Progress in the Application of Targeted Agents in Non-small Cell Cancer

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Abstract: Research subject: primary targeted preparation, that is, the drug is released from the capillary bed into the target site; Secondary targeted preparation, that is, drug release from special cells (such as tumor cells) entering the target; Tertiary targeted preparations are drugs that act on certain parts of cells. Research methods: Compared with traditional preparations, targeted preparations can improve drug selectivity, reduce adverse reactions, enhance efficacy and improve patient compliance, and become the focus of new drug research and development. Therefore, scientific and reasonable targeted evaluation techniques and methods should be established based on this point to improve the safety, effectiveness and quality control of such drug preparations. Objective: This paper reviews the targeted application of anti-tumor targeting agents, and introduces the targeted technology and application from the aspects of targeting and pharmacology, so as to provide reference for the development trend of anti-tumor targeting agents in the future. Conclusion: According to the study, attention should be paid to improving the drug encapsulation rate and drug loading, and increasing the drug stability, so as to obtain drug preparations with large drug loading, good stability and strong targeting.

Keywords: Non-small Cell Lung Cancer; Targeted Preparations; Application Research.

1. Introduction

With the incidence rate of cancer increasing year by year, targeted preparations have become one of the research hotspots in the field of pharmaceutics in the world due to their high efficacy and low side effects. In the treatment of cancer, targeted agents have the following advantages: (1) fast drug delivery, rapid access to the lesion site after drug delivery; (2) High safety, low toxicity and side effects. It only works on cancerous sites and does not cause damage to surrounding normal cells; (3) With a small amount of drugs, appropriate targeted preparations can play a therapeutic role. However, because the research on targeted agents is still shallow and some technical problems have not been broken through, only a small number of targeted agents are used in clinical practice, and most of them are still in the research stage.

2. Targeted Preparation Research based on Pharmaceutical Perspective

2.1. Serine Targeted Preparation

Although serine is classified as non-essential amino acid, serine is essential in cell metabolism and plays a key role in a variety of cell processes. Serine can be converted to glycine through the action of serine hydroxymethyltransferase (SHMT), which provides a "one carbon" unit to promote the synthesis of 5,10-methylenetetrahydrofolate, while 5,10-methylenetetrahydrofolate is a precursor of folate to facilitate the synthesis of purine nucleotides. In addition, serine can react with palmitoyl coenzyme A to provide sphingosine, which is necessary to form sphingolipids of cell membrane. In addition, serine is the precursor of several amino acids, such as glycine and cysteine, which is essential for protein synthesis. Because serine also participates in the production of NADPH, serine can play a role in regulating the redox state. In short, serine can provide nucleotides, lipids, amino acids and cofactor building blocks, so it can promote cell proliferation [1].

Cells can not only obtain serine from foreign sources through amino acid transporters, but also synthesize it from glucose through SSP. Through three consecutive enzymatic reactions, the intermediate of glycolysis, 3-phosphoglycerate is converted into serine. NAD + dependent PHGDH is the key enzyme limiting the first step of its synthesis pathway [2]. The analysis of human cancer shows that PHGDH is located in the genome region with the most common repeated copy number increase in breast cancer and melanoma. In cell lines with high PHGDH expression level, inhibition of PHGDH leads to a reduction in serine synthesis and a significant inhibition of cell proliferation, which has led to the understanding of serine synthesis and downstream metabolites (including "one carbon" unit and α-Ketoglutaric acid). Therefore, the study of PHGDH inhibitors as targeted cancer therapy has shown great clinical research significance and application value [3].

2.2. Research on Low-density Lipoprotein Targeted Preparation

In Fig 1, the structure of LDL is shown.
The structure of LDL is an emulsion particle model, which is composed of about 1600 pericholesterol acetate molecules and a small amount of glycerol triacetate. The surface is covered with about 700 phospholipid molecules, 500 free cholesterol molecules and a polar outer mouth of apolipoprotein B-100 (ApoB-100). The particle size is 18–25nm, and the molecular weight is 3x10^4[4].

Low-density lipoprotein receptor (LDLR) is a multifunctional protein, composed of 836 amino acid residues and a 36hedral structural protein with a molecular weight of about 115kd. It is composed of five different regions. Each region has its unique function as shown in Figure 2.

Fig 2. The structure of LDLR and VLDLR

Ligand-binding domain is the ligand-binding domain consists of 292 amino acid residues, including 47 cysteine (Cys). It contains seven repeat sequences composed of 40 residues similar to complement Cb and Cq. Each repeat sequence has 6 cysteine residues. All 42 cysteine residues have formed disulfide bonds. The repeat sequences 2, 3, 6, and 7 are necessary for binding to LDL. Mutation of any one of them will make the receptor lose the ability to bind to LDL. Repeat sequence 5 is combined with β- VLDL. If the sequence is mutated, the receptor binds β- The capacity of VLDL is lost by 60%. The receptor can not only bind LDL, but also VLDL. β- VLDL and VLDL residues can not only recognize ApoB100, but also identify apoE-containing lipoproteins. ApoE and B100 are ligands of LDL receptor, so LDL receptor is also called ApoB100E receptor [5].

