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# Nuclear Mode of the EGFR Signaling Network: Biology, Prognostic Value, and Therapeutic Implications

**Hui-Wen Lo, Ph.D.**
Division of Surgical Sciences, Department of Surgery, Duke University School of Medicine, Durham, North Carolina 27710, USA

## Abstract

Epidermal growth factor receptor (EGFR) belongs to a large family of receptor tyrosine kinases that mediates many important physiological processes in both normal and cancerous cells. EGFR is best known for its classical role as a plasma membrane-bound receptor that, upon binding to its ligands, recruits and phosphorylates downstream molecules which subsequently regulate protein functions, protein-protein interactions, and gene expression. Built upon this traditional view of the EGFR pathway, a number of therapeutic agents have been developed aiming to target EGFR by blocking ligand-mediated receptor activation or by inhibiting its kinase activity. Unfortunately, most of these interventions have yielded disappointing clinical results in the majority of cancer types evaluated, with the exception of non-small cell lung cancer that carries specific EGFR mutants. Given the notion that these EGFR mutations are absent or very rare in other cancer types, extensive investigations have been directed at other potential mechanisms. Some of these efforts have led to rationales for EGFR-based combination regimens; however, they also demonstrated limited clinical benefits. In this review, we will focus on an emerging line of research that examines a novel mode of EGFR signaling that takes place in the cell nucleus. Specifically, we will outline the findings from a number of reports that have together established nuclear EGFR to be a functionally diversified molecule that regulates the biology of normal and malignantly transformed cells. In light of the fact that the impact of nuclear EGFR on anticancer therapy has recently developed into an area of intensive investigations, this review will also summarize the results of these investigations that suggest a potential role the nuclear EGFR may play in tumor response to radiation, chemotherapy, and EGFR-targeted therapy.

## Introduction

EGFR plays a central role in the tumorigenesis and malignancy biology of many human cancers (Lo, 2010; Lo et al., 2006b; Yarden et al., 2007). In cancer, EGFR is frequently mutated, activated, and over-expressed, and is linked to aggressive biology of the tumors (Lo et al., 2007; Lo et al., 2008). EGFR is also associated with tumor therapeutic resistance and poor clinical outcome of cancer patients (Arteaga et al., 2004; Lo, 2010; Zhu et al., 2010). Consequently, EGFR is an important target of anti-cancer therapy. To date, five EGFR-targeted agents have been approved by the FDA for treating cancer patients, of which three are small molecule inhibitors and two are antibodies. Gefitinib (ZD1839, Iressa), a small molecular weight EGFR kinase inhibitor, is being used for locally advanced and metastatic non-small cell lung cancer (NSCLC). Another small molecule EGFR kinase inhibitor, Erlotinib (OSI-774, Tarceva), was approved to treat metastatic NSCLC as single agent and to be used in combination with gemcitabine for pancreatic cancer that cannot be


huiwen.lo@duke.edu.

removed by surgery or has metastasized. Lapatinib (GW572016, Tykerb/Tyverb) is an EGFR/HER2-dual targeting small molecule inhibitor that is used, in combination with other drugs, for patients with advanced or metastatic breast cancer whose cancer is HER2 positive and has failed to respond to other drugs (Moy et al., 2007). Cetuximab (C225, Erbitux) is a humanized monoclonal antibody that recognizes the extracellular domain of both EGFR (Moy et al., 2007) and EGFRvIII (Patel et al., 2007). It has been approved for squamous cell carcinoma of the head and neck that has metastasized or recurred after chemotherapy and as a first-line treatment with radiation therapy for advanced squamous cell carcinoma of the head and neck. Cetuximab is also used for treating metastatic colorectal cancer that has metastasized, after chemotherapy has failed and, in combination with irinotecan, for metastatic colorectal cancer patients who have not responded to irinotecan alone. Another human monoclonal antibody Panitumumab (ABX-EGF, Vectibix) has been approved to treat colorectal cancer that has failed other therapies and has metastasized (Rivera et al., 2008).

