



Achilles Heel of Cancer

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Abstract

Immunotherapy is the most promising trend in cancer treatments. Checkpoint inhibitors block the blocking molecules, enabling T-cells to target the cancer. MDSC-targeted immunotherapy is a new type of immunotherapy that depletes the blocking cells, enabling NK and T-cells to target the cancer. MDSC accumulates in tumor places and suppresses both adaptive and innate immunity. An oncofetal protein – AFP – was found on host MDSC as well as on majority of cancer cells. This receptor can internalize its ligand: another oncofetal protein – AFP – loaded with nutrients. AFP can be cancer, host or artificial origin; it accumulates in tumor places where it works in a shuttle manner feeding both cancer cells and MDSC. On the opposite, toxin being delivered by AFP instead of nutrient through AFPR depletes MDSC that in its turn unleashes subordinate executive cells both of innate and adaptive immunity to destroy cancer cells. Unlike adaptive immunity T cells innate immunity NK are capable to destroy cancer stem cells that prevent metastases. AFP-toxin drugs can be used to treat metastases, early stage cancers and cancer prophylactics. The use of oncofetal proteins is Achilles hill of cancer and should be reversed against it.

Keywords: Cancer Immunotherapy; Immune Suppression; Oncofetal Proteins; MDSC-Targeted Immunotherapy; Targeted Chemotherapy**Abbreviations:** AFP: Alpha-Fetoprotein; AFPR: AFP receptor; MDSC: Myeloid-Derived Suppressor Cells, NK: Natural Killers

Introduction

Cancer cells have the same genome as normal cells do. Hundreds of mutations are detected in cancer cells that are different in normal cells. These differences are used to detect cancer cells and to destroy them due to these differences. On the other hand there are several similarities between cancer and normal cells that are possibly more important for cells survival. Oncofetal proteins are expressed by embryo and cancer cells and are involved in interactions with immune system. During pregnancy the mother's anti-embryo immune response is neutralized by the oncofetal proteins leading to immune tolerance, while in malignancy oncofetal proteins suppress the host's immune system [1]. Among oncofetal proteins the most known are AFP and AFPR [2, 3]. AFP secreted by yolk sac and embryo liver can grab nutrients from mother's blood and deliver them through placenta and AFPR-mediated endocytosis into embryo cells. AFPR was found on majority of cancer cells while AFP surprisingly was secreted only by the few cancers. AFPR is useless without AFP and possibility of coincidence of two different mutations that re-express AFP and AFPR in one cell is low. In this case what is the source of AFP in the AFP-non-secreting cancers? The answer can be non-detectable small amount AFP secretion by cancer cells and retaining (shuttling) it locally [4], or secretion by the host cells; in any case AFP is accumulated

in the tumor [5]. The assumption about AFP secretion by host is now supported by discovery of AFPR on host MDSC [6]. If AFPR exists on MDSC than some host cells should secrete AFP for them or it can be autocrine loop like in some cancer cells [7]. So, embryo and cancer cells are not alone in using oncofetal AFP-AFPR nutrient delivery system. MDSC [8] are superior suppression cells in immune cells hierarchy and they naturally travel from the bone marrow and accumulates in the places where inflammation and immune attack should be naturally blocked, e.g. placenta [9]. Feeding MDSC through AFP-AFPR nutrient delivery system stimulates local immune suppression. On the opposite, depleting MDSC by AFP-toxin drug can reverse immune suppression. MDSC-targeted immunotherapy is a new type of immunotherapy [10, 11].

Immunotherapy aims to empower the immune system to destroy cancer cells. The modern immunotherapy is still in its infancy. Two types of immunotherapy are drawing most of the interest: checkpoint inhibitors [12], which remove "brakes" from the immune system, allowing it to see and go after cancer; and CAR T-cell therapy, which involves a more customized attack. Both immunotherapies use only adaptive immunity T cells and have shown moderate efficacy, can be unsafe for early stage cancer; complexity and cost also prevent their application to

early stage cancer. MDSC-targeted immunotherapy is prevailing these immunotherapies as it activates both NK and T cells. Now the whole immune system is not blind to the cancer and by generating an aggressive response can fight it. Because of the immune system's unique power this therapy could prove a formidable weapon against many kinds of cancer and offer long-term protection with reduced side effects.

