Progress of Folic Acid-Folate Receptor as Drug Carriers in Targeted Drug Delivery System

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ABSTRACT: Targeted drug delivery system is an effective method for the diagnosis and treatment of cancer, it has received much attention because of its low side effects and therapeutic efficacy. Folic acid receptor is highly expressed on the surface of most cancer cells, but is low or not expressed on the surface of normal cells, and the ligand folate has a high affinity. Folic acid receptor is attached to drug carriers and can be targeted to cancer cells. This paper introduces folic acid and folate receptors, briefly describes the mechanism of action of folic acid receptor-mediated targeted drug delivery, discusses the progress on four types of folic acid-folate receptor-mediated cancer treatment: folate acid-conjugated magnetic nanoparticles, drug binding of small-molecule folic acid, folic acid receptor-bound protein, and folic acid-conjugated polysialic acid. It also analyzes the favorable points and future development trends of each treatment mechanism.

1. Introduction

With the development of society and the continuous progress of science and technology, the number of cancer patients worldwide is increasing due to various factors such as the environment and work pressure. Targeted drugs have received the attention of scholars worldwide as an effective means of treating cancer treatment, who have conducted a lot of research in this field, and many targeted drugs have been successful. In the development of targeted drugs, folic acid receptor-mediated targeted drug delivery is one of the most striking research technologies for targeted cancer therapy.

2. Current status of domestic and international research

Cancer is the leading cause of death and one [1] of the most important barriers to increasing life expectancy in the 21st century.

By far the most commonly used treatment for cancer is chemotherapy, which is used to remove invisible cancer cells after surgery to remove visible lesions. Most of the available chemotherapeutic drugs destroy cells by increasing the value of cells. Receptor-mediated targeted therapy has emerged as an effective strategy for precision medicine to treat cancer [2-4] in a healthier and more effective manner.

Therapeutics based on folic acid receptor targeting nanotechnology are used for the targeted treatment of different cancers and have been proven by many scientists. Tumour targeting by antibodies may be an effective cancer treatment due to targeted antibody-mediated endocytosis and immunotherapy. The drug nanocomposites may improve therapeutic efficiency and reduce cytotoxicity. The interaction of receptor and ligand may be considered the best method for chemotherapeutic drugs to target cancer cells [7-8]. However, the current research of folic acid-coupled anti-tumor drug vector is still in its infancy, most of which are only in cell and animal experiments, and a large number of animal experiments and clinical studies are needed to achieve further results.

3. Mechanism of folate-folate receptor-mediated targeted administration

(1) Folic acid, one of the vitamin B complexes, is pteroylglutamic acid (PGA), which was purified from spinach leaves by H. K. Mitchell (1941), and was named folate [9]. Folic acid is particularly important for pregnant women, as it has a role in promoting the maturation of young cells in the bone marrow, and deficiencies in humans can lead to megaloblastic anaemia and leucopenia.

The folate receptor (FR) is a transmembrane glycoprotein linked by Glycosylphosphatidyll alcohol with a molecular weight of 38-40 kDa, which is present on the surface of most tumour cells and is not or rarely expressed in normal body cells. Folate receptor antibodies can be used for targeting purposes and strengthen the immune response to cancer/tumour cells through modulation of natural killer cells and macrophages. As folic acid receptor are overexpressed on most cancer tissues and have limited expression on health cells, they are one [10-12] of the pivotal targets for drug delivery. Folic acid internalizes changes after attachment to the folate receptor via receptor-mediated endocytosis.

(2) Mechanism of action

There are two mechanisms for the targeted

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administration of folic acid receptors: the transport of dihydrofolate and tetrahydrofolate into cells via low-affinity transmembrane proteins; and the uptake of folic acid into cells mediated by folate receptors (FR), which are high-affinity folate binding proteins. The latter is the main route [14-15] of entry of folate-coupled drugs into cells. Folate acid receptor antibodies are mainly used to target folic acid receptors, and antibodies are generated against purified folic acid receptors which is come from cancer cells.

4. Folate acid-conjugated magnetic nanoparticles

Folate receptors are purified using magnetic affinity purification technology and used in the preparation of anti-folate receptor antibodies. Folic acid receptor purification using nanotechnology ensures the depuration of intact proteins in a bioactive modality. By coupling MNP with MTX and anti-fr antibodies, a new targeted nanopharmaceutical formulation was prepared across antibody mediated endocytosis. The new approach with targeted administration by folic acid receptor can administer MTX on cancer cells and it can also attracts macrophages and natural killer cells to eliminate cancer cells [16-18] by conditioning.

