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Death receptor 5 (DR5) marks the highly pathogenic interacting GM-CSF+ T helper cells and IL-23+ macrophages rendering it as an attractive therapeutic target of Rheumatoid arthritis

The highly pathogenic GM-CSF$^+$IL-17$^+$CD4 T cells and IL-23$^+$IRF5$^+$M1 macrophages exhibit a bidirectional interaction in autoimmunity. Death receptor 5 (.alyzed DR5 expression and apoptosis function of an anti-human DR5 antibody, TRA-8, in macrophages and T cells in humans and humanized DR5 transgenic mice in the context of collagen II-induced arthritis (CIA) and systemic autoimmune diseases. Expression of DR5 was highly correlated with that of GM-CSF in CD4 T cells and that of IL-23 and IRF5 in macrophages from synovia fluid of Rheumatoid arthritis (RA) patients ($p<0.01$). *In vitro* treatment with TRA-8 resulted in 94.1% and 43.4% depletion of GM-CSF+ CD4+ T cells and IL-23$^+$ macrophages, respectively. CIA was induced inhumanized DR5 transgenic mice (Tg$^+$). TRA-8 (0.2 mg/mouse) was I.V. weekly initiated on day 30 until mice were sacrificed 3-mo post CII. TRA-8 treatment resulted in a 60% reduction of CD11b$^+$ macrophages in the draining lymph nodes (LNs) of Tg$^+$ mice. Within the CD11b$^+$ cells, ~60% of the Ly6c$^+$ activated macrophages and ~90% of the IL-23$^+$ macrophages were eliminated by TRA-8. The depletion also leads to elevation of CD4$^+$Foxp3$^+$Tregs (3.6% to 5.9%, $P<0.05$) and reduction of the CD4$^+$IL-17$^+$ Th17 cells (1.4% to 0.6%, $P<0.05$). After TRA-8 treatment, joint histopathology showed a significantly decreased MAC3$^+$ macrophage infiltration, synovial hyperplasia, and destruction (arthritis score: 9.8 versus 1.5, $P<0.01$). In DR5 transgenic mice crossed with the *Shp-1* negative regulator deficient *viable motheaten* mice, 3 doses of TRA-8 (0.1 mg IP, weekly) lead to a 35.7% reduction of GM-CSF$^+$ CD4$^+$ T cells and 45.1% reduction of IL-23$^+$IRF5$^+$ macrophages in the draining LNs. TRA-8 treatment also decreased expression levels of *Csf-2* and *p19* by 74.4% and 94.7% respectively in joints. These findings were associated with amelioration of hemorrhagic pneumonitis and arthritis, reduction of autoantibodies, and increased lifespan in these mice. The study indicated that DR5 expression marks the GM-CSF$^+$CD4$^+$ T cells and IL-23$^+$ macrophages. We also demonstrated the high therapeutic efficacy of an anti-human DR5 antibody in arthritis and other autoimmune diseases.

Biography

Jun Li has received his MD from Sun Yat-sen University and his PhD (Physiology) and postdoctoral training (Immunology & Rheumatology) from University of Alabama at Birmingham (UAB). He is currently a faculty at the Division of Clinical Immunology and Rheumatology, UAB. He focuses on developing novel therapies for Rheumatoid arthritis (RA) and his major research interests include targeting M1 inflammatory macrophages in RA, regulation of macrophage plasticity by fucosylation in RA, and the bidirectional interaction between macrophages and T cells in RA. His research is funded by Arthritis Foundation. He has received multiple awards from The American Association of Immunologists (AAI). His research has also been recognized by Rheumatology Congress UK.He has served as a reviewer for *Arthritis and Rheumatism, Clinical Rheumatology* and other reputed journals.

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