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The Mechanism Of Action Of EGFR In Cancer Development And Targeted Therapy And Its Optimization Strategy

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Abstract. The incidence of cancer has continued to rise, particularly among the elderly population with mortality rates surpassing those of other diseases, drawing significant societal attention. The causes of cancer are complex with approximately 5% linked to genetic factors, while studies on the correlation between histone modifications and mutation rates reveal potential differences in germline and somatic cells. The EGFR a receptor tyrosine kinase on the cell membrane is closely associated with the development of various cancers such as non-small cell lung cancer and colorectal cancer, due to its overexpression or mutations. Although significant progress in EGFR targeted therapy, compound mutations and drug resistance still need improvement. This study examined the relationship between EGFR and cancer, using EGFR as a targeted therapy for cancer, including monoclonal antibodies (mAbs) (cetuximab) and combination therapy (pertuzumab). These findings make EGFR targeted therapy important in inhibiting tumor growth and reducing the incidence rate of cancer. In addition, the study also discussed the different populations and their impact on treatment strategies. This study provides a theoretical basis for optimizing EGFR targeted therapy. The research will further investigate the mechanisms of drug resistance and new combination therapies to improve the accuracy and efficacy of cancer treatment.

Keywords: EGFR targeted therapy; cancer drug resistance; monoclonal antibodies and combination therapy.

1. Introduction

In recent years, the incidence of cancer has been increasing. The incidence rate of cancer is mostly the elderly. The mortality rate caused by cancer is higher than other symptoms. The society has a high level of attention on how to prevent cancer. People reduce cancer risk through vaccination. The cause of cancer has uncontrollable factors; it has 5% of cancers are genetically related. An interesting thing is that many histone modifications are inversely associated with mutation and somatic mutation rate, suggesting a different underlying cause causes [1]. An autonomous consider too proposed that chromatin districts in closed shape tend to have higher foundation change rate in germline [2].

Gene Mutation refers to a permanent alteration in the DNA sequence, involving changes in base pairs, which may disrupt gene function and contribute to diseases such as cancer. Mutations create genetic difference among cells in an individual and contribute to variation between members of the same species. Its evolution is the main cause of disease in humans. How mutations and repair shape patterns of mutations in the human genome and interpret their effect on pathogenicity it knows as pathogenicity remains a mystery [2]. Independent research indicates that tightly packed chromatin demonstrates increase baseline germline mutation frequencies compared to open regions. It may infer from endogenous sources, such as spontaneous reactions, replication mistakes and responsive oxygen species (ROS) assault, as well as exogenous sources, such as UV light, radiation and harmful compounds [2]. It has been estimated that around ten thousand damaging events occur in a mammalian genome per cell per day [3]. If not repaired, these errors will lead to mutations that may contribute to evolution and disease. Mutations that arise from different sources occur at different rates with distinct signatures [4]. The genetic composition can also be altered through external influences.

The Epidermal Growth Factor Receptor (EGFR) is a grow on receptor tyrosine kinase on cell membrane (RTK). It controls cell growth, survival, etc. Its abnormal activity is intimately related to

the incidence rate of cancer. The treatment effect of EGFR-specific (mAb) in cancer the main reason is that inhibition of EGFR generated signaling; the role of antibodies against the immune system appears to play an important role in determining the overall anti-tumour response [5,6]. Overexpression or mutation of EGFR gene can lead to uncontrolled cell growth and trigger cancer.

This study is about the relationship between treatment methods for EGFR and cancer. It focuses on the treatment of cancer with EGFR and will analyze inhibitors, mAbs, and combination therapy with other targets for cancer treatment.

2. The Relationship between EGFR with Cancer

EGFR belongs to the HER family, which is a subclass of receptor tyrosine kinases. EGFR family is necessary for regulating cellular functions such as cell proliferation differentiation and life. It mainly regulates cell proliferation, differentiation, cell cycle regulation, tumorigenesis and angiogenesis. In many cancers, overexpression of EGFR protein leads to sustained activation of downstream signaling pathways, facilitate infinite cell increase and anti-apoptosis, including non-small cell lung cancer (NSCLC), colorectal cancer (CRC) and glioblastoma overexpression of EGFR protein leads to sustained activation of downstream signaling pathways. EGFR mutations are a major cause of cancer development. In about 15 to 50% of patients with advanced non-squamous NSCLC, tumors harbor activating mutations in the EGFR [5]. The viability of EGFR-particular mAb in cancer happens much appreciated to restraint of EGFR-generated signaling; moreover, the impacts of antibodies on the safe framework appear to play vital part in deciding the by and large anti-tumour reaction [6]. In addition, mAbs EGFR provides clinical benefits in cancer.

