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Progress on the EGFR pathway drives targeted therapy for NSCLC

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Abstract. Epidermal growth factor receptor (EGFR) is a key tyrosine kinase receptor that regulates cell survival, proliferation, division, and differentiation. The mutation of the EGFR gene is one of the most common gene mutations responsible for non-small cell lung cancer (NSCLC). Extensive research has been done in the field. Several key EGFR signaling pathways control cell activity, such as MAPK/EPK, PI3K/Akt/mTOR, and JAK/STAT pathways. Mutation of EGFR can cause abnormal activation of signaling cascades, leading to constant cell growth and division, eventually causing tumor growth. Understanding the function of epidermal growth factor receptor and EGFR signaling pathways contributes to the development of targeted treatment for lung cancer. Therefore, through recent research and analysis on the mechanism of action and related pathways of EGFR, this article finds that EGFR tyrosine kinase inhibitor (TKI), a commonly used drug to treat lung cancer, is one of the most effective treatment and it has high potential. However, resistance to TKIs caused by secondary mutations has become a crucial challenge. Novel generations of TKI and combination therapies are needed.

Keywords: NSCLC, EGFR Signaling Pathways, Tyrosine Kinase Inhibitor, Targeted Therapy.

1. Introduction

Lung cancer is the second most common cancer and is one of the death leading cancers in around the world [1]. Lung cancer was a relatively rare cancer type at the beginning of the 20th century. However, lung cancer cases dramatically rose in the following decades due to increased smoking among both males and females [2]. Signs and symptoms of lung cancer typically only occur in later stages as the disease is advanced, including blood coughing, breathlessness, chest infections, unexplained weight loss, bone pain, and persistent tiredness [3]. Lung cancers are commonly categorized in to two types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLS and NSCLC develop differently and needs to be treated with different methods [4].

The EGFR gene, also known as HER1, is one of the most significant genes for the lung cancer. The EGFR is one of the receptor tyrosine kinase family, which contains four members: EGFR (HER1), ErbB2 (HER2/Neu), ErbB3 (HER3), and ErbB4 (HER4). Unlike other gene mutations that are universal to cause all different kinds of cancer, the EGFR gene mutations are highly associated with NSCLC [5]. The EGFR gene is responsible for the production of epidermal growth factor receptor (EGFR), which is a transmembrane protein that transduce signals. The EGFRs can be activated when specific ligands are bound to the receptor domain. The signal pathway is then activated within the cell, and the cell starts to proliferate and replicate. Mutations in the EGFR gene can cause lung cancer. The most common EGFR

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mutations in lung cancer are exon 21 L858R mutation and exon 19 del19 mutation. The mutated genes lead to false protein production, causing the production of constantly activated EGFR. Consequently, mutant cells persistently receive signals to proliferate and divide, leading to tumor growth [6].

EGFR mutation is one of the main causes of adenocarcinoma. Knowing the mechanism of EGFR mutation can lead to a better understanding of tumor growth. Moreover, studying EGFR mutation can help researchers to develop targeted therapy and personalized medicine, which potentially improves patient outcomes. There are still some research gaps in the effective treatment of lung cancer with EGFR mutation, such as the need for more research to improve treatment outcomes for patients with EGFR-mutant NSCLC and more research on acquired resistance to EGFR TKIs.hese guidelines, written in the style of a submission, show the best layout for your paper using Microsoft Word. If you don't wish to use the Word template provided, please use the following page setup measurements.

