Regulation effects of fusion protein IgD-Fc-Ig targeting T cells via IgD-IgDR-Lck-ZAP70-PI3K-NF-ϰB signaling in rheumatoid arthritis

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Abstract

Rheumatoid arthritis(RA) is a chronic systemic autoimmunediseasecharacterized by synovitis and the destruction of small joints.Emerging evidence had shown thatthe stimulation of immunoglobulin D (IgD) induced T cell activation which may contribute to diseases pathogenesis in RA.In this study we demonstrated that IgD could induce the activation of T cells through affecting IgDR-Lck-ZAP70- PI3K-NF-ϰB signaling, IgD-induced CD4+T cells promoted the proliferation of CD19+B cells in RA patients. IgD-Fc-Ig fusion protein (composed of human IgD Fc domain and IgG1 Fc domain, specifically blocks the IgD-IgDR pathway)inhibited the co-expression of IgDR and p-Lck and the expressions of p-Lck, p-ZAP70, p-PI3K on CD4+T cells, and decreased NF-ϰB nuclear translocation in Jurkat cells. Meanwhile, IgD-Fc-Ig down-regulated the protein expressions of CD40L on CD4+T cells and CD40, CD86 on CD19+B cells in RA patients and healthy controls. It also decreased the protein expressions of CD40L on CD4+T cellsand CD40 on CD19+B cells from spleens of CIA mice and reduced IL-17A level in mouse serum. Moreover, in vivo, IgD-Fc-Ig administration dose-dependently down-regulated the protein expressions of CD40, CD40L and IgD in spleens from CIA mice. IgD-Fc-Ig restrains the activations of T cells through inhibiting IgD-IgDR-Lck-ZAP70- PI3K-NF-ϰB signaling, thus inhibiting the activation of B cells.Our data provides experimental evidence for application prospect of IgD-Fc-Ig as a highly selective targeting T cell treatment for RA.

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