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Cancer Treatment with Oncoshuttle

Vladimir N. Pak

Freelance Researcher, Toronto, Canada.

*Correspondence:
Vladimir N. Pak, Freelance Researcher, Toronto, Canada, E-mail: oncoshut@gmail.com.

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ABSTRACT

Oncofetal alpha-fetoprotein (AFP) activates in developing as well as in growing cancer cells. It delivers polyunsaturated fatty acids through specific cell receptors. AFP-binding receptors are also discovered on myeloid-derived suppressor cells which suppress the immune response to the embryo and to the tumor. After AFP receptor-mediated endocytosis these cells release AFP for the next run for nutrients. The AFP natural shuttle delivery manner can be used for cancer treatments. Oncoshuttle is an exogenous AFP able to bind and deliver toxins instead of nutrients to cancer and myeloid-derived suppressor cells in a repeated way. Toxins for shuttling should have a higher than albumin or other blood proteins binding affinity to AFP. AFP wins the competition for the ligand over albumin due to its unique hydrophobic pocket. Injectable AFP-toxin non-covalent complexes, as well as oral porcine AFP-toxin ones, have demonstrated anticancer activity. The possible role of neonatal Fc receptor in transcytosis of oral porcine AFP-toxin complexes to gastrointestinal tract lymph nodes is discussed.

Keywords

Cancer treatment, Alpha-fetoprotein receptor, Myeloid-derived suppressor cell, Neonatal Fc receptor, Targeted chemotherapy, Immunotherapy, Nano-container.

Introduction

Alpha-fetoprotein (AFP) is the main delivery protein produced by the embryo. During pregnancy, it crosses three layers (trophoblast, embryonic connective tissue, and embryonic capillary endothelium) of the human hemochorial placenta which typically separate the two circulations. In the blood, it binds polyunsaturated fatty acids (PUFAs) which the mother has to take by food as she does not produce them herself. AFP-PUFA crosses the placenta without complex dissociation due to neonatal Fc receptor (FcRn) detected on placental syncytiotrophoblasts [1,2]. After transcytosis through the placenta, the AFP-PUFA complex is internalized by embryo cells with an AFP receptor (AFPR)-mediated endocytosis. Embryo cells release AFP back for the next nutrient run. Due to its hydrophobic pocket with 1-3 PUFA molecules capacity and the shuttle delivery manner, natural nano-container AFP brings dozens of PUFAs during several days of the protein half-life [3]. PUFAs can be substituted into toxins in AFP-toxin non-covalent complex to treat cancer.

Injectable AFP-toxin preparations

In adults, AFP is detected only at the minuscular level. During hepatocellular carcinoma and a few other cancers, AFP levels in the blood can be elevated. Unlike AFP, AFPR is detected in the serum of patients with many different cancers. AFP shuttles PUFAs to cancer cells through the same AFPR-mediated endocytosis as embryo cells do. Being injected, exogenous AFP accumulates in the tumor [4]. Based on this observation, AFP- or AFP fragments-toxin chemical conjugates were used for the cancer cells-targeted chemotherapy [3].

Nevertheless, Nature's efficacy and safety in the wrong cell elimination cannot be beaten. In addition to embryo cells, AFP-mediated nutrients delivery to AFPR-positive myeloid-derived suppressor cells (MDSCs) potentiates the latter ability to suppress the mother's immune system and prevent embryo rejection [5]. MDSCs are a heterogeneous population of immunosuppressive cells developing from myeloid progenitors, which are enriched in pathological conditions such as cancer, and are known to inhibit the functions of cytotoxic T and NK cells. A single cytotoxic T or NK cell can destroy hundreds of wrong cells. In cancer, like in pregnancy, those killer cells are suppressed by MDSCs which play a major role in forming the tumor microenvironment (TME).

Suppressive myeloid cells facilitate metastasis and immunotherapy resistance through TME remodeling and inhibition of adaptive immune cells [6].

