Vaccine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Editorial

Personalized cancer vaccines: Targeting the cancer mutanome

Xiuli Zhang [a], Piyush K. Sharma [a], S. Peter Goedegebuure [a,b], William E. Gillanders [a,b,*]

[a] Department of Surgery, Washington University School of Medicine, St. Louis, MO 63110, United States
[b] Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO 63110, United States

ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Personalized
Cancer vaccine
Genome sequencing
Neoantigen

ABSTRACT

The development of next generation sequencing technologies has revolutionized our understanding of how specific genetic events contribute to cancer initiation and progression. Dramatic improvements in instrument design and efficiency, combined with significant cost reductions has permitted a systematic analysis of the mutational landscape in a variety of cancer types. At the same time, a detailed map of the cancer mutanome in individual cancers offers a unique opportunity to develop personalized cancer vaccine strategies targeting neoantigens. Recent studies in both preclinical models and human cancer patients demonstrate that neoantigens (1) are important targets following checkpoint inhibition therapy, (2) have been identified as the target of adoptive T cell therapies, and (3) can be successfully targeted with personalized vaccines. Taken together, these observations provide strong rationale for the clinical translation of personalized cancer vaccines.

1. Introduction

It has long been known that solid tumors can elicit antitumor immune responses, often preventing the outgrowth of early lesions [1–6]. The tumor immunosurveillance concept was dramatically extended by Schreiber and colleagues to more accurately describe the dynamic interplay between tumors and the immune system. Cancer immunoediting is a dynamic process that describes the outgrowth of clinically apparent disease in immunocompetent hosts in three sequential phases: elimination, equilibrium, and escape [4]. Of particular note to the field of cancer immunotherapy is the observation that even in the escape phase tumor cells express antigens that can elicit antitumor immunity. Thus, great emphasis has been placed on identification of relevant tumor antigens and strategies to induce and/or enhance antitumor immunity.

For many years the identity of tumor antigens was only sporadically known. However, in 1991 Boon and colleagues introduced a molecular strategy to identify tumor antigens recognized by T cells [7]. Subsequent studies demonstrated that tumor antigens include both self and nonself antigens. Typically self tumor antigens (tumor-associated antigens) are derived from normal proteins with high expression in the tumor but limited expression in normal tissues. Nonself tumor antigens include both neoantigens and viral antigens. While both types of tumor antigens have been implicated in tumor development and progression, they are distinct from an immunological perspective. Tumor-specific antigens are expressed only in the tumor and immune therapies targeting such antigens are less likely to be associated with autoimmunity, and the repertoire of responding T cells is less likely to have been shaped by thymic selection (Fig. 1). This suggests that the affinity of responding T cells may be higher.

Human neoantigens have been identified in a number of different tumor types over the past 20 years (Reviewed in [8]). Recently, the systematic identification of neoantigens has been dramatically simplified through next-generation sequencing technologies whereby entire cancer exomes (and comparative normal exomes) can be sequenced and compared. The progress in high-throughput sequencing at deep coverage has revolutionized the path toward personalized medicine, and provides unique opportunities to pursue the development of personalized cancer vaccines. At the same time, results from the first clinical studies of checkpoint inhibition using antibodies targeting CTLA4, PD-1, and PDL1 have shown promise and provide proof-of-concept that T cell-based immunotherapy can offer therapeutic benefit in a variety of tumors. We discuss here current strategies for the discovery and validation of neoantigens, and the clinical implications for vaccine development.

DOI of original article: http://dx.doi.org/10.1016/j.vaccine.2015.09.086
* Corresponding author at: Department of Surgery, Washington University School of Medicine, 660 South Euclid Ave, St. Louis, MO 63110, United States.
E-mail address: gillandersw@wudosis.wustl.edu (W.E. Gillanders).

