Biomaterials xxx (2013) 1–18

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

Review

Epidermal growth factor receptor targeting in cancer: A review of trends and strategies

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ARTICLE INFO

Article history:
Received 4 June 2013
Accepted 28 July 2013
Available online xxx

Keywords:
EGFR
Monoclonal antibodies
Tyrosine kinase inhibitors
Immunoconjugates
Antisense oligonucleotides
Cancer

ABSTRACT

The epidermal growth factor receptor (EGFR) is a cell-surface receptor belonging to ErbB family of tyrosine kinase and it plays a vital role in the regulation of cell proliferation, survival and differentiation. However; EGFR is aberrantly activated by various mechanisms like receptor overexpression, mutation, ligand-dependent receptor dimerization, ligand-independent activation and is associated with development of variety of tumors. Therefore, specific EGFR inhibition is one of the key targets for cancer therapy. Two major approaches have been developed and demonstrated benefits in clinical trials for targeting EGFR; monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs). EGFR inhibitors like, cetuximab, panitumumab, etc. (mAbs) and gefitinib, erlotinib, lapatinib, etc. (TKIs) are now commercially available for treatment of variety of cancers. Recently, many other agents like peptides, nanobodies, affibodies and antisense oligonucleotide have also shown better efficacy in targeting and inhibiting EGFR. Now a days, efforts are being focused to identify molecular markers that can predict patients more likely to respond to anti-EGFR therapy; to find out combinatorial approaches with EGFR inhibitors and to bring new therapeutic agents with clinical efficacy. In this review we have outlined the role of EGFR in cancer, different types of EGFR inhibitors, preclinical and clinical status of EGFR inhibitors as well as summarized the recent efforts made in the field of molecular EGFR targeting.

1. Introduction

The epidermal growth factor receptors (EGFR)/Her1/ErbB1 are the cell-surface receptors belonging to ErbB family of tyrosine kinase and they have been of much attention for the molecular targeting of cancer therapeutics owing to their abnormal expression in many epithelial tumors and their influence on the growth and survival in malignant states [1]. Advances in genetic engineering and understanding of the EGFR signaling pathways in cancer have led to the development of many therapeutic agents including monoclonal antibodies (mAbs), small-molecule tyrosine kinase inhibitors (TKIs), antisense oligonucleotides, antibody based immunoconjugates and other agents like FR-18, peptides, affibodies, nanobodies, etc.

mAbs bind to the extracellular domain of EGFR and compete with endogenous ligands to inhibit the ligand-induced EGFR tyrosine kinase activation by blocking the ligand-binding region [2,3]. Cetuximab and panitumumab are the two most advanced mAbs targeting the extracellular domain of the EGFR. Cetuximab (Erbitux), approved in February 2004 by United States Food and Drug Administration (USFDA), is a chimeric (mouse/human) monoclonal antibody for intravenous infusion for the treatment of metastatic colorectal and head/neck cancer [4]. On the other hand Panitumumab (Vectibix), manufactured by Amgen, is a fully human mAb specific to EGFR approved in September 2006 by USFDA for metastatic colorectal cancer. Panitumumab is the first mAb to demonstrate the use of KRAS (Kristen RAS) as a predictive biomarker and it was further approved by the European Medicines Agency in 2007 and by Health Canada in 2008 for the treatment of refractory EGFR-expressing metastatic colorectal cancer in patients with wild-type KRAS. Later in July 2009 USFDA approved Erbitux for treatment of KRAS wild-type (non-mutated) colon cancer.

Second class of agents targeting EGFR are TKIs which have a partially different activity profile than mAbs as they act in intracellular domain to inhibit enzyme tyrosine kinase which is responsible for signal transduction cascade and downstream activation of many proteins [3]. USFDA approved TKIs include gefitinib (Iressa) in 2003 for the treatment of patients with advanced or metastatic non-small cell lung cancer (NSCLC); erlotinib (Tarceva)

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0142-9612/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.biomaterials.2013.07.100

in 2004 for locally advanced or metastatic NSCLC and in combination with gemcitabine for locally advanced or metastatic pancreatic cancer and lapatinib (Tykerb) in 2007 in combination with capecitabine for the treatment of patients with advanced or metastatic Her2-overexpressing breast cancer patients who have received prior treatment with an anthracycline, a taxane, and trastuzumab. Remaining EGFR inhibitors like antisense oligonucleotides, antibody based immunoconjugates, agents like FR-18, peptides, affibodies and nanobodies are under preclinical and clinical investigations.

Recently, mutations and amplification of the EGFR gene have been identified and are implicated in development of resistance against mAbs and TKIs [5]. To address these problems, broader acting inhibitors like dual EGFR HER2 inhibitors, combined anti-pan-ErbB and vascular endothelial growth factor receptor inhibitors are under development. Current research focus is directed towards the selection of optimal dose regimen for particular cancer therapy, to identify molecular markers that can predict patients more likely to respond to anti-EGFR therapy, to find out combinatorial approaches with anti-EGFR agents and to bring new therapeutic agents with better clinical efficacy. In conclusion, there is a need of improved strategies to integrate anti-EGFR agents with traditional therapies to explore better approaches for inhibition of receptor-downstream signal transduction and targeted approaches interfering with other essential drivers of cancer, such as angiogenesis. With consideration of above facets, more attention has been given in this review to the role of EGFR in cancer, different types of EGFR inhibitors, preclinical and clinical status of EGFR inhibitors for different types of cancer, resistance development to EGFR inhibitors and strategies for the prevention of same.