2. Structure and activation of EGFR

The EGFRs have three domains: an EGF-binding domain, a transmembrane domain, and a tyrosine kinase (TK) domain. The EGF binding domain contains subdomains: subdomains I, II, III, and IV. Among these, subdomains II and IV are responsible for ligand binding and dimerization. The intracellular domain contains a C-terminal tail, which has several tyrosine residues that can be phosphorylated upon activation. The structure of the epidermal growth receptor has been extensively studied and is known to adopt a bilobate-fold characteristic of other protein kinase domains. In the inactivated state, the EGFR remains as two separated monomers. The two monomeric units are identical, each with an EGF-binding domain and a tyrosine kinase domain. The binding of epidermal growth factor or other EGF ligands such as transforming growth factor-α (TGF-α) and amphiregulin (AREG), leads to the activation of EGFR; the activation of EGFR causes ligan-induced dimerization, which leads to the autophosphorylation of the c-terminal tail. The phosphorylated c-terminal tail act as a binding sites for different kinds of signaling proteins, which can further conduct the signaling pathway [7]. Figure 1 indicates the structure of the EGFR. The blue monomer represents a single monomeric unit of EGFR in an inactivated state. The red molecule represents extracellular ligands. As extracellular ligands bind to the EGF binding domain of both monomers, the EGFR dimerizes and forms a unified molecule. The c-terminal tails are then phosphorylated.

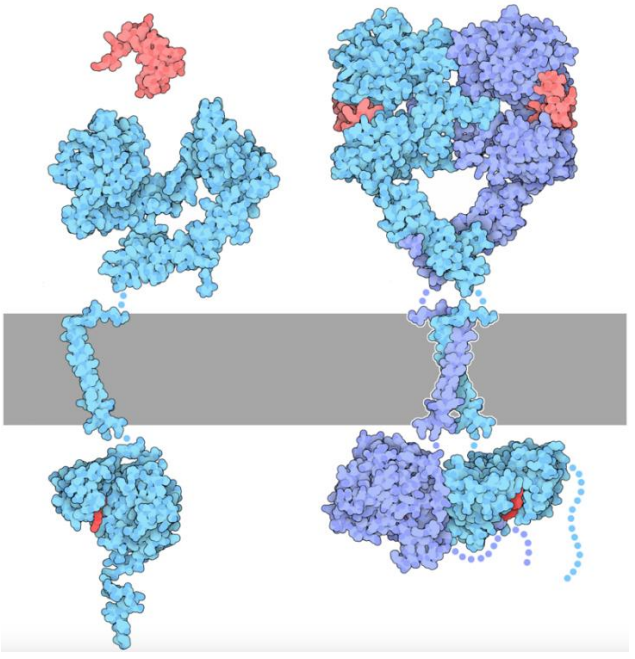

Figure 1. Structure of EGFR [8].

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3. EGFR signaling pathway

3.1. MAPK/ERK pathway

As shown in figure2, the Ras/Raf/MAPK pathway conducts signals from outside the cell to the cell nucleus, and transcription is activated for cell growth. The MAPK pathway starts as the TK domain of EGFR is phosphorylated. The adaptor protein Grb2 then are able to bind to the phosphorylated c-terminal tail, allowing SOS protein to bind to the complex. The active site of SOS protein then recruits and activates Ras protein by interchanging a GDP molecule of Ras protein for a GTP molecule. The activated Ras protein then activates the RAF kinase. The RAF kinase phosphorylates and activates MEKs. The MEK then phosphorylates and activates ERK-1/2, as known as mitogen-activated protein kinase (MAPK). Activated MAPK enters the cell nucleus and stimulates the activities of several transcription factors. As a result, the protein production is increased, which further leads to cell proliferation [9].

