Autoantibodies in psoriatic arthritis: are they of pathogenic relevance?

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A physician in clinical practice does not usually order autoantibody testing to aid subsequent diagnosis or for monitoring disease activity in patients with psoriasis or psoriatic arthritis (PsA), although a variety of autoantibodies are present in these patients. Our understanding of autoantibodies in psoriasis and PsA is limited.

Early investigations of autoantibodies in psoriasis were focused on the known autoantibodies in rheumatic diseases. For instance, anti-nuclear antibodies (ANAs) are often found in patients with psoriasis or PsA, but anti-double-stranded DNA or anti-extractable nuclear antigens are rarely identified. Therefore, ANAs have not been considered valuable in diagnosing PsA or predicting prognosis to manage PsA. Moreover, the roles of ANAs in the pathogenesis of PsA remain unknown. 1, 2 Autoantibodies associated with rheumatoid arthritis (RA) have been investigated in PsA for their presence and association with the disease. For instance, antibodies against citrullinated proteins (ACPAs), which are highly specific to RA, are found in 5.0% to 17.5% of PsA patients. In several studies, a more erosive disease has been observed in PsA patients with ACPAs than in ACPA-negative PsA patients. 3, 4 These findings imply that ACPAs in patients with PsA may be capable of inducing bone loss, which has been observed in RA patients with antibodies against citrullinated vimentin. 5 However, the antigen specificity of ACPAs in PsA has not been clearly reported. In a study with a small number of subjects, levels of anti-citrullinated vimentin antibodies were found to be significantly higher in patients with PsA than in those without PsA. 6 Anti-citrullinated protein (CarP) antibodies are relatively specific for RA, particularly in ACPA-negative patients with RA 7; anti-CarP antibodies are also present in patients with PsA, and their presence has been linked to disease activity. 8 These studies suggest that proteins in the joints of patients with PsA undergo a similar post-translational modification process as in RA. However, the factors that exert the post-translational modification in the joints but not in the skin remain unclear, although inflammation is observed in both sites as neither ACPA nor anti-CarP antibodies were found in psoriasis patients without PsA.

Recently, novel autoantibodies have been described in patients with PsA. Among these autoantibodies that were detected in PsA patients, the antibodies against LL-37 and a disintegrin and metalloprotease (ADAM) domain containing thrombospondin type 1 motif-like 5 (ADAMTS-L5) are particularly interesting as they may be relevant to the pathogenesis of PsA. LL-37 is a cationic antimicrobial peptide of 37 amino acids and is derived from Hcap-18, which is an inactive precursor produced by neutrophils, antigen-presenting cells, mast cells, and keratinocytes in response to infections or tissue injury. LL-37 is overexpressed in psoriatic skin lesions and has been reported to be abundant in the synovial fluid and synovium of patients with PsA. LL-37 in the synovium of joints is associated with myeloperoxidase; this indicates that it may be derived from neutrophils. Autoantibodies to native, citrullinated, or carbamylated LL-37 are present in the synovial fluid of patients with PsA but not in the synovial fluid of those with osteoarthritis. 9 Interestingly, the presence of anti-LL-37 antibodies in synovial fluid has been linked to inflammation and disease activity in patients with PsA. 9 Autoantibodies to LL-37 are also present in the circulatory system of patients with PsA. 9, 10, 11 The presence of anti-carbamylated LL-37 antibodies has also
been linked to PsA. Importantly, anti-LL-37 titers in the blood have been reported to be significantly higher in patients with PsA than in patients with psoriasis alone; this suggests that a higher titer of anti-LL-37 may be an indicator or biomarker for distinguishing between patients with PsA and patients with psoriasis without PsA. Anti-LL-37 antibodies have also been found in PsA patients with early stage disease, suggesting that anti-LL-37 participates in the development of autoimmunity.

ADAMTS-L5 belongs to the ADAMTS superfamily, which binds and modulates microfibril function. Autoantibodies to ADAMTS-L5 have also been reported to be significantly higher in patients with PsA than in patients with psoriasis without PsA.

Both LL-37 and ADAMTS-L5 are autoantigens in the pathogenesis of psoriasis and are upregulated in psoriatic skin lesions. Moreover, expression of LL-37 and ADAMTS-L5 in skin lesions have been reportedly downregulated after the inhibition of tumor necrosis factor (TNF) or interleukin (IL)-17. This suggests that expression of LL-37 and ADAMTS-L5 is regulated by TNF and IL-17 and is involved in the pathogenesis of the disease. LL-37 can induce both CD4+ and CD8+ T cell responses. LL-37-reactive CD4+ T cells produce IL-17A and have been suggested to help B cells produce anti-LL-37 autoantibodies. Moreover, LL-37 can bind to self-DNA and stimulate the production of interferon-α by plasmacytoid dendritic cells (pDCs); this has been considered an early event in the development of psoriasis. Recently, Herster et al. reported that LL-37 forms a complex with RNA released by neutrophil extracellular traps and can induce the production of inflammatory cytokines. ADAMTS-L5 is expressed by melanocytes in psoriasis. Intradermal CD8+ T cells isolated from psoriatic skin lesions have been reported to be able to react against melanocytes and produce IL-17A. The increased levels of autoantibodies against LL-37 and ADAMTS-L5 in patients with PsA may indicate that lymphoid tissue in the arthritic joint plays a key role in autoantibody production. Indeed, ectopic lymphoid-like structures with germinal centers are found in the synovium of patients with PsA and ADAMTS-L5 is overexpressed in the synovium of patients with PsA. However, the overexpression of ADAMTS-L5 in the synovium of patients with PsA is yet to be investigated.

