Gut-derived CD8$^+$ tissue-resident memory T cells are expanded in the peripheral blood and synovia of SpA patients

We read with interest the recently published paper from Qaiyum *et al*[1] demonstrating a novel integrin-expressing mature Crohn's disease (CD)8$^+$ T cell population defined as CD49a$^+$CD103$^+$β7$^+$CD29$^+$ cells in the synovial fluids of ankylosing spondylitis (AS) patients. Although the authors did not analyse gut samples from AS patients, they speculate that these cells might be gut-derived cells. Interestingly, as stated by authors, the transcriptional and phenotypic signature of these cells is reminiscent of human tissue-resident memory T cells (T_{RM}). T_{RM} are a subset of cells important as the first line of defence from infection in mucosal tissues, never studied in spondyloarthritis (SpA).[2] For clarifying whether these cells could be of intestinal original, we set up additional analyses, wondering if we could see similar results in paired samples of patients with SpA.

Paired gut and synovial samples and fluids and peripheral blood samples (PCMCs) were obtained from patients with SpA (HLA-B27 positive; n=6), never treated with biologic agents at the time of sample collection. Gut samples were also obtained from healthy controls (HCs) (HLA-B27 negative; n=6) and synovial tissues from osteoarthritis (OA) patients (HLA-B27 negative; n=6). Peripheral blood mononuclear cells (PBMCs) were also obtained from HCs. CD103 and CD8 expression were assessed by immunohistochemistry. The percentage of T_{RM} T cells (defined as CD8$^+$CD69$^+$CD103$^+$cells) among isolated lamina propria mononuclear cells (LPMCs) and PBMCs from SpA patients and controls were also analysed by flow cytometry.

Part of the results is shown in figure 1. In the gut tissues, the number of CD8$^+$CD103$^+$ cells was consistently increased in the inflammatory SpA samples compared with non-inflammatory samples (figure 1A–E). Tissue distribution confirmed their predominant localisation in the context of epithelial layer (figure 1A–D). Flow cytometric analysis of LPMCs confirmed the expansion of CD8$^+$CD69$^+$CD103$^+$ T_{RM} T cells, mainly

