

EGFR: an Overview and Mutation on Lung Cancer

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Abstract. Cancer is a popular and well-known disease all over the world. It is a genetic disease that mutations occur on patients' genome and cause cells to proliferate uncontrollably and start to invade surrounding tissues which is not commonly seen on normal cells and tissues. It is a common cause of death in the world. In 2020, the number of people died because of cancer is 10 million. Among these deaths, lung cancer account for 2.21 million cases which is the second largest group of all cancer types. Among all lung cancer types, non-small cell lung carcinoma (NSCLC) constitutes around 80 percent lung cancer. EGFR is a gene that mutation on it is often found within the genome of NSCLC patients. According to a report, 30466 patients among 115815 NSCLC patients are found to have EGFR mutation in order to provide suggestion for patients with mutation on EGFR to have a better therapeutic effect, learning the function of a gene and its impact on metastasis is necessary. This review intended to give an overview on the EGFR (epidermal growth factor receptor) which mutation on it is often seen on lung Cancer.

Keywords: Lung Cancer, Oncogene, EGFR, Tyrosine kinase.

1. Introduction

Non-small-cell-lung cancer is a type of cancers that are heterogenous and often considered as one of the most common and dangerous type of all cancers. Patients are often diagnosed with NSCLC at advanced stage therefore people with this cancer type often have a poor prognosis. that the understanding of mutations on genes is of great importance for the research of cancer. The learning of the structure protein that gene encode for, and function of proteins contribute significantly to the understanding of mechanisms of normal functions of cells, tissues and organs. As a result, Mutations occur on the genes could be interpreted from the changes that occur on the conformation of proteins and mechanisms of the mutation that occur on the genes and eventually provide researchers with potential pathways of therapy and even provide direction to the invention of new drugs. Epidermal growth factor receptor (EGFR) is a protein receptor gene located on chromosome 7 of human to form a transmembrane glycoprotein from a protein kinase superfamily. It is a polypeptide that have the ability to increase the rate of cell proliferation and differentiation of tumorous cells and normal cells. By analyzing the mechanisms of its mutation happened on lung cancer, change in pattern of proliferation of cancer cells are revealed.

2. EGFR

There are four transmembrane growth factor receptor proteins in the tyrosine kinase receptor family, including EGFR, HER2, HER3, and HER4. It is a protein composed of a chain of polypeptides with 1186 amino acids and the weight of the molecules is 132012.67Da. EGFR is frequently observed on cell surface. The extracellular, transmembrane, and intracellular domains make up a complete EGFR protein.

2.1. Structure of EGFR

There are four subdomains that make up the extracellular domains, two are domains responsible for ligand binding and two domains for dimerization of receptors. There are several ligands that could binds to EGFR: Epidermal growth factor (EGF), TGF- α , HBEGF, EPN and EPR [1]. The transmembrane domain is a hydrophobic domain that act as a transmembrane-spanning region. The intracellular domain is a conserved and a tyrosine kinase domain is included. When the tail of the

EGFR is activated, it phosphorylates the tyrosine kinase residues and make it as a binding site for proteins which contain phosphoserine binding regions. The cytoplasmic carboxy-terminal region is the place where activation of tyrosine kinase happened, and it is also responsible for the regulatory function of carboxyterminal. Tyrosine kinase region is followed by the autophosphorylation domains

2.2. Activation of EGFR

EGFR is a typical receptor tyrosine kinase (RTK). ligand induced Homodimerization or heterodimerization with different members like HER2 which do not have the ability to respond the binding of ligand due to its lack of specific ligand is the first step of RTK activation. The process stimulates the autophosphorylation of the tyrosine kinase in trans [2]. after interacting with adaptor molecules, they couple and initiate downstream signaling pathways. The main pathway that mediates intracellular signaling are RAS-RAF-MEK-MARK pathway, the PI3K-PTEN-AKT pathway, and transducer of signal and transcription activator (STAT) pathway. Downstream signaling of EGFR eventually results in the proliferation, differentiation, division, survival, angiogenesis, metastasis and decreased apoptosis [3,4]. EGFR have an important role on development of epithelial cells, family members like HER2, HER3 and HER4 are crucial for growth of cardiac. The normal functions of glands and nervous system are highly related to these proteins [2]. Many studies have reported that distinct ligands functions in a selective way. The binding of different ligands produces quantitatively and qualitatively different cellular response. biological process produced by ligands are different among four common ligands, which includes Another ligand that binds to EGFR but with low affinity is AREG.

