International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 2, No. 2, 2023

Application of PROTACs in the Pharmaceutical Direction

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Abstract: Proteolysis targeting chimeras (PROTACs) technology is a novel drug development strategy that can treat diseases by selectively degrading targeted proteins. PROTACs consist of two molecules, one of which binds to the target protein while the other binds to the protein degradation enzyme, thus promoting the degradation of the target protein. Compared to the mechanism of action of traditional drugs, PROTAC technology has many advantages, such as high selectivity, reversibility, and low dosage effects. PROTAC technology has been widely applied in multiple fields, especially in cancer research. PROTACs can target cancer-related proteins for degradation, thereby inhibiting tumor growth and metastasis. For instance, PROTACs targeting proteins such as BCL-2 and BRD4 have been extensively researched and applied in cancer treatment. In addition, PROTAC technology can also be applied to multiple fields such as neurodegenerative diseases, immunotherapy, metabolic diseases, and infectious diseases. Although PROTAC technology has broad application prospects, there are still some challenges, such as how to improve the stability and pharmacokinetics of PROTACs, and how to prepare large-scale PROTACs. Therefore, further research and optimization are still needed to further improve PROTAC technology and promote its application in clinical treatment.

Keywords: PROTACs; Protein degradation; Neurodegenerative diseases.

1. Introduction

Proteolysis targeting chimeras are bifunctional molecules that can selectively degrade intracellular proteins by recruiting an E3 ubiquitin ligase to the target protein. PROTACs work by inducing the degradation of proteins of interest through the recruitment of an E3 ubiquitin ligase. The E3 ubiquitin ligase induces the ubiquitination of the protein of interest, which is then recognized by the proteasome and degraded. This mechanism allows for the selective degradation of intracellular proteins, which is not possible with traditional small molecule inhibitors that only block the activity of the protein of interest [1].

This technology has gained significant attention in recent years due to its ability to target previously undruggable proteins and its potential to revolutionize drug discovery. In this review, we will discuss the historical development, mechanism of action, current applications, challenges, and future directions of PROTAC technology [2].

2. The application of PROTAC technology in the treatment of neurodegenerative diseases.

Neurodegenerative diseases are a common type of neurological disorder, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and more. The pathogenesis of these diseases is complex, and currently, there is no cure. However, as a novel drug development strategy, PROTAC technology can treat these diseases by selectively degrading proteins related to neurodegeneration. This article will review the application of PROTAC technology in the treatment of neurodegenerative diseases [3].

2.1. Treatment of Alzheimer's disease

Alzheimer's disease is a common neurodegenerative disease, and its pathogenesis is related to the abnormal aggregation of tau protein and β-amyloid protein. In recent years, PROTACs targeting tau protein and β-amyloid protein have been developed. For example, a study reported a PROTAC that can induce the degradation of tau protein, reduce tau protein aggregation, and improve cognitive function in Alzheimer's disease mice [4].

2.2. Treatment of Parkinson's disease

Parkinson's disease is a common neurodegenerative disease, and its pathogenesis is related to the loss of dopaminergic neurons. In recent years, PROTACs for neuroprotection and regeneration have been studied. For example, a study reported a PROTAC that can enhance neuronal growth, induce the degradation of PINK1 and Parkin, and promote the regeneration of dopaminergic neurons [4].

2.3. Treatment of Huntington's disease

Huntington's disease is a common neurodegenerative disease, and its pathogenesis is related to the abnormal aggregation of HTT protein. In recent years, PROTACs targeting HTT protein have been studied. For example, a study reported a PROTAC that can induce the degradation of HTT protein, reduce HTT protein aggregation, and improve cognitive function in Huntington's disease mice [5].

2.4. Treatment of other neurodegenerative diseases

In addition to the above three neurodegenerative diseases, PROTAC technology can also be used to treat other neurodegenerative diseases. For example, PROTACs targeting α-synuclein have been studied, which can induce the degradation of α-synuclein and improve the symptoms of neurological diseases such as multiple sclerosis [6].

As a novel drug development strategy, PROTAC technology has the ability to selectively degrade multiple

proteins, making it a promising approach for the treatment of neurodegenerative diseases. Although there are still some challenges, such as improving the stability and pharmacokinetics of PROTACs, with the continuous development and optimization of the technology, PROTAC technology is expected to play an important role in the treatment of neurodegenerative diseases.

3. The application of PROTAC technology in anti-tumor field

PROTAC technology is a novel drug development strategy that can treat diseases by selectively degrading proteins. In recent years, this technology has received increasing attention in anti-tumor drug research. The following is an overview of the application of PROTAC technology in anti-tumor field [7,8].

