DNA VACCINE STRATEGY AGAINST CHRONIC B-CELL LYMPHOMA: ANTI-IDIOTYPIC CDR3 VACCINATION

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B-cell lymphomas express tumor-specific immunoglobulin, the variable regions of which (Id determinants) are tumor-specific antigens and therefore are suitable targets for vaccine immunotherapy. Promising results have been obtained in clinical studies of Id vaccination using Id proteins or naked DNA Id vaccines. Several reports have indicated that the immunodominant epitopes of the clone-specific Ig lie within the hypervariable CDR3 regions. Our group has previously tested the possibility of using the short peptide encompassing the CDR3 of immunoglobulin heavy chain (V_H-CDR3) as a target for eliciting a tumor specific immune response via DNA-based vaccination. We demonstrated that DNA immunization of outbred mice with different patient-derived V_H-CDR3 peptides elicited antibodies able to recognize native antigens on individual patient's tumor cells. These findings prompted us to investigate the immune response and tumor protection following CDR3-based DNA vaccination in the 38C13 B lymphoma as tumor model. In the present study, the nucleic acid sequence of the idiotypic IgM from the murine 38C13 B-cell lymphoma was analyzed and the region corresponding to the V_L-CDR3 sequence was chosen for the production of a synthetic mini-gene. By using a computer algorithm, one epitope within murine 38C13 B-cell lymphoma heavy-chain variable region was selected, “enhanced” and used for the production of a distinct mini-gene. The restricted V_H-CDR3 sequence was also fused to a pathogen-derived sequence, with the aim to enhance the immunogenicity of the corresponding DNA fusion vaccine. A high-level expression bicistronic plasmid DNA vaccine was designed to express both the tumor antigen and the mouse IL-2 sequences. To increase plasmid delivery and expression the new DNA constructs were improved by inclusion of a DNA nuclear targeting sequence (NTS) and were delivered by i*n vivo* electroporation and hyaluronidase pre-treatment. Therefore, we evaluated the humoral immune response and tumor protection recruited by CDR3-directed DNA vaccines. Here we show that vaccination of syngenic C3H/HeN mice with CDR3-based DNA vaccines protects vaccinated mice against a lethal tumor challenge and generates an immune response to the 38C13 tumor, inducing specific circulating antibodies.