A novel nanodrug formulations has been designed by foreign laboratories to exploit the synergistic [19] effects of immunotherapy and targeted drug delivery. Many targeted sites and combinations of targeted drug delivery have been reported, but there is still a large gap in the field of targeted nanomedicine. This laboratory has purified folic acid receptor for studies of antibodies against folic acid receptor. The Applied Molecular Biotechnology Research (AMBR) Laboratory has designed a novel magnetic affinity method to purify the receptors. Antifolate receptor antibodies were prepared by immunization of rabbits with purified protein, which were coupled to MNP after identification by ELISA and Western blot. ELISA and Western blot confirmed the specific reaction [20] of the anti-folate receptor antibodies with the folic acid receptor.

Their results suggest that the final nanomagent successfully target folate receptors and undergo receptor-mediated endocytic MTX endocytosis. This further suggests that the FR antibodies have a more affinity and have better outcome compared to folate. The anti-cancer efficacy of the combined nanodrugs was demonstrated by analysing the cytotoxicity of the cells against cancer cells. The MNP-MTX-FR antibody had the greatest cytotoxicity, confirming the potential affinity of the antibody-coated drug to destroy cancer cells during targeted delivery. These experiments were conducted to further evaluate the effectiveness of novel nanomedicines for in vivo immunotherapy and to make a contribution [21-22] to the treatment of cancer.

5. Folic acid-small molecule drug coupling (SMDC)

Targeted drug delivery united with controlled drug release has a crucial role to play of individualised medicine. Most anticancer drugs interfere with normal life activity of cells and have some damage to normal human cells, normal cells also require life activity [23].

Conventional anti-tumour chemotherapeutic drugs are not selective for tumours and do not preferentially target tumour sites. This drug limitation of chemotherapeutic drugs often leads to toxicity. Over the past 30 years, the development and production of anticancer drugs have undergone tremendous changes, with a focus from traditional chemotherapeutic drugs to selective drugs that have greatly improved both tumor specificity and side effects. Small-molecule drug conjugation is an alternative to the targeted delivery of cytotoxic drugs to malignant tissues.

The cytotoxicity of SMDC is dependent on therapeutic drug loading. Efficacy and metabolism should be considered when choosing the payload, and the mechanism of action is also the main determinant to be considered. Due to the key role of folic acid in DNA replication and repair, it allows to play an important and complex role in the prevention of cancer [24].

SMDC has multiple advantages over conventional untargeted chemotherapeutic agents. Minimal adverse toxicity to ordinary cells, which is one of the advantages of SMDC compared to conventional untargeted chemotherapeutic agents. sDMCs can decrease the exposure [25] of normal cells to cytotoxic drugs by explicitly delivering the drug payload to cancer cells. The development of the SMDC field has attracted researchers from all over the world. An increasing number of deeply studied receptors has been proven to be developed as suitable targets and the development of more targeted ligands, the research intention of SMDC methods will increase and the application of SMDC will extend to other diseases in the coming years.

6. Folic acid-folate binding protein

A team led by Professor Robert J. Lee hasexploited the affinity of folic acid binding protein (FBP) to synthesise a new approach to anti-EGFR immuneliposomes for the treatment of cancer [26]. Liposomes of lipid-soluble folate acid derivatives were prepared by polycarbonate membrane extrusion. The FBP-C225 and folate liposomes were then combined to obtain anti-EGFR immune liposomes, and the uptake and cytotoxicity of U87 human glioblastoma cells overexpressed with EGFR were assessed. It is the high affinity of folate to FBP that novel non-covalently coupled immunoliposomal [27] have been developed.

Combining liposomes with targeting ligands can improve the selectivity of liposomes for tumour cells.

It has been reported that folic acid receptor-targeting liposome can selectively deliver drugs to folic acid receptor-expressing cells.

Folic acid binding protein (FBP) is an endogenous protein with a high affinity for folic acid.

