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Mini Review

Antigens in Immune-Oncotherapy

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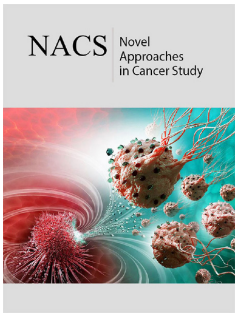

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Abstract

Therapeutic vaccination is admitted to be a promising axis in onco-therapy. Contrary to preventive vaccination, which is mainly effective through the action of antibodies, onco-therapeutic vaccination requires the action of cellular immunity and in particular cytotoxic CD8+ T lymphocytes. Development of such vaccines requires a rational antigenic choice and efficient vaccination vectors to induce robust, high quality and durable T-cell responses, and when necessary to overcome the T-cell tolerance. Here, we review the two categories of antigens that can be targeted by onco-therapeutic vaccines, namely Tumor-Associated Antigens (TAAs) and Tumor-Specific Antigens (TSAs), by giving examples and describing advantages and limitations of each antigen category. Combination of one or more appropriately selected antigens with, for instance, the powerful lentiviral vaccine vector platform, is a novel approach for the development of new generations of onco-therapeutic vaccines.

Keywords: Tumor-associated antigens; Tumor-specific antigens; Self antigens; T-cell responses; Onco-proteins; Tumor regression; Vaccination

Introduction

T-cell based therapeutic cancer vaccines are administered to cancer patients with the aim of generating effector and memory anti-tumor T-cell responses to control tumor growth without destroying non-tumor cells/tissues. Vaccine design should target the most appropriate tumor antigens that ideally possess all of the following characteristics: specifically expressed by cancer cells and essential for their survival, expressed by all cancer cells to avoid escape from immune elimination, and highly immunogenic to induce specific and robust cellular responses [1]. Tumor antigens are classically divided into two groups, namely Tumor-Associated Antigens (TAAs) and Tumor-Specific Antigens (TSAs).

Tumor-Associated Antigens (TAAs)

TAAs are non-mutated self-proteins, abnormally expressed by cancer cells, and are not necessarily tumor specific since they might be expressed by normal cells.

(i) Self-antigens,

(ii) differentiation antigens, and

(iii) cancer testis antigens are the three types of TAAs.

Self-antigens, e.g., Mucin1 (MUC-1), Human Epidermal growth factor Receptor 2 (HER2/neu) and telomerase [2], are normally expressed at low levels in healthy cells. Differentiation antigens, e.g., tyrosinase, glycoprotein (gp) 100, (PSA) and (PAP), are expressed only in tumor cells and in the healthy tissues of origin [1]. Expression of cancer testis antigens, e.g., Melanoma-Associated Antigen (MAGE)-A1, MAGE-A3, and New York Esophageal Squamous Cell Carcinoma-1 (NY-ESO1), is normally restricted to immune-privileged germline cells but becomes aberrant in tumors [3]. Like T cells specific to self-proteins, TAA-specific T cells are submitted to central and peripheral immune tolerance. T-Cell Receptor for antigen (TCR)

that recognize epitopes derived from such self-antigens with high affinity are either deleted from the immune repertoire during the intra-thymic negative selection or maintained anergic under the control of peripheral tolerance mechanisms [4].

Compared to overexpressed proteins or differentiation antigens, cancer testis antigens are mainly expressed in germline cells which do not express Major Histocompatibility Complex (MHC) molecules, and which are located in immune-privileged sites [5]. Therefore, T cells specific to cancer testis antigens are subjected to weaker or more partial tolerance induction. These antigens may thus be more attractive targets for vaccine design.

Tumor-Specific Antigens (TSAs)

Unlike TAAs, TSAs are tumor specific and include oncoviral antigens, neoantigens, as well as antigens derived from Human Endogenous Retroviruses (HERVs) [6]. TSAs are considered as foreign antigens and can be highly immunogenic.

Vaccination against viro-induced carcinogenesis might seem to be the easiest to design, as the oncoviral antigens meet all the criteria listed above, i.e., essential for tumor survival, specifically expressed by all tumor cells, and highly immunogenic, without risk of inducing autoimmunity. About 10% of human cancers are caused by viral infection [7]. Viral antigens have been identified in vitro-induced cancers such as: Human PapillomaVirus (HPV)-associated cancers, including (oropharyngeal) head and neck cancers, cervical or anal cancers, Hepatitis B Virus (HBV)- or Hepatitis C Virus (HCV)-associated hepatocellular carcinomas. In addition, Epstein-Barr Virus (EBV) is linked to hematological cancers, i.e., Hodgkin lymphoma and Burkitt lymphoma, and nasopharyngeal cancers, while Human T cell leukemia/lymphoma virus type 1 (HTLV-1) is responsible for adult T-cell leukemia/lymphoma [8]. Gardasil and Cervarix prophylactic vaccines, targeting the oncogenic HPV16 and HPV18 serotypes provide significant protection against HPV infection and pre-cancerous cervical lesions [9]. This vaccination mainly induces neutralizing antibodies, efficiently preventing host cell infection and the resulting oncogenic transformation. However, therapeutic use of these vaccines in patients with established HPV-induced cancers did not show efficacy [1], the most seemingly because of the lack of efficient T-cell immunity, a requirement to eradicate established tumors. Currently, several HPV vaccine candidates targeting T-cell epitopes, derived from major E6 and E7 oncoproteins, are under investigation in clinical trials [10] and [11].

