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Personalized approaches to active immunotherapy in cancer

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ABSTRACT

Immunotherapy is emerging as a promising anti-cancer curative modality. However, in contrast to recent advances obtained employing checkpoint blockade agents and T cell therapies, clinical efficacy of therapeutic cancer vaccines is still limited. Most vaccination attempts in the clinic represent "off-the shelf" approaches since they target common "self" tumor antigens, shared among different patients. In contrast, personalized approaches of vaccination are tailor-made for each patient and in spite being laborious, hold great potential. Recent technical advancement enabled the first steps in the clinic of personalized vaccines that target patient-specific mutated neo-antigens. Such vaccines could induce enhanced tumor-specific immune response since neo-antigens are mutation-derived antigens that can be recognized by high affinity T cells, not limited by central tolerance. Alternatively, the use of personalized vaccines based on whole autologous tumor cells, overcome the need for the identification of specific tumor antigens. Whole autologous tumor cells could be administered alone, pulsed on dendritic cells as lysate, DNA, RNA or delivered to dendritic cells in-vivo through encapsulation in nanoparticle vehicles. Such vaccines may provide a source for the full repertoire of the patient-specific tumor antigens, including its private neo-antigens. Furthermore, combining next-generation personalized vaccination with other immunotherapy modalities might be the key for achieving significant therapeutic outcome.

1. Background

Cancer immunotherapy aims at utilizing the immune system to reject tumors and/or to prevent their recurrence. Cancer immunotherapy comprises passive, active or immunomodulatory approaches. Passive immunotherapy involves administration of exogenously generated antibodies or adoptively transferred immune cells (typically T cells) to mediate an anti-cancer immune response. Immunomodulatory agents aim at enhancing immune response to increase anti-cancer immunity. As for active immunotherapy (i.e. vaccination), its primary goal is to activate endogenous immune cells to recognize specific tumor-associated antigens (TAAs) and eliminate cancer cells, with minimal detriment to healthy non-tumor cells. While the recent renaissance of cancer immunotherapy is mainly fueled by advances in adoptive T cell therapies and immunomodulatory checkpoint blockade agents, the achievement of systemic, specific and durable anti-cancer immune response, through therapeutic vaccination of patients still holds a great promise [1].

1.1. Therapeutic cancer vaccines

Prophylactic (or preventive) vaccination represents one of the major achievements in the history of medicine. In the context of cancer therapy, prophylactic vaccines have been used efficiently for the prevention of cancers of viral origin [2,3]. In 2009 the FDA approved multi-valent vaccines to prevent infections by the human papilloma virus (HPV) type 16 and 18 which ultimately lead to the development of cervical carcinoma [4–6]. In contrast, only a minority of patients currently benefit from cancer therapeutic vaccination, although for some patients the benefit can be substantial [1,7]. The challenges in developing highly effective therapeutic cancer vaccines, compared to prophylactic vaccines, stem from various reasons including the low immunogenicity of cancer cells, the immunosuppressive micro and macro environment induced by malignant cells, the compromised immune system of the heavily treated patients themselves and finally the choice of the advanced patient population where therapeutic vaccines are

Abbreviations: TAA, tumor associated antigen; HPV, human papilloma virus; DC, dendritic cell; CTL, cytotoxic T cell; TGF-β, transforming-growth-factor-β; MDSC, myeloid-derived-supressor-cells; CT, cancer/testis; Gp100, glycoprotein 100; MS, mass spectrometry; NGS, next-generation sequencing; GM-CSF, granulocyte-macrophage colony-stimulating factor; PAP, prostatic acid phosphatase; TIL, tumor infiltrating lymphocytes; CLL, chronic lymphocytic leukemia; IFN-γ, interferon-gamma; BCG, bacille Calmette–Guérin; PLGA, poly(lactic-co-glycolic acid); TLR, Toll-like receptor; HOCL, hypochlorous acid; VEGF, vascular-endothelial-growth factor; PFS, progression-free-survival.

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administered intending to eliminate large established tumors. Accordingly, clinical evidence indeed shows that patients with less advanced disease are more likely to benefit from active immunotherapy [8–10].

1.2. The biological cascade that leads to an effective anti-cancer immune response

Poor understanding of the biological cascade that leads to an effective vaccination compromised many of the initial therapeutic cancer vaccines attempts in the clinic [11]. However, in recent years, extension of this knowledge has led to more rational design of cancer vaccines. The mechanism that leads to an effective anti-cancer response involves few stages [12]. Dendritic cells (DCs) are key players in this cascade through their capacity to capture, process and present antigens to activate T cells [13]. Thus, to initiate immunity, DCs must capture TAAs derived from the vaccine. As we will discuss along this review, choosing the "right" TAA, or combination of TAAs, for vaccination is a crucial part in the vaccine design.

The second step of efficient anti-cancer immunity will have to involve a proper activation ("maturation") signal delivered to the DCs to allow their differentiation and migration to the lymph nodes. Antigen presentation in the absence of suitable maturation signal typically results in an unwanted immune tolerance due to lack of co-stimulatory molecules expression by the DCs [14] and expansion of regulatory T cells [14,15]. Next, in the lymph nodes, mature TAA-presenting DCs must activate and expand tumor-specific T cells in sufficient numbers to generate therapeutic–meaningful immune response. Of note, spontaneously organized tertiary lymphoid organ features were documented in tumors suggesting that T cell activation can occur within the tumor stroma as well [16]. The exact type of T cell response required for optimal anti-tumor immunity is not entirely clear but obviously $CD8^+$ cytotoxic T cells (CTLs) play a key role in tumor eradication. In addition, it is now known that $CD4^+$ T cells concurrent activation is required to support potent CTLs and memory $CD8^+$ T cells generation and maintenance [17,18]. Furthermore, $CD4^+$ T cells can directly serve as potent anti-tumor effector cells [19–21].