In conclusion, overexpression or mutation of EGFR can lead to sustained activation of downstream signaling pathways, it will promote abnormal cell proliferation, death and tumor progression, it usually seen in the following cancers: non-small cell carcinoma, CRC and glioblastoma.

3. The Mutations in EGFR

There are two main types of EGFR mutation: activating mutation and overexpression of EGFR gene. Among these, the most clinically relevant are the classical activating mutations, which account for the majority of cancer and tumors by EGFR. As of now, the most common sorts of EGFR changes are commonplace enacting changes, counting exon 19 in-frame cancellation (ex19del) around the long-range epigenetically dynamic theme, taken after by the L858R point change in exon 21 [4]. And there are some other not typical mutations include exon 18 mutations and exon 20mutations [4]. EGFR compound mutations are the co-occurrence of multiple genetic alterations within the EGFR tyrosine kinase domain, which are complex mutations involving multiple nucleotide changes at a signal locus, double mutations at distinct sites, or multiple independent mutations distributed across different regions of the kinase domain. The frequency of EGFR compound mutations varies among studies and populations, with previous studies indicating an incidence rate of approximately 4% to 26% among Asians and 5% to 7%among Caucasians with EGFR mutation-positive NSCLC [4]. EGFR gene mutations hold significant clinical implications in NSCLC, primarily categorized into activating mutations and overexpression. Among these, classical activating mutations sever as the main oncogenic drivers, constituting the vast majority of all EGFR mutation cases. The incidence of EGFR compound mutations is notably higher in Asian population compared to Caucasian populations.

The expression of approximately 1000 genes is affected following EGF stimulation of epithelial cells [7,8]. After EGFR stimulation, the immediate- early genes (IEGs) are upregulated in the transcriptional level, leading to the subsequent shutdown of IEGs activation.

4. Targeting Cancer Treatment of EGFR

For cancer targeted by EGFR treatment there are lung cancer, CRC and other cancers. The development of EGFR drugs has Gefitinib, Erlotinib, Afatinib and Brigatinib more than ten types of

drugs, it also obtained usage license in many countries. Over the past 20 years, 20 direct EGFR inhibitors have been developed, including tyrosine kinase inhibitors (TKls) and mAbs [9,10], reflecting the critical importance of EGFR as a specific target for cancer treatment. The TKIs is a class of targeted therapy drugs used to treat cancers with EGFR gene mutations or overexpression, particularly non-small cell lung cancer. The mAbs is a class of bioengineered targeted therapeutics designed to specifically bind to certain antigens. They are used to treat cancers, infectious diseases and autoimmune diseases. They work by blocking the tyrosine kinase activity of EGFR, thereby inhibiting tumor cell proliferation and survival. EGFR TKIs inhibitors are endorsed either within the Joined together States (gefitinib, erlotinib, lapatinib, afatinib et al.) or exterior the Joined together States (icotinib, almonertinib, simotinib, et al.) [11].

4.1. mAb-targeted EGFR Therapy

MAbs targeting EGFR represent an important class of molecularly targeted therapeutics that primarily exert their antitumor effects to the extracellular range of EGFR and blocking it signaling pathways. The clinical treatment with cetuximab involves binding to EGFR in cells, blocking the activation of signaling pathways by EGFR and thereby inhibiting cancer. This leads to down-regulation and reducing the avail-ability of EGFR on the cell surface and preventing activation that of EGFR-associated downstream signaling pathways [6]. It combines with cetuximab to EGFR restrains the movement of the cell period at the G0/G1 boundary, increments expression of the cell cycle controller p27KIP1 and actuates apoptosis by expanding expression of pro-apoptotic proteins or by inactivation of anti-apoptotic proteins actuating diminished expression or phosphorylation [6].

MAbs targeting EGFR such as cetuximab, exert antitumor effects by binding to the receptor's extracellular domain, inhibiting downstream signaling pathways. This leads to receptor internalization and degradation, reducing EGFR surface expression. The treatment induces cell period arrest at the G0/G1 phase cross p27KIP1 upregulation and promotes apoptosis by activating proapoptotic proteins while suppressing anti apoptotic factors. These combined effects block cancer cell proliferation and survival, making EGFR targeted therapy an effective approach in oncology. Clinical applications demonstrate significant efficacy in EGFR overexpressing tumors.