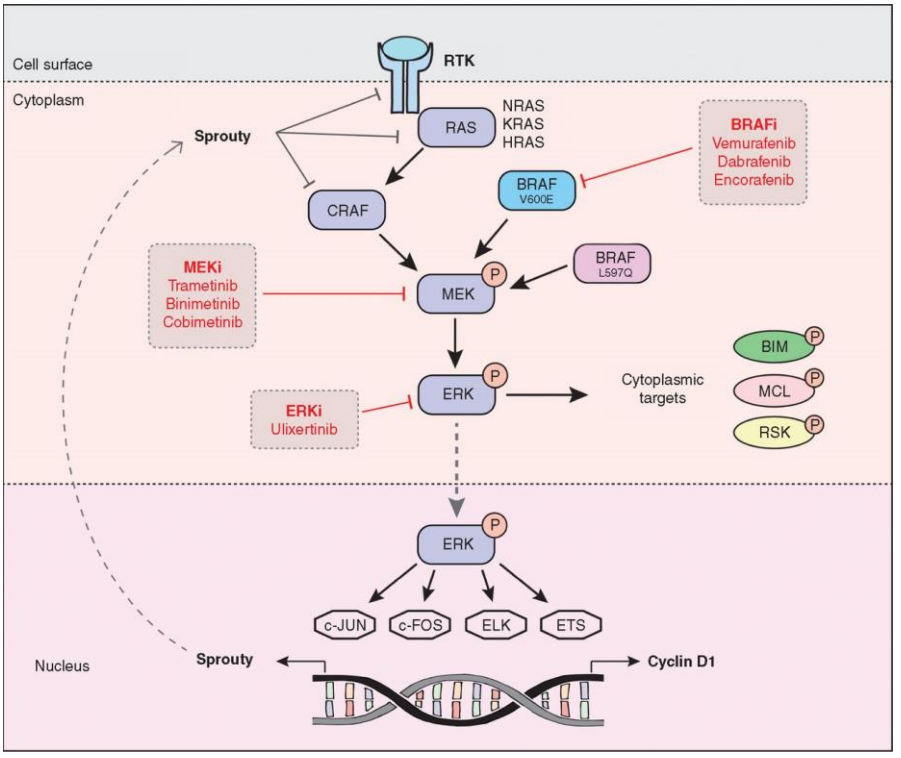

Figure 2. The MAPK/ERK Signaling Pathway [9].

3.2. PI3k/Akt/mTOR pathway

As shown in figure 3, the Phosphoinositide 3-kinase (PI3K)/Akt/mTOR pathway regulates cell metabolism, protein production, and angiogenesis. Same as the MAPK pathway, the PI3K pathway is initiated by the phosphorylation of the TK domain of EGFR. This binds to and phosphates the adaptor protein insulin receptor substrate (IRS) protein. The activated site of IRS then triggers the activation of the p85 subunit and p110 subunit of PI3K. The activated PI3K converts PI2 to PIP3. PIP3 interacts with membrane protein 3-phosphoinositide-dependent protein kinase 1 (PDK1) and PDK2, which drives the recruitment of Akt. Akt has three domains: PH domain, kinase domain and regulatory domain. The PDK1 and PDK 2 protein phosphorylate tyrosine 308 on the kinase domain and serine on the regulatory domain, activating Akt. Activated Akt can translocate from cell membrane to the cytoplasm and nucleus, activating mTOR, which is a significant regulatory molecule that could increase the expression of the growth factors and proteins, driving the replication of DNA. The PI3K/AKT/mTOR signaling pathway can then regulate cell proliferation, division, and differentiation [10].

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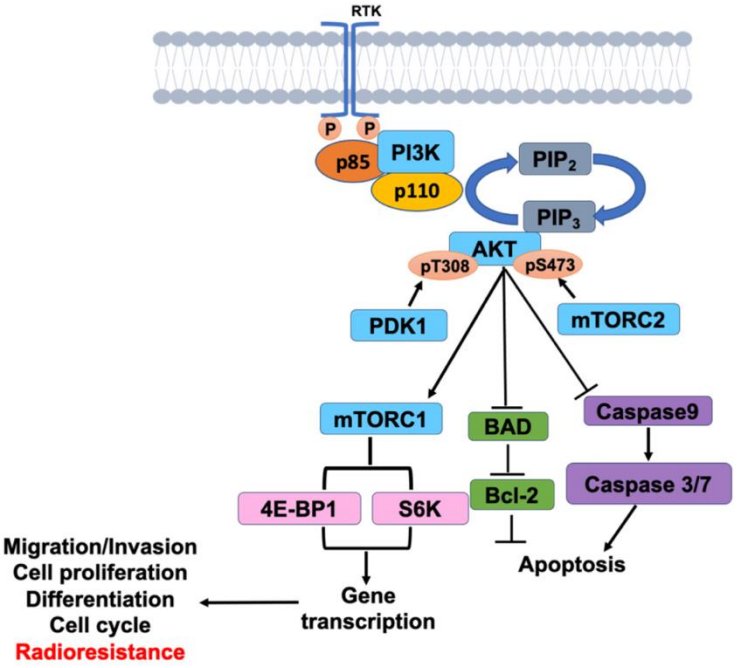

Figure 3. The PI3K/ART/mTOR Signaling Pathway [11].

