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Identification and characterization of agonist epitopes of MUC1-C oncoprotein

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Purpose: The MUC1 tumor-associated antigen is overexpressed in the majority of human carcinomas and several hematologic malignancies. Much attention has been paid to the hypoglycosylated VNTR region of the N-terminus of MUC1 as a vaccine target, and recombinant viral vector vaccines are also being evaluated that express the entire MUC1 transgene. While previous studies have described MUC1 as a tumor-associated tissue differentiation antigen, numerous studies have now determined that the C-terminus of MUC1 (MUC1-C) is an oncoprotein, and its expression is an indication of poor prognosis in numerous tumor types.

Experimental Design: We report here the identification of seven potential CD8+ cytotoxic T lymphocyte epitopes of MUC1: five in the C-terminus and two in the VNTR region, and have identified enhancer agonist peptides for each of these epitopes. These epitopes span HLA-A2 and A3 MHC class I alleles, which encompass two thirds of the population.

Results: The agonist peptides, compared to the native peptides, more efficiently (a) generate T-cell lines from the peripheral blood mononuclear cells of cancer patients, (b) enhance the production of IFN-γ by peptide-activated human T cells, and (c) lyse human tumor cell targets in an MHC-restricted manner.

Conclusions: The agonist epitopes described here can be incorporated in various vaccine platforms and for ex vivo generation of human T cells. These studies thus provide the rationale for the T-cell-mediated targeting of the oncogenic C-terminus of MUC1, which has been shown to be an important factor in both drug resistance and poor prognosis for numerous tumor types.

Biography

I am currently the Head of Cellular Immunology Group at the Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute My research interest is in the role of the human immune response to tumor-associated antigens. We are working to define and develop immunodominant determinants and modifications of those determinants toward the optimal activation of human immune responses to tumor-associated antigens. Additionally, we are involved in studying mechanisms to enhance the potency of antigen-presenting cells for specific T cell activation. We are also developing immunologic methods and immunoassays to better define the efficacy of vaccine therapies for a range of human cancers.

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