DEVELOPMENT OF IL-33 AS A NOVEL IMMUNOTHERAPY OF CANCER

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Background Immune-checkpoint-blockade (ICB) therapy has produced unprecedented survival benefits for cancer patients but such therapy has been limited by low response rates in most cancer. One major obstacle for ICB therapy is the reduced immunogenicity of tumor tissues due to genetically driven down-regulation of epithelial tissue cytokines. IL-33 is a member of the IL-1 gene family and its level is downregulated in many advanced carcinomas such as lung cancer, breast cancer and pancreatic cancer. It has recently been shown that IL-33 plays an important role in mediating cancer immune therapy. In addition, transgenic expression of the active form of IL-33 in tumor cells or administration of the recombinant IL-33 exerts strong antitumor effects. Mechanistically, IL-33 enhances the function of Th1 and CD8+ T cells in vitro and types 1 antitumor immune responses in vivo.

Methods In the current study, we have optimized the pharmacodynamics of IL-33 by engineering a fusion protein, called anti-HSA-IL-33, using IL-33 and an anti-human albumin antibody. We have used preclinical mouse tumor models to determine the efficacy and toxicity of this new molecule.

Results We have shown that anti-HSA-IL-33 has excellent antitumor activities alone and enhances the antitumor function of PD-1 mAbs. Despite causing increased inflammation, anti-HSA-IL-33 is well tolerated with limited toxicity in mice.

Conclusions These studies support further development of IL-33 as a novel cancer immunotherapy.