Overview on Antibody-drug Conjugates Development

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Abstract

Since the 20th century, medical scientists represented by Paul Ehrlich, the father of chemotherapy, have been searching for such a "magic bullet" that distinguishes between pathogens and normal cells. Since the beginning of the new century, more and more people believe that antibody-drug conjugate (ADC) is the answer that has long been sought.

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Since the 20th century, medical scientists represented by Paul Ehrlich, the father of chemotherapy, have been searching for such a "magic bullet" that distinguishes between pathogens and normal cells. Since the beginning of the new century, more and more people believe that antibody-drug conjugate (ADC) is the answer that has long been sought.

The ADC is made by attaching a cytotoxic small molecule drug to a monoclonal antibody via a chemical link, which combines the targeting of antibodies with the lethality of small molecule chemicals.

During the whole process, the antibody is equivalent to the missile's "navigation system", which guides it to find the tumor cells. The small molecule cytotoxic drugs coupled with the antibody are equivalent to the missile's "warhead" and kill the tumor cells. Antibody drug conjugates use the targeting of monoclonal antibodies to target small molecule drugs to pathogens such as tumors, avoiding normal cells, thereby minimizing the damage of drugs to normal cells.

The development of antibody drug conjugates is much more complicated than common drugs. Key processes include: target screening, selection of small molecule chemical drug warheads, design and optimization of coupled molecules, and antibody selection.

ADC drugs are mainly used for anti-tumor, so the ideal target antigen should be expressed at a high level on the surface of tumor cells, with little or no expression in normal cell tissues. Some of the tumor targets currently screened in clinical trials are expressed only in certain types of tumor cells, and many targets are expressed in most types of tumor cells.

Secondly, after binding the antibody to the selected antigen, it can be effectively internalized, facilitating the entry of the ADC into the cell and killing the target cell. However, some studies have shown that in some cases, even if the antibody drug complex and the target are combined, no internalization into the cell can exert a bystander effect and kill the tumor cells.

Selection of drug "warhead"

Currently, antibody drug complexes have a limited number of small molecule chemicals to choose from, some of which are microtubules inhibitors that inhibit mitosis; the other are DNA-damaging agents.

Most of the small molecule cytotoxic drugs used in ADCs are hydrophobic, preventing antibody aggregation, thereby prolonging the shelf life of the drug, increasing the residence time in blood tissue, and enhancing the efficacy of the ADC.

Since only a small portion of the antibody can effectively enter the tumor site after entering the body, the drug needs to have an efficient and sensitive killing effect on the target cell. Common drug warheads include: Auristatins, Tubulysins, Calicheamicins, Duocarmycins, Benzodiazepines, Camptothecin analogues, Doxorubicin.

Antibody selection and optimization

Because the ADC stays in the environment before entering the cell, it is often tissue blood. In clinical trials, the requirement for ADC drugs is to stay in the blood for as long as possible before exposure to pathogenic cells. The antibody drug complex in this process should be in a state of being stable, not decomposing, and not being cleared by the human immune system.

This requires that the selected antibodies need to have relatively low immunogenicity, long half-life, and high stability. The traditional antibody protein subtypes mainly include IG1, IG2, IG3, and IG4, among which, since the half-life of IG3 in tissue blood is only other 1/3 of the antibody type, so clinically IG3 is generally not selected as an ADC drug.

Compared with the development of common drugs, antibody drug conjugates require more research and development investment, but because of the great side effects of ordinary chemotherapy, the body is rapidly weakened during cancer treatment, and the quality of life is greatly affected.

In contrast, the targeting characteristics of antibody drug conjugates can minimize the damage to normal tissues, and reduce the side effects on humans while treating cancer. Therefore, antibody drug conjugates will have a broad future. Application prospects.

About us

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