SIGNIFICANCE STATEMENT

Control of humoral response in renal transplantation by Belatacept depends on a direct effect on B cells and impaired T follicular helper cell (Tfh)-B cells cross-talk. Generation of *de novo* donor-specific antibodies (*dn*DSAs) is the leading cause of late renal transplant failure. Recent clinical trials using the costimulatory blockade agent CTLA4-Ig (Belatacept) have shown that patients treated with Belatacept exhibit better graft survival and function and lower proportion of *dn*DSAs than recipients treated with calcineurin inhibitors. This study of the mechanisms for control of humoral responses by Belatacept found that it affects B cell function by both modulating antigen-presenting capacities and production of antibodies by effector B cells. The results bring new perspectives to the development of immunosuppressive strategies for transplantation and autoimmune disease.