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A novel form of 4-1BB ligand as a potent and safe adjuvant for development of therapeutic cancer vaccines

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Abstract

Subunit cancer vaccine represents an attractive treatment option due to tumor specificity, ability to generate memory, and safety. However, they require potent adjuvants for therapeutic efficacy due to weak immunogenicity of TAAs and potential self-tolerance. Given costimulation is intrinsically evolved to augment antigen specific T cell responses required for antitumor immunity, we tested if a costimulatory molecule 4-1BBL can serve as an effective adjuvant component of the TAA based vaccine formulations. To achieve this goal, we used ProtEx™ for generation of chimeric SA-4-1BBL that exist as stable tetramers and higher structures, and as such can be used as soluble proteins to effectively crosslink 4-1BB receptor on immune cells for potent signal transduction. We herein describe a novel vaccine approach based on the use of this novel SA-4-1BBL protein as adjuvant with various TAAs in several cancer immunotherapy mouse models. One vaccination with the E7 or Survivin with SA-4-1BBL resulted in the eradication of existing E7 expressing cervical and survivin over expressing 3LL lung tumors in >70% of the animals. This efficacy was improved to 100% when multiple vaccinations were used. Importantly, animals with successful immunotherapy developed a robust CTL responses and NK cell cytotoxicity against the tumor and long-term immune memory which was tumor antigen specific. Vaccine was well tolerated and showed no sign of overt toxicity or autoimmunity. Chimeric SA-4-1BBL has the potential to serve as a specific immunological adjuvant to develop T cell based therapeutic vaccines against tumors with well characterized tumor associated antigens.

Biography

Dr. Sharma is a Faculty of Department of Medicine at University of Louisville, Louisville, KY. He completed his Ph.D. in the area of infectious immunology at Banaras Hindu University in India. Dr. Sharma then moved to USA to pursue his postdoctoral studies in the area of cancer immunology/immunotherapy and therapeutic cancer vaccines at the Institute for Cellular Therapeutics, at University of Louisville. Dr. Sharma serves as Editorial Board member and reviewer for various journals. His research interests are in the area of cancer immunology & immunotherapies, particularly development of combinatorial approaches such as chemo-immunotherapy. Dr. Sharma has widely published in journals of Immunology, and Cancer Research.