IMMUNOLOGY

BiP peptides induce epitope-specific T-cell reactions in RA

New research shows that peptides derived from the rheumatoid arthritis (RA) autoantigen immunoglobulin-binding protein (BiP, also known as 78 kDa glucose-regulated protein [GRP78]) are differentially recognized by effector and regulatory T cells, and points to BiP-specific T-cell subsets as potential therapeutic targets in RA.

In the study, peripheral blood mononuclear cells (PBMCs) from patients with RA carrying the *HLADRB1* shared epitope were cultured in the presence or absence of peptides derived from

human BiP for 96 h. Among 42 different BiP-derived epitopes screened, BiP_{336–355} was the strongest inducer of T-cell proliferation, with proliferation higher in cells from patients carrying two copies of the shared epitope than those carrying one copy.

Notably, proliferation of PBMCs in response to BiP_{336–355} correlated with clinical disease activity and serum titres of antibodies against BiP and citrullinated BiP in patients with RA. BiP_{336–355}-induced PBMCs secreted the proinflammatory cytokines IL-17A and IFN- γ , whereas those from healthy donors did not.

Conversely, the regulatory peptide BiP_{456–475} induced production of IL-10 by CD25⁺ PBMCs from patients with RA and healthy donors but did not induce cell proliferation. BiP_{456–475} also suppressed PBMC proliferation and inflammatory cytokine production induced by BiP_{336–355}. In mice with collagen-induced arthritis, oral administration of BiP_{456–475} peptide

during arthritis onset reduced joint inflammation and proliferation of CD4⁺ T cells, and increased IL-10 secretion and numbers of regulatory T cells.

“Our antigen-specific approach revealed an impairment in the homeostatic balance between autoantigen-specific effector and regulatory T cells in RA,” explains corresponding author Keishi Fujio. “This observation suggests that T-cell response to the effector epitope of BiP overwhelms pre-existing tolerance associated with the regulatory epitope under some unknown stimulation in RA. Moreover, we showed the possibility that an enforcement of autoantigen-specific tolerance may result in the improvement of arthritis.”

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