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Review

Mechanisms for oncogenic activation of the epidermal growth factor receptor

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Abstract

The Epidermal growth factor receptor (EGFR) is a membrane spanning glycoprotein, which frequently has been implicated in various cancer types. The mechanisms by which EGFR becomes oncogenic are numerous and are often specific for each cancer type. In some tumors, EGFR is activated by autocrine/paracrine growth factor loops, whereas in others activating mutations promote EGFR signaling. Overexpression and/or amplification of the EGFR gene are prevalent in many cancer types leading to aberrant EGFR signaling. In addition, failure to attenuate receptor signaling by receptor downregulation can also lead to cellular transformation. Heterodimerization of EGFR with ErbB2 inhibits downregulation of EGFR and thereby prolongs growth factor signaling. This also indicates that cross-talk between EGFR and heterologous receptor systems serves as another mechanism for oncogenic activation of EGFR.

Because of its role in tumor promotion, the EGFR has been intensely studied as a therapeutic target. There are currently two major mechanisms by which the EGFR is targeted: antibodies binding to the extracellular domain of EGFR and small-molecule tyrosine-kinase inhibitors. However, tumorigenesis is a multi-step process involving several mutations, which might explain why EGFR therapeutics has only been partially successful. This highlights the importance of pinpointing the mechanisms by which EGFR becomes oncogenic in a particular cancer. In this review, each of the above mentioned mechanisms will be discussed, as a detailed molecular and genetic understanding of how EGFR contributes to the malignant phenotype might offer new promise for the design, development and clinical evaluation of future tumor-specific anticancer approaches.

Keywords: EGFR; Cancer; Mechanism; Oncogenesis; Mutation; Transactivation; Signaling; Downregulation

Contents

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1. Introduction

Carcinogenesis is a multi-step process that requires the accumulation of several genetic alterations in a single cell. Among numerous factors, carcinogenesis involves the activation of oncogenes such as the epidermal growth factor receptor (EGFR), also known as ErbB1/HER1. EGFR is a receptor tyrosine kinase (RTK) that is catalytically active and under tight regulatory control. This receptor belongs to the ErbB/HER family of ligand-activated RTKs, which in addition include ErbB2/Neu/HER2, ErbB3/HER3 and ErbB4/HER4 [1]. EGFR and its family members play essential roles in regulating a number of cellular processes including cell proliferation, survival and migration [2]. Dysregulation of their activity is therefore strongly associated with tumorigenesis, which classifies them as some of the most frequent implicated cell-surface markers of human cancer [3].

The involvement of increased and/or aberrant EGFR activity in human cancers is well documented [4–6] and cancer patients with altered EGFR activity tend to have a more aggressive disease, associated with a poor clinical outcome [1]. Therefore, EGFR is a rational target for anti-tumor strategies. There is a range of mechanisms leading to dysregulated EGFR activity and it is important to know which one is prevalent in a particular tumor in order to give the patients the most appropriate treatment.

Since the vast majority of reviews largely focus on anti-EGFR agents and their clinical outcome, this review will mainly focus on the mechanisms by which EGFR becomes oncogenic and briefly summarize some of the clinical approaches currently used to target tumors with aberrant EGFR activation. A detailed molecular and genetic understanding of how EGFR contributes to the malignant phenotype is important for future design and development of tumor-specific anticancer approaches.

2. EGFR: structure and regulation of activity

The EGFR is a highly glycosylated 170 kDa membrane spanning protein, which consists of a single polypeptide chain of 1186 amino acids [7–9]. Like all RTKs, the EGFR is characterized by three main domains: an extracellular ligand-binding domain, a transmembrane domain and a cytoplasmic domain containing the tyrosine kinase (Fig. 1A) [1,10]. The extracellular domain of the EGFR can be further divided into four subdomains designated I, II, III and IV (Fig. 1A). Crystallographic studies of the EGFR extracellular domain in complex with its ligands have shown that the domains I, II and III form a ligand-binding pocket, wherein ligands bind (Fig. 1A) [7,11].

