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Role Of Epidermal Growth Factor Receptor In Lung Cancer

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Abstract

The epidermal growth factor receptor is a transmembrane glycoprotein with an epidermal growth factor-binding domain on the outside and an intracellular tyrosine kinase domain on the inside that regulates signalling pathways to regulate cellular proliferation. The EGF receptor's tyrosine/kinase activity results in auto phosphorylation upon binding to its ligand, activating several signal transduction pathways. The constant stimulation of these downstream targets is hypothesised to be the source of tumours with more aggressive features. Certain types of lung cancer have been associated with epidermal growth factor receptor mutations. Individuals who are not chosen seem to benefit from the usage of these inhibitors in the case of lung adenocarcinomas with epidermal growth factor receptor mutations. However, a significant survival advantage seems to exist in a minority of individuals (non-smoking Asian women with adenocarcinoma, notably with a bronchioloalveolar carcinoma). EGFR mutations or gene amplification may be present in tumours that respond to tyrosine kinase inhibitors.

Keywords: Inhibitors of tyrosine kinase, receptors for epidermal growth factor, lung cancer

Introduction

Cancer-related mortality is increased in both men and women due to a lack of treatment alternatives for advanced lung cancer. NSCLC, the most prevalent kind of lung cancer (accounting for nearly 75% of all occurrences), has proven difficult to treat due to the absence of obvious pathogenic reasons. Understanding the cell signalling networks that regulate cell survival has revealed genetic and regulatory anomalies that promote cell proliferation, suppress cell death, and contribute to tumorigenesis. One such discovery is the epidermal growth factor receptor (EGFR). In some normal epithelial, mesenchymal, and neurogenic tissues, the transmembrane receptor tyrosine kinase (EGFR) is expressed. Numerous human malignancies, including non-small cell lung cancer (NSCLC), have EGFR ove rexpression, which has been related in studies to the development of those tumours (1-4). In multiple studies, EGFR expression in NSCLC has been associated with poor survival, frequent lymph node metastasis, and lower

chemosensitivity. Gefitinib (Iressa) and erlotinib (Tarceva) are now available in treating patients with advanced non-small-cell lung cancer, and EGFR mutations have been linked to specific forms of lung cancer(5-7). A tremendous lot of time and effort has been spent on discovering markers that may help predict the effectiveness of these drugs. EGFR plays a critical role in the development of lung cancer, and this review summarises the most recent findings on the issue (Figure 1)(8-11).

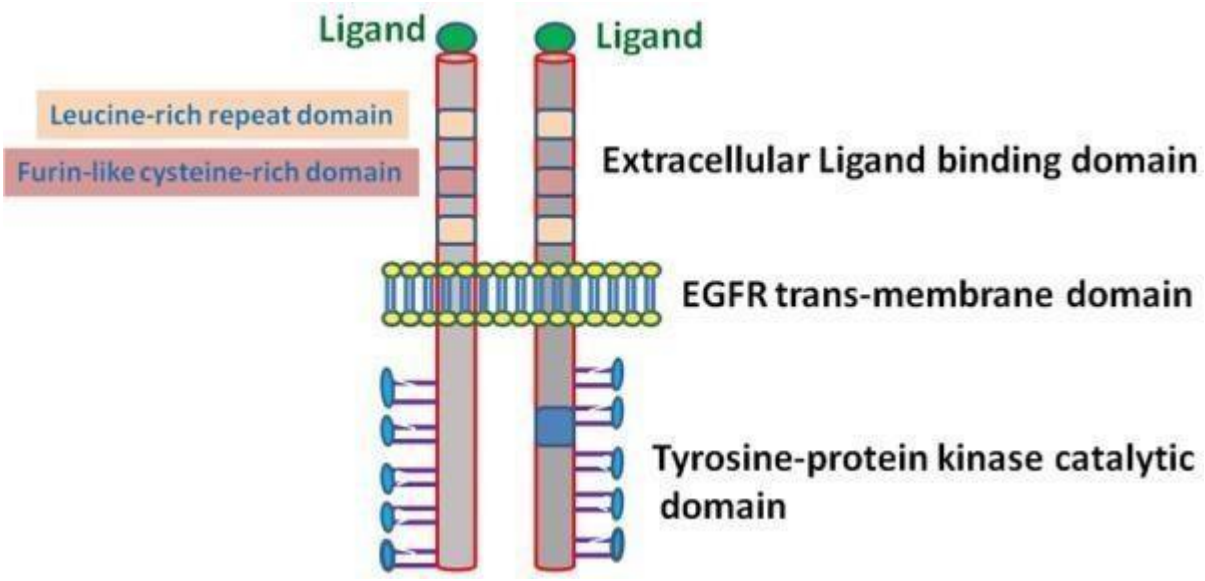

Figure 1: EGFR structure and ligand binding.

