Induction and therapeutic exploitation of PD-1 tolerogenic function

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Abstract

PD-1 is an inhibitory receptor induced in activated T cells and mediates self-tolerance. Therapeutic exploitation of the PD-1 pathway by blocking antibodies has shown great potential in cancer immunotherapy. Although PD-1 is a natural gatekeeper of T cell tolerance, it is currently unknown how to take advantage of the PD-1 pathway to deliver tolerogenic and immunosuppressive signals and inhibit aberrant T cell responses in conditions such as autoimmune diseases. We have embarked in extensive studies to determine how to engage the PD-1 receptor to deliver signals that suppress T cell responses. PD-1-mediated inhibitory effects require concomitant engagement of PD-1 and TCR/CD3, posing a major challenge in the development of such compounds. To overcome this challenge, we engineered a single chain diabody (scDb) that can co-engage PD-1 and CD3 (PD1-scDb) bringing the PD-1 receptor in proximity to the TCR. Using this approach, we generated a mouse scDb (mPD1-scDb) and a human scDb (hPD1-scDb). We found that hPD1-scDb inhibited human T cell proliferation and cytokine production *in vitro*, whereas mPD1-scDb inhibited T cell activation *in vitro*, and reversed pathology in a mouse model of systemic lupus erythematosus (SLE) *in vivo*. These findings open new avenues for therapeutic exploitation of the PD-1 checkpoint to induce tolerance in autoimmune diseases, graft versus host disease (GvHD) and organ transplantation.

Biography

Vassiliki Boussiotis, M.D., Ph.D. is a Professor of Medicine at Harvard Medical School and a Physician Scientist in the Department of Hematology-Oncology at Beth Israel Deaconess Medical Center. She received her MD and PhD from the University of Athens, Greece and completed her postdoctoral training at DFCI, in Dr. Lee Nadler's laboratory, which was generating ground breaking knowledge that changed the route of Immunology: the discovery of the B7 family of costimulatory molecules. Her first postdoctoral project revealed that additional B7 molecules exist forming the B7 family. She had an active role in the discovery that PD-1 ligands are expressed in immune privileged sites and cancer cells. Her ongoing work investigates the effects of checkpoint inhibitors on signaling and immunometabolism in innate and adaptive immune cells in the context of cancer. Dr. Boussiotis is a faculty member of the Immunology Graduate Program at Harvard Medical School and a board-certified oncologist. She has published more than 200 research articles, book chapters and reviews.