MAbs directed against the EGFR that is currently in clinical trials. Another class of MAbs consists of bispecific antibodies that can bind the EGFR and an immunologic effector cell (Negri *et al*., 1995; Tosi *et al*., 1995; Curnow, 1997). Examples of this class of agents include M26.1, MDX-447, and H22-EGF. These agents have shown promising activity in early clinical trials (Negri *et al*., 1995; Tosi *et al*., 1995; Curnow, 1997).

Receptor Tyrosine Kinase Inhibitors

Receptor tyrosine kinase inhibitors compete with ATP for the intracellular catalytic site of the EGFR. In contrast to the MAbs, this class of agents does not downregulate the EGFR.[11] Receptor tyrosine kinase inhibitors differ with respect to reversibility of inhibition and specificity to the EGFR versus the other ErbB receptors. Based on these differences, four different classes of RTK inhibitors can be identified and these include (1) reversible EGFR inhibitors (e.g., gefitinib and erlotinib), (2) irreversible EGFR inhibitors (e.g., EKB-569), (3) reversible dual ErbB inhibitors (e.g., GW2016), and (4) irreversible pan-ErbB inhibitors (e.g. CI-1033) (Mendelsohn and Baselga, 2003).

Comparison of MAb and RTK Compounds

Both these classes of agents result in downregulation of the MAPK, PI3K/Akt, and Jak/Stat signal transduction pathways (Bruns *et al*., 2000; Albanell *et al*., 2001).[12] MAbs also downregulate EGFR expression, while RTKs inhibit receptor phosphorylation without affecting expression. At the cellular level, EGFR inhibitors result in cell cycle arrest at the G1 phase (Wu *et al*., 1995; Busse *et al*., 2000), decrease tumour neovascularization by downregulating expression of angiogenic mediators such as vascular endothelial

growth factor (Perrotte *et al*., 1999; Ciardiello *et al*., 2001a), and promote apoptosis (Moyer *et al*., 1997; Liu *et al*., 2000). While MAbs require an intact EGFR ligand-binding domain to be active, the RTK inhibitors are active against mutated forms of the EGFR. At the clinical level, several differences between RTK inhibitors and MAbs exist.[13] The RTK compounds are orally administered while the MAbs require intravenous administration. While both classes of agents are associated with acneiform rash (Baselga *et al*., 2000, 2002), only RTK inhibitors have been associated with gastrointestinal toxicity (Baselga *et al*., 2002; Herbst *et al*., 2002). The preliminary results of clinical trials also suggest different disease-specific activity for each class of agents. For example, cetuximab (Saltz *et al*., 2001a, 2002) and EMD 72000 (Tewes *et al*., 2002) are both active in colorectal cancer, in contrast.[14]

Role of EGFR Receptor in Early Stage Disease

EGFR inhibitors have demonstrated significant activity in patients with metastatic NSCLC, who have failed cytotoxic chemotherapy.[15] These results raise the possibility of a role for EGFR inhibitors in locally advanced NSCLC. At present, SWOG is conducting a randomized trial in patients with Stage III NSCLC.[16] Patients enrolled in this study will receive definitive chemoradiotherapy, followed by docetaxel with subsequent randomization to either gefitinib or placebo. The low incidence of toxicity associated with the EGFR inhibitors has also raised the possibility of a potential role for these agents in the adjuvant

setting. SWOG is currently conducting a Phase III trial randomizing patients with Stages I and II NSCLC to either gefitinib or placebo after resection.[17] The results of these trials will help define the role of targeted agents after definitive treatment of early stage and locally advanced NSCLC.

CONCLUSION

EGFR family plays an important role in cell linkage determination, the morphogenesis of many organs and in cell survival in the adult follows ERK/MAP kinase pathway, STAT3 pathway, PI3 kinase/AKT signaling pathway, and p38 stress pathway. The past studies shows that ErbB receptors play a pivotal role in cell transformation and progression of many carcinomas including breast, ovarian, renal, NSCLC, head and neck, colorectal, pancreas, brain (glioma), bladder, esophagus, stomach, prostate, melanoma, thyroid, and endometrial cancers, thereby been a major focal point in cancer drug discovery.[18] Till now, two predominant classes of EGFR inhibitors have been developed including monoclonal antibodies that target the extracellular domain of EGFR such as cetuximab and small-molecule TKIs that target the receptor catalytic domain of EGFR which shows clear antitumor activity, and cetuximab and gefitinib have been recently FDA approved for colorectal and lung cancer indications, respectively.[19,20] To date, the FDA has approved only two MAbs for clinical use, cetuximab and panitumumab; two TKIs, erlotinib and gefitinib as EGFR inhibitors.[21] Results from newly reported Phase III trials in 2004 now confirm a survival advantage for the use of EGFR inhibitors in combination with high-dose radiation in head and neck cancer and refractory lung cancer, respectively. It appears likely that EGFR inhibitors (and other rationally designed molecular growth inhibitors) will play a meaningful role in cancer therapy in the years to come.[22,23]