Neoantigens arise from somatic mutations of normal proteins during oncogenesis and theoretically, the host harbors no central tolerance towards them, which potentially leads to robust neoantigen-specific T-cell responses [12]. Even though neoantigens could appear as an optimal choice to design cancer vaccines, several issues need to be highlighted concerning their potential use. The majority of neoantigens are unique to individual patients and required generation of personalized immunotherapy. The latter approaches present logistical and financial obstacles associated to an extended production timeline that could possibly lead to tumor progression before the possibility to initiate the treatment. Neoantigens arise in tumor with high Tumor Mutational Burden (TMB). Increased mutational load may generate neoantigens for T-cell recognition, in turn leading to increased recruitment of CD8+ cytotoxic T cells, major players of efficient cancer immunotherapy. TMB has also been linked to the efficacy of immune checkpoint blockade in melanoma, lung cancer, and colorectal cancer, which are typically cancers displaying high TMB. However, many cancer types, such as breast and prostate cancers, do not exhibit a positive correlation between CD8+ T-cell infiltration and neoantigen load indicating that native anti-tumor immune response exist independently of the TMB. In addition, only a small subset of neoantigens has been shown to be able to elicit robust T-cell responses [13]. In fact, neoantigens need to meet the following criteria.

A. Sufficient degree of foreignness; if the neoantigen has high similarity to the wild-type sequence, the responding T cells will the most probably be tolerant through central or peripheral tolerance mechanisms.

B. Expressed by every tumor cell; if the neoantigen is present in only a proportion of tumor cells, the T-cell mediated tumor elimination will be partial [14].

Shared neoantigens or public neoantigens are derived from recurrent mutations in cancer driver genes, such as KRAS p. Gly12Asp or KRAS p. Gly12Val mutations, which occur in pancreas or lung cancer, respectively. This kind of neoantigens can be an alternative for cancer vaccine design that could be applied to many patients [15].

Another source of TSAs results from the HERV reactivation that can lead to de novo viral protein synthesis by the tumor. Due to their homology with “non self” viral proteins and their limited expression to normal tissues, HERVs may potently elicit antitumor B- and T-cell responses, and positively help tumor regression [16]. HERVs derive from the chromosomal integration of retroviral genetic material upon germline infections and represent 8% of the human genome [16]. Most HERVs are silenced by epigenetic mechanisms in normal cells, however, dysregulated expression of HERVs in human cancers can result from tumor-specific DNA hypomethylation. The expression of tumor specific HERV proteins is found in many tumors, including prostate cancer, melanoma and breast cancer. Several HERVs were found to induce T-cell responses in colorectal or breast cancer patients [17] and [18].

Concluding Remarks

Although many studies have shown that TAAs are able to induce specific T cells, little benefice has been observed in patients [19], probably related to a poor quality of T cells and/or their short duration. For instance, numerous studies use adjuvanted peptide strategies which generally fail to induce antigen cross presentation and CD8+ T cells, crucial in tumor eradication [1]. Cancer vaccines using TAAs have to be able to break the immune tolerance and those using TSAs also need to induce high quality and long-lasting T-cell immunity. mRNA strategy has not been proven to induce durable

and good quality T-cell responses, as shown by the mass vaccination experience against COVID-19 [20,21]. Alternative vaccine platforms including viral vectors [22] and notably the non-cytopathic, non-inflammatory and non-integrative lentiviral vectors, which are not target of pre-existing immunity in the human populations, emerges as a promising platform for cancer immunotherapy [23], [24] and [25]). Lentiviral vectors, due to their particular tropism for dendritic cells and their unique ability to transduce these cells, also at their non-dividing state, induce endogenous expression of antigens of interest. This endogenous antigen expression in dendritic cells is certainly at the origin of the great capacity of these vectors to induce robust and long-lasting T-cell responses with a great potential, not only in anti-infectious vaccination [26] and [27], but also in immuno-oncotherapy [23] and [25].

Conflict of Interest

PC is the founder and CSO of TheraVectys. LD is an employee of TheraVectys. LM has a consultancy activity for TheraVectys.

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