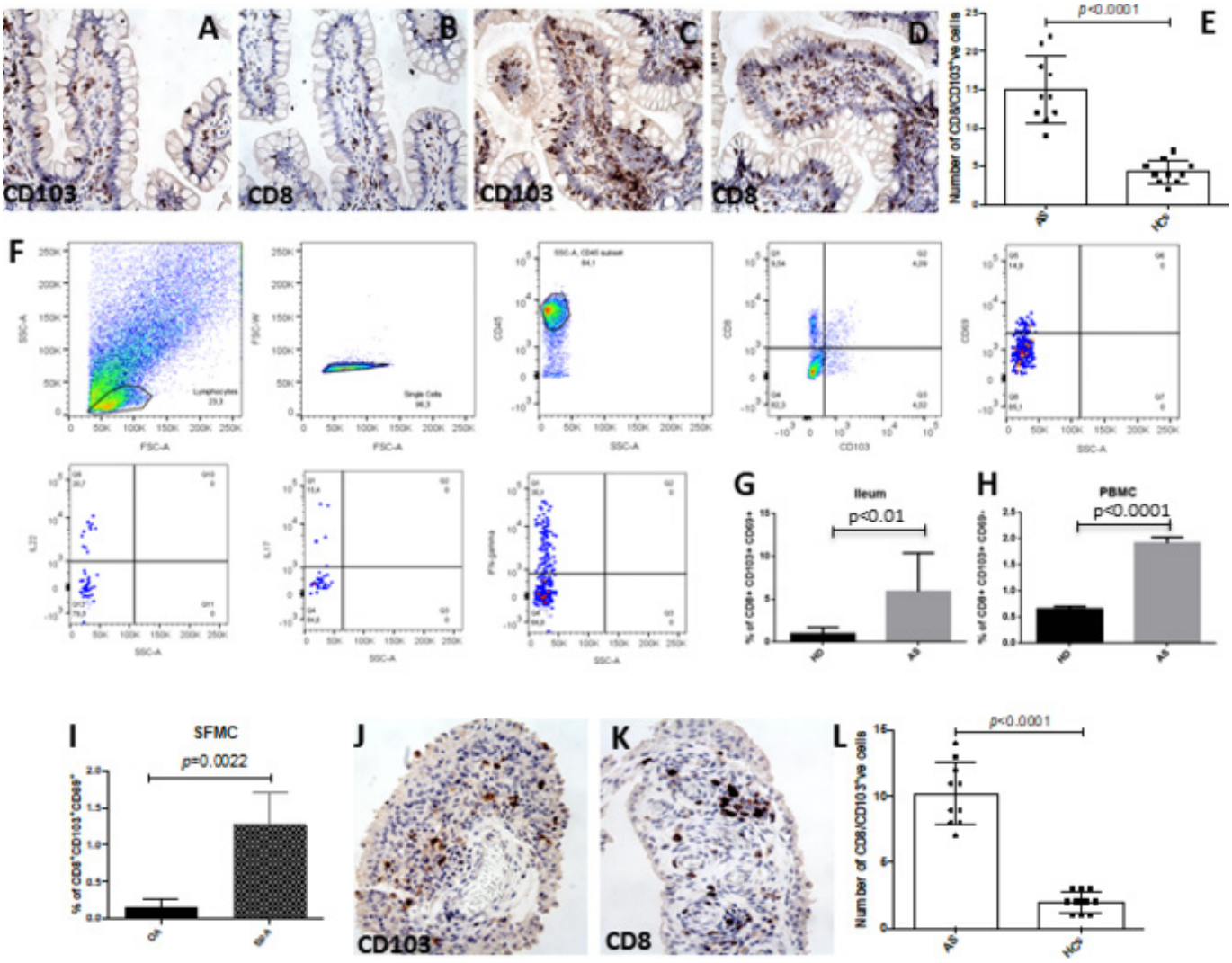

Figure 1 T_{RM}s in the gut, peripheral blood and synovia of SpA patients. (A–D) Representative imaging showing CD103 (A and C) and CD8 (B and D) expression in sequential gut sections of controls (A–B) and SpA patients (C–D). (E) Higher numbers of CD8/CD103 positive cells were observed in SpA patients compared with controls. (F) Representative dot plots showing gating strategy for T_{RM}s in the peripheral blood of SpA patients. (G–I) Percentages of T_{RM}s among LPMC (G), PBMC (H) and SFMC (I) in SpA patients and controls. (J–K) Representative imaging showing CD103 (J) and CD8 (K) expression in sequential synovial sections of SpA patients. (L) Higher numbers of CD8/CD103 positive cells were observed in SpA patients compared with controls. (A–D) and (J–K): Original magnification ×250. LPMC, lamina propria mononuclear cell; PBMC, peripheral blood mononuclear cell; T_{RM}s, tissue-resident memory T cells.

producing IFNγ, in SpA patients compared with HCs (figure 1F–G). The expansion of $CD8^+CD69^+CD103^+$ T_{RM} T cells, mainly producing IFNγ, was also confirmed in SpA PBMCs (figure 1H) and synovial mononuclear cells (SFMC) (figure 1I), compared with HCs. The majority of circulating and synovial fluids $CD8^+CD69^+CD103^+$ T_{RM} expressed the intestinal homing receptor α4β7 (67% and 75%, respectively) suggesting their gut origin (data not shown). Finally, immunohistochemical analysis of sequential synovial samples confirmed tissue infiltration of $CD8^+CD103^+$ cells in the inflamed synovial tissues of SpA patients (figure 1J–L).

The existence of a gut–joint has been hypothesised in SpA patients.[3] The inflamed gut could actively participate in the pathogenesis of SpA through the production of proinflammatory cytokines, such as IL-23p19[4] and IL-9,[5] and the differentiation of potentially pathogenic innate cells producing IL-22 and IL-17.[3] T_{RM} are a critical component of mucosal immune defence by acting as peripheral sentinels capable of rapidly mobilising protective tissue immunity on pathogen recognition.[2] Our data confirm the expansion of T_{RM} in the synovial compartment of SpA patients, providing evidence of T_{RM} expansion in the peripheral blood and the gut. The expression of α4β7 by circulating T_{RM} in SpA might support the re-circulation of these cells from the gut to the peripheral blood and inflamed joints.

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