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Mechanisms of resistance to targeted therapies in non-small cell lung cancer (Pharmacology and Therapeutics)

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A B S T R A C T

Introduction: Targeted therapy for lung cancer is a treatment that kills cancer cells, can also affect normal cells, and can cause unwanted side effects. Before targeted therapy used to treat lung cancer, a common approach to treating lung cancer was to use one or more chemotherapy drugs.

Material and Method: In the current study, the issue investigated by reviewing 35 articles (2018-2025) and considering key words such as "lung cancer", " targeted therapy", "cancer", " cell culture", "PDS model" in Scopus, Google scholar and PubMed databases.

Findings: Meanwhile, researchers at MIT's Institute for Biomedical Engineering recently made headlines for using artificial intelligence to discover a new class of antibiotics. The move is part of the group's larger mission to use artificial intelligence to expand the range of antibiotics available. A 2019 study found that 1.27 million lives saved that year if infections made vulnerable to the drugs. One challenge for researchers in this field is finding antibiotics that can target metabolically dormant bacteria. Most antibiotics target metabolically active bacteria, but now, in a new breakthrough using artificial intelligence, researchers have managed to use drug compounds against dormant microbes.

Conclusion: Lung spheroid models offer hope in the search for personalized cancer treatments and serve as a gateway for the development of anticancer therapies tailored to each individual. The findings also showed that this lung PDS model is an effective in vitro drug-screening tool to identify an optimized treatment for the patient.

Introduction

Doctors have developed more than 80-targeted therapies to treat many types of cancer. In addition, they have developed targeted therapies that treat different mutations that are part of a type of cancer. Before receiving targeted therapy [1], your doctor will confirm whether targeted therapy is a good treatment for the type of cancer, you have. Your doctor may need to take blood tests or some tissue from a biopsy [2]. They will examine the samples for specific gene changes or mutations and look for targets that are likely to respond to specific treatments [3].

About 17 percent of AI use is in the field of Drug Repurposing. AI gives researchers insights into polypharmacology, or the ability to bind to multiple targets, relevant to one or more conditions. As with target identification, a common approach here is to create knowledge graphs that reflect the relationships between genes, diseases, and drugs. The neural network then predicts previously unknown connections [4]. So it's no surprise that all the big pharma companies are investing in AI, especially deep learning, which has the potential to make drug hunting cheaper, faster, and more accurate. For example, Benevolent AI used AI

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algorithms to identify existing drugs that could tackle COVID-19. In just 48 hours, researchers identified Baricitinib (known for rheumatoid arthritis) as the best candidate. Clinical trials confirmed the drug's antiviral efficacy [5].

Material and Method: In the current study, the issue investigated by reviewing 35 articles and considering key words such as "lung cancer", " targeted therapy", "cancer", " cell culture", "PDS model" in Scopus, Google scholar and PubMed databases.

Findings

Depending on the type of cancer, targeted therapy drugs can have specific properties that match the genetics of the cancer cells [6]. These drugs can find cancer cells through their genetic mutations and, unlike other methods such as chemotherapy, only affect these cells and do not harm healthy tissues in the body. Now, after targeted therapy drugs find cancer cells, they can either simply reveal their location to the immune system, so that the body can fight cancer as if it were its own disease (immunotherapy), or they can directly intervene and destroy them by working on proteins on cancer cells.

In direct action, targeted therapy drugs either prevent the message from sent to cancer cells to grow and spread further, they stop the process of building blood vessels in the cancer tumor (Figure 1). Therefore, that the cells do not have a source of food for further growth, or they can compensate for the genetic defect of cancer cells, so that these cells also die at their own specified time, like normal cells [7].

Artificial intelligence drug design is an approach that uses artificial intelligence algorithms to identify and design new and optimal chemical compounds for drug development. This approach can help speed up, improve the process of new drug discovery, and reduce the costs associated with this process. Artificial intelligence drug design first requires collecting chemical data about the chemical compounds of interest [8]. Then, this data is analyzed and processed using artificial intelligence algorithms such as neural networks, machine-learning algorithms, and deep learning. In addition, molecular simulation methods used in the design of new drugs with artificial intelligence. In this method, molecular simulation software used to examine the structure and properties of different molecules and find new and better chemical compounds for drug manufacturing.

