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Ligand-Based targeting in drug delivery system

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Abstract:

Targeted drug delivery system has come up as a new approach that increase the effectiveness of the drug while reducing the side effects of cancer therapy. This review focuses on the application of ligand-based drug targeting, especially antibodies-drug conjugates in the case of ovarian cancer and folate-receptor targeting in the case for tumor cells. This review will provide analytical insights about the effectiveness of two approaches on improving bioavailability, targeting specific tumor cells, and enhancing drug carrying capacity. The findings show that folate receptor targeting does has significant potential in enhancing curcumin's anticancer activity. However, there are still challenges such as rapid decomposition of curcumin. This review also highlights the need for future experiments and research to consolidate the effectiveness of the drug delivery system and explore their potential in broader clinical environment.

Keywords: Ligand-Based, drug delivery system, effectiveness, ligand-based drug targeting, rapid decomposition of curcumin

Introduction:

The important rules that decide whether any new drug can be approved are its efficacy and safety. Nowadays, the best way for researchers to maximize the efficacy of any potential new drug is by "sending" the drug to where it should be to address the disease. To made happen this process, the drugs need to be directed to the specific pathologic cell by connecting to a ligand. Ligand is molecules or atoms attached to the central atom (from Britannica). Usually, a ligand acts as an electron-pair donor in covalent bonds. Some examples of ligands are H_2O, NH_3, and OH^-. However, ligands can also be cations, electron-acceptors, such as NO^+ and $N_2H_5^+$. Moreover, ligands can be neutral molecules. For instance, Folic acid is one type of ligand. Folic acid is a type of vitamin that are significant in terms of biosynthesis of nucleotide bases and cell proliferation (Yan, 2024). It has been widely used as a targeting ligand in the treatment of cancer due to the overexpressed folate receptor in many tumor cells. This made folic acid an attractive approach in the development of effective targeted therapies. Similarly, antibodies are also used to target pathological cells of various cancers. Antibodies are proteins produced by B-cells, B lymphocytes (Britannica), to respond to invading substances in the cells. Specially, monoclonal antibody (MABs) is one of the antibodies used to identify pathological cells. Monoclonal antibodies are immunoglobulins molecules that are secreted by B-cells when B-cells are activated by the presence of antigens. All monoclonal antibodies are made in the laboratory. There are few ways monoclonal antibody can be used for disease treatments. For instance, it can be used to detect where the cancer cells are situated in your body, carry cancer drugs directly to the cell, and even block the signal that "tell" the cancer cells to divide. (Cancer Research UK website) This review will dive into how antibody and folic acid have been used as targeting agents in modern disease treatments, especially in cancer therapies. Meanwhile, this review also aims to discuss the benefits and mechanisms of ligand-based drug delivery systems and discuss the limitations and potential improvements of contemporary research methods and approaches.

First Study:

Ligand-based drug delivery system involves complex designations. In this section, the review will briefly talk about one research study on the relationship of antibody-drug conjugate (ADCs) with ovarian cancer. Then introduce some limitations of this particular experimental ideas of designing and using the drug to treat epithelial ovarian cancer by targeting folate receptor alpha (FRα). "Although absent from normal ovarian epithelium, approximately 80% of epithelial ovarian cancer (EOC) tumors constitutively express FRα[1]." So FRα has been thought of an attractive tool to approach the pathological cells with overexpressed folate receptor alpha. In the research study conducted by Lainie P. Martin et al, researchers collected

1 Kalli KR, Oberg AL, Keeney GL, Christianson TJ, Low PS, Knutson KL, et al., Folate receptor alpha as a tumor target in epithelial ovarian cancer, Gynecol. Oncol 108 (2008) 619–626.

core needle biopsies before and after the treatment of mirvetuximab soravtansine (6 mg/kg once every 3 weeks)[2] from relapsed ovarian tumors patients who are fit for biopsy. According to Penelope M. Webb & Susan J. Jordan, "Globally, ovarian cancer is the eighth most common cancer in women, accounting for an estimated 3.7% of cases and 4.7% of cancer deaths in 2020." Mirvetuximab soravtansine is an antibody-drug conjugate that include humanized anti-FRα antibody which is linked to maytansinoid DM4. One limitation of this study is the sample size. There are a total of twenty-seven pre-treated patients who were enrolled in this study. For a heterogeneous disease like ovarian cancer, the sample size used in this study may not fully reflect the whole patient populations. To fully account for a broader population of ovarian cancer patients, the sample size should be larger, which will provide a more solid and persuading result in the future. Secondly, the adverse effect resulted from the treatment of mirvetuximab soravtansine are dangerous, but it still needs to be cared for. For instance, one of the twenty-seven patients suffered through grade 3 hypokalemia. Although using ADCs will much better lead the drug to the cancer cells rather than using the tradition chemotherapy that will destroy both the cancer/tumor cells and all other healthy cells, the side effects are still a problem that should be resolved in future study and should be one of the major concerns in future research. Finally, the period of the research is overall 4.2 months. However, a median therapy period is usually 12-18 months. So, the period should be longer to fully examine the effectiveness and safety of the treatment used in this study.

