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Novel bispecific proteins that promote crosslinking of CTLA-4 to the TCR inhibit T cell activation, direct FOXP3+ Tregs differentiation, and protect NOD mice from developing autoimmune diabetes

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Crosslinking of ligand-engaged cytotoxic T lymphocyte antigen-4 (CTLA-4) to the T cell receptor (TCR) during the early phase of T cell activation attenuates TCR signaling, leading to T cell inhibition. To promote this event, a bispecific fusion protein comprising a mutant mouse CD80 (CD80w88a) and lymphocyte activation antigen-3 was engineered to concurrently engage CTLA-4 and crosslink it to the TCR. Crosslinking is expected to be attained via ligation of CTLA-4 first to MHCII and then indirectly to the TCR, generating a CTLA-4-MHCII-TCR tri-molecular complex that forms between T cells and antigen-presenting cells during T cell activation. Treating T cells with this bispecific fusion protein in vitro inhibited T cell activation, induced production of IL-10 and TGF-β, and attenuated AKT and mTOR signaling. Intriguingly, the bispecific fusion protein also directed early T cell differentiation into Foxp3 positive regulatory T cells (Tregs) in a process that was dependent on the endogenous production of TGF-β. Treatment of non-obese diabetic (NOD) female mice between 4-13 weeks of age with the bispecific protein significantly delayed the onset of disease or protected animals from developing autoimmune diabetes. Thus, bispecific fusion proteins that engage CTLA-4 and co-ligate it to the TCR during the early phase of T cell activation can negatively regulate the T cell response at multiple levels. Bispecific biologics with such dual functions may therefore represent a novel class of therapeutics for immune modulation. These findings presented here also reveal a potential new role for CTLA-4 in Treg differentiation.

Biography

Yunxiang Zhu has completed his Ph.D. in Cell Biology at University of Miami School of Medicine in 2006 and finished his post-doctoral training in Dr. Stuart Kornfeld's lab at University of Washington School of Medicine in St. Louis from 1996 to 2001. Currently, he is a distinguished fellow at Genzyme, a Sanofi company, working on drug discovery research for rare genetic diseases and autoimmune diseases. He has published more than 20 papers in reputed journals, including Science and PNAS.

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