Paradoxically, the cancer cell itself is not the only and/or the main target. Among many cancer-forming processes (apoptosis failure, proliferation, angiogenesis, metastasis, etc.), immune suppression "is more equal than others". Like any defense system, the immune one has regulatory (monocytes) and executive (lymphocytes) levels. The cancer problem can be solved better rather at the regulatory than at the executive level. The most important target for treatment is a suppressive cell which prevents numerous cytotoxic T and NK cells from naturally executing cancer cells [7]. The relative concentrations of white blood cell types are neutrophils (70%), lymphocytes, monocytes, eosinophils, and basophils. Neutrophils and the innate immune system have been overlooked as immunologists focused on T and B cells of the adaptive immune system. MDSCs depletion harnesses both innate and adaptive immunity to fight tumors. MDSCs are a small subpopulation of monocytes, so it takes fewer doses of targeted chemotherapy to reduce their numbers, reverse the TME, and eventually kill cancer cells. Hence, MDSCs-targeted immunotherapy is more powerful than cancer cells-targeted chemotherapy. Unlike T cell-based immunotherapies, it is not personalized but universal.

The AFP influence on MDSC (the former Natural Suppressor Cell) activity and tumor growth, as well as the approach for cancer treatment by MDSCs depletion, was proposed in [8,9]. The approach was proved with the AFP-daunorubicin conjugate which specifically depleted 50% M-MDSCs (unlike G-MDSCs) in vitro. MDSCs numbers decreased during treatment with this conjugate, and the inhibition of the tumor mass growth was shown in the experimental group compared with the control animals [10]. AFP non-covalent complex with a potent generic chemotherapy drug thapsigargin has shown a significant reduction in MDSCs in vitro also [11].

Meanwhile, the AFP-toxin conjugate is an artificial construction. Like monoclonal-antibodies drug conjugates, it is designed as a one-way "magic bullet". Using AFP as a shuttle nano-container is a different approach. Instead of PUFAs, AFP can bind and deliver selected toxins to both AFPR-positive cancer cells and MDSCs. For example, injections of the PUFA-daunorubicin conjugate in mice with an AFP-producing tumor led to tumor reductions. Attaching toxin to PUFA, which bound to AFP in the blood circulation leads to PUFA-daunorubicin conjugate accumulation in the tumor [12].

It was supposed that the environmental toxin dioxin by some way can enter the pregnant mother's blood, be bound by circulating AFP, cross the placenta, and became an embryo toxin. The assumption was supported by AFP-dioxin non-covalent complex injections which have shown good anti-cancer activity in mice [13]. The same delivery of the embryo toxin diethylstilbestrol to the tumor by AFP can be true also [14,15].

Albumin is a shuttle delivery vehicle for hydrophobic ligands. In cancer patients, visual identification of sentinel lymph nodes is achieved by the injection of dyes that bind avidly to endogenous albumin, targeting these compounds to lymph nodes, where they are absorbed by resident phagocytes. Attaching antigen to a fatty acid, which bound to albumin in the circulation leads to lymph node accumulation of antigen. This approach provides a simple, broadly applicable strategy to simultaneously increase the potency and safety of subunit vaccines, decreasing systemic dissemination relative to their parent compounds, increasing T-cell priming, and enhancing anti-tumor efficacy while greatly reducing systemic toxicity [16]. Nevertheless, albumin delivers drugs to different than AFP sites and through less specific receptors expressed by different cells, such as fibroblasts and endothelial cells [17].

Oncoshuttle is an exogenous AFP able to bind and deliver to sensitive cells more toxins than AFP-toxin conjugates do [18]. AFP shuttle action is different from any other known targeted chemotherapy. Unlike a conjugate, one AFP molecule brings toxins numerous times at the same address. Thus, oncoshuttle technology is an addressed chemo/immunotherapy. The technology exploits simultaneously exogenous AFP and toxins that have a higher binding affinity to AFP than to albumin and other blood proteins.