EGFR can bind several ligands including epidermal growth factor (EGF), transforming growth factor-α (TGF-α), betacellulin (BTC), epiregulin (EPR), heparin-binding EGF like growth factor (HB-EGF) and amphiregulin (AR) [2]. In the absence of ligand, EGFR exist as monomers on the cell surface. Binding of ligand to EGFR leads to the formation of receptor homo- and heterodimers, depending on whether EGFR dimerizes with another EGFR or with other ErbB family members, respectively

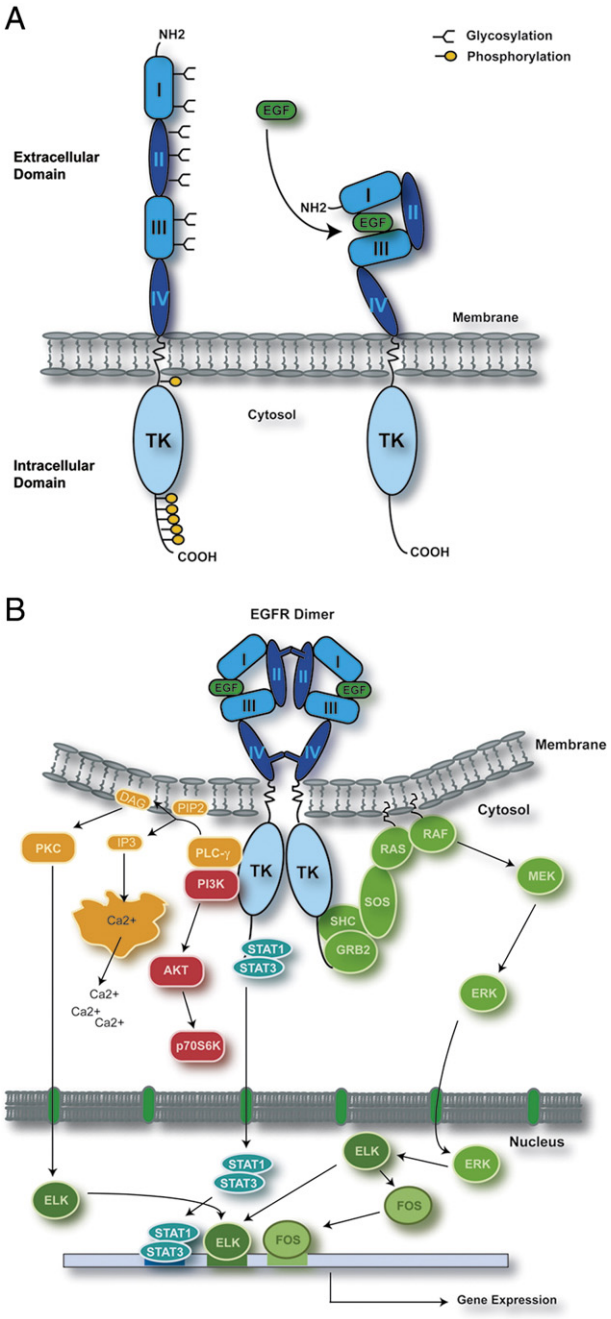

Fig. 1. EGFR Structure and Signaling. A) EGFR is a highly glycosylated membrane spanning protein, which consists of three main domains: an extracellular domain, a transmembrane domain and an intracellular domain containing the tyrosine kinase (TK). The extracellular domain is composed of four subdomains designated I, II, III and IV. The domains I, II and III form a ligand-binding pocket, where a ligand is docked between the domains I and III. B) Binding of ligand to EGFR leads to receptor dimerization, autophosphorylation and activation of several downstream signaling pathways. Only selected pathways and transcription factors are presented.

[2,12]. Ligand induced EGFR dimerization leads to autophosphorylation of several key tyrosine residues in the cytoplasmic domain of each receptor monomer [8,13]. These phosphorylated tyrosine residues then serve as binding sites for a number of adapter and signaling molecules leading to the activation of