REFERENCES

1. Pawson T. Regulation and targets of receptor tyrosine kinases. Eur J Cancer 2002;38 Suppl 5:S3-10.
2. Arteaga CL. The epidermal growth factor receptor: From mutant oncogene in nonhuman cancers to therapeutic target in human neoplasia. J Clin Oncol 2001;19:32S-40S.
3. Arora A, Scholar EM. Role of tyrosine kinase inhibitors in cancer therapy. J Pharmacol Exp Ther 2005;315:971-9.
4. Paul MK, Mukhopadhyay AK. Tyrosine kinase-role and significance in cancer. Int J Med Sci 2004;1:101-15.
5. Yarden Y. The EGFR family and its ligands in human cancer. Signalling mechanisms and therapeutic opportunities. Eur J Cancer 2001;37 Suppl 4:S3-8.
6. Jorissen RN, Walker F, Pouliot N, Garrett TP, Ward CW, Burgess AW, *et al*. Epidermal growth factor receptor: Mechanisms of activation and signalling. Exp Cell Res 2003;284:31-53.
7. Nair P. Epidermal growth factor receptor family and its role incancer progression. Curr Sci 2005;88:890-8.
8. Bates SE, Fojo T. Epidermal growth factor receptor inhibitors: A moving target? Clin Cancer Res 2005;11:7203-5.
9. Riese DJ, Komurasaki T, Plowman GD, Stern DF. Activation ofErbB4 by the bifunctional epidermal growth factor family hormoneepiregulin is regulated by ErbB2. J Biol Chem 2010;273:11288-94.
10. Dutta PR, Maity A. Cellular responses to EGFR inhibitors and their relevance to cancer therapy. Cancer Lett 2007;254:165-77.
11. Schlessinger J. Ligand-induced, receptor-mediated dimerization and activation of EGF receptor. Cell 2002;110:669-72.
12. Tanner KG, Kyte J. Dimerization of the extracellular domain of the receptor for epidermal growth factor containing the membrane-spanning segment in response to treatment with epidermal growth factor. J Biol Chem 1999;274:35985-90.
13. Bargmann CI, Hung MC, Weinberg RA. Multiple independent activations of the neu oncogene by a point mutation altering the transmembrane domain of p185. Cell 1986;45:649-57.
14. Bennasroune A, Fickova M, Gardin A, Dirrig-Grosch S, Aunis D, Crémel G, *et al*. Transmembrane peptides as inhibitors of erbB receptor signaling. Mol Biol Cell 2004;15:3464-74.
15. Bell CA, Tynan JA, Hart KC, Meyer AN, Robertson SC, Donoghue DJ, *et al*. Rotational coupling of the transmembrane and kinase domains of the neu receptor tyrosine kinase. Mol Biol Cell 2000;11:3589-99.
16. Harari PM. Epidermal growth factor receptor inhibition strategies in oncology. Endocr Relat Cancer 2004;11:689-708.
17. Shah MS, Gayathri R, Priya VV. Treating oral cancer by targeting humanepidermal growth factor. Int J Pharm Sci Rev Res 2017;47:7-9.
18. Normanno N, De Luca A, Bianco C, Strizzi L, Mancino M,

Maiello MR, *et al*. Epidermal growth factor receptor (EGFR) signaling in cancer. Gene 2006;366:2-16.
19. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-39.
21. Maheshwari TN. Salivary biomarkers in oral leukoplakia-a review. Int J Pharm Bio Sci 2015;6:999-1004.
22. Grandis JR, Tweardy DJ. Elevated levels of transforming growth factor alpha and epidermal growth factor receptor messenger RNA are early markers of carcinogenesis in head and neck cancer. Cancer Res 1993;53:3579-84.
20. Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, *et al.* EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. Science 2004;304:1497-500.
23. Pawson T. Protein modules and signalling networks. Nature 1995;373:573-80.

Source of support: Nil; Conflict of interest: None Declared