Response to: 'Polyfunctional TEM cells in psoriatic arthritis synovium skewed towards Th17 cells' by Raychaudhuri *et al*

We read with interest the research letter by Raychaudhuri *et al*, which examines the frequencies of cytokine producing CD4+ memory T cells in psoriatic arthritis (PsA) and rheumatoid arthritis (RA) synovial fluid mononuclear cells (SFMC) compared with peripheral blood mononuclear cells (PBMC).[1] The authors examined the frequencies of single cytokine-producing T cells, specifically interleukin (IL)-17A+, IL-22+, tumour necrosis factor (TNF)+, interferon gamma (IFNγ)+ or IL-23R+ and report that Th17 cells are enriched in PsA SFMC, while RA is skewed to a Th1-like profile. In our previous publication, Wade *et al*,[2] we reported the frequencies of both single cytokine-producing and multiple cytokine (polyfunctional)-producing T cells, in addition to the frequencies of Th1, Th17 and exTh17 cells by using the Th17 lineage marker CD161. In our study, however, we reported these findings in synovial tissue biopsies from PsA patients, as opposed to PsA SFMC (reported by Raychaudhuri *et al*), demonstrating enrichment of polyfunctional T cells, specifically triple-positive cytokine-producing T cells isolated from PsA synovial tissue.

While discrepancies in immune cell frequencies and phenotypes have been reported between SFMC and synovial tissue,[3] the study by Raychaudhuri *et al* report an increase in CD4+ IL-17a+ T cells in PsA SFMC compared with PBMC, an observation which we also described in PsA synovial tissue.[2] Moreover, Raychaudhuri *et al* also report a decrease in TNFα production in PsA SFMC compared with PBMC, similar to that observed in our study in PsA synovial tissue .[2]

However, we noted that while Radchaudhuri *et al* report the identification of polyfunctional T cells in PsA and RA, we believe these data should be interpreted cautiously. Radchaudhuri *et al* demonstrate an increase in a number of single cytokine-producing T cells, specifically IL23R, 1L-17A and IL-22 in PsA compared with RA, however, they do not show that these cytokines are being co-produced by the same T cells (ie, polyfunctionality). Polyfunctionality or co-production of multiple cytokines within the same T-cell population is best evaluated using advanced flow cytometric algorithm analysis.[2 4] In this manner, polyfunctionality within a specific T cell can be accurately analysed. Moreover, we reported that it is these polyfunctional T cells that correlate with disease activity for psoriatic arthritis (DAPSA) and not the single cytokine-producing T cell subsets. Additionally, when we used a PDE4 inhibitor in our ex vivo synovial tissue single cell cultures, again it was the polyfunctional T-cell population and not the single-producing cytokine populations which responded, suggesting that the polyfunctional T cells are significantly contributing to disease pathogenesis and response in PsA. Further studies by Radchaudhrui *et al* to examine polyfunctional T cells within their dataset in addition to the single positive cytokine-producing T cells which they have reported in their study would extend their current findings. This would allow the comparative evaluation of these polyfunctional effector memory T cells in the periphery versus site of inflammation providing additional insight into their potential role in autoimmune disease.

Interestingly, in addition to examining the synovial environment in PsA, the authors also examined T effector memory (TEM) cells within RA SFMC and report a more Th1-like profile. Previous studies by Basdeo *et al* report an accumulation of ex-Th17 cells or non-classical Th1 cells in RA SFMC.[4] It is now known that Th17 cells can lose their ability to produce IL-17 and instead switch to predominantly producing IFNγ.[5] These ex-Th17 cells can no longer be distinguished from Th1 cells purely on the production of IFNγ, given that both subsets produce this cytokine in high amounts. Therefore, the Th17 plasticity marker CD161 is used to delineate Th1 cells (CD161− IFNγ+) from ex-Th17 cells (CD161+ IFNγ+). Thus, future analysis of the IFNγ+ TEM population in the Raychaudhuri *et al*'s study could be performed to ascertain through the use of CD161 expression if the RA SFMC in their study display increased levels of Th1 cells or non classical Th1/exTh17 cells.

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