EDITORIAL

PD-1$^+$ T cells contribute differently to the pathogenesis of rheumatoid arthritis and psoriatic arthritis

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Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are 2 chronic autoinflammatory diseases that result in erosive inflammatory arthritis, severe pain, and chronic fatigue, where PsA is often further complicated by persistent painful skin lesions and can display characteristics consistent with spondyloarthropathy.[1] While both diseases have prominent synovitis characterized by lymphocyte and monocyte infiltration of the synovial membranes, there are nonetheless significant differences in joint involvement, molecular and cellular immunology, and seropositivity. Patients with RA often present with serum autoantibodies, in particular antibodies against citrullinated peptides and rheumatoid factor,[2] whereas most patients with PsA lack any serum autoantibodies.[3] The reasons for this difference are slowly being elucidated, and it has been suggested that there are fewer T–B-cell aggregates in PsA compared with RA.[1] These aggregates can form functional ectopic germinal centers (EGCs), which are known to result in the local in situ production of autoantibodies.[4] Thus, fewer T–B-cell aggregates in PsA result in fewer EGCs and lower levels of serum autoantibodies.

T follicular helper (Tfh) cells are essential for the generation of high-affinity antibodies, and cognate Tfh- and B-cell interactions in EGCs are thought to be required for the production of high-affinity autoantibodies in autoimmune diseases.[5] Tfh cells express the receptor for CXCL13, CXCR5, which positions them into B-cell aggregates within developing EGCs, while B-cell interactions are facilitated by inducible T-cell costimulator (ICOS), CD40, and programmed cell death protein 1 (PD-1) (expressed on Tfh cells) ligation to ICOS-L, CD40L, and PD-L1 (expressed on B cells), respectively.[6] A recent interest in the modulation of PD-1 signaling in autoimmune diseases has stemmed from immunotherapies for cancer which target PD-1. Checkpoint inhibitors blocking PD-1 signaling have been shown to unleash antitumor T-cell responses, and there is now a considerable interest in the development of PD-1 agonists which activate the regulatory signaling effect of PD-1 in order to attenuate T-cell activation in autoimmune disease.[7] Moreover, exacerbation of autoimmune disease in patients treated with checkpoint inhibitors highlights the importance of PD-1 in regulating T-cell responses and immune tolerance.[7]

In RA, Tfh-like cells have been identified in the synovial tissue[8,9] and elevated levels of circulating Tfh cells and serum interleukin 21 have been reported.[10,11] Furthermore, a recent report demonstrating attenuation of disease in a T–cell-specific CXCR5-deficient animal model of RA strengthens the already compelling case for Tfh involvement in the pathogenesis of RA.[12,13] Tfh-cell involvement in PsA is less well studied and restricted to the recent identification of circulating Tfh cells in psoriasis only.[13] Moreover, there are unanswered questions regarding the role of PD-1 expression in RA as well as PsA, where a correlation between decreased expression of PD-1 on T cells and disease severity in RA has been reported.[14] Thus, in both diseases, the contribution of PD-1 (and to a lesser extent of Tfh cells) to disease progression and maintenance remains to be clarified.

In the current issue of the *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Bartosińska et al[15] reported using flow cytometry to investigate PD–1-expressing T cells both in patients with RA and those with PsA. The study included the analysis of peripheral blood from 100 patients with RA classified using the American College of Rheumatology 1987 criteria, 31 patients with PsA that fulfilled the official Classification of Psoriasis Arthritis criteria, and 52 healthy controls. Importantly, the investigators demonstrated that both CD4$^+$ and CD8$^+$ T cells expressing

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Received: November 17, 2017.
Revision accepted:
November 17, 2017.
Published online:
December 21, 2017.
Conflict of interests: none declared.
Pol Arch Intern Med. 2017;
127 (12): 813-814
doi:10.20452/pamw.4172

PD-1 are more abundant in patients with RA compared with controls, whereas patients with PsA had fewer $CD4^+$ and $CD8^+$ T cells expressing PD-1 compared with controls. Moreover, PD-1 expression levels were also elevated on both $CD4^+$ and $CD8^+$ T cells in patients with RA compared both with patients with PsA and controls.

The results show considerable heterogeneity in PD-1 expression on $CD4^+$ and $CD8^+$ cells in patients with RA compared with the relatively homogeneous results in healthy controls and patients with PsA. This is likely due to the heterogeneity of treatments the patients with RA were receiving, and this treatment heterogeneity along with the long disease duration and the variability in disease activity (not really addressed in this paper) in this RA patient group makes it more difficult to assign the high expression of PD-1 directly to pathogenetic processes in RA. The question would be better addressed by studying a treatment-naive population of patients with RA with early disease and following changes in PD-1 expression as a result of treatment with a standardized regimen.

