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A critical role of leptin in promoting B cell response during the development of autoimmune arthritis

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Activation of autoreactive B cells leads to plasma cell (PC) formation and autoantibody production, contributing to the development of autoimmune diseases. Increasing evidence indicates a crucial role of leptin in immune response and autoimmune pathogenesis via enhancing $CD4^+$ T cell responses, but whether and how leptin regulates B cell response in autoimmune pathogenesis remains largely unclear. Using collagen-induced arthritis (CIA) mice, we detected increased levels of leptin and anti-collagen II (CII) antibodies in the synovial fluid (SF) and sera of mice at acute and chronic stages of CIA. Higher percentage and cell number of PCs were observed in the SF of CIA mice. Leptin receptor-deficient (*db/db*) mice exhibited ameliorated CIA development with reduced PCs responses and CII-specific antibody production. Intra-articular injection of recombinant leptin enhanced PCs responses and CII-specific antibody production and joint damage. Importantly, intra-articular injection of a soluble leptin blocker (ObR:Fc) deceased PCs responses, CII-specific antibody production and joint damage. Mechanistic studies revealed that leptin promoted $CD138^+IFR4^+$ PC generation from $GL\text{-}7^+Fas^+$ germinal center B cells via activating Akt-mTOR-IRF4 axis. Moreover, rapamycin treatment attenuated leptin-induced IRF4 expression and PCs generation. In RA patients, leptin levels and autoantibody production were positively correlated with disease activity (DAS28 score) with increased $CD38^+CD27^+$ plasmablasts detected in the synovium of active RA patients. Together, these findings demonstrated a critical role of leptin in enhancing PCs responses and CIA progression via ObR-Akt-mTOR-IRF4 axis, indicating that leptin blockade may serve as a potential therapeutic strategy for the treatment of autoimmune arthritis.

Biography

Liwei Lu is an internationally recognized expert in the field of Autoimmunity. His research is focused on studying immune dysregulations in autoimmune diseases. During last ten years, his laboratory has been exploring novel strategies for the treatment of rheumatoid arthritis. His team was among the first to successfully treat autoimmune arthritis by targeting the cytokine B-cell activating factor in a preclinical study, which has significant therapeutic implications for the effective treatment of rheumatoid arthritis. He is the Councillor of Federation of Immunological Societies of Asia-Oceania and has served as the Chairman of Hong Kong Society for Immunology. He has published over 120 peer-reviewed papers in leading immunology and rheumatology journals.

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