4.2. Therapeutic Targeting of EGFR and Other Molecular Targets

Pertuzumab can modulate EGFR activity, effectively reducing tumor growth and cancer progression. Pertuzumab has been shown to effectively inhibit the proliferative and anti-atrophy effects by EGFR/ErbB2and ErbB2/ErbB3 heterodimers and in clinical studies have demonstrated its robust anti-tumor activity against ErbB2-expressing breast and prostate cancers and against lung cancers co-expressing ErbB2and ErbB3 [1].

In the context of metastatic colorectal cancer, the Erbitux Plus Irinotecan for metastatic colorectal cancer study conducted a multi-country phase III clinical trial to evaluate the efficacy of cetuximab in combination with irinotecan as a second-line in treatment to metastatic colorectal cancer (MCRC) patients with EGFR expression.

Results showed that cetuximab treatment improved the progression-free survival and health-related quality of life [6]. In expansion, cetuximab illustrated movement in CRC

patients with other medicines have fizzled and moving forward PFS, reinforce by and large survival movement and quality of life over best strong care [6]. And results demonstrated that this combination regimen significantly improved PFS, objective response rate, and improvement healthy associated quality of life in patients. For mCRC patients who have failed previous treatments, cetuximab can prolong PFS and OS, while improving quality of life, compared to best supporting therapy. It confirms the clinical value of anti EGFR therapy in refractory.

In a Phase III randomized clinical trial evaluated cetuximab in permutation with radiotherapy for advanced neck, head cancer and the efficacy of cetuximab in patients with progressed head and neck squamous cell carcinoma. In the study, samples of 424 patients were divided into two different

treatment regimens, one receiving with radiation therapy alone and one receiving adjuvant cetuximab. During an average follow-up of 54 months, survival rates were observed in patients who received cetuximab compared to those who received radiation therapy alone. Therefore, the cetuximab group demonstrated superior locoregional control. This is the first study to use a statistically significant survival benefit rate for patients treated with curative intent using an anti-EGFR antibody [6]. A milestone phase III randomized clinical trial evaluated the efficacy of cetuximab combined with radiotherapy in the treatment of advanced head and neck cancer. The study included 424 patients who were randomly divided into a radiotherapy group and a radiotherapy combined with cetuximab group. After a middle take after up of 54 months the study achieved breakthrough results the median survival time of patients in the combination therapy group was remarkable prolonged contrast with the radiotherapy group alone.

Moreover, both local area control rate and PFS showed statistically significant improvement. This study confirms for the first time that use of anti EGFR antibody drugs for curative treatment can significantly improve the survival of patients with head and neck cancer, which has important clinical significance. The research results have established cetuximab as an important treatment option for prolonging survival and maintaining local disease control, which has a profound impact for advanced head and neck cancer. The research has a rigorous design and statistically significant results, providing high level evidence-based evidence for the clinical benefits of cetuximab combined with radiotherapy. Furthermore, these findings open up new avenues for personalized treatment approaches. By identifying biomarkers that predict the response to cetuximab, clinicians can better custom-made therapies to individual patients, maximizing efficacy while minimizing side effects. It ongoing studies are now focused on refining combination therapies and exploring cetuximab's potential in other cancer types.

5. Conclusion

This research mainly explores the relationship between EGFR and cancer, as well as its application in cancer treatment. It mainly includes the association types, targeted therapy methods targeting EGFR (tyrosine kinase inhibitors and mAbs) and combination therapy strategies with other molecular targets. Research has found that overexpression or mutation of EGFR can lead to sustained activation of downstream signaling pathways, thereby promoting abnormal cell proliferation and tumor development, especially in NSCLC, CRC and glioblastoma. Targeted therapy drugs such as gefitinib, erlotinib and cetuximab have shown significant clinical efficacy by inhibiting EGFR activity. Besides, combination therapy (combining pertuzumab with other targets) further enhances the therapeutic effect.

The significance of this study lies in its systematic review of the role of EGFR with cancer development and treatment, providing a crucial reference for understanding EGFR driven tumor mechanisms. The research demonstrates that EGFR targeted therapies can effectively suppress tumor growth. The limitation of this study is the insufficient analysis of how EGFR mutations affect the tumors. There is insufficient evaluation of the long-term effectiveness of EGFR targeted therapies, as well as the mechanisms underlying acquired resistance, which limits a comprehensive understanding of treatment durability. The study does not sufficiently examine the interplay between EGFR and other critical signaling pathways, which could reveal additional therapeutic vulnerabilities.

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