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α -fetoprotein-binding toxins and teratogens against cancer

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“Delivering toxins in a way that is right for the patient – safe, painless, reliable, targeted, efficient and cost effective can be done with AFP.”

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A tumor is ‘an embryo’s evil twin’, so teratogens (or small molecule embryo toxins) that can damage or even destroy the embryo cells can be used for the suppression of cancer cells. A teratogen is an agent that can produce a permanent abnormality of structure or function in an organism exposed during embryonic or fetal life. Teratogens can appear in the blood of pregnant woman from the food, drugs or air. They damage embryo cells but are tolerated by the adult mother cells. Teratogens have definite advantages over other chemical agents because they can cross the placenta. Human hemochorial placenta has three cells layers and not too many agents can cross it themselves. Currently, there are 4194 teratogens available on the TERIS system, including 200 of the most frequently prescribed drugs [1]. It is assumed that during pregnancy teratogens are transported by albumin to placenta, where the exchange of the nutrients from albumin to α -fetoprotein (AFP) that is synthesized by the embryo yolk sac, fetal liver and the gastrointestinal tract naturally occurs [2]. The AFP-binding affinity can correlate with teratogenic properties of the toxin.

The AFP is a 69 kDa major fetal serum glycoprotein that serves as a pregnancy and tumor marker. During the fetal period, the AFP binds and transports nutrients of high nutritional value from the mother’s blood through placenta into the embryo’s blood. The AFP has multiple ligand-binding sites and a plasma half-life of approximately 3–5 days [3]. After nutrient delivery into the cell, it takes approximately 1 h for AFP to be released back in its undamaged form, and it can continue to transport dozens of ligands in a ‘shuttle-like’ manner. The AFP is a very effective shuttle for omega-3 docosahexaenoic acid (DHA), which is not synthesized by the mother and should be taken with food as it is a vital nutrient for growing embryos. The AFP is considered as an ‘embryo albumin’ because it serves like album transport protein in adults, but AFP overcomes albumin in binding affinity to DHA. That is why AFP takes DHA from albumin and transports it through placenta into the embryo’s blood. For this purpose, AFP has the hydrophobic pocket that binds 1–2 hydrophobic [4] and amphiphilic molecules even in the presence of the huge albumin excess. The ligands noncovalently bound outside the hydrophobic pocket will be shared with serum proteins. Most molecules do not bind to the AFP (e.g., out of 125 molecules tested by Hong *et al.* only 53 could bind AFP) [5], whereas the AFP-ligand binding affinity is crucial to cross placenta transport. Chemotherapy drugs: cyclophosphamide, fluorouracil, doxorubicin, bleomycin, vincristine and etoposide are fairly safe to the fetus [6], which can indicate the poor AFP-binding affinity of these drugs.

Embryo cells internalize the AFP–ligand complex through the AFP receptor (AFPR)-mediated endocytosis. Cancer cells regain this ability [7]. The AFPR is a number one oncofetal antigen because, unlike AFP (which is also oncofetal antigen, testicular cancer and hepatocellular carcinoma marker), it is re-expressed by most types of cancer, though it is not a universal tumor marker [8]. The AFPR is mostly absent in normal adult cells, except for a small population of regulatory immune cells – myeloid-derived suppressor cells (MDSC). Therefore, AFP and AFPR are not just nutrient transport system proteins and tumor markers, but they are also involved in the regulation of cell growth, differentiation and immune regulation.

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The MDSC are the top regulatory immune cells that inhibit nonspecific and various immune reactions including those during pregnancy [9]. They originate from hematopoietic stem cells and then can leave the bone marrow and spread throughout the body becoming immune response calmers. The MDSC accumulation in the tumor microenvironment is a general and dominant process that prevents executive immune cells from erasing cancer cells. So, regulatory MDSC elimination is an urgent oncology problem [10]. The recent AFPR discovery of M-MDSC has helped to explain how AFP-toxin medicines work [3,11]. The MDSC depletion unleashes not only adaptive immunity executive T-cells but innate immunity executive natural killer cells too, which are necessary to support modern T-cells cancer immunotherapy [12]. Moreover, AFP-toxin MDSC-targeted immunotherapy eventually erases more cancer cells than AFP-toxin cancer cells-targeted chemotherapy.

The AFP accumulates in tumor sites [13] as well as MDSC. Toxins bound *in vivo* with AFP can destroy embryonic cells, MDSC and cancer cells. The AFP as an ‘oncoshuttle’ can bind and deliver toxins dozens of times utilizing its physiological delivery manner. This is an advantage over other chemical conjugates, which are limited to a few toxins, that cannot increase AFP-toxin conjugate immunogenicity. The good perspectives of this therapeutic delivery of the selected small molecule toxins in humans have been demonstrated with amphotericin B [14], atractyloside, thapsigargin and betulinic acid [15]. In animals, AFP noncovalent complexes with 1-S-1-acetoxychavicol acetate [16], paclitaxel and thapsigargin [17], curcumin and genistein [18], dioxin [19], diethylstilbestrol [4], rotenone and ajoene (Pak VN, Unpublished Data) have shown anticancer efficacy also.

Delivering toxins in a way that is right for the patient – safe, painless, reliable, targeted, efficient and cost effective can be done with AFP. Phase I clinical trials have demonstrated the safety of recombinant human AFP (MM-093) at doses significantly higher than the AFP serum concentrations during pregnancy [20]. The AFP is simple in design, biodegradable, not immunogenic, and it has been shown to have an excellent safety profile (MM-093, today it is ACT-101 [17]). Therefore, it is a very attractive ‘oncoshuttle’ vehicle for targeted delivery of toxins to MDSC and cancer cells.

The AFP delivery of the selected small molecules through the naturally existing mechanism working during pregnancy can also be exploited for drug–drug interactions in cancer patients. This requires AFP and AFP-binding toxin to be simultaneously present in the blood of the cancer patient. The AFP can be injected to accumulate at the tumor/metastases site. The AFP-binding toxin can be delivered to the blood through injection, orally or other ways of administration. Total of 200 registered drugs with teratogenic properties (e.g., accutane, warfarin, thalidomide, etc. [1]) are the candidates for AFP-toxin combinations. The registered drug-data package can shortcut clinical trials and accelerate the US FDA approvals. To be useful for anticancer treatment, an AFP-toxin binding affinity should be competitive to albumin’s one. Ideally, a potent toxin should substitute DHA in the AFP hydrophobic pocket and follow its way. The results could be more impressive than those demonstrated with the moderate toxin amphotericin B (response in six out of eight cancer patients) [14]. On the other hand, it can be AFP-binding small molecules with low or moderate toxic activity from food (e.g., capsaicin, artemisinin, genistein, resveratrol, etc.). Being taken on a regular basis, AFP presence in the blood can demonstrate synergetic anticancer effects. The AFP–toxin noncovalent complexes promise to be especially effective in metastasis treatment, as they require low concentrations of AFP and toxins (like teratogens in pregnancy).

Conclusion

Recombinant human AFP is close to becoming a registered drug [17]. Then it could be provided to patients together with registered drugs-teratogens and AFP-binding toxins during cancer treatments. The toxins shuttle delivery by AFP to MDSC and cancer cells is expected to be a potent cancer immunotherapy and targeted chemotherapy approach.

Financial & competing interests disclosure

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