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Opinion

Alpha-Fetoprotein/Receptor Vital Duo

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Oncofetal proteins serve as pregnancy and tumor markers. However, they are of critical importance not only in pregnancy and tumor growth. The main two of these oncofetal proteins are alpha-fetoprotein (AFP) and alpha-fetoprotein receptor (AFPR). During pregnancy, AFP functions as both a maintenance molecule and a biological response modulator of fetal growth. In benign and malignant tumors, it serves as a growth-regulating molecule [1]. AFP is synthesized by the embryo yolk sac and liver. It has many functions including the transport of docosahexaenoic acid (DHA), which is essential for embryo cells growth. The mother's organism does not synthesize DHA and hence should take it from food. AFP takes DHA from albumin in mother's blood and transports it through placenta. Embryo cells internalize AFP-DHA non-covalent complex through AFPR-mediated endocytosis. AFP transports nutrients multiple times in a "shuttle" manner. AFP-AFPR duo serves as a delivery system also to cancer cells because AFP is an oncomarker for several cancers while AFPR is found in majority of them, though it is not a universal tumor marker [2]. So, AFPR instead of AFP should be considered the number one oncofetal protein.

Nevertheless, human AFP deficiencies and/or absence during pregnancy reveal that full-term pregnancies could still occur. In the AFP gene knockout rodents models it was shown that AFP was not a requirement for full term delivery. The knockout rodent females were found to be sterile (unlike males) that was attributed to anovulation due to an AFP regulatory absence in the hypothalamic-pituitary-gonadal axis [3]. On the other hand, there is no data that could reveal the AFPR requirement for survival or full term delivery of AFPR-deficient rodents. AFPR-negative organisms probably could not survive at all.

The recently discovered AFPR on myeloid-derived suppressor cells (MDSC) [4] can provide additional AFP-negative rodent females sterility explanation that is based on the AFP-AFPR duo role in the cells of immune system. The AFPR existence on the normal MDSC assumes that AFP is locally synthesized during lifetime and that it is not restricted by pregnancy or tumor growth periods. Hence, AFP gene knockout rodents could grow due to mother's AFP supply. Moreover, regulatory MDSC facilitate maternal-fetal immune tolerance [5]. The AFP gene knockout females should be sterile not only due to AFP absence in their brains which affect ovulation but also due to its absence in the immune tolerance "shield" normally generated by recruited MDSC over embryo. The embryo will be destroyed by the innate immunity that is not properly suppressed by MDSC lacking AFP-nutrient supply. For example, MDSC have a poor source of polyunsaturated fatty acids that are needed for suppressive cytokines synthesis. In any case, not AFP alone but AFP-AFPR duo is vital for embryo growth.

The same is true for the tumor growth. Tumor- or mother-synthesized AFP supply AFPR-positive cancer cells with nutrients and they grow freely in immune suppressive microenvironment generated by AFPR-positive MDSC. Cancer treatments with AFP-toxin drugs were successful not only due to direct chemotherapy drug action but mostly due to MDSC-targeted immunotherapy that destroyed tumor immune suppressive microenvironment. At the same time the regulatory cells-targeted immunotherapy "unleashes" both innate and adaptive immunity that should prevail separate executive natural killer and T cells immunotherapies in efficacy [6].

The presence of MDSC is not restricted to cancer, but can occur in every form of chronic inflammation, including autoimmune diseases, pathogenic infection, and other diseases [7], so AFP-AFPR duo can be used for the treatment of these diseases [8]. AFP loaded with definite ligands (e.g. polyunsaturated fatty acids and/or their derivatives) can potentiate immunosuppressive cytokines synthesis by MDSC and/or their direct suppressive activity.

Summary

AFPR should be considered oncofetal protein number one. AFP-AFPR delivery system serves not only during pregnancy and tumor growth but during the entire lifetime. AFPR-positive MDSC

are effective targets for cancer and other diseases' treatment with AFP-ligand drugs.

Conflict of Interest

The author declare no conflict of interest.

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