Magic Targets for Magic Bullet

Vladimir N Pak
Freelance researcher, Toronto, Canada.

Corresponding Author: Freelance researcher, Toronto, Canada. E-mail: oncoshut@gmail.com

Abstract

The “magic bullet” by Paul Ehrlich is a chemotherapeutic, which can precisely locate and destroy tumor cells. For over 100 years, a great number of approaches have been developed for targeted delivery of toxins. Nevertheless, the progress in the battle with cancer is moderate. In reality, the magic bullet is unable to destroy cancer cells with 100% efficacy. However, cancer cells are neither an optimal nor the only possible target. The magic bullet needs a “magic target”.

Keywords: cancer immunotherapy; myeloid-derived suppressor cells; neonatal Fc receptor; alpha-fetoprotein; lymphatic system

Introduction

The “magic bullet” by Paul Ehrlich is a chemotherapeutic, which can precisely locate and destroy tumor cells. For over 100 years, a great number of approaches have been developed for targeted delivery of toxins. Nevertheless, the progress in the battle with cancer is moderate. In reality, the magic bullet is unable to destroy cancer cells with 100% efficacy. However, cancer cells are neither an optimal nor the only possible target. The magic bullet needs a “magic target”.

Billions of cells die and are recycled every day. Each of the newborn cell inevitably accumulate mutations. During a human lifetime, two anti-cancer systems: apoptosis and immunity, are perfectly able to protect the majority of us. In case of cancer, both systems are damaged and do not eliminate “wrong” cells. The magic bullet can destroy cancer cell, but it is only one side of the coin. Immune system should be repaired too.

Immune checkpoint inhibitors (ICIs), CAR-T cells, natural killer (NK) cells and other approaches are used for cancer immunotherapy.

A number of patients do not respond to ICIs treatment due to profound immunosuppression, which is mediated by myeloid-derived suppressor cells (MDSCs). MDSCs can largely inhibit anti-tumor activities of cytotoxic lymphocytes (CTLs) and NK cells, and stimulate regulatory T cells (T-regs), leading to tumor progression [1].

CAR-T cells therapy provokes fever and elevated IL-6 levels that are often followed by life-threatening cytokine-release syndrome (CRS) and neurotoxicity [2]. Monocytes are the major source of IL-6 during CRS and their depletion can prevent syndrome [3].

Both ICIs and CAR-T cells rely on adaptive immunity, carry risk of serious side effects and have limited efficacy in the majority of patients. In the hierarchy of innate and adaptive immunity cells, large numbers of executive NK cells and CTLs are controlled by lesser quantity of T-regs and a smaller number of MDSCs. MDSC and monocyte depletion can improve ICIs and CAR-T cells therapy [1, 3]. MDSC depletion is a powerful immunotherapy strategy itself [4, 5, and 6] and it should prevail over ICIs or CAR-T cells immunotherapies in efficacy, as it initiates additional attacks by NK cells on cancer stem cells and metastases [7, 8].

MDSCs as an immunotherapy target.

MDSC background, its physiologic function, roles in cancer and important progress in cancer research related to MDSC targeting are well described [9, 10, and 11]. MDSCs play a major role in the profound immune suppression during pregnancy and cancer, even ahead of T-regs[12]. They can be regarded as the main tumor-induced negative regulators of cancer immunity, as well as the suppressors of innate immunity NK cells [13].

MDSCs depletion can reverse immune suppression and activate the second natural anti-cancer defense system – our own immunity. Unlike chemotherapy, it does not require 100% efficacy. MDSCs play a pivotal role in the balance of pro- and anti-cancer immune forces at the tumor site [14]; while even partial reduction of regulatory suppressor cells can shift the tumor microenvironment balance into desired active state, and unleash an army of subordinate executive cells. Taking into account the considerably smaller quantity of MDSCs compared to the quantity of cancer cells, we can assume that MDSC-depleting immunotherapy needs less magic bullets to achieve massive cancer cells elimination. Low dosesensure treatment safety and reduce cost.