No need for a chemical reaction of liposomes or high-temperature treatment is an important advantage of this non-covalent coupling approach, but it has limited

stability. This new conjugation method can similarly make available for the composition of other immunoconjugates, and may outperform the extensively used biotin-affinity systems at present. It has gradually become a fast, efficient and sensitive tool for the identification and 3 haracterization of tumor-specific antibodies to non-covalently coupled liposomes. Nevertheless, this method currently has defects in nickel potential toxicity.

7. Folic acid coupled with polysialic acid (folate-polysia)

Calcification is one of the important biological processes in breast, and it plays a role in the formation of the teeth and bones [28]. Folate-conjugated polysialic acid absorbs calcium from the blood and selectively induce biomineralization on tumor cells, leading to pathological calcification of the tumor. Cancer cells die due to extracellular calcification triggered by macromolecules. Its role is to intervene in the glycolytic process of cancer cells. Systemic folic acid injection suppressed the growth of cervical cancer and breast tumors in mice and significantly increased the survival of mice.

Folate-polysialic acid polysaccharide conjugate (polySia) to complete tumor calcification at physiological concentrations of blood calcium and phosphate. Folic acid is selective for cancer cells because the folic acid receptor is suppressed in common cells but overexpressed in tumours, polySia provides some carboxylic acid groups to enrich blood calcium and induce calcification [29] in cancer cells spontaneously and selectively.

Extracellular therapies for the treatment of malignant diseases by calcification are fully prepared for the development of clinical trials and offer novel perspectives on the discovery of large molecule anti-cancer drugs.

8. Conclusions

In conclusion, the folate-folate receptor-mediated targeted carrier system has received widespread attention for its high specificity to tumor cells, but most studies in this area are still in its infancy. In vivo experiments with mice as an experimental model demonstrated the advantages of a folate-folate receptor-mediated targeted administration system with strong selectivity and small adverse effects, but more animal models as well as human trials are needed before entering clinical therapy.

References

1. Wang Wei. (2016). Study on green synthesis process of folic acid.(Doctoral dissertation, Southeast University).
2. Xu Lihui, Xie Liqu, & Lin Lihua.(2013).Progress in folic acid research.Fujian Animal Husbandry and Veterinary Medicine (2), 3.
3. Strong jade chai.Study on the synthesis of folic acid.(Doctoral dissertation, Hebei University of Technology).
4. Luo Jiajie, Zhang Bin, Wang Jie, & Chen Dengke. (2013).Progress in the application of folic acid in animal production. Guangdong Feed, 22 (2), 27-29.
5. Folate acid (folic acid), also called vitamin B9, is a water-soluble vitamin.. Folic acid (folic acid), also called vitamin B9, is a water-soluble vitamin
6. Advani, P.G., Schonfeld, S.J., Curtis, R.E., Dores, G.M., Linet, M.S., & Sigel, B.S., et al.(2019).Risk of therapy-related myelodysplastic syndrome/acute myeloid leukemia after childhood cancer: a population-based study. Leukemia.
7. Morgan, G., Ward, R., & Barton, M..(2004).The contribution of cytotoxic chemotherapy to 5-year survival in adult malignancies. Clin Oncol, 16(8), 549-560.
8. Lee Peng-hee, Wan Chuan, Chen Benshou, & Li Donghong.(2018).Study on tumor microenvironment stimulation-responsive folic acid-targeted precursor drugs.Chinese Pharmacy, 29 (21), 7.
9. Fu Liqiang, Ding Shi, & Yang Yushe. (2013). Advances in folate receptor-mediated small-molecule antitumor drugs. Chinese Journal of Pharmaceutical Chemistry, 23 (3), 9.
10. Coumar, M.S., Tsai, F.Y., Kanwar, J.R., Sarvagalla, S., & Cheung, C..(2013).Treat cancers by targeting survivin: just a dream or future reality?.Cancer Treatment Reviews, 39(7), 802-811.
11. Wang Hongwu. (2004).Modern tumor-targeted therapy technology. China Medical Science and Technology Press.
12. Wang Hongwu. (2002).Ct guided by percutaneous targeted treatment of lung cancer.Chinese tumors, 11 (8), 3.
13. Wu Yilong, Yang Jin Ji, Lin Jiaying, Huang Yujuan, Liao Riqiang, & Huang Yisheng, etc.(2007).Clinical study of gefitinib targeting for non-small cell lung cancer.The Chinese Journal of Tuberculosis and Breath, 30 (2), 98-102.
14. Qian Huimin, Chen Haiyan, Wang Min, & Gu Yueqing.(2006).Application of near-infrared labeling technology in biomedicine.Drug Biotechnology, 13 (4), 4.
15. Reddy, J.A., Xu, L.C., Parker, N., Vetzel, M., & Leamon, C.P..(2004).Preclinical evaluation of (99m)tc-ec20 for imaging folate receptor-positive tumors.Journal of Nuclear Medicine Official Publication Society of Nuclear Medicine, 45(5), 857.
16. Wan Danjing, Zhong Gaoren, Zhu Jianhua, Ding Jianhui, & Zeng Meng Su.(2006).Initial evaluation of the folic acid receptor-targeted MR contrast agent 157gd-dtpa-folate to enhance tumor signaling in nude mice.Nuclear technology, 029 (008), 605-608.
17. Zwicke, G.L., Mansoori, G.A., & Jeffery, C.J.. (2012). Utilizing the folate receptor for active targeting of cancer nanotherapeutics. Nano Reviews, 3(3).
18. Zhang, Y., Li, M., Gao, X., Chen, Y., & Liu, T..(2019).Nanotechnology in cancer diagnosis: progress, challenges and opportunities. Journal of