Modern immunotherapies need combinational therapy, e.g. with chemotherapy. AFPR was detected on majority of cancer cells that is why AFP-toxin drug already works as combination of the targeted chemotherapy [13] and MDSC-targeted immunotherapy [10]. Nevertheless, the immunotherapy impact is much more powerful because one magic bullet (targeted chemotherapy) can hit only one MDSC or cancer cell while MDSC depletion has greater consequences. That is the reason of high anti-cancer efficacy of low doses AFP-toxin preparations demonstrated in practice [6].

90% of cancer patients die of metastases that arise from cancer stem cells. Unlike T cells, innate immunity NK are able to deplete cancer stem cells [14]. That is an opportunity for MDSC-targeted immunotherapy to treat metastases, early stage cancers and cancer prophylactics. Moreover, cancer stem cells are close to embryo and normal stem cells by the early stage of differentiation when they can possibly express the same oncofetal protein - AFPR. It means that AFP-toxin drug can serve as targeted chemotherapy for cancer stem cells.

Conclusion

Cancers hijack the immune system for their benefit. The different pathways of immune response blocking are not well understood yet. Nevertheless modern immunotherapy can shift the balance of "attackers" vs. "defenders" to favor ability of "attackers" to overcome "defenders". Unlike artificial checkpoint inhibitors and CAR T-cell therapies MDSC-targeted immunotherapy use AFP-toxin drug that naturally activates a full strength immune response combining both NK and T-cell anti-cancer attackers. Moreover, AFP-toxin drug serves as targeted chemotherapy against majority of cancers and metastases (possibly hitting cancer stem cells through AFPR). Achilles hill of cancer is in using oncofetal proteins and cancer can be

beaten through this weakness. MDSC-targeted immunotherapy + targeted chemotherapy (AFP-toxin drug) can help in creating the medicine of tomorrow.

Reference

1. Govallo VI (1993) The immunology of pregnancy and cancer. New York: Nova Science Publishers Commack, USA.
2. Mizejewski GJ (2004) Biological roles of alpha-fetoprotein during pregnancy and perinatal development. *Exp Biol Med* 229(6): 439-463.
3. Mizejewski GJ (2010) Review of the putative cell-surface receptors for alpha-fetoprotein: identification of a candidate receptor protein family. *Tumor Biol* 32(2): 241-258.
4. Jassam N, Jones CM, Briscoe T, Horner JH (2006) The hook effect: a need for constant vigilance. *Ann Clin Biochem* 43(4): 314-317.
5. SeverinSE, Kulakov VN, Moskaleva Elu, Severin ES, Slobodianik II, et al. (2012) The distribution of iodine-125 labeled alpha-fetoprotein in the animal organism and its accumulation in the tumor. *Vestn Ross Akad Med Nauk* 4: 11-15.
6. Pak VN, Belyaev NN (2016) Alpha-fetoprotein-mediated immune tolerance and its reversal. In: Lakhi N, Moretti M, Nova Science Publishers Inc, New York, USA pp: 353-374.
7. Esteban C, Geuskens M, Uriel J (1991) Activation of an alpha-fetoprotein (AFP)/receptor autocrine loop in HT-29 human colon carcinoma cells. *International Journal of Cancer* 49(3): 425-430.
8. Marvel D, Gabrilovich, DI (2015) Myeloid-derived suppressor cells in the tumor microenvironment: expect the unexpected. *J Clin Invest* 125(9): 3356-3364.
9. Kostlin N, Hofstadter K, Ostermeir A-L, Spring B, Leiber A, et al. (2015) Granulocytic Myeloid-Derived Suppressor Cells Accumulate in Human Placenta and Polarize toward a Th2 Phenotype. *The Journal of Immunology* 196(3): 1132-1145.
10. Pak V (2016) Magic Bullet and Immunotherapy against Metastasis. *J Cancer PrevCurr Res* 6(3).
11. Wesolowski R, Markowitz J, Carson III WE (2013) Myeloid derived suppressor cells – a new therapeutic target in the treatment of cancer. *Journal for Immuno Therapy of Cancer* 1:1-10.
12. Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJ, et al. (2014) PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature* 515: 568-571.
13. Pak V (2014) The use of alpha-fetoprotein for the delivery of cytotoxic payloads to cancer cells. *Ther Deliv* 5(8): 885-892.
14. Jewett A, Tseng HC (2011) Tumor Induced Inactivation of Natural Killer Cell Cytotoxic Function; Implication in Growth, Expansion and Differentiation of Cancer Stem Cells. *J Cancer* 2: 443-457.



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