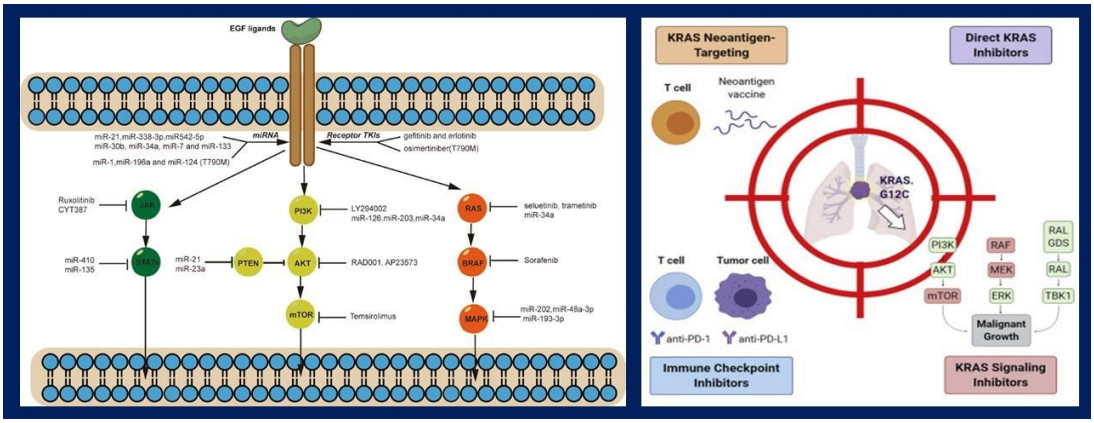

Figure 1. Molecularly targeted therapy

Artificial Intelligence in Drug Targeting

The use of AI in drug discovery and development enables the faster identification of new compounds with medicinal potential. By analyzing biological and chemical data, AI can help determine molecules that are likely to be successful in treating specific diseases. This technology can also predict potential toxicity profiles and drug interactions, and facilitate the optimization of drug formulations. In addition to drug discovery [9],

AI also has significant applications in drug development stages, including the design of clinical trials and analysis of results. AI can help identify appropriate patient groups to participate in trials and, by analyzing the complexities of laboratory and clinical data, help speed up drug development decisions.

Ultimately, the impact of AI on drug discovery and development promises developments that can accelerate access to new treatments and reduce the financial burden of drug research. These developments are promising not only for the pharmaceutical industry but also for patients around the world, as they facilitate access to innovative and effective treatments. Artificial intelligence (AI) is playing an increasing role in the development of anticancer drugs, which, with its unique capabilities in analyzing large and complex data, is contributing to significant advances in this field [10].

The use of AI in the development of anticancer drugs includes several key aspects that help accelerate and optimize the drug discovery process, as well as improve the accuracy of cancer diagnosis and treatment. AI can quickly analyze data on molecules

and chemical compounds to identify promising candidates for anticancer drugs. This process includes predicting the effectiveness of molecules against cancer cells and reducing their potential toxicity to healthy cells [11].

AI can predict drug toxicity profiles with high accuracy and assess the possibility of drug interactions. This helps reduce the time and costs associated with clinical trials and ensures that new drugs are safer and more effective. By analyzing patients' genomic data and biomarkers, AI can help develop anti-cancer treatments that specifically tailored to each patient's genetic or biological characteristics. AI can help optimize the design of clinical trials, including selecting the best patient groups to participate in trials and analyzing trial results to gain a better understanding of the effectiveness and safety of drugs.

By analyzing data on patients' responses to different treatments, AI can help doctors choose the best treatment strategy for each patient, which can improve treatment outcomes and reduce side effects (Figure 2).

QSAR modeling tools have been used to identify potential drugs and have evolved into AI-based QSAR approaches, such as linear discriminant analysis (LDA), support vector machines (SVMs), random forest (RF), and decision trees, which can be used to speed up the analysis. When the ability of six AI algorithms to rank unknown compounds for biological activity compared with traditional approaches, a statistically insignificant difference found [12].

