British Journal of Cancer Research
2019; 2(2): 274 - 276. doi: 10.31488/bjcr.130

Minireview

Think outside the cancer cell

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Received: March 15, 2019; Accepted: April 25, 2019; Published: April 29, 2019

Abstract

Chemotherapy destroys cancer cells from inside, but that is not enough to beat cancer. We should also consider immunotherapy, which attacks cancer cells from outside. The complex and sophisticated interactions between immune system and cancer cells makes the best immunotherapy strategy choice hard. Nevertheless, it is clear that regulatory immune cells are more powerful than executive ones. Regulatory myeloid-derived suppressor cells-targeted immunotherapy should prevail over check-point inhibitors immunotherapy in efficacy. This mini-review is focused on myeloid-derived suppressor cells immunotherapy targeted through their alpha-feto-protein receptors.

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

Introduction

Myeloid-derived suppressor cells (MDSC) comprise a small group of innate immune cells that are closely involved in immune tolerance induction and maintenance. MDSC are the major immunity pacifiers, but their identity, heterogeneity and biology is still poorly understood. It is established that MDSC are the essential participants of tumor immune suppression microenvironment [1]. They were shown to play an important negative regulatory role in cancer development, even upstream of regulatory T-cells. MDSC regulate both innate and adaptive immune responses, and their elimination unleashes numerous executive cells including NK and T-cells. MDSC have several surface markers through which they can be specifically targeted, but recently-discovered alpha-fetoprotein (AFP) receptor (AFPR) [2, 3] is of special interest.

AFPR as an Immunotherapy Target

AFP and AFPR are the main oncofetal proteins that serve as a nutrient delivery system for embryo and cancer cells. AFP is synthesized by the yolk sac and the embryo/fetal liver and crosses placenta to mother's blood to transport back essential nutrients, e.g. polyunsaturated fatty acids. Majority of cancer cells re-express AFPR and can internalize AFP-nutrient non-covalent complex through receptor-mediated endocytosis as embryo cells do. After internalization and nutrient unloading, AFP returns to the blood to shuttle another nutrient while AFPR returns to the cell surface. Unlike AFP, AFPR is re-expressed by majority of cancer cells making it the number one oncofetal protein [4]. Like embryo, stem and low differentiated cells MDSC (which are precursors of hematopoietic and lymphoid cells) demonstrate AFPR for attracting nutrients-loaded AFP. AFP-AFPR nutrient delivery system works for MDSC not only in onco/fetal period, but throughout the entire lifetime, and MDSC create tolerance to embryo, tumor, inflammation, autoimmune and other conditions [5-8]. That is why AFPR is an immunotherapy target.

Govallo vaccinated terminal patients with AFP, AFPR and other placental proteins that generated antibodies which erased cancer cells. In 35 patients he achieved a 77.1% 5-year survival rate, and a 65.4% 10-year survival rate [9]. Not only could antibodies to AFPR destroy cancer cells, but also affect AFPR-positive MDSC, which implies immunotherapy. "Normogen" preparation (antibodies to AFPR) injections improved the quality and longevity of patient's life. Total anti-tumor activity of "Normogen" preparation in 15 patients reached 73.34% [10]. The authors proposed that antibodies to AFPR destroyed cancer cells through complement-dependent cytotoxicity [11]. Nevertheless, AFPR-targeted therapy inevitably resulted additionally in MDSC immunotherapy.

Unlike antibodies that destroy AFPR-positive cells through complement-dependent cytotoxicity AFP-toxin complexes use cell inbuilt self-destruction pathways. AFP transports selected toxins molecules inside the hydrophobic pocket [12]. After receptor-mediated endocytosis AFP have been reported within coated pits of the plasma membrane, tracked to vesicles, multi-vesicular bodies, and the trans-Golgi network [13]. On this intracellular pathway AFP releases toxins that activate self-destruction mechanisms. The toxins that ruin organelle membranes and cell compartmentalization are effective in cell self-destruction. For example, most evidence suggests that Golgi disruption occurs prior to cell death [14]; or mitochondrion break is a known "point of no return" in the intrinsic apoptosis pathway. Amphotericin B is a pore-forming anti-fungal antibiotic which presumably ruins organelle membranes which

close to fungal membrane by physic-chemical structure. AFP-amphotericin B non-covalent complex infusions have shown response in 6 out of 8 (75%) cancer patients [15]. The numerous metastases elimination could not be explained through cancer cells-targeted chemotherapy because of low AFP dose (0.001-0.004 mg/kg) and one "magic bullet" can hit only one target. On the contrary, massive cancer cells destruction is possible if this target is MDSC. MDSC depletion unleashes subordinate numerous executive NK and T cells, which in turn can destroy a lot of cancer cells. AFP-amphotericin B complex infusions were sometimes accompanied with the immediate acute phase immune response (chill, shiver) that could be explained by MDSC depletion in the blood. So, MDSC-targeted immunotherapy should be responsible for AFP-amphotericin B non-covalent complex anti-cancer efficacy. Similarly, the high anti-cancer efficacy demonstrated by low doses of AFP-thapsigargin (Golgi is a target), AFP-atractyloside and AFP-betulinic acid (mitochondrion is a target) non-covalent complexes [16] should be also due to MDSC depletion [17].