3.3. JAK/STAT pathway

As shown in figure 4, the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway regulate immunity, cell division and cell death. JAK interacts with and is phosphorylated by hormone, cytokine and growth factor receptors, including EGFR. Activated JAK proteins then phosphorylate STAT proteins. Once phosphorylated, STAT proteins dissociate from the receptor and form homodimers or heterodimers in the cytoplasm through SH2-domain–phosphotyrosine interactions. The STAT dimers then are able to move into the nucleus, where they regulate transcription processes [12]. Intriguingly, phosphorylated JAK can interact with and activate PI3K and Ras. The interaction of signaling pathways composes a signaling networks that influence each other.

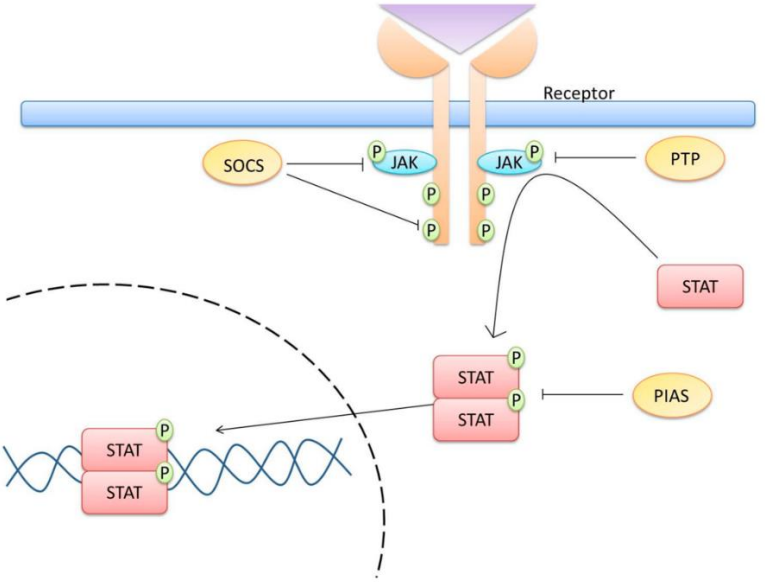

Figure 4. The JAK/STAT Signaling Pathway [13].

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4. Typical EGFR mutations

Common EGFR mutations are EGFR L858R mutation and EGFR del19 mutation, which accounts for 85% of the EGFR mutation. The L858R mutation is a single nucleotide mutation in the exon 21 in the TK domain of EGFR gene. This mutation leads to a missense mutation -a nucleotide change from thymine to guanine, which further influences the protein synthesis substituting leucine to arginine at codon 858. The L858R mutation increases the activity of the EGFR kinase. Research has shown that L858R mutated EGFR kinase is fifty times more active than a normal EGFR kinase due to the disruption of stabilization of the inactive EGFR monomers, so that kinase maintains in a constitutively active state. EGFR L858R mutation also enhances the binding of inhibitors to the kinase, resulting induced cell invasion and metastasis. EGFR del19 mutation is caused by the deletion in exon 19, which destabilizes the inactive EGFR monomeric structure, leading increased receptor dimerization. Del19 mutation also locks the kinase domain in an active conformation, causing the continuous activation of EGFR signaling pathways and cell proliferation [14].

5. Current treatment strategies

The current treatment for lung cancer caused by EGFR mutation includes but is not limited to surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy and combination therapy. To this article's extent, targeted therapy will be primarily discussed due to the particularity of EGFR mutation. EGFR tyrosine kinase inhibitor (TKI) is a type of targeted therapy that is used as a treatment for NSCLC. TKI can specifically inhibit the TK domain of EGFR in order to prevent tumor cell growth. TKI has three generations along development, each with different characteristics [15]. The choice of TKI often depends on the patient's condition and resistance to the medicine. Figure 5 shows the chemical structures of TIKs.

