

The potential relationship between PU.1 and IL-9 in the development of arthritis

Sirs,

RA is a chronic inflammatory joint disorder in which several immune cells act as key players in the inflammatory responses underlying the disease (1). A few years ago, our group demonstrated the role of IL-9 and Th9 cells in RA pathogenesis (2). Th9 cells were shown to be abundantly found in the peripheral blood, synovial fluid, and synovium of RA patients; the frequency of Th9 positively correlated with disease activity and the degree of histological organisation of B and T cells into ectopic lymphoid structures (2). These results were then confirmed in a mouse model of CIA, on DBA1 mice, in which IL-9 was over-expressed in the swollen joints of mice developing arthritis and treatment with anti-IL-9 significantly improved the arthritis score (3). Specifically, the development of Th9 cells from naive T cells occurs under stimulation by transforming growth factor β (TGF β) and interleukin-4 (IL-4), or directly in the presence of thymic stromal lymphopoietin (TSLP). Following activation, the cells are primed for the production of IL-9 and require transcription factors, including PU.1, to promote the optimal differentiation of Th9 cells (4).

In their recent study, Tu *et al.* (5) elegantly demonstrated how PU.1 is a key transcriptional factor that promotes joint inflammation, as evidenced in arthritis models. Indeed, PU.1 knockdown mice showed attenuation of collagen antibody-induced arthritis (CAIA) symptoms, and the PU.1 inhibitor DB2313 significantly repressed the development of arthritis in both CAIA and CIA models.

In support of the above-described findings and of our previously published observations, we have further shown that mice with deficiency of PU.1 were protected from CIA, as the arthritis score was significantly reduced in PU.1^{-/-} mice compared with wild type (WT) C57BL/6 mice at week 4 (Fig. 1), corroborating the role of this transcription factor in arthritis development.

It has recently been suggested that PU.1/FMS-like tyrosine kinase 3 (FLT3) is a crucial proinflammatory axis in RA that promotes inflammatory features in macrophages and malignant changes in RA fibroblast-like synoviocytes (FLS), contributing to the maintenance of the inflammatory

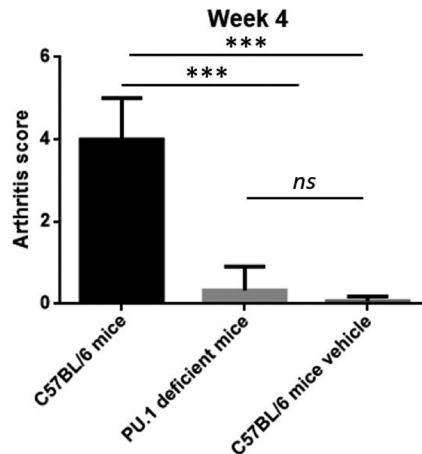


Fig. 1. PU.1 deficiency confers protection against CIA. Arthritis score at week 4 in PU.1^{-/-} mice, C57BL/6 CIA mice and C57BL/6 mice. *** $p < 0.0001$.

microenvironment and the development of synovitis (5). In addition, PU.1-dependent production of IL-9 by T cells, previously demonstrated in other autoimmune diseases (6) and confirmed in our model, strengthens the role of PU.1 and IL-9 in CIA models and supports the immunopathogenic role of IL-9 in RA. The specific self-relevance of PU.1 in multiple cells in RA provides new insights into the pathogenesis of RA and discloses new potential therapeutic targets. These data may seem to be in conflict with a published study. Specifically, in an experimental model of adjuvant induced arthritis (AIA) (7), (a model of self-resolving arthritis called “acute” experimental arthritis), IL-9 deficiency appeared to be responsible for the chronicity of the lesions, negatively correlating with the resolution of arthritis. However, it is plausible that the results obtained in the AIA model, an acute model of arthritis induced by a non self-antigen (methylated bovine serum albumin) which spontaneously resolves within 16 days after immunisation, are not automatically applicable to human chronic inflammatory diseases, such as RA or psoriatic arthritis (PsA), and therefore the suggested protective effect for IL-9 is not viable in these conditions.

Certainly, in light of its potential implications, the relationship between PU.1 and IL-9, which has already been confirmed in many autoimmune diseases, deserves further investigation. However, despite the controversial role of IL-9 in joint inflammation, the above-mentioned evidence supports the production of PU.1-driven IL-9

by Th9 cells as important mediators of inflammation and joint damage in RA through pleiotropic effects that need to be further elucidated.

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