http://dx.doi.org/10.1016/j.vaccine.2016.05.073
0264-410X/

2. Next generation sequencing and identification of neoantigens

Massively parallel or next generation sequencing technologies have transformed nucleic acid sequencing, significantly decreasing the cost and time required to sequence human genomes [9]. In the field of cancer genomics, the realization that somatic mutations present in cancers contribute to cancer initiation and progression has spurred efforts to sequence cancers. Cancer genome sequencing rapidly progressed from patients with hematologic malignancies in 2008 [10] to solid malignancies with more complex mutational landscapes such as breast cancer [11]. Since then, cancer sequencing studies have been performed in multiple different types of cancer, with the largest effort being through The Cancer Genome Atlas (TCGA), a program launched in 2006 by the NIH and NHGRI to comprehensively characterize the genomic and molecular features of various cancer types. In order to define the somatic mutations present in the tumor, it is necessary to compare tumor and germline DNA. To confirm that the mutations are expressed, tumor RNA is required. For whole exome sequencing, and in particular RNA sequencing, a high quality sample is critical. Traditionally tissue obtained at surgery has been used. Currently, adequate DNA/RNA can often be obtained from fresh and/or paraffin-embedded core biopsy samples. Through TCGA, exome or whole-genome sequencing has been completed for close to 30 different cancer types [12]. Similar efforts are ongoing in other countries such as the UK [13]. These efforts also include detailed analyses of the molecular subtypes of cancers such as breast and pancreas [14,15]. Of note, the mutational landscape varies considerably among the different histologic types of cancer; analysis of 27 cancer types showed that the median frequency of somatic mutations in cancers ranged from 0.1/megabase (approximately one mutation in the entire exome) in pediatric tumors to over 100/megabase in lung cancer and melanoma [12]. To facilitate analysis of sequencing results, novel bioinformatics programs have been developed in parallel to analyze and interpret the vast amount of data obtained. Together, these technologies are now being used to explore the potential of personalized therapeutics. The recently announced NCI-MATCH (Molecular Analysis for Therapy Choice, www.cancer.gov/nci-match) trial will use next generation sequencing technologies to identify the mutations present in individual patient's cancers, and then use this information to treat patients with molecularly targeted cancer drugs specifically designed to target the mutations present [16].

An equally exciting therapeutic opportunity is the design of personalized vaccines based on the identification of mutations present in individual patient's cancers. Of all the genetic changes that have been observed in the cancer genome, single nucleotide variations (SNVs) that encode missense mutations have the highest likelihood of being expressed and recognized by the immune system. In a recent study of 47 luminal breast cancer genomes, approximately 31 nonsynonymous SNV mutations were present in each breast cancer genome, similar to the number identified in previous studies of a basal-like breast cancer [11], and similar to the number predicted by limited exome sequencing [17], and statistical models [18]. The question as to whether somatic mutations can be processed and presented by the immune system was first addressed by *in silico* analysis of the consensus coding sequences of human breast and colon carcinoma [19]. Using computer algorithms, the authors analyzed data from limited exome sequencing studies of breast and colorectal cancer to determine how many mutations detected by sequencing could be meaningfully presented by HLA-A2, the most common HLA class I allele. In these studies, Segal et al. predicted that approximately one new HLA-A2-restricted epitope was generated for every 10 mutations identified by sequencing [19], and individual breast cancers accumulate approximately

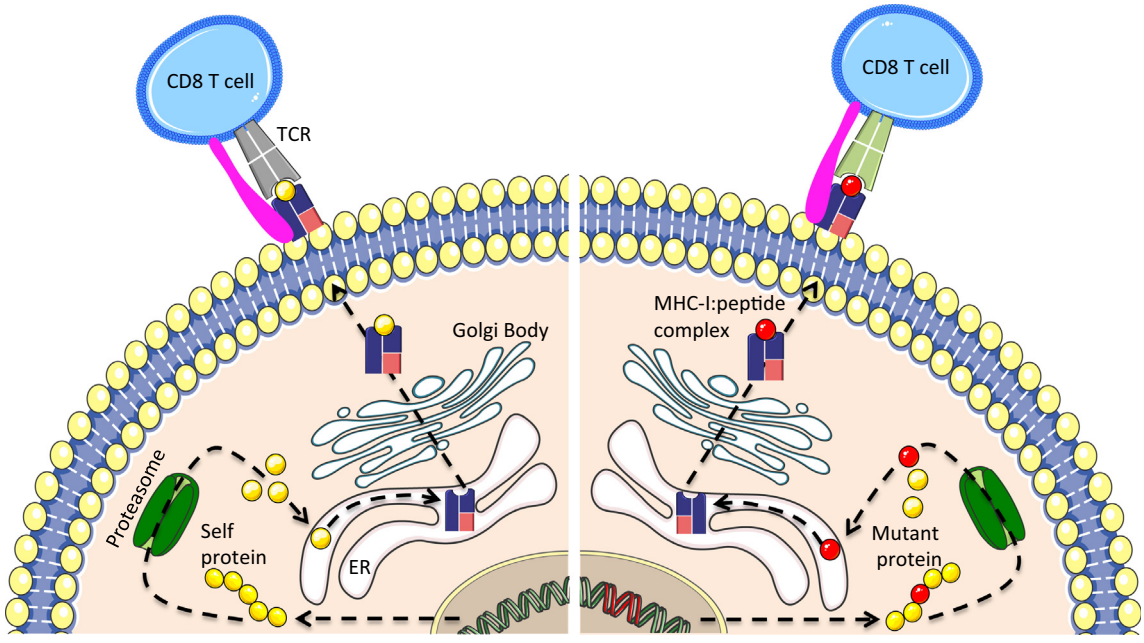

Fig. 1. Neoantigen presentation. Schematic representation of tumor-associated and neoantigen presentation.

Please cite this article in press as: Zhang X et al. Personalized cancer vaccines: Targeting the cancer mutanome. Vaccine (2016), http://dx.doi.org/10.1016/j.vaccine.2016.05.073