2.3. Inactivation of EGFR

EGFR down-regulation is a process partially completed by internalization of EGFR that are activated, and they are degraded by lysosomes after this process. After the fusion with lysosomes, endocytosis of EGFR spanning on the cell surface happens at the region called coated pits on the cell surface. An EGFR C-terminal is needed to endocytosis [5].

2.4. Mutation of EGFR

The EGFR activity of tyrosine kinase could be disturbed by oncogenic mechanisms, containing mutation on EGFR gene, increasing of copy number of genes, and overexpression of EGFR protein. Deletion mutation on EGFR mRNA is found in breast cancer, glioblastoma, and non-small cell lung carcinomas. Unwanted activation of EGFR on cells inhibits the cell apoptosis and contributes to tumor progressions. The deletions on mRNA are found to be located on the extracellular region of EGFR and in sites which encodes intracellular region of EGFR. The mutation on TK domain of EGFR is often recognized as short deletions in exon 19 and point mutations (G719S, L858R, and L861Q) in exon 19 and 21 [6]. The mutations are categorized into three types. (Deletions, insertions and missense point mutations) [7]. deletion includes short in-frame deletions in exon 19 which is the most obvious type. Missense mutation usually appears as a single nucleotide substitution L858R in exon 21 and sometimes on G719X in exon 18. L858R mutation is in a place close to a DFG motif which is a conserved sequence that stabilizes the A-loop whereas G719X mutation is on the glycine-rich sequence in the p-loop of the protein. Insertion mutation are mutations that are found mostly in exon 20 and 21 and it occupy only around 5 percent of all mutations. All of three types of mutations target the structures around ATP binding cleft. mutation of EGFR gene may be gain-of-function or activating and it appears in some of the NSCLCs.

3. Mechanisms of uncontrolled activation of EGFR.

On cells of cancer patients, excessive growth, invasive behavior and aberrant blood vessel formation was found in cells with EGFR mutation [8]. The activation of EGRFR kinase domain caused by increase in the local concentration or the Leucine (L834R) mutation that happen on the

activation loop which the process of phosphorylation is not needed for the activation process; This suggest that the conformation of the TK domain results in the intrinsic autoinhibition. The suggestion is proofed experimentally by replacing the Leu834 which is a residue that mutation happen to replace an arginine to glutamine. The kinase domain of EGFR change from a low basal activity to a substantially increased state. This shows that wild type kinase domain is in an autoinhibited state and tyrosine kinase domain mutation of EGFR cause a change in the conformation of the protein which cause a destabilization of the domain conformation and subsequently constitute abnormal activation of activity of kinase and signaling cascade at cancer cells. Among all downstream signaling pathways, antiapoptotic pathways (PI3K/AKT and JAK-STAT) are preferentially activated [9].

4. Inhibition of EGFR

The two main inhibitors used in inhibiting activity of EGFR are small-molecule tyrosine kinase inhibitors (TKIs) and a group of monoclonal antibodies. Tyrosine kinase inhibitors are molecules that bind to the ATP-binding site of tyrosine kinase domain of EGFR and stop the activity of EGFR. Clinical trials of TKIs were conducted a few years ago and several TKIs have been successfully approved to be used; containing 4-anilinuiazolines gefitinib, erlotinib, lapatinib, pyridopyrimidine AEE788, and irreversible HKI-272. The presence of mutations including L858R, Gly719, that concentrate on the active site cleft of TK domain perform higher affinity to the TKIs comparing to cells with wild-type tyrosine kinase. Another type of TKIs is called reversible inhibitors, including CL-387, CL785, HKI-272 and BIBW 2992. These are TKIs used when tumor cells have developed resistance the former TKIs. Mutations such as secondary mutation T790M on exon 20, are conferred with a steric interference to drug binding. A covalent bonding could be formed between irreversible inhibitors and residues-Cys797 located in EGFR or Cys805 within ERBB2 which is in the active site of the respective enzymes. Research have shown that problem of resistance to gefitinib gained from T790M in cis with L858R mutation could be solved by some irreversible inhibitors [10].