EGFR-targeted therapy has demonstrated only modest effects on most cancer types (Reardon et al., 2009; van den Bent et al., 2009), with the exception of NSCLC that expresses gain-of-function mutants of EGFR (Lynch et al., 2004; Mitsudomi et al., 2010; Mok et al., 2009; Paez et al., 2004). However, the lung cancer-associated EGFR mutations are either absent or very rare in other tumor types. Consequently, the mechanisms underlying tumor resistance to anti-EGFR agents are still under extensive investigations. Several mechanisms, including one involving the loss of phosphatase and tenson homolog (PTEN), have been shown to play a role in resistance to EGFR-targeted therapy (Guillamo et al., 2009; Mellinghoff et al., 2007); however, the results have been mixed and inconclusive (Reardon et al., 2009; Thiessen et al., 2009). Interestingly, emerging evidence suggests that nuclear EGFR, a result of either constitutive presence or treatment-induced nuclear translocation, may play a role in the therapy-resistant phenotype (Carpenter et al., 2009). For example, nuclear EGFR has been shown to associate with tumor resistance to radiation therapy (Dittmann et al., 2005a; Wanner et al., 2008) and to EGFR-targeted therapeutic antibodies (Li et al., 2009). Given the facts that the nature of the nuclear EGFR pathway is still not well understood and that its role in cancer drug resistance remains unclear, this review will summarize our current knowledge of the nuclear EGFR pathway and also provide a timely outline on its impact on tumor response to anti-cancer therapy.

## Discovery and Biological Properties

The presence of EGFR in cell nuclei was first detected in regenerating livers (Marti et al., 1991) and later in placenta (Lin et al., 2001), keratinocytes (Lo et al., 2005a), thyroid (Marti et al., 2001) and in a variety of cancerous cells and tissues (Cordero et al., 2002; de la Iglesia et al., 2008; Hanada et al., 2006; Lin et al., 2001; Lo et al., 2005c; Lo et al., 2006a; Lo et al., 2010; Psyrri et al., 2005; Xia et al., 2009). Nuclear EGFR has been detected in glioma (de la Iglesia et al., 2008; Lo et al., 2010) and cancers of the breast (Lo et al., 2005a; Lo et al., 2005c), epidermoid (Hanada et al., 2006; Kim et al., 2007), bladder (Kim et al., 2007), ovary (Xia et al., 2009), and oral cavity (Lo et al., 2005c; Psyrri et al., 2005). More recent studies also reported that the constitutively activated EGFR variant, EGFRvIII, is present in the nuclei of glial cells (de la Iglesia et al., 2008) and glioblastoma (de la Iglesia et al., 2008; Lo et al., 2010). In addition to the nucleoplasm (Liao et al., 2007; Lin et al., 2001; Lo et al., 2005a; Lo et al., 2006a), nuclear EGFR can also be localized on the inner nuclear membrane (Cao et al., 1995; Klein et al., 2004).

Evidence to date indicates that EGFR has three key nuclear functions (Figure 1): (1) gene regulation (Hanada et al., 2006; Hung et al., 2008; Lin et al., 2001; Lo et al., 2005c; Lo et al., 2010), (2) kinase function leading to tyrosine phosphorylation of target proteins (Wang et al., 2006), and (3) protein-protein interactions leading to DNA repair (Dittmann et al.,

2005a; Dittmann et al., 2005b). As a transcription co-factor with a functional transactivation domain (Lin et al., 2001), nuclear EGFR activates expression of a number of genes, including cyclin D1 (Lin et al., 2001), inducible nitric oxide synthase (iNOS) (Lo et al., 2005a), B-Myb (Hanada et al., 2006), aurora A (Hung et al., 2008), and cyclooxygenase-2 (COX-2) (Lo et al., 2010). Consistent with the fact that EGFR lacks a DNA-binding domain, nuclear EGFR interacts with DNA-binding transcription factors to activate gene transcription. In this context, nuclear EGFR cooperates with signal transducer and activator of transcription-3 (STAT3) to upregulate expression of iNOS (Lo et al., 2005a) and COX-2 (Lo et al., 2010) genes, with E2F1 to activate B-Myb gene expression (Hanada et al., 2006), and with STAT5 to enhance aurora A gene expression (Hung et al., 2008). Our recent study (Lo et al., 2010) using a systemic unbiased approach has identified additional candidates as nuclear EGFR target genes that can potentially be up- or down-regulated by nuclear EGFR. Ongoing investigations are conducted to validate whether these candidate genes are indeed regulated by nuclear EGFR and the outcome could shed new light on the physiological and pathological functions of nuclear EGFR that is still not well understood. Another mechanism underlying nuclear EGFR-mediated gene regulation could be attributed to its interaction with mucin 1 (MUC1) (Bitler et al., 2010). This interaction may promote the accumulation of chromatin-bound EGFR and significant co-localization of EGFR with phosphorylated RNA polymerase II.

