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New approaches to identification of antigenic candidates for future prostate cancer immunotherapy

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ABSTRACT

Prostate cancer is currently the most commonly diagnosed malignancy, and the second leading cause of cancer-related death, of men in the United States. There is a great deal of interest in the development of molecularly targeted approaches, including immunotherapies, to the treatment of prostate cancer. Immunotherapies can be broadly classified into passive and active treatments. Passive approaches generally involve the infusion of monoclonal antibodies with specificity to a desired target antigen, or adoptive transfer of antigen- or tumor-specific lymphocytes. Vaccines represent an active immunotherapeutic approach in which the goal is to elicit, rather than exogenously supply, antigen-specific antibodies or lymphocytes. In this article, we review recent developments and methods for the identification of antigens for both passive and active immunotherapies. In addition, we highlight some of the current ongoing clinical applications of several of these approaches.

Abbreviations:
AMACR, α-methylacyl-CoA racemase; cDNA, complementary deoxyribonucleic acid; CTA, cancer-testis antigen(s); CTL, cytolytic T lymphocyte; ELISPOT, enzyme-linked immunosorbent spot assay; EpCAM, epithelial cell adhesion molecule; HLA, human leukocyte antigen; HPLC, high-pressure liquid chromatography; IFNγ, interferon-gamma; IL-X, interleukin-X; MALDI-TOF, matrix-assisted laser desorption ionization-time of flight; MHC, major histocompatibility complex (antigen); mRNA, messenger ribonucleic acid; PAP, prostatic acid phosphatase; PBMC, peripheral blood mononuclear cell(s); PCR,

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polymerase chain reaction; PSA, prostate-specific antigen; PSCA, prostate stem cell antigen; PSMA, prostate-specific membrane antigen; SAGE, serial analysis of gene expression; SEREX, serological analysis of recombinant cDNA expression libraries; SMARTA, serological mini-arrays of recombinant tumor antigens; TIL, tumor-infiltrating lymphocyte(s)

1. Introduction

Prostate cancer is currently the most commonly diagnosed malignancy, and the second leading cause of cancer-related death in men, in the United States [1]. There is a great deal of interest in the development of molecularly targeted approaches to the treatment of cancer, including prostate cancer. Immunotherapies represent a class of molecularly targeted approaches to cancer therapy that can be broadly classified into passive and active types of treatments. Passive approaches generally involve the infusion of monoclonal antibodies with specificity to a desired target antigen or adoptive immunotherapy with antigen- or tumor-specific lymphocytes. Vaccines represent an active immunotherapeutic approach in which the goal is to elicit, rather than exogenously supply, antigen-specific antibodies or lymphocytes. In this section, we review recent developments and methods for the identification of antigens for both passive and active therapies. In addition, we also highlight some of the current ongoing clinical applications of several of these approaches.

2. Identification of cell surface prostate cancer antigens for passive immunotherapy

The treatment of cancer with monoclonal antibodies directed at cell surface antigens has revolutionized the treatment of cancer in the last decade. Specific advances have led to FDA approval of an antibody targeting CD20 (rituximab) for non-Hodgkin's lymphoma, an antibody targeting HER-2/neu (trastuzumab) for breast cancer, an antibody targeting CD33 (gemtuzumab) for myeloid malignancies, and antibodies targeting the epidermal growth factor receptor (cetuximab) and vascular endothelial growth factor (bevacizumab) for colorectal cancer. These therapies have been generally safe, without the frequency or severity of adverse events typically associated with cytotoxic chemotherapies. Currently, over 100 monoclonal antibody therapies are in various stages of clinical evaluation for various cancers. Several of these antibodies, notably those targeting the epidermal growth factor family of receptors, including cetuximab [2], trastuzumab [3], and a newer monoclonal antibody targeting HER-2/neu, pertuzumab, have been investigated in clinical trials for patients with prostate cancer, as we have recently reviewed [4]. In addition, a novel antibody-based treatment, including the immunocytokine EMD 273006 (a monoclonal antibody specific for the epithelial cell adhesion molecule (EpCAM) genetically fused to IL-2) has recently entered clinical testing for patients with prostate cancer and other solid tumors [5]. Unfortunately, most of these agents have been disappointing in their efficacy against prostate cancer compared with other common solid tumors [5,6]. In fact, prostate cancer has been curiously absent from the list of successes of monoclonal antibody therapies. However, there is currently significant enthusiasm among researchers attempting to identify new prostate cancer cell surface antigens that may be better targets for antibody-based therapies, as well as developing newer antibody-based therapies targeting previously identified antigens. We will summarize these approaches to the identification of novel target antigens below, highlighting specific antigens that have been identified as targets that are now in clinical development.

2.1. *Antibody screening: prostate-specific membrane antigen (PSMA)*

The primary approach to identifying cell surface antigens has involved immunizing rodents with human tumors and subsequently characterizing and purifying tumor-specific antibodies [7]. This type of approach was applied in the past with human prostate cancer cells and characterized cell lines, and several tissue-specific monoclonal antibodies were identified [8–10]. Among these studies, Horoszewicz et al. immunized mice with the LNCaP human prostate cancer cell line, and identified a monoclonal antibody, 7E11, with strong reactivity to prostate cancer cells compared with other tissues, including normal prostate tissue [10]. The protein recognized by this antibody, prostate-specific membrane antigen, was identified and has been subsequently evaluated by several groups as a diagnostic marker for prostate cancer cells [11]. ^{111}In-labeled 7E11 monoclonal antibody has become commercially available (Prostascint®, Cyt-356, Cytogen Corp., Princeton, NJ) as a diagnostic test for prostate cancer. However, the epitope recognized by this antibody is displayed in the cytoplasmic domain of the protein [12]. Consequently, in order to develop a therapeutic antibody to PSMA, more recent studies have characterized panels of PSMA monoclonal antibodies for avidity to and recognition of extracellular epitopes. Fracasso et al. reported the results of in vitro studies with several PSMA-specific monoclonal antibodies conjugated to a