1.1. Biochemical and structural characterization of EGFR

EGFR is a 170 kDa protein containing approximately 20% of carbohydrate of its molecular mass and is heavily N-glycosylated [6]. Glycosylation is important in case of protein–protein interactions that occur between protein ligand and their cognate receptors, because it plays a role in determining protein structure and known to affect the three-dimensional configuration of proteins. Eight of the eleven canonical N-linked sites of the receptor are glycosylated with two sites unglycosylated and one site glycosylated in a fraction as observed by mass spectrometry characterization in A431 cell line [7]. The extracellular region of EGFR is divided into four domains; Domain I, II, III and IV (DI, DII, DIII and DIV). DI and DIII are the members of the leucine rich repeat family, and hence termed L1 and L2. They are similar to the domains found in the insulin receptor family [8]. Both DI and DIII contribute to ligand binding [9]. However, most of the binding energy is contributed by DIII alone, having affinity approximately 400 nM for EGF [10]. DII and DIV are similar to those in laminin, containing multiple small disulfide-bonded modules and are called cysteine-rich domains [11]. Both monomer and dimer forms of the EGFR ectodomain have been crystallized [12]; monomer exists in a tethered, closed and autoinhibited state [13], while dimer exists in an untethered open or extended conformation. Although most cytokine receptors dimerize through the ligands spanning the two receptor monomers [14], all the dimerization contact in the EGFR dimer are full receptor mediated. The dimer exists in receptor to ligand ratio of 2:3, with multiple contacts through the DII dimerization arm. In dimer structures, DIV was either unresolved or not present in the crystallized protein Ref. [15].

The binding of ligand occurs between DI and DIII allowing the formation of dimer which stabilizes the extended conformation, exposing the DII dimerization arm and other residues. However, it was demonstrated through mutations and deletion of DIV that the breaking of the tether is necessary but not sufficient for dimer formation [15–17]. It also seems that certain types of receptor glycosylation can shift the equilibrium towards the extended form [18,19] and subsequently it has been found that the DII-DIV tether interaction is not necessarily responsible for maintaining the receptor in the autoinhibited conformation. In fact mutating every interaction in soluble EGFR still leads to an autoinhibited conformation [20]. Fig. 1 schematically shows the EGFR conformation and ligand-based activation. Ectodomain crystal structure is also available for other EGFR family members, Her2, Her3 and Her4. The Her2 monomer adopts an extended conformation in contrast to EGFR monomer which is similar to that of EGFR in the dimer structure. Her2 is extended and poised to interact with other ErbB

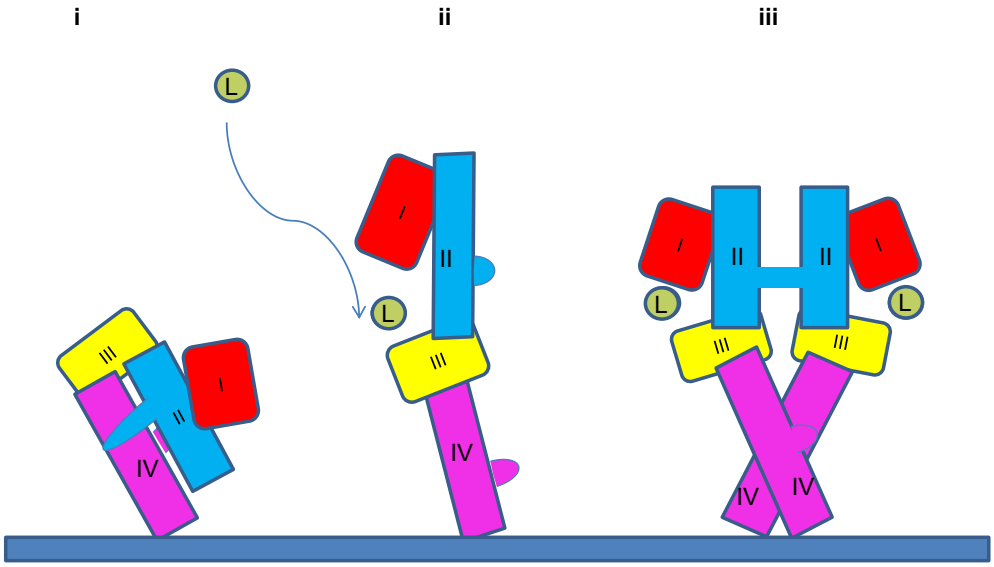

Fig. 1. EGFR conformation and ligand-based activation. The extracellular domain of ErbB receptor consisting of four domains. Showing the unligated receptor form in an autoinhibited or tethered conformation, in which the dimerization arm of domain II buried into domain IV. Ligand (L = EGF) binding to domains I and III induces the spatial rearrangement of these domains, forming an extended and stabilized conformation of the entire ectodomain. Consequent exposure of dimerization arm in domain II, to form the core of the dimer interface with another receptor.

Please cite this article in press as: Yewale C, et al., Epidermal growth factor receptor targeting in cancer: A review of trends and strategies, Biomaterials (2013), http://dx.doi.org/10.1016/j.biomaterials.2013.07.100