CANCER VACCINE CO-TARGETING PRAME AND PD-L1 EXERTS SIGNIFICANT TUMOR GROWTH INHIBITION IN SYNGENEIC MOUSE HEPATOCELLULAR CARCINOMA MODELS

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Background Preferentially expressed Antigen in Melanoma (PRAME) is a cancer-testis antigen highly expressed in many different types of cancers and has been associated with different oncogenic processes. Over the past decade, PRAME has become an attractive target for various cancer immunotherapeutic strategies, including therapeutic cancer vaccine and T-cell therapy. Programmed death-ligand 1 (PD-L1) represents one of the most important immune checkpoint antigens highly expressed on cancer cells to limit T-cell activation in tumor microenvironment. In this preclinical study, we investigate whether dual-antigen cancer vaccines co-targeting PRAME and PD-L1 can suppress tumor growth in both prophylactic and therapeutic syngeneic mouse hepatocellular carcinoma (HCC) models.

Methods Recombinant fusion protein vaccines comprised of PD-L1 and PRAME with or without GM-CSF (PD-PR and PD-PR-GM) were expressed in an Escherichia coli based system as inclusion bodies. After purification, the fusion protein vaccines (30 microgram) were formulated with a Toll-like receptor 9 agonist CpG oligodeoxynucleotide (30 microgram) and aluminum hydroxide (300 microgram) for vaccination. In the prophylactic tumor model study, the vaccines were administrated subcutaneously twice at a two-week interval before implantation of mouse HCC cells expressing PRAME, followed by weekly vaccination. In the therapeutic model study, the vaccines were administrated weekly into the animals after tumor cell implantation. Body weight and tumor volume were measured three times a week.

Results All mice experienced a recoverable body weight loss without any abnormal behavior or reduction of activity after vaccination. In the prophylactic model (n=10 mice), both PD-PR and PD-PR-GM fusion protein vaccines significantly inhibited tumor growth, with 76.4% (P<0.01) and 59.5% (P<0.05) tumor growth inhibition (TGI) compared to control group, respectively. Importantly, there were some mice vaccinated with PD-PR without palpable tumor mass (less than 30 mm³) at the end of the study. These results were consistent with that found in the therapeutic model study (n = 10 mice), in which both vaccine formulations significantly inhibited tumor growth with 43.4% (PD-PR, P<0.01) and 40.7% (PD-PR-GM, P<0.05) TGI and prolonged animal survival compared to the control group (P<0.01).

Conclusions The results of this preclinical study clearly highlighted the potential of simultaneously targeting PRAME and PD-L1 by fusion protein vaccination in cancer immunotherapy. Both fusion protein vaccines are currently being evaluated in an aggressive B16/F10 melanoma model.

Ethics Approval This study was approved by the Animal Committee of the National Health Research Institutes; approval number NHRI-IACUC-108157-AC1-M1-A-S04.

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