Lung cancer, the function of the EGFR, and its involvement

Members of the receptor tyrosine kinase (erbB) family include erbB1 (EGFR), erbB2 (HER2), erbB3 (HER3), and erbB4 (HER4). Their essential structures are the same, but their properties, especially their tyrosine kinase activity, are distinct. The tyrosine kinase and regulatory domains are located in the protein's intracellular and extracellular regions. When a specific ligand (e.g. epidermal growth factor) is bound, the normally functioning EGFR undergoes conformational changes and phosphorylation of the intracellular domain, resulting in downstream signal transduction through numerous pathways. Stat factors such as Raf1 and PI3K/Akt have been involved in this process. Depending on the technique, cell proliferation or cell maintenance through apoptosis may be accomplished. A polymerase chain reaction (PCR) test may be used to detect DNA mutations in the EGFR protein that affect both the extracellular and intracellular domains(3, 12, 13). It has been shown that 43–89% of non-small cell lung cancer cases have EGFR over expression or intracellular changes(14, 15). According to previous research, the EGFR tyrosine kinase domain mutations seen in 25% of NSCLC patients were associated with a 75% increase in receptor expression. At codon 858, the short in-frame deletion in exon 19 results in the substitution of arginine for leucine, while the point mutation in exon 21 results in the substitution of arginine for leucine (L858R). Even in the absence of an external ligand, these alterations may result in cell growth or anti-apoptosis. These mutations have the potential to activate signal transduction pathways constitutively. Although mutations in exons 18 or 21 are uncommon, they do occur. Notably, EGFR and KRAS mutations do not seem to be connected(16-19).

FISH and chromogenic in situ hybridization (CIH) may also be used to detect EGFR gene amplification (CISH). Along with EGFR mutations, increased EGFR gene copy number, defined as polysomy or amplification, has been associated with increased responsiveness to TKIs. In certain cases of adenocarcinoma, EGFR mutations and increased gene copy number are seen, however, they are not usually detected in conjunction with other kinds of malignancy. According to a recent investigation, around half of EGFR-mutated patients had an increased EGFR copy number, while approximately 75% of individuals with an increased gene copy number have mutations (Figure 2)(20-22).