In addition to transcriptional regulation, nuclear EGFR retains its tyrosine kinase activity and phosphorylates proliferating cell nuclear antigen (PCNA) to promote cell proliferation and DNA repair (Wang et al., 2006). Chromatin-bound PCNA protein is phosphorylated on the Tyr211 amino acid residue by nuclear EGFR, leading to increased PCNA stability. This important finding raised the possibility that additional nuclear proteins may be phosphorylated by nuclear EGFR and their functions, stability, and/or subcellular localization altered as a consequence of tyrosine phosphorylation. Future efforts are needed to explore this possibility. Furthermore, nuclear EGFR also plays a role in DNA repair following radiation therapy (Dittmann et al., 2005a; Dittmann et al., 2005b). Since this has been an active area of cancer research, an entire section is dedicated to summarizing findings in this field and is included in a later part of this review.

## Nuclear EGFR: Indicator for Poor Clinical Outcome of Cancer Patients

While the functional aspects of nuclear EGFR are still under intense investigations, several studies involving primary patient tumors suggest that nuclear EGFR may serve as a prognostic indicator for poor clinical outcome. Using a cohort of 130 breast carcinomas and immunohistochemical analyses, we showed for the first time that 37.7% of the cohort were immunostained positively for nuclear EGFR, 6.9% had high levels of expression of nuclear EGFR, and, importantly, a significant inverse correlation existed between high nuclear EGFR expression and overall survival (Lo et al., 2005c). In contrast, expression of non-nuclear EGFR did not significantly correlate with the overall survival rate. In another cohort of 37 oral squamous carcinomas, we found that 24.3% of the cases contained moderate/high levels of nuclear EGFR and those with high EGFR had the tendency to survive poorly (Lo et al., 2005c). In line with these observations, a study (Psyrri et al., 2005) using 95 oropharyngeal carcinomas indicated an inverse correlation between nuclear EGFR and disease-free survival. Most recently, Xia et al. (2009) investigated 221 cases of ovarian cancer tissues and observed that 28.3% of the cohort had high levels of nuclear EGFR and that there was an inverse correlation between high levels of nuclear EGFR and overall survival. These promising results not only suggest a use of nuclear EGFR as a prognostic indicator for poor clinical outcome, but also highlight the possibility that nuclear EGFR mediates physiological processes that enable the aggressiveness of tumor cells. These results

also call for future investigations that examine the pathological role of nuclear EGFR in other tumor types and potentially other human diseases.

## Nuclear EGFR in Resistance to Radiotherapy and DNA-damaging Agents

The first two studies that reported radiotherapy-induced EGFR nuclear transport in cancer cells and the consequences of this event were conducted by Dittmann and colleagues (Dittmann et al., 2005a; Dittmann et al., 2005b). Radiation therapy induces EGFR nuclear translocalization and, while in the nucleus, EGFR undergoes protein-protein interactions with DNA-dependent protein kinase (DNA-PK), leading to repair of radiation-induced DNA double-strand breaks in bronchial carcinoma cells. Interestingly, a non-steroid anti-inflammatory drug celecoxib has been shown to facilitate tumor cell radiosensitization by inhibiting radiation-induced nuclear EGFR transport and DNA repair (Klaus et al., 2008). This action of celecoxib appears to be independent of its COX-2 inhibitory effect given the observation that radiosensitization was not correlated with COX-2 expression nor prostaglandin E2 levels. A recent study (Hsu et al., 2009) further showed that nuclear EGFR is required for tumor resistance to DNA damage induced by the DNA alkylator, cisplatin. Collectively, these studies suggest a negative impact of nuclear EGFR on tumor sensitivity to DNA-damaging radiation therapy and anti-cancer alkylating agents.

In contrast to the negative impact of nuclear EGFR on radiation therapy, nuclear presence of EGFR may protect normal cells from unwanted DNA damage caused by ultraviolet and $\gamma$ irradiations. Ultraviolet irradiation has been shown to induce EGFR nuclear translocation in human keratinocytes (Xu et al., 2009). While the exact mechanisms by which nuclear EGFR facilitates DNA repair in normal cells are still elusive, nuclear EGFR has been shown to associate with p53 and MDC1 protein (Figure 1), an essential protein for the recruitment of DNA repair foci, following irradiation and treatment of the radioprotector Bowman-Birk proteinase inhibitor (Dittmann et al., 2008). Another radioprotector O-phospho-l-tyrosine (P-Tyr) has been shown to activate PKCepsilon, which triggers nuclear EGFR accumulation and concurrent phosphorylation of DNA-PK at amino acid residue Thr2609, and leads to repair of DNA double-strand breaks (Wanner et al., 2008).

