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Albumin-binding prodrugs' use in treating cancer

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Abstract. Throughout the past few decades, the use of targeted delivery methods for cancer therapies has dramatically increased. Prodrug, a type of drug that can apply the targeting therapy, is defined as chemicals that undergo chemical transformations after enters the patient's body. They will be activated and release the parent drug after reached the targeted site. Both passively and actively targeted therapies are explored. The albumin-binding prodrug, a model of prodrug applying passively targeted therapy, this paper introduces the enhanced permeability and retention (EPR) effect to target the tumor site. Besides, since the human serum albumin is an endogenous substance originated from human body, its nanoparticles is able to carry the anticancer drugs to elongate the circulatory half-lives of drugs since it will not be rejected by the immune system. However, the activated compound's systemic toxicity and the dearth of information regarding the biodistribution of prodrugs are two possible disadvantages. Moreover, some exogenous albumin formulations are prohibited from participating in clinical trials because of their very poor delivery efficiency. In conclusion, the albumin-binding prodrug is a cancer treating therapy that has great promise and great capability despite the potential risks.

Keywords: albumin-binding prodrugs, anticancer, the EPR effect.

1. Introduction

Recent decades, scientists have explored extensively in the targeted drug delivery system. Now, they can deliver the anticancer drugs to the tumor tissue efficiently [1]. The nanomaterials such as polymeric nanoparticles, dendrimers, micelles, liposomes and other inorganic nanoparticles are especially focused [2]. The prodrug, which is defined as a chemical that is transformed before it has pharmacological effects, are used in the targeted therapy since the side-effects of the toxic drugs can be reduced when the number of drugs is reduced.

The passively targeted therapy is developed with the help of the EPR effect. The nanoparticles are able to penetrate the cleavage between the endothelia cells in tumor tissue and finally accumulate in them, due to the enhanced permeability and retention. There are also some approaches to deliver the activating enzymes, which are considered actively targeted therapy. For example, by using the chemical trigger, the therapy may let the enzyme be a conjugate to an antibody, a polymer-based nanoparticle, a virus or even an entire cell [3]. In addition, the physical trigger can be used to activate the prodrug from the exterior. The photodynamic therapy (PDT) is now extensively explored and has become an effective treatment to many types of solid tumors. By using this therapy, the unreactive prodrug will be activated by visible lights or near-infrared light and then be converted to toxic drug [3]. Advantages of using PDT includes less harmful radiation. Also, PDT will not weaken the immune system like what the

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radiotherapy does, since it will not decrease the amount of white blood cells (WBCs) and other immune system cells.

However, there are some shortcomings in this system, such as the potential toxicity of the nanocarriers and the complex structures which has limited the mass-production of the drugs. Also, only a few drug candidates are allowed to be used in clinical trials.

This paper explains what prodrugs are and focuses on an example of albumin-binding prodrug called Aldoxorubicin. Besides, this paper gives accounts of the hydrazone linker, doxorubicin drug, the EPR effect applied, and the positives and negatives of prodrugs.

2. Prodrugs

When body cells are growing and spreading in a human's body uncontrollably, this person is considered getting cancer. Cancer cells are multiplying and invading abnormally, they sometimes form malignant tumors, which can continuously spread to adjacent tissue. The energy and nutrients the tumor cells needed is increasing dramatically at time passed. One difficulty of treating cancer is the poor tumor site selectivity [4]. One direction that scientists are exploring is to improve the targeting ability of drugs, which means the drug should precisely attacking the cancer cells instead of the normal cells.

Prodrug is drug molecules that undergo enzymatic and chemical transformations to release the active parent drug [5]. Prodrugs are designed in two ways, one is called bioprecursor, another one is called carrier-linked prodrug. The bioprecursor is a simple compound that transforms into an active parent drug metabolically or chemically [6]. The carrier-linked prodrug is an active molecule linked to a carrier through a covalent linkage. It will release parent drug and the carrier to become active drug after metabolic hydrolysis [7]. The carrier-linked prodrug is pH-sensitive, which means it utilize the unusual acidic environment caused by cancer to cleavage hydrazone linkage.

3. The construction of an albumin-binding prodrug aldoxorubicin

The construction of the albumin-binding prodrug includes a drug, linkers, and a peptide. The specific prodrug this paper introduced as an example is called Aldoxorubicin, a prodrug of doxorubicin (DOX). In this prodrug, the linker to albumin is maleimide moiety, the linker to drug is hydrazone, and the prodrug binds with human serum albumin [8]. The maleimide moiety of the prodrug reacts rapidly and selectively with the cysteine-34 position of endogenous human serum albumin (HSA) via Michael addition. After that, DOX is released from the albumin carrier by the cleavage of hydrazone bond in the acidic environment of cancer cells. The Aldoxorubicin has been investigated in clinical trials. It can improve the pharmacokinetics and biodistribution of mice with tumor and can effectively bind with endogenous albumin. Comparing with free DOX, the prodrug Aldoxorubicin has greater targeting ability and better therapeutic effect.

