Review

Towards progress on DNA vaccines for cancer

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Received 2 April 2007; received after revision 14 May 2007; accepted 21 May 2007
Online First 14 June 2007

Abstract. Cancer immunotherapy faces many obstacles that include eliciting immune reactions to self antigens as well as overcoming tumor-derived immunosuppressive networks and evasion tactics. Within the vaccine arsenal for inhibiting cancer proliferation, plasmid DNA represents a novel immunization strategy that is capable of eliciting both humoral and cellular arms of the immune response in addition to being safely administered and easily engineered and manufactured. Unfortunately, while DNA vaccines have performed well in preventing and treating malignancies in animal models, their overall application in human clinical trials has not impacted cancer regression to date. Since the establishment of these early trials, progress has been made in terms of increasing DNA vaccine immunogenicity and subverting the suppressive properties of tumor cells. Therefore, the success of future plasmid DNA use in cancer patients will depend on combinatorial strategies that enhance and direct the DNA vaccine immune response while also targeting tumor evasion mechanisms.

Keywords. DNA vaccines, cancer, immunotherapy, non-human primates, animal models.

Introduction

The use of plasmid DNA to elicit the immune system against disease provides a variety of practical benefits for large scale vaccine production that are not as easily manageable with other forms of vaccines including recombinant protein or whole tumor cells [1, 2]. DNA vectors are capable of encoding a number of needed immunological components and are easily engineered and produced for administration using bacterial expression systems. Their safety in terms of adverse reactions after injection has also been demonstrated in animal models and human clinical trials. More importantly, neutralizing immune responses to plasmid DNA is rarely observed, making repeated injections possible; however, continued use of viral vectors such as vaccinia and adenovirus can direct the immune response to viral coat proteins and produce anti-vector responses, limiting the vaccine’s efficacy. Viral vaccines of these types have been used in prime-boost strategies or, if available, been constructed from less common serotype backgrounds [3]. In its simplest description, immunization with a naked DNA vector prompts the host cell harboring the vector to express the gene constructs of the plasmid. The expressed protein enters into proper immunological presentation pathways that cause specific antibody and cell-mediated immune responses, which may prove necessary for alleviating disease. These vaccination outcomes are in contrast to immunizing with recombinant soluble protein that enters
into exogenous presentation pathways and predominately induces humoral immunity [1]. Historically, Wolff and colleagues [4] first demonstrated that long-term gene expression in mouse skeletal muscle could be achieved with direct intramuscular injection of plasmid DNA. This and other early studies demonstrating the feasibility of DNA vaccination propelled the first vaccination studies utilizing plasmid DNA in protection scenarios involving influenza [5] and HIV-1 [6]. Years later, with an accumulation of plasmid DNA studies in animal models, the first human clinical trial was initiated to monitor the safety and efficacy of a DNA vaccine against HIV-1 infection [7]. DNA immunization studies in animal models involving cancer and infectious disease have demonstrated preventative and therapeutic success [8]. In contrast, the crossover application of DNA vaccines in humans has faced many obstacles and difficulties, leading to their less-than-desired efficacy in the clinical setting. Although human administration of DNA vaccines as prophylactic and therapeutic tools is in its infancy, much understanding and progress has been made concerning the use of DNA vectors to target specific illnesses. The scope of this review focuses on the advancements and challenges facing DNA vaccines, particularly against human cancer.

Inherent difficulties associated with cancer

It is estimated by the American Cancer Society that over 550,000 individuals in the United States will die from some form of cancer in 2007 [9]. As, on a whole, standard therapeutic procedures currently in practice, including surgery, radiation, and chemotherapy, have not greatly impacted the spread and recurrence of progressive malignancies, newer strategies are needed to improve upon the current treatment success rate [10]. Immunotherapeutic strategies including the use of DNA vaccines hold great promise as an alternative or additive agent to the standard treatment regime. The nature of immunotherapy is designed to specifically target cancer types using components of the immune system. However, the inherent properties of tumorigenic cells pose problems for immunological-based vaccines.

The idea of self

The cellular pathways that ultimately lead to cancer could be initiated by intrinsic genetic abnormalities [11] or extrinsic factors such as viral infection or carcinogen exposure. Indeed, oncogenic viruses, such as Epstein-Barr virus and human papilloma virus, have been found to be etiological agents for certain human neoplasms [12]. These viral infections result in tumor cells that express foreign viral proteins and represent ideal targets for vaccine development. In contrast, for the broader cancer types, the majority of tumors arise from other defined factors that do not impart an evident immunogenic phenotype based on the host’s central tolerance system. Such tolerance to self antigens expressed by the host is primarily achieved through early immune processes that remove self-reacting lymphocytes from the bone marrow and thymus [13, 14]. Nevertheless, self-reacting lymphocytes do survive central tolerance mechanisms of the host and are present in the periphery, allowing self tolerance to potentially be broken. These populations, for example, represent positively selected lymphocytes that react to self antigen weakly or foreign antigen, which cross-reacts with naturally occurring proteins [15].

Many obstacles exist with regard to choosing the appropriate DNA vaccine to target a specific type of malignant cell. The nature of the antigen and its tissue expression profile within the body are important guiding principles for vaccine candidacy. Ideally, one would wish to target an antigen both presentable to the immune system and expressed only by a particular neoplasm. Unfortunately, these preferences are not always achievable as many tumor self antigens are also expressed by normal cells [16–18]. Therefore, in a relatively broad outlook, DNA vaccines are faced with the difficult task of (i) breaking self tolerance to generate an appropriate immune response, and (ii) not initiating therapeutically uncontrollable autoimmune reactions within the body.

To date, a growing list of tumor self-antigens has been compiled by investigators and provides potential vaccine targets against specific human cancers [16, 18]. Many of the more common self antigens are described in Table 1 and are classified based upon antigen type. For example, MAGE-A1 was the first reported gene to encode a human tumor antigen recognized by T lymphocytes and is characterized as a cancer/testis (CT) antigen [19]. This antigen class is denoted by expression in tumor cells and germline tissues (e.g., testis, placenta, ovary). CT antigens represent ideal conditions for vaccine use since the antigen is typically not transcriptionally active in normal adult cells and germline tissues do not express the proper receptors for antigen presentation to the immune system [20]. Interestingly, antibodies and T cells specific to CT antigens such as NY-ESO-1 have been found in cancer patients [21]. Although the protein is derived from the host, the increased immunogenicity to NY-ESO-1 is hypothesized to result from the primary expression in immune-privileged sites such as the testis, thereby, evading central tolerance mechanisms that take place in somatic