Second Study:

Nowadays, there are novel approaches for folate receptor targeting strategies. In this section, the review will briefly talk about a study about folic acid receptor targeting. In the study, the researchers attempted "to improve the bioavailability, biosafety, and drug loading capacity of curcumin"[3] by using a novel folate receptor targeting called "folate receptor-targeted β-cyclodextrin (β-CD) drug delivery vehicle."[4] In the introduction part, the research discussed the drawbacks about current cancer therapeutics, including poor selectivity, serious side effects, and drug resistances. Then, the main focus of this paper is curcumin. Curcumin, a kind of polyphenol, is a yellow chemical found in Curcuma longa species. The researchers pointed out that curcumin get most attention for its anticancer activity. Moreover, its anticancer activity has the ability to handle different tumors, such as stomach, liver, and breast cancer. However, due to "the low water solubility, rapid decomposition, and lack of specific targeting"[5], curcumin was limited in certain clinical trials due to the limitations under physiological condition. The researchers did a lot of experiments to overcome this obstacle in this study. I will introduce the process in which the researchers used different synthesis methods to overcome this obstacle. They synthesized both β-CD-CL-FA Nanoparticles (FA-Cur-NPs) and Curcumin Loaded β-CD-CL Nanoparticles (Cur-NPs). The presence of Curcumin Loaded β-CD-CL Nanoparticles (Cur-NPs) function as a control group compared to β-CD-CL-FA Nanoparticles (FA-Cur-NPs). According to the experiments the researchers did, 1 mL of β-CD-CL-FA Nanoparticles (FA-Cur-NPs) lasted for 72 hours in 37 degrees Celsius. The results showed that the stability of FA-Cur-NPs is extraordinary. Later, the researchers did two experiments to look for the targeting efficacy and the overall therapeutic effectiveness of curcumin. In the first experiment with mice, the researchers examined three types of curcumin, β-CD-CL-FA Nanoparticles (FA-Cur-NPs). In the test, mice with tumors were selected. They were then injected "Cur-DMSO [0.2 mL of 6.25 mg/kg; DMSO: H2O 1:1000(v/v)] aqueous solution (control group), Cur-NPs, or FA-Cur-NPs"[6] through tail veins. Then, researchers also took small images in vivo to look into the biodistribution of three types of cur-

2 Martin, Lainie P et al. "Characterization of folate receptor alpha (FRα) expression in archival tumor and biopsy samples from relapsed epithelial ovarian cancer patients: A phase I expansion study of the FRα-targeting antibody-drug conjugate mirvetuximab soravtansine." Gynecologic oncology vol. 147,2 (2017): 402-407. doi:10.1016/j.ygyno.2017.08.015

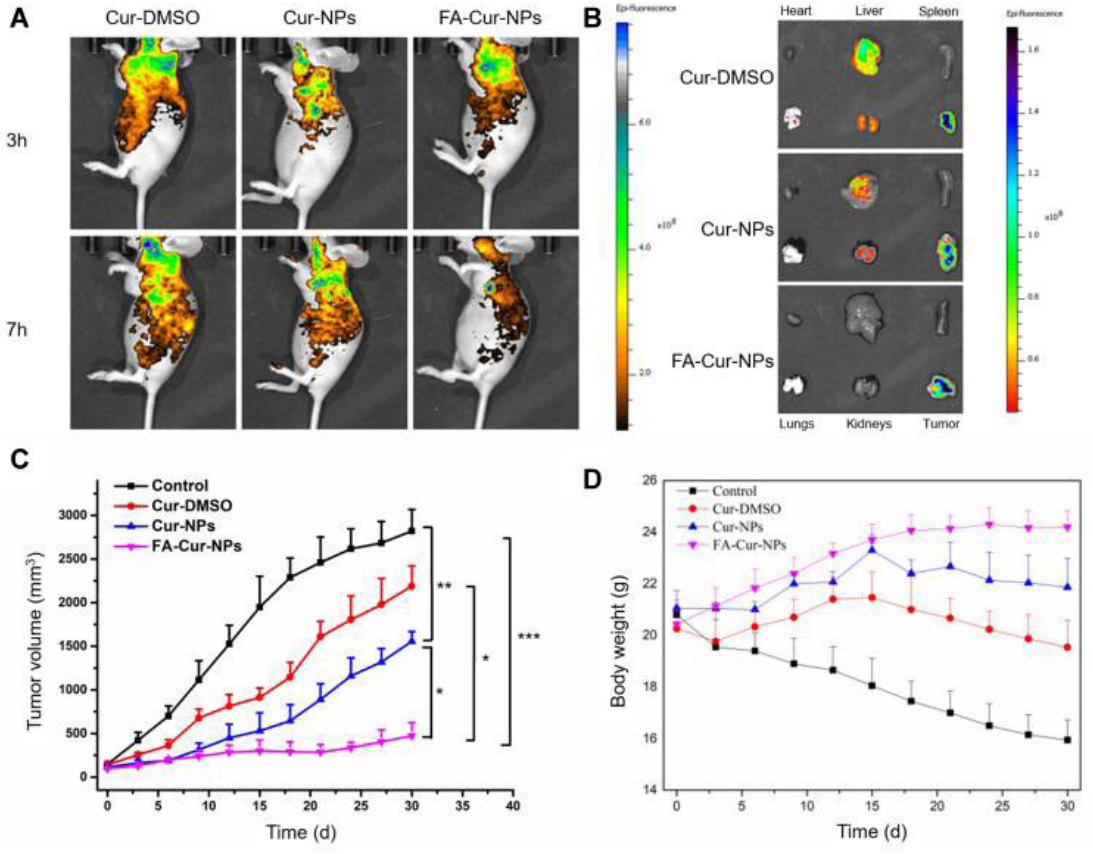
3 Hong, Weiyong et al. "A Novel Folic Acid Receptor-Targeted Drug Delivery System Based on Curcumin-Loaded β-Cyclodextrin Nanoparticles for Cancer Treatment." Drug design, development and therapy vol. 15 2843-2855. 30 Jun. 2021, doi:10.2147/DDDT.S320119