3.1. Hydrazone

The reason why hydrazone is chosen to be the linker of drug is due to its chemical property. The hydrazone relates to ketones and aldehydes, it releases free drug through hydrolysis once an ADC is transported to acidic endosomes (pH 5.0–6.0) and lysosomes (pH about 4.8).

At the same time, cancer cell will always create acidic environment. The rapid growth of cancer cells requires a lot of oxygen and energy, which leads to three properties: hypoxia, glycolytic tumor cell metabolism, and inefficient blood perfusion.

Another mechanism for cancer cells to create acid is the Warburg effect. In normal cells, energy was produced through the usual citric acid cycle and oxidative phosphorylation in the mitochondria. However, the Warburg effect explained that most cancer cells go through a less efficient process of "aerobic glycolysis" consisting of high level of glucose uptake and glycolysis followed by lactic acid fermentation taking place in the cytosol, even in the presence of abundant oxygen [9]. To increase the rate of glucose uptake, lactate join the final electron transfer chain in the aerobic glycolysis. So, the byproduct is lactic acid and lactate.

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Hydrazone linkage is pH-sensitive, it will only break in acidic environment, which is formed by the lactic acid produced by tumor cells. Thus, the hydrazone linkage will only release the drug at where the cancer cell exists, which represents the targeting ability of the hydrazone linkage.

3.2. Human serum albumin

HSA, also known as human serum albumin, is an essential nutrition supply for the body. Due to its numerous benefits, such as good biodegradability, easy surface modification, and high biocompatibility, albumin has been intensively researched as a natural medication delivery mechanism [2].

The target site of cancer cell. It is a global plasma protein, and the structure is shown in Figure 1.

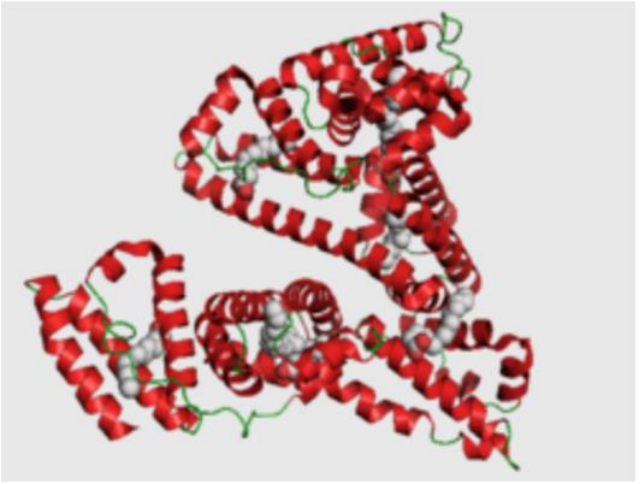

Figure 1. The structure of human serum albumin [10].

Through the protein nanoparticle generation, HSA as the carrier will pack the drug inside and enter the cell by endocytosis. After getting into the tumor cell, the HSA nanoparticles and drugs will accumulate.

One of the reasons HSA is selected is because it is an endogenous substance, which means it can be produced by human body itself. Thus, the prodrug carried in the HSA will not be recognized as enemy by the immune system. So, the advantages of using HSA have included increased stability and activity, decreased enzymatic degradation, decreased immunogenicity, decreased phagocytosis, and decreased renal clearance.

4. The EPR effect

EPR effect, also known as enhanced permeability and retention effect, is an important mechanism that plays an important role when the HSA nanoparticles are functioning [10]. In normal tissue, there are densely connected vascular endothelium and healthy lymphatic system. The closely packed endothelial cells prevent the nanoparticles from crossing the blood vessel, and the lymphatic system allows body fluid returns to the circulatory system.

However, in tumor tissue, there are hyper-vascular, abnormally organized leaky vasculature, and ineffective lymphatic system. There will be leakages between the endothelial cells which allow nanoparticles with diameter 100-800nm to pass through, and that's what the permeability on the name of the EPR effect means. When tumor has a volume that is larger than 2 mm3, its diffusion will be limited [11]. This limitation will affect nutrition intake, waste excretion, and oxygen delivery. To overcome this limitation, the tumor will increase the surrounding vasculature which is called angiogenesis, and thus get more excess to the energy, nutrients and oxygen. The tumor cells undergo angiogenesis have basement membrane that are abnormal and has distorted shape and do not have normal amount of pericytes lining endothelial cells. In different tumor types, the gap may have a size of a range from 100 nm to 2 μm.

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The retention effect is due to the ineffective lymphatic system. The tumor cells do not have well-developed lymphatic system. So, there will be a high interstitial pressure which will force out the fluid and causing a convective interstitial fluid flow towards the periphery of the tumor, which prevents the accumulation of drugs toward the center of the tumor. However, the nanoparticles will have longer retention time due to the leaky vasculature and poor lymphatic drainage. They limited the nanoparticles to return to the tissue fluid (Figure 2). Finally, the nanoparticles, including the prodrugs, which are smaller than the leakage will reach the interstitium and be packed in the tumors [12].

