Identification and Characterization of the Tissue Resident Memorial T Cells in Psoriatic Arthritis: Regulatory Role in Chronicity and Treatment Response

Krishna Sah[1,2], Christine Abria[1], Smriti K Raychaudhuri[1] and Siba P. Raychaudhuri[1,2]

[1]Division of Rheumatology & Immunology, VA Medical Center, Mather, CA, [2]Division of Rheumatology , UC Davis School of Medicine, Davis, CA

Background

Tissue-resident memory T cells (TRM) are site-specific T cells that take up long-term residence in peripheral tissues and aid in pathogen defense. TRM cells can drive localized, recurrent inflammation. Thus, the TRM in autoimmune disease is critical in respect to induction, chronicity, remission and relapse.

Objective

Cellular/molecular biology of TRM in respect to their growth/cytokine network in autoimmune disease is a new field and remains largely unknown. Here we have investigated the regulatory role of TRM in PsA; and have studied Rheumatoid arthritis (RA, as a positive control) and osteoarthritis (OA, as a negative control).

Methods

From untreated/active, age/sex matched patients with PsA, RA, OA (n=12/each) synovial fluid mononuclear cells (SFMC) were collected. SFMC cells (10*6 cells/mL) were activated with antihuman CD3/CD28 cocktail; cells were cultured for 3 days. Hi-D FACS studies were done (i) to identify TRM (CCR7-CD69+CD103+/CD49a+) T cells (CD3+CD4+/CD8+) and (ii) to evaluate relevant Th1/Th17 cytokines (TNFα, IFNγ,IL-17A, IL-22) in TRM. MFI and the percentages of each cell population were analysed using FlowJo software. Results are described as Mean±SEM.

Figure 1A

Figure 1 A. Here, we characterized the synovial tissue-resident memory T cells (TRM) in PsA. First live lymphomononuclear cells were gated and then CD4+ and CD8+ TRM were characterized. In this FACS plot of CD4+ and CD8+ TRM (CCR7-CD69+ CD103+/CD49a+) cells are identified. CD4+TRM cells (CCR7-CD69+) are characterized by high expression of CD49a whereas CD8+ TRM cells (CCR7-CD69+) are positive for both CD49a and CD103.

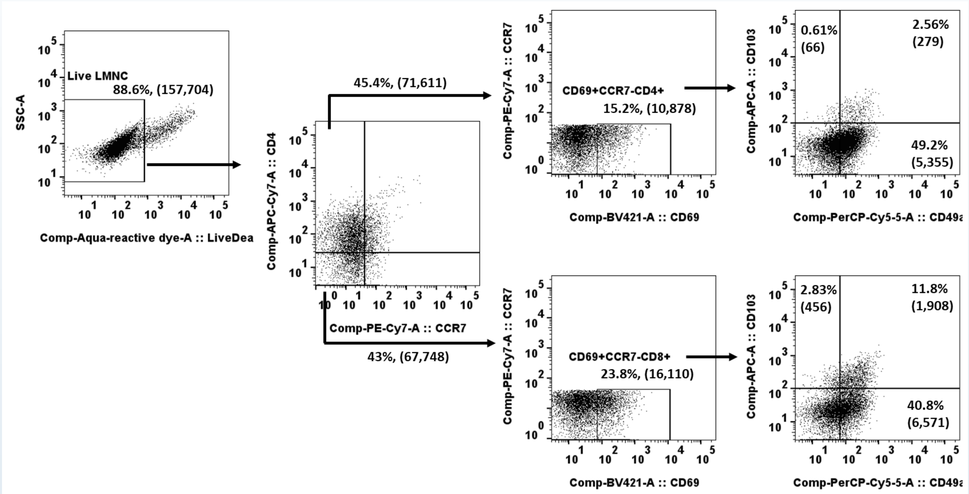
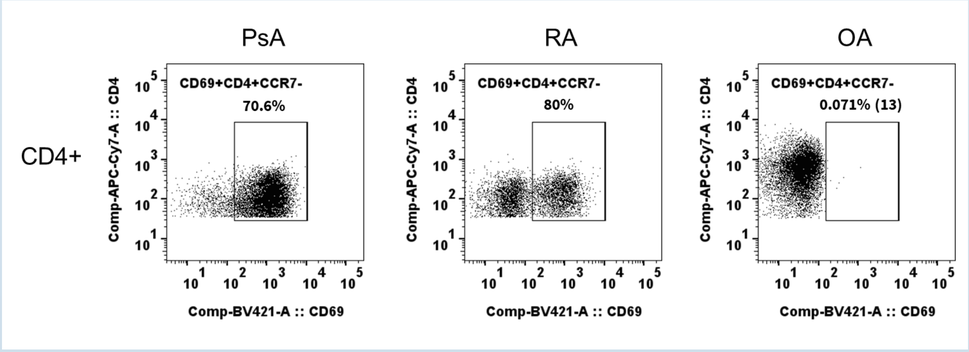


Figure 1B

Figure 1B. Here gated live CD4+CCR7-CD69+ are studied to identify TRM cells in PsA, RA and OA. As expected the OA synovial fluid T cells did not have TRM cells; whereas both PsA and RA demonstrated CD4+TRM cell.



Results

1). Here we phenotyped CD8+/CD4+ TRM cells (CCR7-CD69+CD103+ /CD49a+) in PsA and RA, and have noticed that they were of heterogeneous population characterized by multiple distinct phenotypes and functions (Figure 1A,1B). 2.) In live gated SFMC in PsA and RA the CD4+TRM cells were 20.5%±2.5 and 18.5%±4.4 respectively compared to <1% in OA ($p<0.001$). Majority of the CD3+ SFMC TRM cells in both PsA and RA were CD4+ (>70%). Thus the major source of the TRM cell derived Th1/Th17 cytokines were the CD4+TRM cells. 3.) In PsA CD4+TRM cells; IL-17A (20.5%±1.4) and IL-22 (8.4%±1.3) secreting cells were significantly higher ($p< 0.01$) than RA (IL-17A 5.9%±1.2), IL-22 (2.5%±0.5)); whereas RA CD4+TRM cells had higher numbers of TNFα(24.3%±0.2) and IFNγ producing cells(11.8%±0.5); TNFα and IFNγ CD4+TRM cells in PsA were respectively 8.16±0.11 and 4.5% ($p< 0.01$).

Conclusion

Here we identified the synovial TRM cells in autoimmune arthritis including in PsA. This is the first study to substantiate the regulatory role of TRM cells in PsA. TRM cells are capable of site-specific flare after remission. Thus, our observations provide a novel insight that depletion of TRM cells as a potential long term remission for PsA. Further we noticed that TRM cells are skewed more towards the Th17 cells compared with RA; which indicates the impact of IL-23 on TRM cell growth/apoptosis and its therapeutic relevance in PsA.