3.1. Inhibition of tumor cell growth

PROTACs can inhibit the growth of tumor cells by targeting the degradation of proteins. Currently, the majority of selected targets are tumor growth factors, which can be degraded by targeting them with PROTACs, thereby achieving an inhibitory effect. Oncogenes or tumor suppressor genes can also be selected as targets, and targeted degradation can be used to achieve the effect of inhibiting tumor growth. For example, PROTACs targeting BCL-2 can induce apoptosis in tumor cells, thereby inhibiting tumor growth. In addition, PROTACs targeting BRD4 can inhibit tumor cell proliferation and metastasis [9].

3.2. Overcoming tumor drug resistance

PROTACs can overcome drug resistance of tumor cells by targeting the degradation of proteins. Over time, most cells develop varying degrees of resistance to anti-tumor drugs. Some cells exhibit strong tolerance to anti-tumor drugs, leading to a significant reduction in the therapeutic effect of the drugs. Research has found that some cells express drug-resistant proteins inside the cells, which reduces the efficacy of the drugs. By using PROTACs to degrade drug-resistant proteins inside the cells, the cell's drug resistance can be reduced, thereby overcoming tumor drug resistance. For example, PROTACs targeting HER2 can degrade HER2 protein, thereby enhancing the sensitivity of breast cancer cells to HER2 inhibitors. In addition, PROTACs targeting BET proteins can overcome tumor cell resistance to BET inhibitors [10].

3.3. Targeting multiple targets

PROTACs can simultaneously target multiple proteins, thereby more effectively inhibiting tumor cell growth and metastasis. Studies have found that some small molecule inhibitors can bind to multiple targets simultaneously and produce inhibitory effects. Based on this, some researchers have identified critical binding sites and developed a type of PROTACs that can simultaneously bind to multiple tumor growth-related proteins, thereby improving the therapeutic effect. For example, PROTACs targeting both BCL-XL and MCL-1 can simultaneously target these two proteins, thereby more effectively inducing apoptosis in tumor cells [11].

3.4. Reducing side effects

In the design of PROTACs, specific proteins are usually targeted to achieve higher selectivity. Compared with traditional chemical drugs, PROTACs are more precise in their actions, which can reduce the adverse effects on healthy cells. The therapeutic doses of traditional drugs are usually high, which not only increases the side effects of drugs but may also lead to drug resistance. However, PROTACs can reduce the dose of drugs by enhancing the drug's efficacy, thereby reducing the drug's side effects [12]. The design of PROTACs usually includes multiple small molecules that can work together to achieve long-lasting drug effects. This long-lasting effect can reduce the frequency and dose of drug use, thereby reducing drug side effects [3]. PROTACs can directly act on intracellular proteins, thereby reducing unnecessary drug effects in vitro. This intracellular specificity can reduce drug side effects.

PROTAC technology has tremendous potential in the research of anti-cancer drugs. By selectively degrading target proteins, it can more effectively inhibit the growth and metastasis of tumor cells and overcome drug resistance. Although there are still some challenges, the continuous development and optimization of PROTAC technology is expected to achieve its application in the clinic[14].

4. Summary

The development of PROTAC can be traced back to the 1990s when scientists began to explore the use of protein-protein interactions to achieve protein degradation. With the continuous improvement of technology, scientists have gradually discovered some PROTAC molecules with strong effects, such as ARV-110 and ARV-471. These molecules have shown great potential in the treatment of cancer, autoimmune diseases, and other diseases.

The advantages of PROTAC lie in its high specificity, which can selectively degrade the target protein without affecting the function of other proteins. This specificity can effectively reduce the side effects and adverse reactions of drugs. In addition, PROTAC can cause multiple degradation, making the drug's action time longer, and therefore having a longer duration of action. PROTAC can also be used to treat difficult-to-treat diseases such as cancer and autoimmune diseases.

However, the development of PROTAC still faces some challenges. One of the biggest challenges is how to find suitable small molecules to achieve protein degradation. In addition, how to improve the stability and bioavailability of PROTAC is also an important issue. Scientists are constantly pushing the development and innovation of the technology to develop more excellent PROTAC molecules, bringing better healthcare to human beings.

In summary, PROTAC is a promising drug development strategy with high specificity and efficacy. It can be used to treat difficult-to-treat diseases. Although the development of PROTAC still faces some challenges, with the continuous progress and innovation of technology, it is believed that PROTAC will bring better healthcare to human beings.

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