Correspondence to 'Normal human enthesis harbours conventional CD4+ and CD8+ T cells with regulatory features and inducible IL-17A and TNF expression'

We read with great interest the work by Watad *et al*,[1] which the authors demonstrated the characterisation of enthesis-resident T cells and their corresponding cytokine responses upon stimulation. This commendable work mimicked enthesitis-involved inflammatory pathogenesis of spondyloarthritis, for instance, psoriatic arthritis (PsA). Particularly, the authors proposed that entheseal T cells may secrete interleukin (IL)-17 and much more tumour necrosis factor α (TNF-α) in response to anti-CD3 and anti-CD28 (as suggested in figure 3 by Watad *et al*[1]); furthermore, phosphodiesterase 4 (PDE4) inhibitors suppressed the expression of the above mentioned inflammatory cytokines (as suggested in figure 5 by Watad *et al*[1]). As PDE4 inhibitors have been used to treat autoimmune diseases and advanced malignancies,[2] we are highly interested in whether infliximab, a neutralised antibody for TNF-α and a widely prescribed biologic disease-modifying antirheumatic drugs for a number of autoimmune diseases, would as well modulate the immunity of entheseal or synovial T cells in patients with PsA in clinical settings.

We compared the RNA-sequencing profiles of synovial biopsies from patients with PsA naive to anti-TNF-α agents before and 10 weeks after infliximab treatment registered in the National Center for Biotechnology Information-Gene Expression Omnibus database. Overall, we identified 39 significantly expressed pathways using p value and Z-score visualisation, with 26 pathways up-regulated at a Z-score of above 1, and 13 pathways down-regulated at a Z-score of less than −1 (figure 1). Among the 26 upregulated pathways after infliximab treatment, well-documented immunomodulatory signalling pathways, including adrenomedullin signalling pathway,[3] transforming growth factor-β (TGF-β) signalling and aryl hydrocarbon receptor signalling, were noted; furthermore, B cell-involved pathways, including B cell receptor signalling and systemic lupus erythematosus-associated B cell signalling pathway, were as well activated after TNF-α blockage. Among the 13 downregulated pathways after infliximab treatment, both Tec kinase signalling and signalling by Rho family GTPases were significantly inhibited at a Z-score of less than −2. These findings are consistent with previous studies reporting that Tec kinases regulate signalling pathways downstream of T cell receptor (TCR) activation, followed by T cell development, cytokine production and T-helper cell differentiation.[4] On the other hand, these findings are in line with the fact that Rho GTPases initiate signalling following TCR activation, which allow them to modulate pathways responsible for T cell development, differentiation and activation.[5] Moreover, as IL-23 signalling, a pathway upstream of Th17 induction,[6] was also downregulated after infliximab treatment, it was suggested that reciprocal regulation between TNF-α and IL-17 took place in synovial T cells during anti-TNF-α therapy.[7]

In conclusion, our data supported that the activity of entheseal and synovial T cells was suppressed in patients with PsA treated with TNF-α inhibitors, potently accompanying with an overall downregulation in pathways underlying the pathogenesis of PsA.

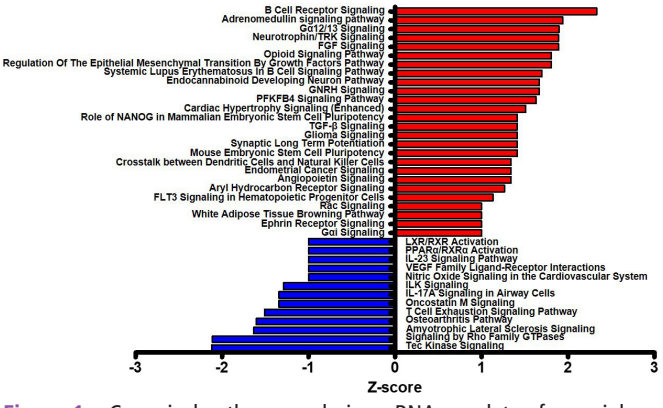

Figure 1 Canonical pathway analysis on RNA-seq data of synovial biopsy from patients with psoriatic arthritis receiving infliximab treatment after a follow-up of 10 weeks. Upregulated pathways are labelled in red. Downregulated pathways are labelled in blue. FGF, fibroblast growth factor; FLT3, FMS-like tyrosine kinase 3; GNRH, gonadotropin-releasing hormone; IL, interleukin; ILK, integrin-linked kinase; LXR, liver X receptor; NANOG, homeobox transcription factor Nanog; PFKB4, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4; PPARα, peroxisome proliferator-activated receptor α; RXR, retinoid X receptor; TRK, tropomyosin receptor kinase; VEGF, vascular endothelial growth factor.

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