While this study could have benefited from a larger (particularly for PsA) and more defined cohort (additionally in RA to compare Tfh abundance and PD-1 expression in seropositive RA vs seronegative RA), the authors highlighted the fact that immune dysregulation in RA and PsA is different and suggested that the autoantibody titers absent in PsA reflect the absence of PD–1--expressing cells as compared with RA. Furthermore, they suggested that recent reports of secreted PD-1 detected in the serum and synovium of patients with RA could result in secreted PD-1 competing with PD-1 expressing T cells for PD-L1 in the microenvironment, resulting in T cells that are hyperactive and thus can drive autoantibody responses in RA, but not PsA.[16] Unfortunately, this study did not substantiate the authors' claims with measures of $PD\text{-}1^+$ T-cell activation (eg, proliferation, cytokine production, and apoptosis) in RA vs PsA, and a further mechanistic evaluation of PD–1-mediated dysregulation of immune responses in these autoimmune pathologies is still required.

Critically, the site of inflammation in both RA and PsA is the synovial membrane.[1] Although synovial tissue is challenging to obtain, it represents the best opportunity for elucidating disease pathogenesis and identifying novel cellular and molecular targets for therapy. Indeed, a recent publication revealed a new $CXCR5^-$ $PD\text{-}1^+$ T-helper subset in the synovium of patients with RA, termed "T peripheral helper" (Tpf).[17] Interestingly, despite high levels of PD-1 expression, these cells were still able to provide effective B-cell help, and the absence of CXCR5 was postulated to provide a mechanism by which Tph cells can enter synovial tissue and start EGC formation without an already established microarchitecture to support T–B-cell interaction. While, this study demonstrated Tph cells in patients with late-stage RA, other groups including ours (unpublished data) are beginning to report on the presence of Tph cells in treatment-naive patients with early disease. This is critical as the long-term outcomes of both RA and PsA are improved with a successful early treatment, and the identification of targets for therapy in the future should focus on early--disease cohorts. Nonetheless, peripheral characterization of PD–1-expressing T cells in autoimmune diseases can, as the authors have demonstrated, provide valuable insights to disease pathogenesis and, where possible, should be used in combination with tissue analysis.

Note The opinions expressed by the author are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

REFERENCES

1 Veale DJ, Fearon, U. What makes psoriatic and rheumatoid arthritis so different? RMD Open. 2015; 1: e000025-e000025.

2 Sanmartí R, Graell E, Perez ML, et al. Diagnostic and prognostic value of antibodies against chimeric fibrin/filaggrin citrullinated synthetic peptides in rheumatoid arthritis. Arthritis Res Ther. 2009; 11: R135.

3 Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006; 54: 2665-2673.

4 Pitzalis C, Jones GW, Bombardieri M, Jones SA. Ectopic lymphoid-like structures in infection, cancer and autoimmunity. Nat Rev Immunol. 2014; 14: 447-462.

5 Ueno H. T follicular helper cells in human autoimmunity. Curr Opin Immunol. 2016; 43: 24-31.

6 Crotty S. Follicular helper CD4 T cells (TFH). Ann Rev Immunol. 2011; 29: 621-663.

7 van der Vlist M, Kuball J, Radstake TR, Meyaard L. Immune checkpoints and rheumatic diseases: what can cancer immunotherapy teach us? Nat Rev Rheumatol. 2016; 12: 593-604.

8 Manzo A, Vitolo B, Humby F, et al. Mature antigen-experienced T helper cells synthesize and secrete the B cell chemoattractant CXCL13 in the inflammatory environment of the rheumatoid joint. Arthritis Rheum. 2008; 58: 3377-3387.

9 Chu Y, Wang F, Zhou M, et al. A preliminary study on the characterization of follicular helper T (Tfh) cells in rheumatoid arthritis synovium. Acta Histochem. 2014; 116: 539-543.

10 Liu R, Wu Q, Su D, et al. A regulatory effect of IL-21 on T follicular helper-like cell and B cell in rheumatoid arthritis. Arthritis Res Ther. 2012; 14: R255.

11 Ma J, Zhu C, Ma B, et al. Increased frequency of circulating follicular helper T cells in patients with rheumatoid arthritis. Clin Dev Immunol. 2012; 2012: 827480.

12 Moschovakis GL, Bubke A, Friedrichsen M, et al. T cell specific Cxcr5 deficiency prevents rheumatoid arthritis. Sci Rep. 2017; 7: 8933.

13 Wang Y, Wang L, Yang H, et al. Activated circulating T follicular helper cells are associated with disease severity in patients with psoriasis. J Immunol Res. 2016; 2016: 7346030.

14 Li S, Liao W, Chen M, et al. Expression of programmed death-1 (PD-1) on CD4+ and CD8+ T cells in rheumatoid arthritis. Inflammation. 2014; 37: 116-121.

15 Bartosińska J, Zakrzewska E, Król A, et al. Differential expression of programmed death 1 (PD-1) on CD4+ and CD8+ T cells in rheumatoid arthritis and psoriatic arthritis. Pol Arch Intern Med. 2017; 127: 815-822.

16 Greisen SR, Rasmussen TK, Stengaard-Pedersen K, et al. Increased soluble programmed death-1 (sPD-1) is associated with disease activity and radiographic progression in early rheumatoid arthritis. Scand J Rheumatol. 2014; 43: 101-108.

17 Rao DA, Gurish MF, Marshall JL, et al. Pathologically expanded peripheral T helper cell subset drives B cells in rheumatoid arthritis. Nature. 2017; 542: 110-114.