Non-specific chemotherapeutics administered in low doses deplete MDSCs, which supports MDSCs role in cancer immunotherapy [15, 16, and 17].

Selective targeting TRAIL receptor 2 with antibody eliminate MDSCs in the patients with advanced stages of cancer. MDSCs depletion with antibody administered intravenously resulted in MDSCs subsets reduction without affecting the number of neutrophils, monocytes, and other populations of myeloid and lymphoid cells. A transitory decrease of the elevated MDSCs numbers was inversely correlated with the length of patients' survival [18].

AFP-binding regulatory immune cells.

Alpha-fetoprotein (AFP) was used for toxin specific delivery into AFP receptor (AFPR)-positive cancer cells [19, 20]. MDSCs were found to be AFPR-positive too and they were specifically targeted with AFP+toxins drugs. In mice, AFP+daunorubicin chemical conjugate decreased MDSCs population and unleashed NK cells to destroy tumors [21].

Low doses of the AFP non-covalent complex with amphotericin B were applied as infusions to cancer patients [22]. The complex did not provoke toxicity or immunity and hemopoiesis depression. A full or a partial clinical effect was achieved in six patients out of eight. One bullet can hit only one target, so AFP+amphotericin B complex could not have affected a lot of AFPR-positive cancer cells. A more viable explanation of such a disproportionate effect in tumor and metastases reduction is thatthe AFP+toxin complex deplete MDSCs [23].

Unlike injectable forms, oral administration cannot provide direct contact of AFP+toxin complex with AFPR-positive cancer cells or MDSCs. Unenhanced bioavailability for oral routes of administration forprotein/peptide pharmaceuticals accounts to no more than 0-1% [24]. Proteins enzymatic instability and gastro intestinal (GI) permeation are the main challenges. Nevertheless, oral administration of the AFP+atractyloside non-covalent complex in suboptimal doses was well- tolerated and produced major objective responses in six out of twelve liver metastatic colorectal cancer patients [25, 26].

An investigation conducted into the possible reasons for such disproportionate response have shown that AFP was not absorbed into themice blood after per oral administration, neither in free form nor in a complex with toxin [Unpublished]. Moreover, unlike in the blood and tumor site, MDSCs are sparsely distributed in the intestinal lymphatic system, which contains majority of immune cells of the body. So, there should be different AFP-binding immune cells which depletion leads to distant metastases reduction.

Discussion

In the adult human gut, both enterocytes in a thin layer of connective tissue of the GI tract and dendritic cells (DCs) in lymphatic system express neonatal Fc receptor (FcRn), which specifically binds IgG, albumin [27] and AFP [28]. These three proteins can bind and deliver their ligands from the gut into the lymphatic system. For example, IgG can deliver antigens from the gut to lymphatic system in a shuttle manner[29]. AFP has a stronger binding affinity to FcRn than albumin [28], it can compete with IgG for FcRn binding and hence, its ligand (e.g. toxin bound with AFP) can be transferred from the gut to lymphatic system.

In the lymphatic system FcRn is mainly present in DCs but it isalso expressed by monocytes, macrophages and neutrophils [30, 31]. Human peripheral monocytes and macrophages also possess AFPR which is involved with the physiological regulation of the immune response [32].

In the draining lymph nodes AFP+atractyloside complex should be absorbed by AFP-binding immature monocytes, macrophages, DCs, orother cells. Similar to MDSCs depletion in the blood these cells subsequent death can possibly induce innate immunity-mediated sterile inflammation and generate response which eventually reduces distant metastases.

Depletion of the hierarchy top immune cells in both injectable and oral AFP+toxin administrations and subsequent anti-cancer effect prevails over their magic bullet one. The regulatory AFP-binding cells can be considered the "magic targets" for immunotherapy. In the case of injectable AFP+toxin drug a traditional magic bullet is combined with themagic bullet hitting the "magic target" - MDSCs. This therapy can fix both natural anti-cancer systems – apoptosis and immunity.

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