

Expression and Immunogenicity of the Tumor Associated Antigens in Lung Cancer Patients.

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Background

The number of patients with malignant lung cancer is increasing each year and lung cancer is currently the leading cause of cancer related death [1]. Non-small-cell lung cancer (NSCLC) is the most common type of lung cancer and is associated with poor outcome, thus there is a need to explore new treatments and to look again at older treatments, such as immunotherapy, with improved technology. Vaccine immunotherapy, as an approach to cancer treatment, has evolved over the last 10 years as the basic biology of immune response has been elucidated.

To develop new strategies for the immunotherapy of lung cancer, we need to identify novel antigens and understand which kind of lung tumors exhibit good reactivity to immunotherapy [2]. It is necessary to define tumor associated antigens (TAAs) which are highly expressed in cancer cells and can evoke a strong antitumor immune response in patients with lung carcinoma. A number of TAAs have now been identified, including MAGE and BAGE families, gp 100, SART-1, tyrosinase, MUC-1 and others. Some of them are used to target immunotherapy for cancer. However, the outcome of the clinical therapeutics targeting these TAAs is not satisfactory [3]. In lung carcinoma, no available TAAs to target have been identified.

NSCLC is a non-immunogenic tumor. NSCLC cells have not been subjected to immune attack and therefore; have not been able to evolve evasion mechanisms for the effectors response of the immune system. Thus, if an immune response can be generated by a vaccine approach against non-immunogenic NSCLC, it may be effective because tumor cells have not been able to develop resistance mechanisms. Many vaccine studies assess clinical outcomes, but only few of them have focused on the measurement of an immune response. The question of an immune response is important because numerous accounts in literature have reported general of tumor specific immune unresponsiveness in tumor-bearing individuals [4].

Anti-tumor immune responses may result in the induction of autoantibodies directed against various TAAs. Previous reports showed that several autoantigens trigger the generation of autoantibodies among patients with malignant disease. For example, antibodies reactive with cancer testis (CT) antigens, such as MAGE, GAGE, BAGE, SSX, and NY-ESO-1, were found in 4,2-12,5% of sera of patients with melanoma and a variety of others tumors, including lung cancer [5,6].

Main Objective

To investigate the possibility of the Tumor Associated Antigens (TAAs) clinical use as a tumor markers and target antigens in lung cancer immunotherapy.

Results

- Tumor-associated antigens have been identified by serological analysis of recombinant c DNA expression libraries (SEREX), using tumor mRNA and autologous serum from a patients with NSCLC. SEREX analysis of a range of different human tumor types has identified a number of tumor antigens with diagnostic and therapeutic potential. Using expression libraries of testis rather than tumor as the antigen source has extended the range of defined antigens, particularly those with the characteristic features of cancer/testis antigens [7].
- The expression of TAAs in lung cancer was assessed by RT-PCR. Tumor tissues of NSCLC have been obtained from surgical resection or biopsies, and characterized by RT-PCR for the expression of MAGE-1, MAGE-3, MAGE-10, NY-ESO-1, LAGE. All tumor samples have been subjected to *in vitro* culture for the establishment of stable tumor cell lines.
- TAAs that are capable of eliciting cytotoxic T cell responses have been identified. Among the most frequently expressed were MAGE antigens. Some MAGE antigens (MAGE-3) are expressed in about 40% of non-small-cell lung cancer (NSCLC) cases [8]. MAGE-3 belongs to the growing class of CT antigens that are expressed only in testicular germ cells and no other normal tissue, yet aberrantly found in broad variety of tumors. Also MAGE-3 is the most commonly expressed CT antigen and thus represents a prime target for cancer vaccines [9].
- Lymphocyte and serum samples have been collected from patients, whose tumors expressed at least one of the antigens tested, and HLA typing have been performed.
- Antigen-specific spontaneous CD4+ and CD8+ T cell responses against those antigens expressed in individual cancers have been assessed in patients whose HLA class I/II alleles allow for testing of peptide-specific reactivates.
- According to the frequency of antigen expression in relation to spontaneous immune responses against these in patient with lung cancer, strategies for the development of vaccines against this disease have been developed.

Among tumor antigens identified to date, cancer testis (CT) antigens are recognized as a group of highly attractive targets for cancer vaccines. CT antigens are found to be expressed in a significant proportion of various human cancers, their normal tissue expression is generally restricted to the testis. Some MAGE antigens are expressed in about 40% of non-small-cell lung cancer (NSCLC) cases [8]. In summary, this analysis provided further insights in the immunogenicity of lung cancer with respect to antigen-specific humoral and cellular immune responses

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