5. TKIs

5.1. Determinants of sensitivity to TKIs

A typical example of difference in sensitivity to TKIs is the L858R mutant, which show significantly more obvious response to gefitinib and erlotinib when compared to cell expressing wild-type kinase. An exception is the exon 20 insertion mutation which is resistant to both TKIs [11]. The sensitivity to TKIs is affected by differences in the mutations. Exon 21 L858R point mutation has a poorer respond to both of the TKIs than deletion mutation on exon 19. The overall conformation of mutant L858R and G719S are similar to the conformation of active site of wild-type tyrosine kinase. the activation of kinase is caused by the disturbance of L858R and G719S mutant which change inactive conformation of the protein and destabilize it. Change in structure of mutants increase the affinity to the TKIs. The sensitivity of EGFR mutant tumors is also partially affected by an “oncogene addiction” effect and differences in structure of mutant kinases which may be the source of the sensitivity to particular inhibitors. Most of response are observed from NSCLC patients that are East Asians, non-smoker or females after clinical trials of erlotinib and gefitinib. People experienced second or third-line monotherapy of gefitinib shows Significant and lasting response. Gain-of-function mutations were observed from EGFR gene sequencing of tumor samples of these patients. Susceptibility of tumorous cells to TKIs are affected by the presence of EGFR mutation. Around 20 percent of patients that don't have recognizable EGFR mutations express a response to gefitinib, which give a hint that mutations of EGFR are just a component of determinants [12].

5.2. Mechanisms of TKIs resistance

Recurrent resistance of disease to TKIs therapy is sometimes developed. Research illustrated that the resistance is the result of secondary mutations. T790M that located on exon 20 of the Tyrosine

kinase domain is a mutation that disturb binding of TKIs, but it does not eradicate the activity of kinase in vitro. T790M mutation in some of the patients seem to appear spontaneously as none of the patients are given TKIs treatment [13].

6. Characteristics of patients with mutations.

EGFR mutation rate differs from areas, ethnicity, sex and histology. From a report, 38.4 percent of Asian patients in a total of 30466 patients have EGFR mutation. Prevalence was also higher for females than men (43.7% versus 24.0%), for past or current smokers than non-smokers (21.5% versus 49.3%) and for patients with adenocarcinomas than those who do not have adenocarcinomas (44.7% versus 12.5%) Stage of disease of patient at diagnosis, history of patient with chemotherapy and methods that mutations are detected has a less impact on the EGFR mutation prevalence rates.

EGFR mutated NSCLCs is 2-3 times more frequently detected in Asia and those patients have better response to gefitinib and erlotinib. More than 75 percent of NSCLC patients with EGFR mutation have response. treatment with gefitinib and erlotinib are readily apparent in Asian which has a larger fraction of mutant cases. The response to TKIs usually last for 6 to 12 months before resistance of tumor cells develop. However, mutations spanning P-loop and A-loop within BCR-ABL kinase domain are observed, which indicate that except for T90M, TKI resistance in patients with relapsed lung cancer are influenced by unidentified EGFR mutations.

7. Conclusion

lung cancer account for 2.21 million cases which is the second largest group of all cancer types. Among all lung cancer types, non-small cell lung carcinoma (NSCLC) constitutes around 80 percent lung cancer. EGFR is a gene that mutation on it is often found within the genome of NSCLC patients. The prognostic role of mutated EGFR is affected by the status of smoking as the status of smoking is in an inverse relation with the incidence of lung cancer with mutated EGFR. the role of mutated EGFR on prognosis are understood after patient groups are compared. Several studies report in patients that never received TKIs treatment before, prognosis of patients that have mutated EGFR NSCLC are better than patients of wild-type EGFR [11]. More studies are in urgent need to develop novel therapies of cancer.

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