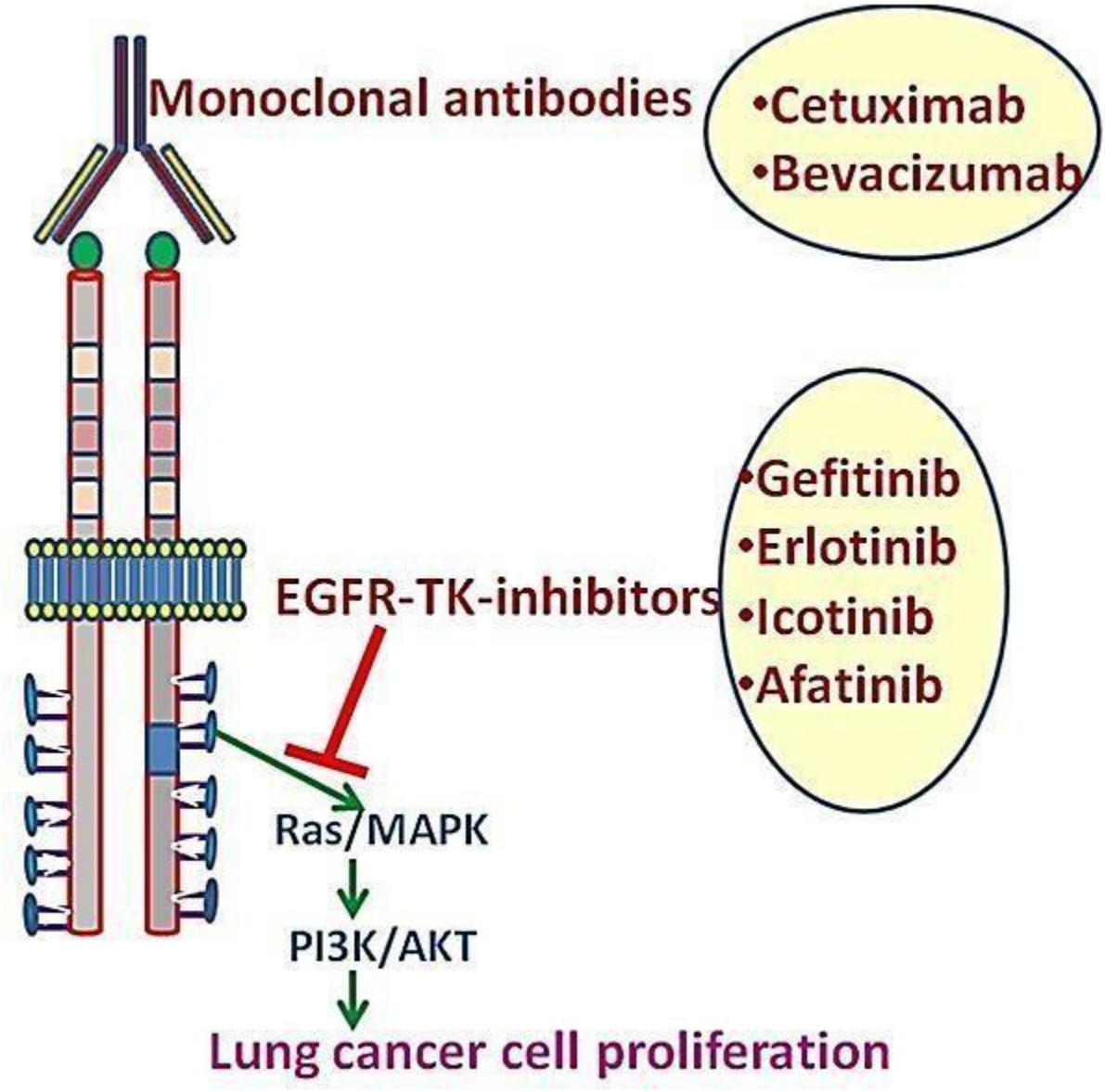

Figure 2: Targeting EGFR in lung cancer. Monoclonal antibodies block EGFR functioning EGFR-inhibit EGFR signalling.

EGFR tyrosine kinase inhibitors

Following the discovery of the EGFR TKIs gefitinib and erlotinib, about 1,700 patients with advanced-stage lung cancer were recruited in a large phase III trial comparing gefitinib to a placebo. Gefitinib had no survival benefit for any kind of lung cancer in the group treated with it. Only a tiny fraction of patients with adenocarcinoma, namely those with bronchioloalveolar carcinoma, were shown to have a survival benefit(23, 24).

Three seminal studies published in 2004 demonstrated that gefitinib and erlotinib were effective against lung adenocarcinomas harbouring mutant EGFR. Patients with EGFR mutations who underwent chemotherapy with erlotinib or gefitinib vs chemotherapy alone demonstrated a survival advantage independent of the drug used in prior phase III clinical trials. Between 65 and 90% of EGFR-mutant adenocarcinomas respond to TKIs. Even though these drugs increase response rates, they may not enhance overall survival in individuals with NSCLC who have an EGFR mutation. In one study, the incidence of EGFR mutations was not associated with survival, however people with an exon 19 deletion exhibited a trend toward shorter survival. According to previous studies, gefitinib relieved symptoms and generated a radiologic response in only 10% of NSCLC patients, suggesting that EGFR activation is a minor component of the tumorigenic process(4, 25).

The orally administered small molecule EGFR tyrosine kinase inhibitors gefitinib and erlotinib have been approved as second-and third-line therapies for advanced lung cancer, respectively. Exon 19 and exon 21 of the EGFR gene seem to confer a greater affinity for these drugs, indicating that the efficacy of the therapies may be contingent upon these changes. The most often occurring acquired resistance mutation in malignancies treated with TKIs is the threonine to methionine switch at codon 790. (T790M). Up to 50% of cancers have acquired resistance to gefitinib(26, 27).

