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MUC1 peptide vaccine mediated antitumor activity in non-small cell lung cancer

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Abstract

Lung cancer is the most common cause of cancer mortality worldwide for both men and women, causing approximately 1.2 million deaths per year. With the existing therapeutic efforts, the long-term survival for lung cancer patients remains low with only 15% surviving for 5 years following diagnosis. Therefore, new therapeutic strategies are needed. One such approach is the development of immune therapy for lung cancer. Immune approaches for lung cancer remain attractive because although surgery, chemotherapy and radiotherapy alone or in combination have response rates in all histological types of lung cancer, relapse is frequent. Immunologic targeting of lung cancer has the potential for nontoxic and specific therapy. Strategies that harness the immune system to react against tumors can be integrated with existing forms of therapy for optimal responses toward this devastating disease.

Keywords

cancer vaccine; immune therapy; lung cancer

1. Therapeutic cancer vaccine

In the US and the world, lung cancer remains the leading cause of cancer death. More than 200,000 new cases occur every year in the US and worldwide more than 1.2 million people die from lung cancer annually [1]. The median survival following diagnosis is eight months, and only 15% of patients are still alive after five years. Only 25% of patients are eligible for a curative treatment such as tumor resection. The remaining patients are not eligible for resection due to local, regional or metastatic spread of disease, or their overall state of health. Despite diagnostic and therapeutic advances, the stage distribution and survival rate for patients with non-small cell lung cancer (NSCLC) has not improved substantially in the last 15 years. Immune therapy, the active harnessing of the power of the immune system and

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its focused ability to destroy cancer cells, is at the forefront of experimental cancer therapies. Activating immune effector mediated tumor destruction has the potential for long term protection and survival.

Immune therapy for lung cancer has potential; however, there have not been Phase III trial-documented improvements in survival. Tumor-induced immune suppression may have contributed to the limited efficacy of the approaches. Many tumors, including lung cancer, have the capacity to promote immune tolerance and escape host immune surveillance. Tumors utilize numerous pathways to inhibit immune responses, including the elaboration of immune inhibitory cytokines as well as inducing host cells to release immune inhibitors. It is becoming increasingly clear that immune suppression through regulatory T cells (Tregs), myeloid derived suppressor cells (MDSC) and M2 macrophages has a crucial role in promoting tumor progression. The success of immune therapy for cancer will depend on integrating strategies that generate T cell responsiveness and downregulate immune suppression.

Another important explanation for tumors that remain refractive to immune therapy is the concept of cancer stem cells. Cancer stem cells have tumor growth-initiating potential and treatment that is not directed to this target population may explain why tumors recur even after a sizeable shrinkage following therapy. Identification of the cell type capable of sustaining neoplastic growth and directing immune therapy to cells that possess tumor-initiating potential may improve current immune-based therapeutic approaches. Before cancer stem cells can serve as an immunotherapeutic target, further research is required to identify and separate cancer stem cells from normal stem cells and other cancer cells. Identification of the genetic signatures in cancer stem cells will unravel novel antigens for exploitation in immune therapy protocols with the eventual goal of eliminating residual disease and recurrence.

A variety of novel approaches are being investigated to improve the outcome of NSCLC. Vaccine therapy has recently re-emerged as a potential therapeutic approach. A vaccine is an agent that elicits the adaptive host immunity (B or T cell responses) against specific disease. A good vaccine has the following attributes: i) ability to elicit the appropriate immune response to the antigen; ii) induce long term protection; iii) non-toxic; iv) stable-retain immunogenicity, despite adverse storage conditions prior to administration; v) inexpensive so that it is widely accessible.

