Doctoral thesis/dissertation Abstract

Thesis/dissertation Title

Sensitization with allogeneic MHC class I molecule H-2K^{d} induces anti-tumor immunity in the context of PD-1 blockade

Student's Name

Komang Alit Paramitasari

Abstract

Immune response to cancer is induced upon recognition of antigen-bound major histocompatibility complex class I (MHC-I) by the T-cell receptor (TCR). Following the killing activity of T cells towards cancer cells, an inhibitory receptor, such as programmed death-1 (PD-1) is expressed on the surface of activated T cells. This immune checkpoint pathway can be coopted by cancer cells in order to escape the antitumor immune response. More recently, the field of cancer immunotherapy has been harnessing the PD-1 pathway to re-stimulate the host immune response to cancer antigens which resulted in remarkable outcomes. However, subsets of patients are refractory to the benefits of the PD-1 therapy. Thus, it is important to improve the success rate of PD-1 blockade in a wide variety of cancer. In this study, I have attempted to bolster the responsiveness to PD-1 checkpoint inhibitors by exploiting an exogenous murine MHC-I gene.

To investigate the effect of MHC-I overexpression to augment immune sensitivity, I have generated expression vectors harboring cDNA of H-2K^{d}, an allogeneic mouse MHC-I molecule. Flow cytometric analysis of the stably transfected MC38 cancer cells confirmed the high expression levels of H-2K^{d}. Next, the tumorigenicity of transfected clones was tested *in vivo* by subcutaneous administration into the flank of PD-1 knockout and wild-type mice in a C57BL/6 genetic background (H-2^{b}). The expression of H-2K^{d} in MC38 clones provided full protection to both naïve PD-1 KO and WT mice, indicated by spontaneous tumor regression. In the context of concomitant tumor immunity, PD-1 KO mice were sensitized for the challenge of unresponsive parental cancer cells (MC38 PT) by administering the highly immunogenic MC38 H-2K^{d} inoculums. Intriguingly, all PD-1 KO mice gained immunity against the aggressive MC38 PT tumor and became tumor-free. Furthermore, to assess long-term immunity, about 5 months following the sensitization, all PD-1 KO mice that had survived the first tumor injection were subjected to a second tumor challenge. Surprisingly, sensitization with cell debris of MC38 H-2K^{d} evidently showed the strongest protective anti-tumor immunity against the re-challenged MC38 PT cells thus conferring the highest survivability. Moreover, the absence of PD-1 activity and specific immunity against tumor antigens are mandatory to elicit protective antitumor immunity in MC38 H-2K^{d}–sensitized mice. Most excitingly, my results provide compelling evidence for the potential augmentation of antitumor immune response mediated by allogeneic mouse MHC class I.