## Nuclear EGFR and EGFR-targeted Therapy

The effect of cetuximab on EGFR nuclear translocalization has been investigated, with the results being mixed. Liao and Carpenter (Liao et al., 2009) showed that cetuximab activates EGFR nuclear transport by binding to the ectodomain of the receptor, initiating receptor endocytosis and activating receptor intracellular trafficking to the endoplasmic reticulum and nucleus. In contrast, an earlier study (Dittmann et al., 2005b) reported that cetuximab inhibits radiation-induced EGFR nuclear translocalization. Another study (Li et al., 2009) found that non-small cell lung cancer cells that have acquired resistance to cetuximab express increased levels of nuclear EGFR. Ectopic expression of a nuclear localization sequence-tagged EGFR renders cetuximab-sensitive cells resistant to cetuximab both *in vitro* and in mouse xenografts. Lapatinib, a dual EGFR and HER2 tyrosine kinase inhibitor, has been shown to inhibit nuclear translocation of both EGFR and HER2 (Kim et al., 2009). Collectively, these data suggest that the effect of cetuximab on EGFR nuclear transport remains inconclusive and the underlying mechanisms are likely to be complex and dependent on cellular context. The reported positive association between nuclear EGFR and tumor resistance to cetuximab is interesting and potentially important in the context of predicting tumor response to cetuximab. Furthermore, it is likely that EGFR-targeting antibodies and small molecule tyrosine kinase inhibitors differ in their effects on EGFR nuclear transport.

Despite the fact that the effect of EGFR-targeted antibodies and tyrosine kinase inhibitors on the extent of EGFR nuclear translocation appears to be unclear, nuclear presence of EGFR can be a constitutive event attributed to ligand-activated nuclear transport (Hanada et al., 2006; Lin et al., 2001; Lo et al., 2005a; Lo et al., 2006a; Lo et al., 2010) and may lead to therapeutic resistance. In this regard, it is becoming clear that nuclear existence of EGFR is beneficial to the tumors encountering EGFR-targeted therapeutic antibodies and small molecule inhibitors, as well as DNA-damaging radiation therapy and alkylators. Consequently, overcoming nuclear EGFR-mediated therapeutic resistance constitutes an urgent task in order to sensitize tumor cells to anti-cancer therapy. This task can potentially be accomplished via two approaches: blocking EGFR from entering the cell nucleus and inhibiting nuclear actions of EGFR. With regard to the former approach, two recent studies suggest that lapatinib (Kim et al., 2009) and the Src family kinase inhibitor, dasatinib (Li et al., 2009), block EGFR nuclear entry. Celecoxib has been shown to inhibit radiation-induced nuclear EGFR transport (Klaus et al., 2008). These observations provide rationales for selecting novel combination treatments that overcome nuclear EGFR-mediated therapeutic resistance.

## Perspectives and Future Directions

Despite the fact that the nuclear mode of EGFR signaling has been overlooked for more than 20 years, studies conducted in the past decade have uncovered some important biological aspects of the nuclear EGFR pathway and some of these discoveries were paradigmchanging (Lo et al., 2005b; Wang et al., 2009). For example, Hung and colleagues reported in their milestone study that nuclear EGFR associates with cyclin D1 gene promoter and functions as a transcription factor that activates cyclin D1 gene expression (Lin et al., 2001). This study has since attracted much attention to and genuine interests in this novel mode of EGFR signaling. Importantly, these profound interests have shaped the nuclear EGFR pathway into an active area of research. They have also generated experimental evidence that links nuclear EGFR to normal cell physiology, cancer pathology, and tumor therapeutic resistance. On the other hand, mixed results have also been reported, indicating that future investigations are needed.

During the course of gaining new insights into the pathological impact of nuclear EGFR on human cancers, many questions were also promoted. The major ones are the followings. (1) What is the relationship between nuclear EGFR and anti-cancer therapy (chemotherapy, radiotherapy, and various targeted therapies)? Knowing the answer to this question will help us stratify patients for personalized medicine. (2) Are there common factors besides ligands that activate EGFR nuclear transport? Targeting these factors could potentially overcome nuclear EGFR-mediated resistance to various therapies. (3) Are there additional functions that nuclear EGFR possesses? Are there yet to be identified nuclear EGFR-targeted genes? Are there additional nuclear proteins phosphorylated and functionally modulated by nuclear EGFR? Elucidation of these aspects of nuclear EGFR will help us better understand the nature of the pathway and determine the advantages (and disadvantages) of targeting the pathway. (4) Is nuclear EGFR involved in tumorigenesis, embryonal development, or stem cell biology? (5) Does nuclear EGFR play a role in the pathogenesis of other human diseases besides cancer? Addressing these questions will not only advance the field of nuclear EGFR, but also help provide insights into the nature of other plasma membrane-bound receptors that also undergo nuclear translocalization, such as rat p185neu, HER2, HER3, HER4, FGFR, TrkA/B, FGFR, VEGFR-2, type I TGF-β receptor, and cytokine receptors for IL-1, IL-5, and interferon-γ (Jans et al., 1998; Maher, 1996; Ni et al., 2001; Ni et al., 2003; Offterdinger et al., 2002; Pillai et al., 2005; Raabe et al., 2004; Rakowicz-Szulczynska et al., 1988; Schausberger et al., 2003; Wells et al., 2002; Xie et al., 1994; Zwaagstra et al., 2000).