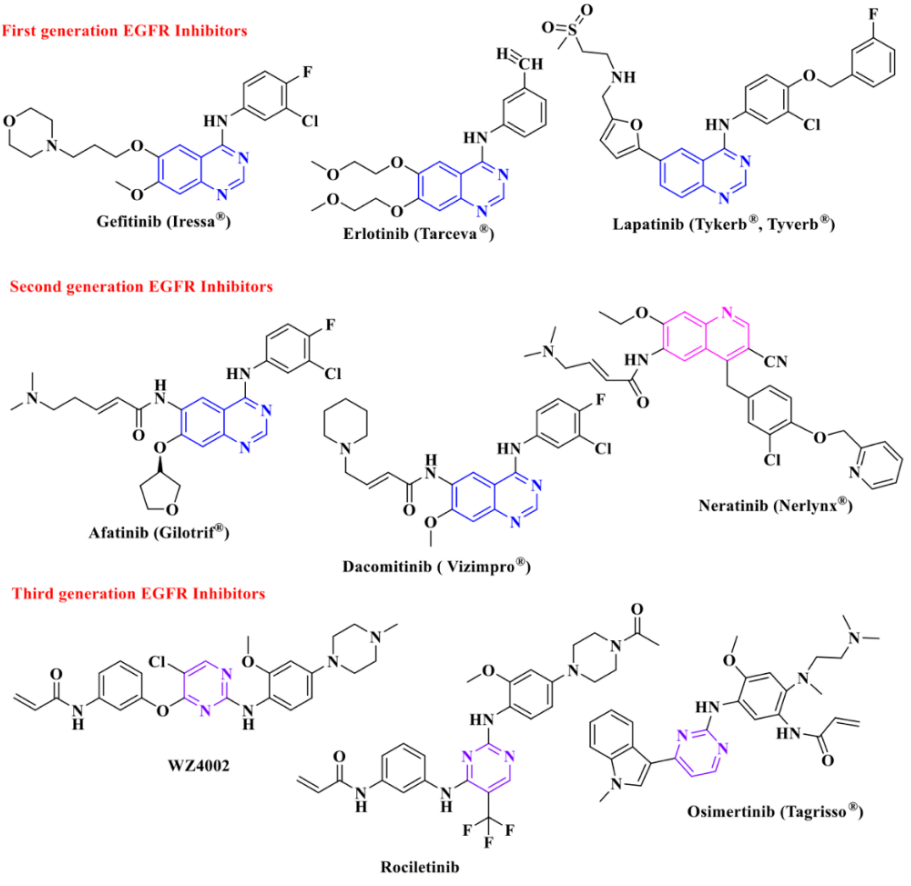

Figure 5. Chemical Structures of TIKs [15].

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5.1. First generation EGFR TKI

First generation TKIs, such as gefitinib, lapatinib, and erlotinib, have been used extensively in the treatment of NSCLC. The first generation TKIs stick to the EGFR TK domain reversibly and inhibit the binding of ATP to the TK domain in order to interrupt cell proliferation and stimulate apoptosis, inhibiting the growth of cancer cells. However, majority of the NSCLC patients have grown resistant to the first-generation TKIs and the chance of recurrence is usually high due to the point mutation of T790M, most commonly.

5.2. Second generation EGFR TKI

Dasatinib, nilotinib, and afatinib are typical second generation TKIs. Second generation TKIs were mainly developed to overcome the resistance that occurs in first-generation TKIs. Second generation TKIs are generally more potent and can achieve quicker responses. Different to the first generation, second generation TKIs bind to the TK domain irreversibly, overcoming T790M or other secondary mutations caused by the resistance of first generation TKIs. However, the efficacy is limited because of the dose-limited toxicity, and it has a higher risk of side effects, particularly cardiovascular complications. Therefore, the use of second-generation TKIs is often more nuanced and may depend on patient's age and medical condition [16].