Therapeutic vaccines for cancer differ from the classical concept of vaccines. In contrast to prophylactic vaccines, which elicit protective immunity, therapeutic vaccines aim to induce strong antigen-specific immune responses against active disease. Cancer vaccination stimulates adaptive immunity in the host against the vaccine component. The identification of tumor associated antigens (TAA), advances in cellular and molecular immunology and an improved understanding of tumor immunity has facilitated the development of promising vaccine strategies. However numerous challenges still preclude cancer vaccine efficacy that include: i) correct identification of optimal antigens and immune adjuvants; ii) quantification of the appropriate immune response to be generated; iii) elicitation of long term antitumor memory; and iv) tumor induced immune suppression and immune evasion. For an ideal cancer vaccine strategy, the requirements for i) immune cell activation, homing and accumulation in the tumors; ii) disruption of the regulatory mechanisms that limit immune responses; and iii) the ability to direct a coordinated and effective attack against tumors engaging multiple components of the immune system should evolve in parallel. This will only be achieved through combinatorial approaches. While there has been a multitude of lung cancer immunization studies, clinical trials focused on inducing a specific antitumor immune response can be categorized into the following vaccine types: i) dendritic cell (DC);

ii) modified tumor cell; iii) tumor protein and peptide; iv) immune adjuvant; and v) DNA. Disappointingly, decades of research has not delivered an approved cancer vaccine for NSCLC therapy.

After a long developmental phase, mucin 1 (MUC1) peptide vaccine candidate in NSCLC patients has demonstrated increased survival in Phase II clinical trials [2,3] that provided the rationale for the initiation of Phase III trials in large cohorts of lung cancer patients. The vaccine targets MUC1, an antigen widely expressed in lung carcinomas. Therapeutic peptide cancer vaccines aim at inducing strong CD8 and CD4 T-cell responses and require the involvement of host antigen presenting cells (APC) to efficiently present the peptide antigens for the activation of the respective T cell subsets. The rationale for the use of peptide vaccines is based on extensive preclinical studies that have demonstrated the requirement of T-lymphocytes for the eradication of solid tumors. Cytotoxic T-lymphocytes (CTLs) or CD8 T cells represent the primary effector cells involved in tumor-specific immune-mediated destruction of cancer cells. CTLs recognize, engage and destroy target cells through the trimolecular interaction of the antigen-specific receptor (TCR) on the CTL and peptides that are presented by the target cell to the CTL in the context of class I major histocompatibility complex antigens [(MHC) also referred to as human leukocyte antigens or HLA]. All somatic cells express HLA molecules on their surfaces and use them to present antigens to T cells. Whole proteins within the cell are processed into small peptide fragments (8 to 10 amino acids in length) that are displayed on the cell surface in the context of HLA molecules. The HLA-peptide molecular complex enables CTLs to recognize tumor-associated antigens and results in the targeted destruction of the cancer cell expressing these antigens by the CTL. Many primary cancers express adequate HLA molecules and are capable of being recognized and destroyed by TAA-specific CTLs. The identification and reintroduction of tumor associated specific peptides in increased concentration to the immune system via vaccination activates and deploys the appropriate CTLs to destroy cancer cells. The use of a single peptide antigen or a few peptide antigens in the therapeutic cancer vaccine is based on the assumption that the initial induced antitumor response to one or few antigens will eventuate into a broad immune response to a multitude of TAAs after uptake of dying tumor cells and presentation by host APC. This however has not been the case in many cancer vaccine trials as tumor associated mechanisms suppress or block antitumor responses. The full determination and understanding of the cellular and molecular networks in the tumor microenvironment that dampen the antitumor activity of therapeutic cancer vaccines will offer potential targets for exploitation through combinatorial approaches to realize the full benefit of therapeutic vaccines.

The BLP25 liposomal vaccine (L-BLP25) approach for lung cancer is a peptide liposomal vaccine to target the exposed core peptide of MUC1 tumor-associated antigen in lung cancer. MUC1 is a cell membrane glycoprotein overexpressed in many types of cancers including NSCLC, breast, colorectal, prostate, pancreatic, ovarian, and multiple myeloma. MUC1 expression in tumors promotes growth and survival and is associated with disease progression and poor prognosis. The relevance of MUC1 as an anti-tumor target is based on preclinical and clinical studies. MUC1 expression pattern in tumor cells is different from normal cells. More than 80% of the tumor cells express MUC1 with greater than 60% of NSCLCs express MUC1 [4]. The BLP25 lipopeptide vaccine consists of a 25-amino acid MUC1 sequence (STAPAHGVTSAPDTRPAGSTAPP) that provides MUC1 specificity. It is slightly larger than one tandem repeat of MUC1 protein and contains a palmitoyl lysine residue at the carboxy terminal to enhance the incorporation of the lipopeptide into the liposome particle. The vaccine is a lyophilized preparation consisting of BLP25 lipopeptide, immunoadjuvant monophosphoryl lipid A, and three lipids (cholesterol, dimyristoyl phosphatidylglycerol, and dipalmitoyl phosphatidylcholine). The lipids serve as adjuvants, to enhance the immunogenicity of the peptide MUC1 vaccine. The monophosphoryl lipid A