The registered injectable drug AFP together with amphotericin B taken in excess (molar ratio = 1:60) for shuttling led to tumor reduction in cancer patients [19]. Recombinant human AFP injected in mice together with 1′-S-1′-acetoxychavicol, paclitaxel, curcumin, and genistein has led to more tumor reductions than parent compounds [20-23]. In the study 2 groups of mice were treated with saline (control group) or AFP-thapsigargin non-covalent complex. 5 out of 6 AFP-thapsigargin-treated tumors show complete regression of tumors by day 7 of treatment with no further growth thereafter. One tumor was unresponsive and continued to grow. In the cited experiments AFP: toxin ratio was 1:1-5, but results can possibly be better if toxins for shuttling were taken in excess. AFP-toxin conjugates or non-covalent complexes are likely to have both, direct cytotoxic effect on cancer cells and an immune checkpoint inhibition effect without toxicity [11].

Per oral AFP-toxin preparations

On the other hand, mucosal drug applications are preferable to injections. There has been a great desire for enabling the non-invasive delivery of therapeutics across mucosal surfaces. FcRn mediates much more interesting biology than its name implies. FcRn is shuttling its ligands across the protective epithelial cell layer and enhances the transport of biologics across mucosal surfaces, improves drug absorption or distribution. For example, intestinal enterocytes use FcRn for IgG-antigen complexes transcytosis to the lymph nodes dendritic cells (DCs) without complexes dissociation [1,2].

FcRn controls the fate of three very distinct proteins: IgG, albumin, and AFP through a highly similar mode of binding. Fusions to IgG Fc or albumin have proven effective in pulmonary, oral, genital,

and in utero delivery of therapeutics or vaccines. Meanwhile, AFP has a higher binding affinity to FcRn than albumin [24,25]. This fact opens an opportunity for AFP-toxin non-covalent complexes transcytosis without dissociation to the lymph nodes after the oral administration.

Porcine AFP (pAFP) has a high similarity of the amino acid structure with epitopes common to human AFP [26]. PAFP is close to human protein functions and immunologic properties. PAFP has an isoelectric point of pH 4.6 and no micro heterogeneity [27]. So, mono-type glycosylated pAFP is responsible for both immunosuppressive and nutrient delivery activity.

Unlike AFP, pAFP possibly is not suitable for injections. On the other hand, FcRn-mediated transcytosis can work for peroral porcine pAFP-toxin non-covalent complexes. PAFP is a better nano-delivery vehicle than AFP as it transfers complexes with PUFAs through six tissue layers (maternal capillary endothelium, maternal uterine connective tissue, uterine endometrium, trophoblast, embryonic connective tissue, and embryonic capillary endothelium) of the porcine epitheliochorial placenta.

Injectable AFP-toxin drugs can target MDSCs in the blood, while GI tract lymph nodes are lacking MDSCs. The presence of FcRn mainly in DCs indicates that it directly implicates FcRn in IgG-mediated immune responses. After the neonatal period, FcRn is also abundant in cells of bone marrow origin in adult humans. FcRn is expressed by monocytes, macrophages (both tissue-resident and splenic), neutrophils, DCs, and B lymphocytes but not by T or NK cells [29-31]. AFP did selectively induce a rapid downregulation of surface MHC class II antigens (which are the key molecules in antigen presentation) in their expression on human monocytes. By reducing the antigen-presenting capacity of monocytes/macrophages, AFP functions as an essential factor in the downregulation of the entire immune system [28]. On the opposite, AFP-toxin drugs deplete monocytes/macrophages in lymph nodes and upregulate the entire immune system.

Depletion with pAFP-toxin drug of unidentified AFPR-positive immune suppressive cells in the GI tract lymph nodes eventually leads to distant metastases reduction by an unknown mechanism. PAFP-atractyloside, pAFP-thapsigargin, pAFP-betulinic acid, and pAFP-rotenone complexes peroral administration led to tumors/metastases reduction/elimination in mice [18,32] and in patients with metastatic colorectal cancer [33].

