

Alpha-Fetoprotein and its Receptor: More Than Oncofoetal Antigens.

Vladimir N Pak^{1,*}

¹Research scientist, Toronto, Ontario, Canada

Oncofetal antigens are proteins which are typically present only during fetal development. However, they are also found in adults with certain kinds of cancer. These proteins are often measurable in blood of individuals with cancer and may be used to both diagnose and follow treatment of the tumors. Oncofetal antigens and clinical tumor markers include alpha-fetoprotein (AFP), carcinoembryonic antigen, beta-human chorionic gonadotropin, trophoblast glycoprotein precursor, immature laminin receptor protein, etc. AFP is produced by hepatocellular carcinoma and some germ cell tumors (its level increases during pregnancy in cases of spina bifida and other fetal malformations) [1]. Carcinoembryonic antigen is produced by colon/rectum cancer, pancreas, breast, ovary or lung cancer. Beta-human chorionic gonadotropin is produced by germ cell tumors, testicular cancers and neuroendocrine islet cell tumors. Oncofetal antigens in the human body are synthesized for a different purpose, but they prove to be very convenient in detection, diagnosis, and management of some types

of cancer or pregnancy defects. The most important two of the tumor markers are AFP and alpha-fetoprotein receptor (AFPR), which serve as nutrient delivery system to embryo and cancer cells. AFP originated from embryo yolk sac and liver can grab small molecules and essential nutrients from mothers' blood and deliver them through placenta specifically into the AFPR-positive cells in a shuttle manner [2].

AFP was found only in few tumors (in liver, gonads and in cases of embryonic carcinoma). On the contrary, AFPR is present in over 80% of cancers (breast, lung, prostate, ovarian, stomach, etc.). Although it is not a "universal" tumor marker [3], AFPR has higher presence in cancer than any other oncofetal protein. That is why AFPR should be considered as the number 1 oncofetal protein. AFPR-positive embryo and cancer cells have definite benefits of targeted nutrient delivery.

In adults AFP normally persists at 5-10 ng/ml and stimulates tissue regeneration or hematopoiesis. This body-synthesized AFP can be co-opted by cancers

Corresponding author: Vladimir N Pak, Research scientist, Toronto, Ontario, Canada, Email: oncoshut@gmail.com

Keywords: alpha-fetoprotein receptor, oncofetal antigens, myeloid-derived suppressor cells, cancer, immunotherapy.

Received: Jun 27, 2019

Accepted: Aug 18, 2019

Published: Aug 20, 2019

Editor: Qingwen Xu.

thus feeding them with growth stimulating ligands. Moreover, myeloid-derived suppressor cells (MDSCs) which are the precursors of hematopoietic and lymphoid cells in bone marrow are AFPR-positive [4] and migrate to tumor sites. MDSCs are essential participants of tumor immune suppression microenvironment (TME) [5]. The AFPR existence on the host hierarchy top suppressors of immune system - MDSCs – assumes that AFP is locally synthesized during lifetime, and that the synthesis is not restricted by pregnancy or tumor growth periods. MDSCs comprise a small group of innate immune cells that are closely involved in immune tolerance induction and maintenance during pregnancy [6, 7], tumor growth [8], and other conditions. MDSCs were shown to play an important role in TME and cancer development, even upstream of regulatory T-cells. MDSCs suppress both innate and adaptive immune responses, and their elimination unleashes executive cells including NK and T-cells. Hence, MDSCs depletion is a hot topic of cancer immunotherapy [9] and should prevail over T-cells immunotherapies in efficacy. MDSCs have several surface markers through which they can be specifically targeted. MDSCs AFPR and AFP-binding receptor CCR5 [10] are perfect candidates to serve as natural targets.

The use of oncofetal proteins is an 'Achilles heel' of cancer and these proteins are promising targets for several types of cancers. AFPR is an ideal immunotherapy target [11]. AFP-toxin drugs were successfully used for anti-cancer targeted chemotherapy [12].

However, oncofetal proteins are of critical importance not only in pregnancy and tumor growth. Utilization of its physiological delivery function makes AFP a highly promising carrier that can be used for immune suppression during autoimmune and other MDSC-mediated diseases treatments [13, 14]. AFP or AFP–drug complexes can potentiate the major immunity pacifiers – MDSCs- suppression functions during inflammation, transplantation, autoimmune and infectious diseases, etc. Therefore, AFP and AFPR are not just nutrient transport system proteins serving during pregnancy and tumor growth, but they are also involved in the regulation of cell growth, differentiation, and immune regulation throughout the entire lifetime.

They can serve not only as oncofetal antigens but additionally as immunotherapy targets (AFPR) and AFP-drugs for cancer and other MDSC-dependent diseases.

It should be noted that other oncofetal proteins also serve as immune modulators, for example human chorionic gonadotropin (hCG) eventually contributes to peripheral immune tolerance development [15]. Placenta-produced pregnancy-associated plasma protein A (PAPP-A) shares mechanisms of immune evasion with cancer cells [16]; trophoblastic b1-glycoprotein (PSG) determines differentiation and maturity of naive T-cells in memory T cells [17], etc.