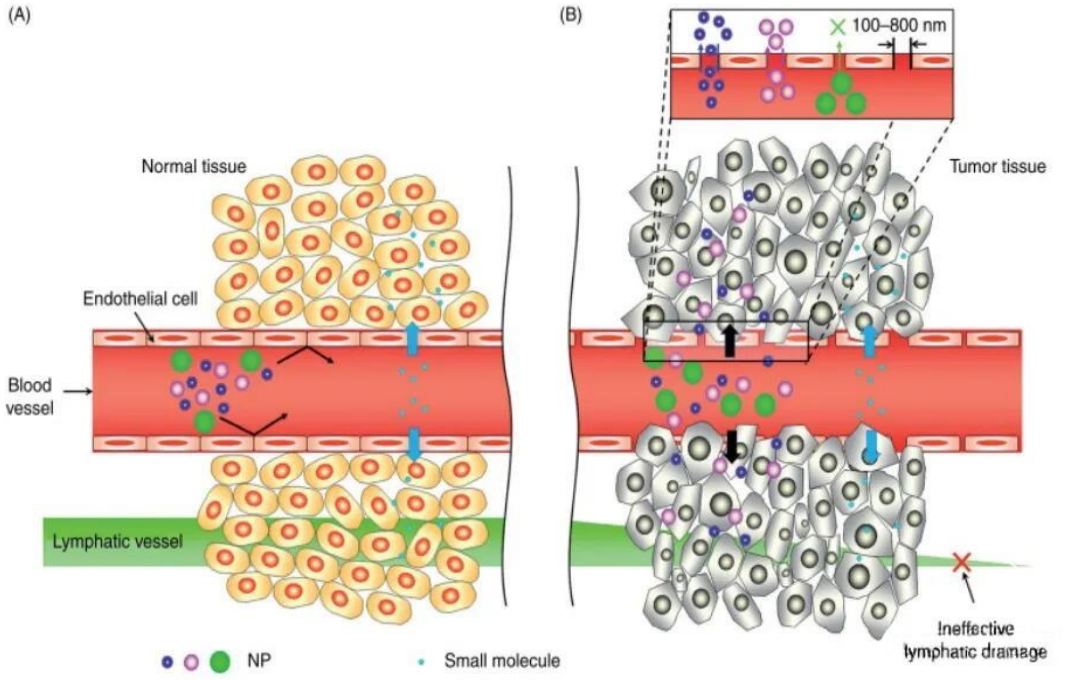

Figure 2. (A) The comparison between the condition of normal tissues; (B) the condition of tumor tissues [13].

The EPR effect is the strategy that the researchers have explored the most [1]. However, although some tumor cells are in high-EPR xenografted tumors, the nanoparticles can only accumulate a small percentage, even less than 1%. One reason may be the physical barriers such as the endothelial barriers, cellular barriers, or the Kupffer cell. Another reason may be the significant stochasticity in the extravasation of NCs across the tumor vascular.

5. The receptors of HSA

After the drugs pass through the endothelium cells, they are able to bind with special receptors over-expressed on the tumor cells, going through a pathway of GP60 receptor, cavoline-1, and SPARC receptor. Some of them can increase the half-life of the albumin.

The glycoprotein (GP) 60 receptor, also known as albondin, is an albumin that exists on the membrane of the vascular continuous endothelia cells and alveolar epithelial cells. It can allow the biodegradable albumin be transported and recycled without being degraded by lysosome [2, 12]. The GP60 can bind with the HSA nanoparticles and form caveolae called cavoline-1, which is an albumin-containing vesicle. The cavoline-1 enters the cytoplasm, fuse with the basement membrane, and thus transport the albumin to the interstitium [14].

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6. Positives and negatives of prodrugs

6.1. Positives

About 10% of drugs in the world is prodrug. The prodrugs have two main benefits: increased effectiveness and decreased side-effects. It can help medications travel to the target site (where they need to work), and impact how medications are distributed at the specific site [15].

6.2. Negatives

At the same time, there are some potential drawbacks such as systemic toxicity of the activated compound and the lack of data about the biodistribution of prodrugs. In addition, some exogeneous albumin formulation are not allowed to do clinical trials due to its unexpected low efficiency of delivery.

7. Conclusion

This paper discussed the albumin-binding prodrugs' use in treating cancer, including the explanation of prodrug and an example called Aldoxorubicin. The construction and reaction mechanism of Aldoxorubicin has been discussed respectively, such as the hydrazone and the human serum albumin. To sum up, although only a few candidates are used in clinical trials, the albumin-binding prodrug is still a promising cancer treatment due to its targeting ability. In the future, scientists may not only focus on the toxicity that needs future experiments to reduce, but also make more efforts on exploring the ways to improve the targeting ability of the prodrugs.

To improve this paper, more detailed information about the use of doxorubicin and maleimide moiety may be added. Also, there could be more discussion and more data on the positives and negatives of prodrug by referring larger variety of papers.

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