Oncoshuttle can potentiate the activity of the traditional medicines and substances with the known anti-cancer properties from food, spices, or supplements. It binds 1′-S-1′-acetoxychavicol, which are used as spices in cooking and traditional medicines, curcumin from turmeric, genistein from soy, gossypol from cottonseed, sinigrin from mustard seeds, etc. For example, feeding mice with the pAFP-ajoene from garlic, or pAFP-tocotrienol, and pAFP-vitamin D3 led to greater tumor reduction than in control groups [18].

Conclusion

AFP or AFP complexes with selected toxins can be injected to treat cancer. The treatment is supported by AFP-binding drugs/toxins excess in the bloodstream. AFP-toxin non-covalent complexes destroy AFPR-positive immune suppressive and cancer cells. This approach provides a simple, broadly applicable strategy to simultaneously increase the potency and safety of toxins, decreasing systemic dissemination relative to their parent compounds, increasing chemo/immunotherapy, and enhancing anti-tumor efficacy while greatly reducing systemic toxicity. Moreover, treatments with injectable AFP-toxin complexes can be enhanced by the diet containing the anticancer substances able to bind AFP in the blood. Addressed chemo/immunotherapy using AFP or pAFP as oncoshuttle for the toxins is a promising cancer treatment approach.

References

1. Pyzik M, Rath T, Lencer WI, et al. FcRn the Architect Behind the Immune and Nonimmune Functions of IgG and Albumin. Journal of Immunology. 2005; 10: 4595-4603.
2. Pyzik M, Sand KMK, Hubbard JJ, et al. The Neonatal Fc Receptor FcRn a Misnomer. Frontiers in Immunology. 2019; 10: 1540.
3. Lakhi N, Moretti M. Alpha-Fetoprotein Functions and Clinical Application. Protein Biochemistry Synthesis Structure and Cellular Functions. Hauppauge New York. Nova Science Publisher's Inc. 2016.
4. Uriel J, Villacampa MJ, Moro R, et al. Uptake of radiolabeled alpha-fetoprotein by mouse mammary carcinomas and its usefulness in tumor scintigraphy. Cancer Res. 1984; 44: 5314-5319.
5. Ostrand-Rosenberg S, Fenselau C. Myeloid-Derived Suppressor Cells Immune-Suppressive Cells That Impair Antitumor Immunity and Are Sculpted by Their Environment. The Journal of Immunology. 2018; 200: 422-431.
6. Fleming V, Hu X, Weber R, et al. Targeting Myeloid-Derived Suppressor Cells to Bypass Tumor-Induced Immunosuppression. Frontiers in Immunology. 2018; 9: 398.
7. Pak VN. Selective targeting of myeloid-derived suppressor cells in cancer patients through AFP-binding receptors. Future Sci OA. 2018; 5: FSO321.
8. Belyaev NN, Bogdanov AY, Savvulidi PhG, et al. The Influence of Alpha-Fetoprotein on Natural Suppressor Cell Activity and Ehrlich Carcinoma Growth. The Korean Journal of Physiology & Pharmacology Official Journal of the Korean Physiological Society and the Korean Society of Pharmacology. 2008; 12: 193-197.
9. Belyaev NN. Myeloid-Derived Suppressor Cells MDSC as a Main Tumor Induced Negative Regulators of Cancer Immunity and Possible Ways for Their Elimination. KazNU Bulletin. Ser Biol. 2014.
10. Belyaev NN, Abdolla N, Perfilueva Yu, et al. Daunorubicin conjugated with alpha-fetoprotein selectively eliminates myeloid-derived suppressor cells MDSCs and inhibits experimental tumor growth. Cancer Immunol. Immunother. 2017; 67: 101-111.

