Response to: 'Regulatory role of the JAK STAT kinase signalling system on the IL-23/IL-17 cytokine axis in psoriatic arthritis' by Raychaudhuri *et al*

In their correspondence, Raychaudhuri *et al*[1] describe an alternative mechanism for the role of Janus Kinase and Signal Transducer and Activator of Transcription (JAK/STAT) signalling in the pathogenesis of psoriatic arthritis (PsA). The interleukin (IL)-23/IL-17 cytokine axis is a well-documented and prominent pathway in the understanding of the pathogenesis of PsA, indicated by the approval of the monoclonal antibody (mAb) ustekinumab, a fully human Ig G1k mAb against the common subunit p40 of IL-12 and IL-23, for the treatment of psoriasis and PsA by the European Medicines Agency and Food and Drug Administration.[2] In addition, IL-17 itself is also a direct therapeutic target for the treatment of PsA and psoriasis, with IL-17A mAb secukinumab now approved also for PsA and psoriasis.[3 4] We agree that the tofacitinib may function by inhibiting JAK2/STAT3, leading to an inhibition of the functional effects of IL-23 on memory T cells, with an ultimate consequence of reduced IL-17 production, as they suggest. Although there are no studies demonstrating the direct effect of tofacitinib on IL-23 secretion from dendritic cells (DCs), a recent study in psoriasis supports this data, having observed that expression of IL-12B, the IL-12/IL-23 p40 subunit and IL-17 were decreased following tofacitinib treatment, which was paralleled by improvements in clinical and histological features of psoriasis.[5]

However, it is important to note that in our study, we use an ex vivo synovial tissue model, which maintains synovial architecture and cell–cell contact. Our model uses undigested tissue, still structurally intact, which is obtained at keyhole arthroscopy and cultured immediately.[6] Consequently, immune/stromal cells within the PsA ex vivo biopsies are highly active and spontaneously release proinflammatory mediators such as cytokines, chemokines and growth factors, closely reflecting the inflamed PsA synovium in vivo. Raychaudhuri *et al* investigate the role of tofacitinib on a specific subset of lymphocytes in peripheral cells of patients with PsA. However, the pathogenesis of PsA involves a complex interaction of multiple innate and adaptive cell types, and it is likely that the exact mechanistic function of tofacitinib is not restricted to a single cell type within the synovium, and that the anti-inflammatory effects of tofacitinib on PsA synovial tissue that we have previously described are due to a complex interplay between the numerous cell types within the joint.

In our study, we demonstrate the inhibitory effect of tofacitinib on the proinflammatory mechanisms using PsA explants and PsAFLS, including migration, invasion, matrigel network formation, matrix metalloproteinase (MMP)/cytokine secretion and key signalling pathways such as nuclear factor kappa B (NFkB). While the precise mechanisms by which tofacitinib inhibits these key destructive processes in PsA is still unknown, it is likely that the IL-23/IL-17 cytokine axis may in part mediate some of these effects. Mechanisms may also involve inhibition of key cytokines including IL-6 resulting in negative feedback inhibition or through the observed inhibition of NFkB, which is known to mediate proliferative and invasive mechanisms in other cell types such as cancer cells.[7]

Raychaudhuri *et al* have previously demonstrated the existence of functional IL-17 receptors in synovial fibroblasts of patients with PsA and have further exhibited the proinflammatory effects of IL-17 in the joint pathology of PsA via induction of IL-6, IL-8 and MMP-3 on exposure to IL-17 in cultured Fibroblast-like synoviocytes (FLS) from patients with PsA.[8] These studies are in line with previous studies by our group which have also established that IL-17 itself can promote synovial inflammation and can drive matrix and cartilage degradation by inducing the production of MMPs.[9] These studies combined with the present data provided by the authors suggest evidence that tofacitinib may have an effect on IL-17-producing cells within the PsA synovial tissue, which can then negatively feedback on PsAFLS to inhibit MMP production and subsequent cartilage degradation in the joint.

Therefore, while we agree that tofacitinib may function to inhibit the IL-23/IL-17 cytokine axis in PsA, it is likely that tofacitinib also operates in a manner that is independent of both IL-23 and IL-17, depending on the cell type and inflammatory milieu. Further studies in a multicellular ex vivo system are needed to fully delineate the mechanistic role of tofacitinib in PsA. It would be interesting for the authors to investigate the direct effect of tofacitinib on IL-23 secretion from DC derived from the PsA inflammatory environment, either from synovial fluid or in synovial tissue. Furthermore, co-culturing PsA DC with T cells in the presence of tofacitinib and measuring specific T-cell subset cytokine secretion would provide strong evidence of JAK/STAT involvement in the IL-23/IL-17 cytokine axis in PsA.

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