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RESEARCH HIGHLIGHT

Transferrin, a cell pilot and iron provider based on its interaction with the overexpressed transferrin receptors

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Transferrin (Tf) is a serum protein responsible for delivering iron to the erythron and peripheral tissues. Transferrin receptor (TfR), a key receptor in the regulation of iron and is activated by the ferric ion loaded Tf, is overexpressed on the surface of various cancer cells due to their malignant transformation. Based on the Tf-TfR transport mechanism, Tf has been projected to be dually used as a pilot for nanoparticles to target the tumor cells with over expressed TfRs and an intracellular iron provider. Dihydroartemisinin (DHA) is believed a promising tumor therapeutic agent for its unique mechanism of cytotoxicity. When DHA chemically damaging cells, ferrous ions are required to react with the drug. In this research highlight, we discuss our latest published findings which demonstrate the enhanced cytotoxicity of DHA helped with a nanographene oxide carrier and the Tf-TfR transport system, and the potential for its anti-tumor application. This approach gives a further understanding on the role of ligand and receptor in tumor treatments.

Keywords: Transferrin; Transferrin receptor; Dihydroartemisinin; oncotherapy

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The major feature of cancer cells is rapid cell growth and proliferation. Cancer cells need lots of nutrient to meet its requirement. Iron is the one of essential nutrient and plays a key role in cell growth and proliferation. Physiological iron exists regularly in two forms: ferrous iron (Fe^{2+}) and ferric iron (Fe^{3+}) [1]. By the change between these two states, iron participates in a wide variety of cellular processes, including macromolecule biosynthesis and as an important cofactor for several key enzymes in cellular respiration and metabolism. Therefore, iron is necessary for cancer cell growth and division [2].

To obtain necessary iron ions, Transferrin-Transferrin receptor (Tf-TfR) transport system plays a key role. TfR, a key receptor in the regulation of iron, is overexpressed on the surface of cancer cell [2, 3]. Transferrin (Tf), a ~80 kDa protein, is an important iron transport protein. Tf is consist of four subdomains (N1, N2, C1 and C2), which form two lobes (termed N- and C-lobes). Each Tf can bind two Fe^{3+} tightly, yet reversibly [4]. Iron-free Tf is not recognized by TfR. TfR only has a high affinity for the iron ion binding Tf. The affinity of Tf and Fe^{3+} is dependent on the pH of microenvironment. Tf can bind Fe^{3+} more tightly at pH7.4. Once the pH drops to 5.5, the combined Fe^{3+}would be released reversibly.

The process of iron uptake by cells through the Tf-TfR transport system is described as follows: Tf combined with Fe^{3+} in blood, specifically binds to the TfR on the surface of cells (pH 7.4) [4, 5]. The complex is then endocytosed, and the acidic pH of the endosomal lumen induces a conformational change in Tf that accompanies iron release. The released iron

is reduced to Fe^{2+} by ferrireductase within the endosome [5]. The Fe^{2+} can then be delivered to the cytoplasm from the endosome by the divalent metal transporter (DMT1) for use by the cell. The Tf un-containing iron remains tightly bound to the TfR at acidic pH and is recycled back to the cell surface. Upon exposure to the slightly basic pH (7.4), Tf is released or displaced from the TfR and free to bind more Fe^{3+} [4].

In recent years, Tf and TfR interaction is widely used in nanoparticle specific delivering. Cui *et al* applied Tf as targeting molecule for magnetic silica PLGA nanoparticles loaded with doxorubicin and paclitaxel for brain glioma treatment [6]. Du *et al* used TfR specific nanocarriers conjugated with functional peptide for oral drug delivery [7]. Liu *et al* modified Tf on the sheet of Graphene oxide (GO) for glioma-targeted drug delivery [8]. Tf-TfR transport system has shown great tumor specificity and improved the therapeutic effect of the fabricated nanoparticles.

In this study, Tf as a targeting molecule is modified on GO to construct a smart delivery carrier to enhance the therapeutic effect of Dihydroartemisinin (DHA). Among them, GO offers abundant active groups and large surface area for DHA and Tf loading [9, 10]. The Tf provides the specific delivery of the nanoparticles. DHA is the main active metabolite of Artemisinin, which is the unique sesquiterpene lactone isolated from the plant Artemisia annua [11]. DHA has been widely used as an effective anti-malarial drug since the 1970's, and been investigated as an alternative tumor therapeutic agent for its unique mechanism of cytotoxicity in recent years [12, 13].

The cytotoxicity of DHA is endoperoxide-dependent and depend on the level of iron ion [13]. Although the uptake of body iron can be increased to meet the requirement of cancer cells, the intracellular concentration of iron still lies at a low level for the quick utilization of the rapid cell growth and proliferation. Therefore, the cytotoxicity of DHA as an anti-tumor drug is normally limited.

To solve the problem above, based on the TfR overexpression of cancer cells and Tf transporting iron, Tf is chosen to not only make the nanoparticle specifically target tumor cells, but also increase the intracellular available iron to interact with DHA [11, 14]. This ultimately enhances the DHA cytotoxicity. With *in vivo* animal models, a preferential tumor uptake of the nanoparticle was observed and the treatment resulted in a complete tumor cure with no observable side effects in normal tissues and organs [15].

In conclusion, by integrating Tf and DHA on one nanoplatform, the synergistic relationship of the both is used successfully for oncotherapy. This novel nanoparticle may serve as a potential alternative tumor treatment modality, and the full use of targeting ligand could provide a new thinking for tumor therapy.

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Conflict of interests

The authors declare that there is no conflict of interests.

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