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Cancer vaccine development in solid tumors

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Abstract

The analysis of spontaneous and vaccine-induced immune responses against cancer has led to the identification of a large number of tumor antigens that are classified according to their expression pattern, function or origin into five different categories: 'cancer-testis' (CT) antigens (i.e. MAGE, BAGE, NY-ESO-1); differentiation antigens (i.e. Melan A/MART-1, tyrosinase, CEA, NY-BR-1); mutational antigens (i.e. MUM-1, p53, CDK-4); overexpressed 'self' antigens (i.e. HER-2/neu, p53); viral antigens (i.e. HPV, HCV). Since antigen-specific CD8+ T-cell responses were first identified to be associated with tumor regression in single patients, multiple approaches have been initiated to develop specific and non-specific cancer vaccines.

Antigenic peptides derived from MAGE, Melan A/MART-1, tyrosinase, and gp100, that are recognized by CD8+ T lymphocytes in the context of defined MHC class I molecules, have been used first to immunize patients with advanced melanoma. Objectives of the first clinical studies were the induction of local and systemic peptide-specific immune responses, and the correlation of these with the clinical development. Delayed-type hypersensitivity (DTH) reactions were frequently observed after intradermal injection of antigenic peptides. The intensity of DTH reactions was later identified to be indicative for the quality of the peptide-specific CD8+ T-cell response detectable in the peripheral blood. Strong CD8+ T-cell responses induced after prolonged immunization were associated with tumor regression in single patients. The standardization of assay systems (ELISPOT, tetramer analysis) has set the basis for the objective evaluation and comparison of immune responses observed in different clinical studies. The analysis of patients with tumor progression despite detectable immune responses to vaccination has led to the identification of prognostic tumor parameters, i.e. homogenous expression of target antigens and MHC class I molecules, which will help to select the most promising candidates for specific cancer immunotherapy.

In recent years, NY-ESO-1 has evolved as a model antigen for cancer immunology for several outstanding characteristics. Spontaneous humoral immune responses, which are associated with detectable CD4+ and CD8+ T-cell reactivity, are found in approximately 50% of patients with NY-ESO-1+ cancers. Strong peptide-specific DTH- and CD8+ T cell responses were induced in the majority of patients without spontaneous immunity against NY-ESO-1 after intradermal immunization with HLA-A2 restricted NY-ESO-1 peptides alone. Studies investigating modified vaccine schedules (intensive course peptide vaccination), different adjuvants (GM-CSF, poly-arginine, CpG), and viral vaccine constructs (vaccinia-NY-ESO-1, fowlpox-NY-ESO-1) have been initiated to evaluate their immunological and clinical efficacy. Future perspectives of clinical cancer vaccines are focused on the design of more immunogenic vaccine constructs targeting multiple antigens expressed in individual cancers. Based on preliminary results of ongoing studies, viral vaccine constructs, which effectively introduce whole antigens to the presentation pathways of individual MHC profiles, may emerge as promising candidates for the vaccination of broader patient populations.