The EGF precursor domain is a peptide segment composed of about 400 amino acid residues, with five repetitive sequences, each of which contains 25 amino acid residues. The EGF precursor domain is homologous with the mouse epithelial growth factor and the EGF precursor, hence the name of this region. In vitro experiments confirmed that the peptide segment in this region belongs to extracellular structural protein and plays a supporting role [6].

The glycosyl domain is composed of 58 amino acid residues, which is a peptide segment close to the cell membrane surface, with 18 serine or threonine, forming an O-linked sugar chain, and also supporting the LDL receptor [7].

The transmembrane structure is composed of 22 amino acid residues, rich in hydrophobic amino acid residues, belonging to transmembrane proteins, which play an "anchoring" role in the cell membrane. If this region is defective, it will affect the extracellular secretion of the receptor [8].

The cytosolic domain is located at the cytoplasmic side of the cell membrane and consists of 50 amino acid residues. The C-terminal is located in the cytoplasm and "deeply buried" in the cytoplasm [9].
the high concentration GSH environment, and rapidly releases the anticancer drugs contained in it into the cell. In terms of improving the stability of micelles, the cross-linking of shell or core can prevent the loss of drugs before reaching the target area, making this kind of micelles a stable and sensitive drug delivery carrier [14].

3.2. Application Research on Temperature Transfer of Targeted Preparations

Temperature is also a widely used factor in drug delivery systems. When some part of the body has pathological changes or such signal stimulation is given in vitro, the temperature will rise. If a polymer is water-soluble below a certain temperature, but becomes insoluble and causes phase transition above that temperature, this temperature becomes "low critical solution temperature (LCST)". If the opposite behavior occurs with temperature change, it is called "upper critical solution temperature (UCST)". Among the polymers with this characteristic, polyisopropylacrylamide (PNIPAM) is the most commonly used temperature-sensitive medical material because of its LCST close to human body temperature (about 33°C) [15]. The polymer and nucleic acid complex can be prepared at a temperature lower than the LCST of the polymer, and the drug will be released when the polymer structure changes under the physiological temperature transported to the cell. Ana et al. 38, based on PNIPAM, added (3-propenylaminopropyl) trimethyl chloride (AMPTMA) to adjust the critical dissolution temperature of the copolymer, and provided more positive charges for the whole complex, so as to better combine with biological molecules with negative charges such as nucleic acid. The temperature-sensitive polymer complex carrying siRNA was prepared at 25°C. The experimental investigation on human fibrosarcoma cells (HT1080 cells) at 37°C showed that the expression of GFP protein in the cells was inhibited under the effect of this temperature-sensitive material, and the expression meter was 32% of the control group [16].

3.3. Related Research based on Liposome Targeted Drug Delivery

The lung targeted drug delivery system uses chemical or pharmaceutical means to release the drug in the lung tissue to improve the local concentration of the lung capsule, reduce the dosage of the drug in the whole body, reduce the side effects of the whole body. There are many ways to release the drug in a targeted way, such as preparing the drug into liposomes, microspheres, cyclodextrin inclusion or structural modification [17].

Liposomes are mainly composed of phosphorous brain, and phosphorous fetus is an important component of alveolar surfactant. Therefore, liposomes are particularly suitable for the release of lung energy drugs. Because of the function of reducing the surface tension of sulfur-lipid substances, it can make the liquid quickly spread on the surface of the alveoli, and make the lipid particles disintegrate, so that the drug can be rapidly absorbed on the surface of the alveoli to achieve the goal of lung targeting aging drugs. In addition, it is confirmed that lipid components can partially activate alveolar macrophages on the surface of the lung. Therefore, liposomes are the most studied tumor-directed drug delivery system [18].

There are two main ways of administration of liposome lung targeted preparations that have been studied. One is intravenous administration, which reaches the lungs through blood circulation. The particles with particle size of more than 7 m are mechanically filtered by the lungs to achieve the purpose of fertilization. This method is gradually abandoned because the particles with larger particle size may cause blood vessel congestion, which has a major safety problem, and the other is direct swelling of the drug. In this study, aerosol inhalation was used for direct lung administration.

4. Conclusion

The research of targeted drug preparations mainly focuses on how to solve the defects of many adverse reactions and poor targeting in vivo of traditional anti-tumor drugs, and at the same time, pay attention to improving the drug encapsulation rate and drug loading, and increase drug stability, in order to obtain drug preparations with large drug loading, good stability and strong targeting.

References

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