Finally, in the last stage of anti-cancer immune response, activated cancer-specific T cells must leave the lymph nodes, infiltrate the tumor microenvironment, and perform there their effector function that will end up in tumor eradication. At this stage, potent tumor-mediated immune suppression becomes a challenge. Tumors use various strategies in order to escape the immune response by interfering with multiple steps required for an effective immunity [22]. Tumors promote the establishment of a physical barrier at the endothelium, that hampers T cell extravasation and homing [23,24], mainly by secreting angiogenic factors that leads to down-regulation of vascular adhesion molecules [25,26], a phenomenon that was termed endothelial cell anergy [27]. In addition, cancer cells produce immunosuppressive molecules (including Indoleamine 2,3-dixoxoygenase [28] and transforming growth factor-beta (TGF-β) [29]) and upregulate inhibitory ligands, such as PDL1, to mediate the suppression of extravasated T cells [30]. Moreover, the tumor microenvironment attracts increased levels of immunosuppressive cells including regulatory T cells [31] and myeloid-derived suppressor cells (MDSCs) [32]. Thus, treatments that target tumor-mediated immunosuppressive mechanisms could enhance the efficacy of active immunotherapy.

1.3. Tumor-associated antigens as targets in active immunotherapy

Tumors are recognized by T cells through various TAAs. In general, TAAs can be separated into two main classes (Fig. 1): non-mutated self-antigens and mutated neo-antigens [33]. Tumors express non-mutated self-antigens as a result of tissue (lineage)-specific gene expression or transformation-induced gene deregulation. To be therapeutically meaningful, cancers must preferentially express these non-mutated antigens, while T cell precursors must be available to recognize them, due to incomplete thymic deletion or peripheral tolerance toward these antigens. Tumor self-antigens can be divided into three major subclasses (Fig. 1) [33,34]: 1) Antigens whose expression is normally restricted to male germline cells (e.g MAGE antigens, NY-ESO-1). These germline or "cancer/testis" (CT) antigens are frequently upregulated in tumors due to promoter demethylation events [35]; 2) Overexpressed antigens, i.e. normal proteins whose expression is elevated in cancer cells but are also expressed in lower levels in healthy tissue (e.g Her2/Neu, WT1); 3) Tissue-specific or lineage antigens, which are antigens shared between tumors and the tissue they originated from. Melan-A/MART-1 and glycoprotein 100 (gp100) are examples of antigens that are expressed in melanoma but also in healthy melanocytes.

Conversely, neo-antigens result from the large number of somatic mutations found in human cancer cells and therefore are fully tumor-specific. Recent deep sequencing analyses have revealed that solid tumors harbor usually between 10 and few thousand private somatic mutations, most of which differ even among tumors of the same histotype [36,37]. Massive parallel sequencing can now reveal with precision the mutational spectrum of individual tumors (i.e. the mutanome). The definition of epitopes derived from the mutanome on a patient-specific basis can be achieved by analyzing the HLA ligandome of tumor cells (direct identification) integrated with cancer genome data identifying mutations that may lead to candidate peptides (reverse identification) [38,39]. The former method requires the elution of the peptides from HLA molecules derived from the tumor tissue of the patient, followed by reversed phase HPLC fractionation and mass spectrometry (MS). Of note, direct identification still needs to be

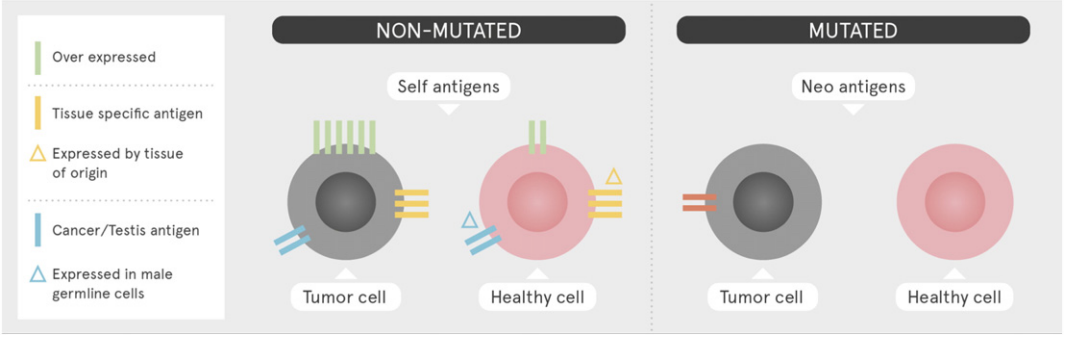

Fig. 1. Tumor associated antigens. Tumor-associated antigens (TAAs) can be separated into two main classes: non-mutated self-antigens and mutated neo-antigens. Tumor self-antigens can be further divided into three major subclasses: 1) overexpressed antigens; 2) tissue-specific antigens, which are antigens shared between tumors and the tissue they originated from; and 3) antigens whose expression is normally restricted to male germline cells ("cancer/testis") antigens. Neo-antigens result from the large number of somatic mutations found in human cancer cells and are therefore tumor-specific.