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Fucosylation, a key player and a novel therapeutic target in Rheumatoid Arthritis

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Inflammatory macrophages (MΦ) play key roles in the pathogenesis of rheumatoid arthritis (RA). We have observed an up regulation of Fucosyltransferases (*FUTs*) expression in RA synovial tissues compared to that of osteoarthritis (OA). There is a highly positive correlation between *TNFα* with *FUTs* 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12(p=0.0001), but not *FUTs* 8 and 13in human RA synovial tissues. In sorted cells from human RA synovial fluid, *FUTs* 1, 3, 5, 7, 9 were highly expressed in M1 inflammatory MΦ, but not in M2MΦ, synovial fibroblasts, and T cells (p<0.01), whereas *FUTs* 8 and 13were predominately expressed in synovial fibroblasts. This highly indicated that expression of subsets of *FUTs* might associate with the inflammatory M1 MΦ characteristics and that inhibition of these *FUTs* might result in the resolution of inflammation. Indeed, a FUT1/2 inhibitor, 2-Deoxy-D-galactose (2-D-gal), precluded the differentiation of M1 MΦ derived by GM-CSF from mouse bone marrow or human PBMC monocytes. Additionally, 2-D-gal treatment of fully differentiated M1 MΦ for 2 days significantly reduced their uptake, processing and presentation of GFP-Eα(from I-Edα)and FITC-Collagen II (CII) antigens (p<0.01). *In vivo*, 2-D-gal treatmentdramatically blocked bovine CII-induced arthritis (scores 9.5±1.7 vs 0.5± 0.3, p<0.01) with reduced inflammatory MΦ in draining LN (1.3±0.3% vs 0.5±0.1%, p<0.05), decreased TNF-α (130 vs 39 pg/ml, p<0.05), and anti-CII in the serum. Together, our study indicated that fucosylation orchestratesM1 MΦ differentiation and function, andis a novel therapeutic target in RA.

Biography

Jun Li received his M.D. from Sun Yat-sen University and his Ph.D. and postdoctoral training from University of Alabama at Birmingham (UAB). He focuses on developing novel therapies for autoimmune diseases including rheumatoid arthritis. He is currently an Instructor of Medicine at UAB. His major research interests include targeting M1 inflammatory macrophages in RA, determining the pathogenic roles of fucosylation in RA, and identifying the bidirectional interaction between macrophages and T cells in RA. His work is supported by an Arthritis Foundation Post-doctoral Fellowship Award.

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