4 Hong, Weiyong et al. "A Novel Folic Acid Receptor-Targeted Drug Delivery System Based on Curcumin-Loaded β-Cyclodextrin Nanoparticles for Cancer Treatment." Drug design, development and therapy vol. 15 2843-2855. 30 Jun. 2021, doi:10.2147/DDDT.S320119

5 Hong, Weiyong et al. "A Novel Folic Acid Receptor-Targeted Drug Delivery System Based on Curcumin-Loaded β-Cyclodextrin Nanoparticles for Cancer Treatment." Drug design, development and therapy vol. 15 2843-2855. 30 Jun. 2021, doi:10.2147/DDDT.S320119

6 Hong, Weiyong et al. "A Novel Folic Acid Receptor-Targeted Drug Delivery System Based on Curcumin-Loaded β-Cyclodextrin Nanoparticles for Cancer Treatment." Drug design, development and therapy vol. 15 2843-2855. 30 Jun. 2021, doi:10.2147/DDDT.S320119

cumins in their bodies. After eight hours, the mice were sacrificed. And the researchers then collected their tumor, heart, liver, spleen, lungs, and kidneys. The purpose of this test is to compare whether the targeting is effective by examining the accumulation of three types of curcumin in the targeted tumor. The second experiment focused on the therapeutic effects of curcumin formulations on tumor growth. The tumor mice were randomly separated into 4 groups. The researchers injected "saline (negative control) or a 6.25 mg/kg of Cur-DMSO, Cur-NPs, or FA-Cur-NPs was injected via tail vein (0.2 mL) every three days"[7] into the mice. After 30 days, the mice were sacrificed. Then, the main organs were weighted which were used for histological analysis to determine whether the normal tissues were damaged and the effects of the treatments on tumors. The results of this study clearly address the problem mentioned before. FA-Cur-NPs not only very effective in reducing tumor cells, but also show no major damages to other healthy cells during the delivery. This study offers a new way to approach drug targeting for other researchers. However, there are still limitations and drawbacks. First, this study used mice as experimental subjects to test their drug. That is, they cannot explain whether the drug will function just the same in human body. Therefore, more clinical trials need to take place to ensure the safety and effectiveness of FA-Cur-NPs in human's body. Secondly, the period of mice testing lasted for 30 days. To ensure the safety and effectiveness of the drug and its targeting, the period should be longer than 30 days. Mentioned in the first place, curcumin is known for its fast metabolism. Further research should focus more on the modification of nanoparticle to lessen the effect of fast metabolism on drug efficacy. The last drawback is that folate receptors can also be found in normal cells, such as kidneys and lungs cells. So, it is still possible that the drug cause side effects because it hit normal cells that are not the target. Despite the fact that there are some parts to improve in this study, folate targeted drug delivery system provides us a brand-new way to the designation of drug delivery system. [8]



7 Hong, Weiyong et al. "A Novel Folic Acid Receptor-Targeted Drug Delivery System Based on Curcumin-Loaded β-Cyclodextrin Nanoparticles for Cancer Treatment." Drug design, development and therapy vol. 15 2843-2855. 30 Jun. 2021, doi:10.2147/DDDT.S320119

8 Hong, Weiyong et al. "A Novel Folic Acid Receptor-Targeted Drug Delivery System Based on Curcumin-Loaded β-Cyclodextrin Nanoparticles for Cancer Treatment." Drug design, development and therapy vol. 15 2843-2855. 30 Jun. 2021, doi:10.2147/DDDT.S320119

Conclusion:

Overall, the first study provided evidence about antibodies-drug conjugate can be an effective way to approach cancer treatments. The second study provided that FA-Cur-NPs enhance curcumin's specificity and bioavailability. And this review has a few limitations. Such as the lack of originality and limited scope of focus. Although my review offers different insights about these two studies, the depth of the discussion is limited due to the interpretations and methodologies of other study. Secondly, the scope of the focus of this paper is limited. Although the papers deeply discussed two specific studies relating to the topic "Ligand-Based targeting in drug delivery system", there are still many other important strategies not mentioned, such as peptide, aptamer, and gene therapy.

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