5.3. Third generation EGFR TKI

The third generation TKIs are the most recent treatment strategy. Typical drugs approved by FDA are ponatinib and osimertinib, in which osimertinib is the most commonly used medicine in the treatment of NSCLC. They are particularly effective against both unmutated EGFR and T790M resistance variants. However, acquired resistance to third generation TKIs also occurs in clinical. The C797S mutation in exon 20 is a typical and representative resistance mutation identified. The C797S mutation eliminates the binding ability of TKIs, leading to resistance. On the other hand, the efficacy of third generation TKIS is also limited to patients who have already developed resistance to the first and second generations of TKIs [7].

In conclusion, EGFR TKIs are relatively more selective and effective treatment of NSCLC. Regarding toxicity, the third generation TKIs have shown a decreased rate of severe morbidity compared to several first and second generation TKIs [17]. However, imatinib, a first-generation TKI, has shown significantly lower toxicity, and it may be a better option for NSCLC patients with comorbidities [18]. Efficacy wise, the third generation TKIs are more effective than earlier generations due to the new mechanisms against cancer cell gene mutations. However, resistance development has been shown in all generations of TKIs. The tumor cell gene mutates all the time. Novel medicines and treatments are needed to be done as soon as possible.

5.4. TKI Resistance in lung cancer

Resistance to TKIs is a crucial obstacle for researchers to develop new generation TKIs or other types of targeted drugs. Two types of TKI resistance are commonly seen in the literature: intrinsic and acquired. Around 25% of the cases are intrinsic resistance due to the lack of initial response to TKI treatment of the patient, while acquired resistance is caused by the development of resistance a period after the treatment. Acquired resistance can occur due to secondary alterations within the gene, which detaches the previous inhibitor from the receptor, resulting reactivation of the signaling pathway or activation of alternative signaling pathways [19].

The T790M mutation in the EGFR gene is one of the most common causes of resistance. A missense mutation changes methionine to threonine at site 790 in exon 20 of the EGFR gene, which decreases the efficacy of the treatment by increasing the ATP affinity to a level that more closely resembles wild-type EGFR. Approximately 60% of recurrences of cancer are caused by T790M mutation [14].

The C797S mutation is another common resistance mechanism, particularly to osimertinib. C797S mutation occurs as the cysteine at codon is substituted by serine, invalidating the binding between osimertinib and EGFR, thereby conferring resistance to the drug. As mentioned, the emergence of the

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C797S mutation can result in resistance to all current EGFR TKIs, but most commonly happens to third generation TKIs such as osimertinib [20].

5.5. Fourth generation TKIs

The fourth generation TKIs are new class of medicine developed to overcome resistance to earlier generations of TKIs. BT-176, OBX02-011, BBT-207, BDTX-1535, BLU-945, and Bi-732 are several drugs that are being developed and have shown promising efficacy in preclinical trials. Most of them have shown high potentials in selecting and overcoming resistance caused by C797S mutation [21].

5.6. Immunotherapies

Immunotherapy combined with TKIs is also a promising solution to the high resistance rate of TKIs. Immunotherapy can help TKI to function even under high resistance due to the tumor mutation. The combination of Afatinib and cetuximab, EAI045 and cetuximab, Brigatinib and cetuximab are widely researched [8].

6. Conclusion

As the technology progresses, novel treatments, including targeted therapy, have been developed. Understanding more about the function of EGFRs and EGFR signaling pathway machinery can lead to more approaches to treating lung cancer. Currently, TKI resistance is a crucial challenge in treating lung cancer. Understanding the molecular and genetic mechanisms of TKI resistance is the key to the development of novel therapeutic strategies. In some cases, reintroducing first-generation TKIs has shown to be effective in cases of T790M loss. However, this approach is still under investigation, and more clinical trials are needed to ensure the result. On the other hand, further research of new drugs and combinatorial therapies is required to improve lung cancer treatment outcomes.

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