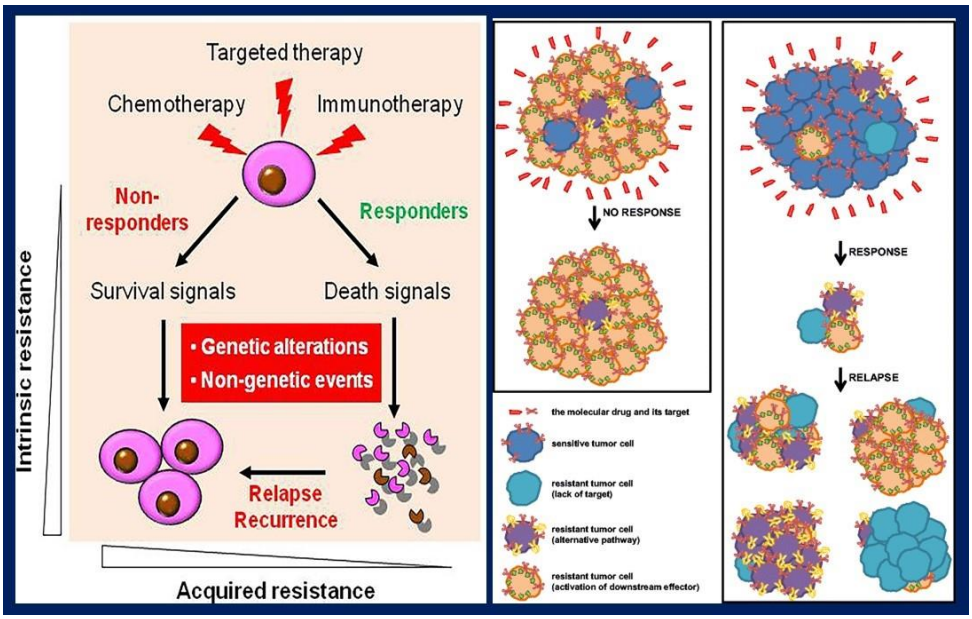

Figure 2. Success rates of targeted therapy for lung cancer

Testing for mutations in the EGFR gene to target cancer treatment

EGFR testing is not a diagnostic test, but it provides information about tumor status, disease progression and appropriate treatment options to the treating physician. Screening for EGFR gene mutations recommended for all patients with colorectal cancer (CRC), non-small cell lung cancer (NSCLC), glioblastoma, head and neck cancer, breast cancer and pancreatic cancer who treated with an EGFR antagonist or in cases where the degree of malignancy of the disease desired. In patients with cancer who do not have mutations in the EGFR gene exons 18 to 21, the likelihood of responding to treatment with monoclonal antibodies increases, and the presence of the mutation increases resistance to treatment [13].

Cellular mechanisms of the drug in eliminating lung cancer

Induction of apoptosis (programmed cell death): DNA damage and oxidative stress can activate various apoptotic pathways in cancer cells. These pathways include A series of biochemical events that ultimately lead to the activation of caspases. Caspases are enzymes responsible for initiating the apoptosis process and modulate various signaling pathways. These enzymes ultimately regulate cell survival and death.

Calpain activation: This substance activates calcium-dependent proteases called calpains. Calpains cleave a number of proteins involved in cell survival, such as Bcl-2 and p53, ultimately leading to the induction of apoptosis.

Immune response: Induction of apoptosis in cancer cells stimulates the immune response. Dying cancer cells release signals that attract immune cells to the tumor site. This feature increases the body's ability to recognize and destroy cancer cells.

Lysosomal rupture: This drug ruptures lysosomes, which are organelles that contain degrading enzymes. The release of these enzymes into the cytoplasm can damage cellular components and induce apoptosis [14].

Designing a Nanoparticle-Based Drug Delivery System for Lung Cancer Treatment

Our challenges lay not only in finding an effective therapeutic agent, but also in precisely delivering it to lung cancer cells. The next step in our study continued by investigating the use of different nanoparticles as carriers to transport and release the desired drug product approximately lung cancer cells. The focus of this innovation was on developing a nanoparticle-based drug delivery system that is capable of not only delivering the drug to the lung cells, but also facilitating its release near the cancer cells. In the early stages of the research, various drug delivery methods investigated, each with its own set of challenges [15]. However, considering the potential of each of them to overcome the barriers of lung drug delivery while ensuring proximity to the cancer cells, a specific type of nanoparticle ultimately used for drug delivery [16].

A series of experiments conducted to optimize the ability of the nanoparticle to nebulize and delivered to the lung tissue. Notably, our final nanoparticle candidate demonstrated a remarkable ability to nebulize effectively, as well as efficiently, uniformly distributed into the lung tissue. Further experiments conducted to assess the safety, efficacy, and efficiency of the nanoparticle structure. Detailed laboratory analyses demonstrated the nanoparticle's bioavailability and its potential to release the drug in a controlled manner [17].

Discussion

Scientists at Spudgen have discovered a definitive cure for lung cancer, representing the pinnacle of medical innovation. Unlike previous ineffective treatments, this therapy has the extraordinary ability to address the diverse challenges that experts have faced throughout the history of lung cancer treatment. This treatment uses extensive medical information and data, clinical experiences and its processing with ultra-advanced technology, relying on the analysis of a large group of scientists at Espagen and the command, control system based on artificial intelligence and using a unique innovation in the use of nanoparticle drug delivery system, succeeded in definitively treating lung cancer at all stages with an astonishing 92.7% result, which is patented [18].

