Antigen-Specific Modulation of Autoimmunity by TCR-Like Antibody Targeting Autoreactive T-Cell Epitope

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Abstract

The development and application of human TCR-like (TCRL) antibodies recognizing disease-specific MHC-peptide complexes may prove as an important tool for basic research and therapeutic applications. Multiple sclerosis is characterized by aberrant CD4 T-cell response to self-antigens presented by MHC class II molecules. This led us to select a panel of TCRL Abs targeting the immunodominant autoantigenic epitope MOG35-55 derived from myelin oligodendrocyte glycoprotein (MOG) presented on HLA-DR2, which is associated with multiple sclerosis (MS). We demonstrate that these TCRL Abs bind with high specificity to human HLA-DR2/MOG35-55-derived MHC class II molecules and can detect APCs that naturally present the MS-associated autoantigen in the humanized EAE transgenic mouse model. The TCRL Abs can block ex vivo and in vivo CD4 T-cell proliferation in response to MOG35-55 stimulation in an antigen specific manner. Most significantly, administration of TCRL Abs to MOG35-55 induced EAE model in HLA-DR2 transgenic mice both prevents and regresses established EAE. TCRL function was associated with a reduction in autoreactive pathogenic T-cell infiltration into the CNS, along with modulation of activated CD11b+ macrophages/microglial APCs. Collectively, these findings demonstrate the combined action of TCRL Abs in blocking TCR-MHC interactions and modulating APC presentation and activation, leading to a profound antigen specific inhibitory effect on the neuroinflammatory process, resulting in regression of EAE. Our study constitutes an in vivo proof of concept for the utility of TCR-like antibodies as antigen-specific immunomodulators for CD4-mediated autoimmune diseases such as MS, validating the importance of the TCR-MHC axis as a therapeutic target for various autoimmune and inflammatory diseases.