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TNFR Costimulatory ligands as a platform for the development of vaccines

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Protein-based subunit vaccines against cancer and infections are attractive because of their safety profile as well as rapid, cost-effective, and large-scale production. However, they are weekly immunogenic and their immunogenicity is further compromised by various immune evasion mechanisms employed by cancer and chronic infections. Importantly, accumulating evidence suggests that both prophylactic and therapeutic vaccines may benefit from their ability in modulating all the three arms of the immune system; innate, adaptive, and regulatory. In this context, the efficacy of subunit vaccines may require formulations that include adjuvants having pleiotropic effects on various cells of the immune system. We have hypothesized that costimulatory ligands of TNF family may serve as effective adjuvants due to their critical roles in modulating all the three arms of the immune system. We focused on 4-1BBL as a test case due to its ability to generate effective $CD8^+$ T cell primary and memory responses and the critical role $CD8^+$ T cells play in the eradication of tumors and chronic infections. Inasmuch as 4-1BBL functions as a cell membrane-bound protein and have no function in soluble form, agonistic antibodies to the receptor have been used extensively in preclinical models and several clinical trials for cancer. However, the use of such antibodies is associated with appreciable toxicity. We, therefore, hypothesized that natural ligands may have better efficacy and less toxicity as compared with agonistic antibodies, and generated a chimeric molecule where the extracellular functional domain of 4-1BBL fused C-terminus with a modified form of streptavidin. This molecule exists as tetramers/oligomers with demonstrated pleiotropic effects on cells of innate, adaptive, and regulatory immunity. As adjuvant component of tumor associated antigen-based vaccines, chimeric 4-1BBL had robust therapeutic efficacy and performed better than an agonistic antibody to 4-1BB receptor as well as TLR agonists CpG and MPL in cancer models in mice. These studies provide strong rationale for further developing TNF costimulatory ligands as adjuvants for prophylactic/therapeutic vaccines.

Biography

Dr. Shirwan is Dr. Michael and Joan Hamilton Endowed Chair in Autoimmune Disease, Professor of Microbiology and Immunology, the Director of the Molecular Immunomodulation Program at the Institute for Cellular Therapeutics, and member of James Brown Cancer Center, University of Louisville, KY. Dr. Shirwan is also the Founder and CSO of ApoVax, Inc., Louisville, KY. Dr. Shirwan is widely published and, lectured at numerous national/international conferences, served on study sections for various federal and non-profit funding agencies, and is on the editorial boards of 12 scientific journals. He is member of several national and international societies and recipient of various awards.

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