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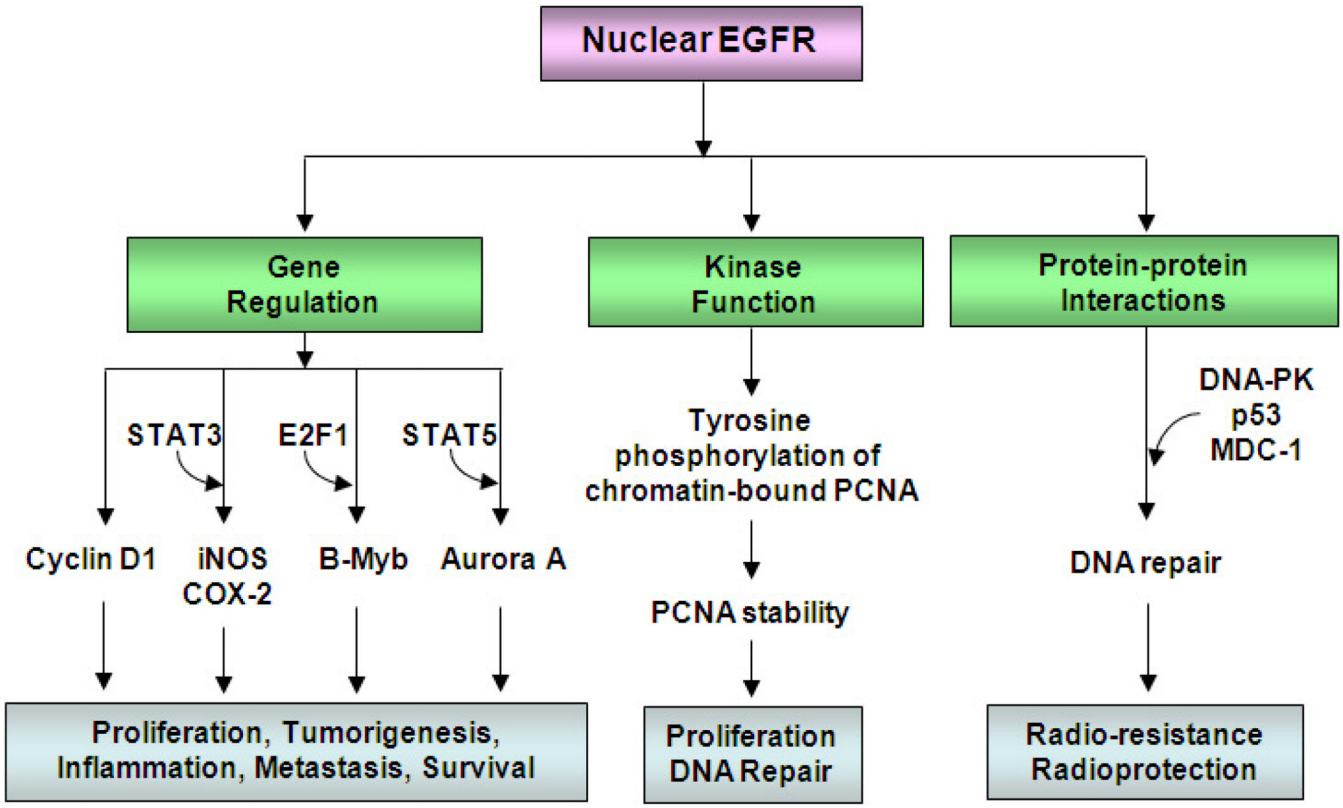


**Figure 1.**
The nuclear EGFR signaling network. Nuclear EGFR has three major functions: (i) gene regulation, (ii) kinase function, and (iii) protein-protein interactions. Via these actions, nuclear EGFR is implicated in a number of physiological and pathological processes, such as proliferation, tumorigenesis, metastasis, inflammation, DNA repair, and resistance to DNA-damaging radiation and alkylating anti-cancer agents.