Conclusion

AFPR should be considered the number one oncofetal protein. MDSCs markers list should include AFP-binding proteins: AFPR and CCR5. AFP and AFPR are more than oncofetal antigens, they are used during entire lifetime by host MDSCs. AFPR and AFP-drug complexes should be used for treatment of all of the MDSC-dependent disorders.

Conflict of Interest

The author declares no conflict of interest.

References

1. Alpha-Fetoprotein: Functions and Clinical Application. (2016) Ed: Nisha Lakhi and Michael Moretti, Nova Science Publishers Inc.
2. Pak VN. α -fetoprotein-binding toxins and teratogens against cancer. (2019) *Ther. Deliv.* 10(1):1-3.
3. Smrkolj T, Gubina B, Bizjak J, Kumer K, Fabjan T. et al. (2017) Tumor marker α -fetoprotein receptor does not discriminate between benign prostatic disease and prostate cancer. *Adv. Clin. Exp. Med.* 26(7), 1085–1090.
4. Belyaev NN, Abdolla N, Perfilueva Yu, Tleulieva R, Krasnoshtanov VK. et al. (2018) Daunorubicin conjugated with alpha-fetoprotein selectively eliminates myeloid-derived suppressor cells (MDSCs) and inhibits experimental tumor growth. *Cancer Immunol. Immunother.* 67(1):101–111.
5. Clappaert EJ, Murgaski A, Van Damme H, Kiss M, Laoui D. (2018) Diamonds in the rough: harnessing

- tumor-associated myeloid cells for cancer therapy. *Front Immunol.* 9:2250.
6. Ostrand-Rosenberg S, Sinha P, Figley C, Long R, Park D. et al. (2017) Frontline Science: Myeloid-derived suppressor cells (MDSCs) facilitate maternal-fetal tolerance in mice. *J Leukoc Biol.* May;101(5):1091-1101. doi: 10.1189/jlb.1HI1016-306RR. Epub 2016 Dec 22.
 7. Köstlin-Gille N, Dietz S, Schwarz J, Spring B, Pauluschke-Fröhlich J. et al. (2019) HIF-1 α -deficiency in myeloid cells leads to a disturbed accumulation of myeloid derived suppressor cells (MDSC) during pregnancy and to an increased abortion rate in mice. *Front Immunol.* 10:161.
 8. Awad RM, De Vlaeminck Y, Maebe J, Goyvaerts C, Breckpot K. et al. (2018) Turn back the TIME: targeting tumor infiltrating myeloid cells to revert cancer progression. *Front Immunol.* 9:1977.
 9. Fleming V, Hu X, Weber R, Nagibin V, Groth C. et al. Targeting myeloid-derived suppressor cells to bypass tumor-induced immunosuppression. *Front Immunol.* 2018; 9:398. 10.3389/fimmu.2018.00398.
 10. Mizejewski GJ. Protein binding and interactions with alpha-fetoprotein (AFP): A review of multiple AFP cell surface receptors, intracytoplasmic binding, and inter- molecular complexing proteins. (2019) *J Mol Cell Biol Forecast.* 2(1): 1016.
 11. Pak VN. Selective targeting of myeloid-derived suppressor cells in cancer patients through AFP-binding receptors. (2018) *Future Sci OA.* 5 (1):FSO321.
 12. Pak VN. The use of alpha-fetoprotein for the treatment of autoimmune diseases and cancer. *Ther Deliv.* 2017; 9(1):37-46.
 13. Wegner A, Verhagen J, Wraith DC. (2017) Myeloid-derived suppressor cells mediate tolerance induction in autoimmune disease. *Immunology.* 151: 26–42.
 14. Linson EA, Hanauer SB. More than a tumor marker. A potential role for alpha-fetoprotein in inflammatory bowel disease. *Inflammatory Bowel Diseases.* izy394, <https://doi.org/10.1093/ibd/izy394>.
 15. Zamorina S, Timganova V, Bochkova M, Khramtsov P, Raev M. (2018). The role of human chorionic gonadotropin and its peptide fragments in the regulation of IDO expression by human monocytes. *Rossiiskii immunologicheskii zhurnal* 12 (3), pp.306-310 DOI: 10.31857/S102872210002400-5.
 16. Heitzeneder S, Sotillo E, Shern JF, Sindiri S, Xu P, et al. (2019) Pregnancy-Associated Plasma Protein-A (PAPP-A) in Ewing Sarcoma: Role in Tumor Growth and Immune Evasion. *Journal of the National Cancer Institute, J Natl Cancer Inst.* Jan 30, dgy209, <https://doi.org/10.1093/jnci/dgy209>
 17. Timganova V, Bochkova M, Khramtsov P, Kochurova S, Rayev M, Zamorina S. (2019). Effects of pregnancy-specific β -1-glycoprotein on the helper T-cell response. *Archives of Biological Sciences.* 19-19. 10.2298/ABS190122019T.