AFP-thapsigargin non-covalent complex (ACT-902) lead to complete regression of 5 out of 6 (83%) highly resistant to chemotherapy POP-92 xenografts by day 7 of treatment with no further growth thereafter in mice; ACT-902 has also demonstrated direct cytotoxic action on MDSC [18].

The antitumor effect of paclitaxel is attributed to the suppression of microtubule formation resulting in defects in cell division. At conventional dose (15 mg/kg) paclitaxel has demonstrated direct cytostatic or cytotoxic effects on melanoma cells. In contrast, paclitaxel in ultralow non-cytotoxic concentrations (1 mg/kg, weekly × 3) intraperitoneal administration significantly decreased accumulation and immunosuppressive activities of tumor-infiltrating MDSC [19]. Paclitaxel in ultralow doses is not able to directly suppress tumor cell proliferation, induce their apoptosis in vivo or alter the bone marrow hematopoiesis but affects immune regulators in the tumor microenvironment. Ultralow non-cytotoxic dose paclitaxel modulated MDSC functions in primary skin tumors and lymphoid organs, effected on the production of mediators of chronic inflammation and T cell activities in the tumor microenvironment in vivo. Paclitaxel applied at ultra-low, non-toxic doses demonstrated a remarkable anti-tumor effect in vivo, prolonged mice survival and reduced melanoma burden. In a low dose paclitaxel reduced the immunosuppressive potential of MDSC in vivo, and reversed immunosuppression and chronic inflammation. Taking into account paclitaxel's ability to be solubilized (or bound in the blood) by AFP [20, 21] we can assume that in vivo paclitaxel first binds AFP; then AFP-paclitaxel is endocytosed by MDSC through AFPR, and this works as immunotherapy.

The low doses of toxins bound to AFP have shown good results in cancer treatments [22, 23]. In the above examples MDSC-targeted immunotherapy exceeded in efficacy checkpoint inhibitors with its 20-30% response to treatments. Other AFPR-targeted immunotherapy advantage is that it is not personalized and can be applied to patients having different cancers and especially metastases.

AFP together with active ingredients from spices/food can be used to treat cancer. Many of the small molecules with anti-cancer properties known from medicine literature are hydrophobic or amphiphilic by nature and can bind AFP. Their anti-cancer activity can be explained and potentiated by AFP-AFPR delivery system. The natural moderate cytotoxins like genistein from soya, curcumin from turmeric [24], 1-S-1-acetoxychavicol acetate [25], ajoene from garlic (Pak VN, Unpublished Data), etc. have demonstrated anti-cancer properties while complexed with AFP. In other words, AFP and toxin jointly present in the blood can effectively destroy (or neutralize like paclitaxel low doses) AFPR-positive MDSC which implies immunotherapy.

Because cancer during pregnancy is rare, not a lot of research has been done. In one anecdotal case the early stage cancer growing in the lady's womb disappeared due to pregnancy. The doctors inferred that the pregnancy hormones had caused this miracle and a tumor to disintegrate [26]. The role of pregnancy-associated AFP and AFPR was not discussed. We can speculate that AFP together with pregnancy hormones or AFP non-covalent complexes with the drugs or moderate cytotoxins from the spices/food the lady took during cancer treatment could impact cancer disintegration. Unlike cancer cells embryo ones had less damage caused by AFP-toxin complexes as they were behind the placenta (like bone marrow hematopoiesis was not altered by paclitaxel low doses). Moreover, cancer could be disintegrated through MDSC-targeted immunotherapy that was discussed before.

Conclusion

Immunotherapy based on major regulatory MDSC prevail executive cells-based immunotherapies as it unleashes subordinate both innate and adaptive immunity including NK and T-cells. MDSC and cancer cells can be depleted by antibodies to AFPR, AFP-toxin non-covalent complexes and others. MDSC-targeted immunotherapy is a novel efficient therapeutic approach for decreasing the pro-tumorigenic potential of the tumor microenvironment and increasing the efficacy of associated anti-cancer therapies.

Conflict of Interest

The author declare no conflict of interest.

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To cite this article: Vladimir N Pak. Think outside the cancer cell. British Journal of Cancer Research. 2019: 2:2.