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IDENTIFICATION OF AND VACCINATION WITH ANTIGEN SPECIFIC TH1 SELECTIVE EPITOPES IN BLADDER CANCER: A STEP TOWARDS A MULTI-ANTIGEN VACCINE FOR BLADDER CANCER PREVENTION

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Background Bladder cancer is a frequently diagnosed malignancy. Half of patients responding to standard therapy develop recurrence within 5 years. Vaccination for secondary prevention of bladder cancer could reduce recurrence. We developed an epitope identification approach for vaccine construction from non-mutated tumor associated proteins combining in silico prediction of Class II epitopes with functional screening to edit out sequences inducing regulatory responses. The method allows the identification of Th1 selective epitopes which elicit an antigen specific IFN-gamma response without IL-10 secretion. We aimed to identify bladder cancer antigens and determine Class II binding peptides for use in a multi-antigen Th1 selective vaccine.

Methods Seven datasets (GEO); 38 normal bladder, 229 NMIBC and 86 muscle invasive non-metastatic bladder cancers were studied. Genes with at least 2-fold upregulation in cancer compared to normal with a corrected p-value < 0.1 and found in >50% of cancer samples were identified (n=159). We prioritized those upregulated in >75% of cancers (n=15). Nine genes encoded proteins with known overexpression in human bladder cancer; CDC20, TOP2A, CCNB2, MAPK13, CDK1, AURKA, CEP55, PRC1, and MELK. We evaluated expression by IHC in OH-BBN induced mouse bladder tumors. Eight proteins were expressed in tumors and the murine MB49 bladder cancer cell line. Using a multi-algorithm approach, we selected 24 putative class II epitopes, associated with high binding affinity across multiple MHC class II alleles, derived from these proteins. All epitopes had >88% homology between species.

Results We screened PBMC (12 donors/9 bladder cancer patients) by IFN-g/IL-10 ELISPOT. Th1 selective epitopes were identified for 5 antigens, CDC20, TOPO2A, CCNB2, CDK1, and CEP55. We evaluated immunogenicity of single-antigen vaccines in C57BL6 mice to identify any epitopes inducing selective Th1 immunity. Five peptides generated significant antigen-specific Th1 with no evidence of Th2. To evaluate anti-tumor activity, single-antigen vaccines were given four times, two weeks apart, with CFA/IFA. Two weeks after vaccination, mice were implanted with MB49. All vaccines could significantly inhibit tumor growth as compared to PBS control; CDC20 (p=0.0001), TOPO2A (p<0.0001), CCNB2 (p<0.0001), CDK1 (p<0.0001), and CEP55 (p<0.0001). We admixed epitopes into a single vaccine, BLADVAC, immunizing mice to discern epitope competition. Significantly elevated levels of antigen-specific IFN-g secreting T-cells were detected for all epitopes except CDK1 (p<0.001 compared to HIV control).

Conclusions We identified bladder cancer antigens covering the majority of tumors with clinically effective Th1 selective vaccines constructed. Prevention trials in the OH-BBN model are ongoing.

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