Lung cancer is one of the major global health challenges and continues to require innovative therapeutic strategies that can effectively target cancer cells while also leveraging the patient's immune system for greater efficacy. In this therapeutic approach, the drug used has emerged as a promising agent due to its unique ability to induce apoptosis in cancer cells as well as enhance the immune response [19].

The dual mechanism of action of the drug makes it an effective drug product in the treatment of lung cancer. Using in vitro cell culture assays and in vivo analyses, a wide range of concentrations of the substance evaluated for their effect on lung cancer cell lines, to investigate its effect on cancer cell death and immune regulation [20].

Our experimental results showed that the resulting product induces apoptosis pathways in cancer cells. This phenomenon accompanied by a concomitant upregulation of immune-related markers, which significantly indicates the potential for immune system activation in response to treatment with this product in the environment of lung cancer cells. The findings of the efficacy of the resulting product in killing cancer cells provided a springboard for our research efforts aimed at killing lung cancer [21].

A recent paper published in the journal Biomaterials uses four different machine learning (ML) methods to develop models that predict and understand the influencing factors affecting the properties of PLGA-based nanoparticles. These models were trained using parameters related to nanoparticle size, encapsulation efficiency (E.E. %) and drug loading (D.L. %) [22]. Metrics such as "least shrinkage" and "selection operator" used to identify the most influential features affecting these parameters. These models validated using a validation method and evaluated using metrics such as absolute error, mean absolute error and R-square [23]. Among these types of materials, polylactic-co-glycolic acid (PLGA)-based nanoparticles hold promising prospects in targeted drug delivery systems [24]].

Conclusion

Artificial intelligence (AI) plays a key role in the design of targeted drugs, which leads to more precise treatments with fewer side effects. Targeted drugs seek to interfere with specific biological pathways involved in diseases such as cancer. In this approach, AI helps researchers discover and design these drugs more quickly and accurately. By analyzing big and complex data, AI can rapidly identify molecules and compounds that have high therapeutic potential. This technology identifies biological targets associated with diseases with greater precision and designs drug molecules to interact with these targets. As a result, targeted drugs delivered with higher efficacy and fewer side effects. In addition, AI helps predict the toxicity of drug molecules and complex drug interactions,

leading to optimized drug formulations and more effective clinical trial design. Hence, AI acts as a driving force in advancing personalized medicine and improving patient outcomes. Genprex's gene therapy for diabetes has shown encouraging preclinical results in mice and nonhuman primates (NHPs). The results show that the cells' glucose tolerance is improved and the need for insulin reduced. GPX-002/003 gene therapy could be a long-term solution for diabetes, potentially helping many patients who need insulin replacement therapy. The company's lead treatment option, Reqorsa, has received FDA accelerated review approval as a combination therapy with Keytruda and Tagrisso. Reqorsa uses the Oncoprex nanoparticle delivery system to develop a gene therapy targeting non-small cell lung cancer. NSCLC is any type of epithelial lung cancer other than small cell lung cancer (SCLC). The company has completed two pilot clinical trials and is currently testing the drug as a combination therapy for the underlying cancer. The active ingredient in Reqorsa is a plasmid expressing the TUSC2 gene, which encapsulated within positively charged lipid nanoparticles. It then injected intravenously and targets cancer cells. Reqorsa's mechanism of action combines the properties of gene therapy and immunotherapy, creating a multifaceted mechanism of action. Research has shown that the treatment inhibits cell-signaling pathways that drive cancer growth. It also enables programmed cell death and regulates the anti-cancer immune response. It has also shown to overcome various mechanisms that lead to drug resistance. Developed via the Oncoprex drug delivery system, Reqorsa potentially balances toxicological and transfection efficiency. Preclinical findings and early clinical results demonstrate the mechanism of action of Reqorsa/TUSC2 as inhibiting cancer growth and stimulating immune responses. Furthermore, when used with other targeted therapies or immunotherapies, it shows better results and can overcome drug resistance. The researchers believe that these features are likely to reflect in the results of the Acclaim 1 and Acclaim 2 clinical trials, thus placing Reqorsa in a large yet competitive market. In addition, GPX-002/003 has high potential and may be the first gene therapy to evaluate in people with diabetes. Given the different approaches of Oncoprex and GPX-002/003 gene therapy, researchers are very optimistic about the company's long-term prospects.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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