is the toll-like receptor-4 agonist that activates DC and macrophages. The liposomal delivery system is designed to facilitate uptake by APC such that the lipopeptide is delivered into the intracellular space for presentation by MHC molecules to activate specific T-cells that will identify and target cancer cells expressing MUC1.

2. Expert opinion

It is encouraging to see that the L-BLP25 cancer vaccine is currently being evaluated in a Phase III trial for the treatment of unresectable, stage III NSCLC [5]. There is much optimism for this vaccine based on the favorable toxicity profile in patients treated with this drug and the benefit in survival in patients with local and regional stage III non small cell lung cancer. In studies described to date on the L-BLP25 vaccine there has not been adequate immune monitoring of vaccination responses. The studies lack data on immune responses to the vaccine component through quantification of the frequency of MUC1 specific CTL pre and post vaccination in PBMCs and how it correlates with overall performance of the patients. Hopefully the omission in quantification of immune responses will be improved as the studies progress. A good quality vaccination response should generate a high frequency of specific effector cells capable of targeting the cancer cells. In monitoring immune responses, there are several important questions that need to be addressed to determine what additional mechanisms are needed to improve the efficacy of the L-BLP25 vaccine. This will be achieved through quantification of: i) T cell responses to the specific vaccine component as well as various antigenic epitopes expressed by the NSCLC to determine if epitope spreading has occurred; ii) Tregs cells and MDSC to determine their contribution to the dampening of the immune responses at disease progression; and iii) the antigens expressed by the tumors at disease progression to determine if they could serve as targets for future vaccines. This data will be informative for the development of future trials using this approach in a variety of antigen delivery platforms and in the evaluation of combinatorial approaches to improve the efficacy of therapeutic vaccines.

Cancer immunotherapy offers an attractive therapeutic addition, delivering treatment of high specificity, low toxicity and prolonged activity. Effective immunotherapeutic strategies for cancer will result from a basic understanding of the mechanisms that sustain tumor growth kinetics. Tumor growth and invasion into surrounding tissue promotes an inflammatory response that is important for tumor development and progression. Dysregulated inflammation in cancer leads to hypo responsiveness of the tumor. Strategies that reprogram the tumor niche could alter the inflammatory infiltrate in the tumor microenvironment making it permissive for immune destruction of tumors. It is likely that combination therapies that focus on methods to address the immune deficits in the lung cancer microenvironment will be required to develop effective therapies for this disease. The future of immune therapy for cancer holds promise with novel combined approaches that simultaneously target cancer-initiating stem cells, restore APC immune-stimulating activity, expand tumor-reactive T cells with γ c homeostatic cytokines such as IL-7, IL-15 and IL-21 and downregulate suppressor pathways to generate effective therapy. A vaccine that uses some of the combined approaches is the DNA vaccine TG4010, a modified vaccinia Ankara virus vector that expresses the entire MUC1 gene sequence along with the sequence coding for the cytokine Interleukin-2 to stimulate specific T cell responses to all antigenic epitopes of MUC1. In a Phase I clinical trial, the TG4010 was well tolerated and extended survival in 75% subset population of patients with normal activated circulating NK cell levels that formed the basis for a pivotal TG4010 Phase IIb/III clinical trial for NSCLC. The optimal way to integrate novel immune targeted combinations will be the major focus of future studies and will require a coordinated and cooperative multidisciplinary effort by the international scientific community. Objective cancer regressions and extensions in survival

should be correlated with multiple predictive and prognostic molecular and cellular biomarkers of response. This information will prove useful in improving therapy.

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