Hematology & Oncology, 12(1).

19. Wang, N., Hu, J., Oppong-Gyebi, A., Zhu, X., & Ye, S..(2020).Elevated blood urea nitrogen is associated with recurrence of post-operative chronic subdural hematoma. BMC Neurology, 20(1).Sinha, R., Kim, G.J., Nie, S., & Shin, D.M..(2006).Nanotechnology in cancer therapeutics: bioconjugated nanoparticles for drug delivery. Molecular Cancer Therapeutics, 5(8), 1909-1917.
20. Neuberger, T., B Schöpf, Hofmann, H., Hofmann, M., & Von, B.R..(2005).Neuberger t, schöpf b, hofmann h, hofmann m, von rechenberg bsuperparamagnetic nanoparticles for biomedical applications: possibilities and limitations of a new drug delivery system.j magn magn mat 293:483-496. Journal of Magnetism & Magnetic Materials, 293(1), 483-496.
21. Khan, I., Saeed, K., & Khan, I..(2017).Nanoparticles: properties, applications and toxicities.Arabian Journal of Chemistry(7).
22. Kalantari, K., Saleh, B., & Webster, T.J..(2021). Biological applications of severely plastically deformed nano-grained medical devices: a review. Nanomaterials, 11(3), 748.
23. Singh, H., Rai, V., Nooti, S.K., & Agrawal, D.K..(2021). Novel ligands and modulators of triggering receptor expressed on myeloid cells receptor family: 2015-2020 updates. Expert Opinion on Therapeutic Patents(8).
24. Dorozhkin, S.V., & Epple, M..(2002).Biological and medical significance of calcium phosphates. Hüthig & Wepf Verlag, 41(17), 3130-3146.
25. Nakanishi, K., Nakagawa, K., Asakura, K., Yoshida, Y., Watanabe, H., & Watanabe, S.I..(2019).Is calcification in the regional lymph nodes a benign feature in patients with lung cancer?. World J Surg.
26. Zhou, Y., Zhang, J., Dan, P., Bi, F., Chen, Y., & Liu, J., et al.(2019).Tumor calcification as a prognostic factor in cetuximab plus chemotherapy-treated patients with metastatic colorectal cancer. Anti-Cancer Drugs.
27. Zhao, R., Wang, B., Yang, X., Xiao, Y., Wang, X., & Shao, C., et al. (2016). A drug-free tumor therapy strategy: cancer-cell-targeting calcification. Angewandte Chemie.
28. Garinchesa, P., Campbell, I., Saigo, P.E., Jr, L.J., Old, L.J., & Rettig, W.J..(1993).Trophoblast and ovarian cancer antigen lk26. sensitivity and specificity in immunopathology and molecular identification as a folate-binding protein. American Journal of Pathology, 142(2), 557.
29. Kadio, B., Yaya, S., Basak, A., K Djè, Gomes, J., & Mesenge, C..(2016).Calcium role in human carcinogenesis: a comprehensive analysis and critical review of literature.Cancer & Metastasis Reviews, 35(3), 391-411. b Havard, R.E., & Reay, G.A.. (1925). Normal variations of the inorganic phosphate of blood. Biochemical Journal, 19(6), 882-887.