Analyses of EGFR gene variants

While gefitinib and erlotinib both have the potential to benefit some patients with non-small cell lung cancer, their efficacy is limited. Numerous studies have connected certain morphological characteristics to EGFR mutations or increased response rates to TKIs. Adenocarcinomas include non-mucinous bronchioloalveolar carcinomas, the hobnail cell type, and papillary and micropapillary patterns. According to research published in the Journal of Clinical Pathology, tumours with an amplification of the EGF receptor (EGFR) are more aggressive.

IHC may or may not be beneficial for detecting EGFR over expression. While IHC has been demonstrated to be beneficial in predicting response to TKIs in certain studies, it is ineffective in others. To improve the prediction of targeted treatment success, there has been tremendous interest in the creation of novel antibodies that can more reliably identify abnormal EGFR or detect over expression(28, 29).

Anomalies in the EGFR have been investigated in several approaches. A meta-analysis and systematic review of 27 studies were conducted to determine the utility of EGFR testing in predicting response to targeted therapy in patients with advanced lung cancer. All three procedures (IHC, FISH, and PCR) demonstrated a substantial correlation with TKI response. Positive predictive values were from 6.5 to 82 percent for IHC, 11 to 89 percent for FISH, and 7 to 100 percent for PCR. According to the authors of the review, significant discrepancies in study design were discovered, emphasising the need tost and ardise

these methodologies. Additional study is required to determine the optimal method for selecting patients who will benefit from TKIs. Genomic mutations may be directly sequenced using PCR to discover specific variations associated with increased TKI response rates. Cancers with EGFR exon 19 mutations, for example, exhibited a higher overall survival rate when TKIs were used(30, 31).

PCR may also be used to identify TKI-resistant mutations, including the exon 20 insertion that confers primary resistance and the acquired mutation T790M. Because KRAS mutations cannot coexist with EGFR mutations, the presence of one indicates that a patient has established primary resistance to TKIs. On the other hand, TKIs do not function in all malignancies with EGFR mutations, and some tumours respond to TKIs despite the absence of an EGFR mutation on direct sequencing. There are various possible explanations for this. An early stage of lung carcinogenesis has been hypothesised to be caused by mutations in the EGFR tyrosine domain, which have been identified in almost half of atypical adenomatous hyperplasia and normal lung tissue around it. Additionally, mutations may be missed if less than 25% of tumour cells are present in a sample submitted for direct sequencing. This is because, although PCR is capable of detecting particular mutation status in many cases since DNA sequencing is not yet available for routine clinical use in the majority of laboratories, it is not an ideal method for predicting TKI response(32-34).

Additionally, it has been shown that the copy number of the EGFR gene, as determined by FISH or CISH, is associated with TKI response. In other studies, the EGFR gene status as determined by FISH analysis did not seem to alter survival. The distinction between mutation status and gene amplification status continues to be a source of contention. Approximately half of the malignancies with EGFR mutations also have an increased copy number of the gene, while approximately 75% of tumours with an increased copy number also have mutations, indicating some coexistence(35-37). According to the notion that EGFR mutations develop early in lung carcinogenesis, EGFR amplification occurs later. According to a recent study, EGFR mutations were detected in eight out of every 10 cases of adenocarcinoma in Asian women who did not smoke, and nine of those cases had FISH-confirmed gene amplification. Each amplified case included an exon 19 deletion mutation. Patients with tumours having amplified EGFR had a significantly lower overall survival than patients with tumours including non-amplified EGFR and were more likely to have a solid growth pattern on histology and a prominent staining pattern on IHC. The fact that increased EGFR was not associated with acinar or BAC patterns, the latter of which has been demonstrated to predict TKI response, was an intriguing discovery. Amplification of the EGFR gene after a mutation may result in a more aggressive tumour with a higher grade(1, 2, 5, 38, 39).

Conclusion

There has been a great amount of research and publication as a result of EGFR inhibitors and the subsequent discovery of mutations in non-small cell lung cancer. Too far, direct sequencing of EGFR mutations has been the most thoroughly explored and most reliable method for predicting response to TKIs. Gene amplification may occur later in the carcinogenesis of some lung tumours than previously believed, according to data from more recent investigations. When it comes to determining whether tumours will respond to TKIs, both genetic abnormalities and gene amplification may be critical aspects to consider. Additional study is required to standardise methodologies to mutation and gene

amplification analysis. Additionally, IHC markers that properly detect abnormal EGFR and recommend the use of targeted therapies are being developed.

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