11. http://alpha-cancer.com/pre-clinical-studies/act-901-3-pre-clinical-io-studies/
12. Deutsch HF, Tsukada Y, Sasaki T, et al. Cytotoxic Effects of Daunomycin-Fatty Acid Complexes on Rat Hepatoma Cells. Cancer Research. 1983; 43: 2668-2672.
13. Sotnichenko AI, Severin SE, Posypanova GA, et al. Water-Soluble 2,3,7,8-Tetrachlorodibenzo-p-Dioxin Complex with Human Alpha-Fetoprotein: Properties Toxicity in Vivo and Antitumor Activity in Vitro. FEBS Letters. 1999; 450: 49-51.
14. Terentiev AA, Moldogazieva NT, Levtsova OV, et al. Modeling of three dimensional structure of human alpha-fetoprotein complexed with diethylstilbestrol docking and molecular dynamics simulation study. J Bioinform Comput Biol. 2012; 10: 1241012.
15. Pak VN. α-fetoprotein-binding toxins and teratogens against cancer. Ther Deliv. 2019; 10: 1-3.
16. Liu H, Moynihan KD, Zheng Y, et al. Structure-based programming of lymph-node targeting in molecular vaccines. Nature. 2014; 507: 519-522.
17. Larsen MT, Kuhlmann M, Hvam ML, et al. Albumin-Based Drug Delivery Harnessing Nature to Cure Disease. Molecular and Cellular Therapies. 2016; 4: 3.
18. Pak VN. Alpha-fetoprotein and Its Receptor in Fixing the Cancer Brakes. Cambridge Scholars Publishing. 2021.
19. Pak VN, Pak NA, Reshetnikov SS, et al. Method of treatment of malignant neoplasms and complex preparation having antineoplastic activity for use in such treatment. 2005.
20. Arshad NM, In LLA, Soh TL, et al. Recombinant human alpha fetoprotein synergistically potentiates the anti-cancer effects of 1-S-1-acetoxychavicol acetate when used as a complex against human tumours harbouring AFP-receptors. Oncotarget. 2015; 6: 16151-16167.
21. Dudich IV, Semenkova LN, Tatulov E, et al. Improved delivery of poorly water soluble drugs with alphafetoprotein stabilized with metal ions. World Intellectual Property Organization. 2015.
22. Kotra LP, Paige CJ, Bello AM, et al. Drug complexes comprising alpha-fetoprotein. Patent. 2016.
23. Dudich E, Semenkova L, Dudich I, et al. Method of reducing cancer cell proliferation by administering recombinant alphafetoprotein. 2018.
24. Blumberg RS, Pyzik M, Gandhiet A, et al. Blockade of alphafetoprotein AFP interactions with beta2-microglobulin associated molecules. United States Patent Application. 2019.
25. Blumberg R, Baker SK, Pyzik M, et al. Methods to Manipulate Alpha-Fetoprotein AFP. United States Patent Application. 2020.
26. Yazova AK, Goussev AI, Poltoranina VS, et al. Human α-Fetoprotein Epitopes as Revealed by Monoclonal Antibodies. Immunology Letters. 1990; 25: 325-330.
27. Carlsson RN, Ingvarsson BI, Karlsson BW. Isolation and Characterization of Alpha-Foetoprotein from Foetal Pigs. Int J Biochem. 1976; 7: 13-20.
28. Laan-Pütsep K, Wigzell H, Cotran P, et al. Human α-fetoprotein AFP causes a selective down regulation of monocyte MHC class II molecules without altering other induced or noninduced monocyte markers or functions in monocytoid cell lines. Cell Immunol. 1991; 133: 506-1810.
29. Zhu X, Meng G, Dickinson B, et al. MHC class I-related neonatal Fc receptor for IgG is functionally expressed in monocytes intestinal macrophages and dendritic cells. J Immunol. 2001; 166: 3266-3276.
30. Latvala S, Jacobsen B, Otteneder MB, et al. Distribution of FcRn across species and tissues. J Histochem Cytochem. 2017; 65: 321-333.
31. Castaneda DC, Dhommee C, Baranek T, et al. Lack of FcRn impairs natural killer cell development and functions in the tumor microenvironment. Front Immunol. 2018; 9: 2259.
32. Pak VN. Compositions of alpha-fetoprotein and inducers of apoptosis for the treatment of cancer. European Patent. 2015.
33. Pak VN, Molchanov O, Vincent M. Treatment of Metastatic Colorectal Cancer with Aimpila a Glycoside/Alpha-Fetoprotein Complex. Journal of Clinical Oncology. 2007; 25: 3589-3589.