In summary, there is a large knowledge gap regarding autoimmunity in psoriasis. The antigen array assay reported by Yuan et al. offers an advantage in finding novel autoantibodies that are specific to a variety of antigens. In contrast, a study by Dolcino et al. autoantibodies against a shared epitope in the skin were reported. Dolcino et al. also reported that there may be hints in joints that would explain why some patients with psoriasis develop PsA. Insightful studies on autoantibodies in PsA are required to determine whether the production of these autoantibodies in PsA is an epiphenomenon or they directly participate in the pathogenesis of arthritis. For example, the increased production of anti-LL-37 autoantibodies in PsA patients is potentially useful to distinguish patients with PsA from those with psoriasis without PsA. Increasing evidence suggests the direct involvement of autoantibodies against LL-37 in the pathogenesis of PsA. Moreover, anti-LL-37 antibodies in systemic lupus erythematosus have been proposed to activate neutrophils such that LL-37 is released via extracellular trap formation, after which LL-37 and DNA complexes are formed that trigger pDCs to produce type I interferon; a similar mechanism by anti-LL-37 is yet to be demonstrated in the pathogenesis of PsA.

Conflicts of interest
None.

References

1. Johnson SR, Schentag CT, Gladman DD. Autoantibodies in biological agent naive patients with psoriatic arthritis. Ann Rheum Dis 2005;64:770–772. doi: 10.1136/ard.2004.031286.
2. Silvy F, Bertin D, Bardin N, Auger I, Guzman MC, Mattei JP, et al. Antinuclear antibodies in patients with psoriatic arthritis treated or not with biologics. PLoS One 2015;10:e0134218. doi: 10.1371/journal.pone.0134218.

3. Behrens F, Kochm M, Thaci D, Gmann H, Greger G, Maria Wittig B, et al. Anti-citrullinated protein antibodies are linked to erosive disease in an observational study of patients with psoriatic arthritis, Rheumatology (Oxford) 2016;55:1791–1795. doi: 10.1093/rheumatology/kwe229.

4. Perez-Alamino R, Garcia-Valladares I, Cuchacakovic R, Iglesias-Gamarra A, Espinoza LR. Are anti-CCP antibodies in psoriatic arthritis patients a biomarker of erosive disease? Rheumatol Int 2014;34:1211–1216. doi: 10.1007/s00296-014-2956-8.

5. Harré U, Georgess D, Banh H, Bozec A, Axmann R, Ossipova E, et al. Induction of osteoclastogenesis and bone loss by human autoantibodies against citrullinated vimentin. J Clin Invest 2012;122:1791–1802. doi: 10.1172/JCI60975.

6. Dalmady S, Kiss M, Kepiro L, Kovacs L, Sonkodi G, Kemeny L, et al. Higher levels of autoantibodies targeting mutated citrullinated vimentin in patients with psoriatic arthritis than in patients with psoriasis vulgaris. Clin Dev Immunol 2013;2013:74028. doi: 10.1155/2013/74028.

7. Shi J, Knevel R, Suwannalai P, van der Linden MP, Janssen GM, van Veenen PA, et al. Autoantibodies recognizing carbamylated proteins are present in sera of patients with rheumatoid arthritis and predict joint damage. Proc Natl Acad Sci U S A 2011;108:17372–17377. doi: 10.1073/pnas.1111446108.

8. Chimenti MS, Triggianese P, Nuccetelli M, Terracciano C, Crisanti F, et al. Auto-reactions, autoimmunity and psoriatic arthritis. Autoimmun Rev 2015;14:1142–1146. doi: 10.1016/j.autrev.2015.08.003.

9. Frasla L, Palazzo R, Chimenti MS, Alivermini S, Toloumbo B, Bui L, et al. Anti-LL37 antibodies are present in psoriatic arthritis (PsA) patients: new biomarkers in PsA. Front Immunol 2018;9:1936. doi: 10.3389/fimmu.2018.01936.

10. De Santis M, Iaslovic N, Generali E, Ceribelli A, Guarino MD, et al. Higher levels of anti-ADAMTSL5 IgG4 anti-gliadin autoantibody as a potential biomarker of psoriasis in an autoantigen array. Proteomics Clin Appl 2020;4:2203–2212. doi: 10.1002/pca.2526.

11. Yuan Y, Qiu J, Li Y, Haley C, Swali R, et al. Discovery of IgG4 anti-gliadin autoantibody as a potential biomarker of psoriasis. Scand J Immunol 2020;92:e12945. doi: 10.1111/sji.12945.

12. Cheung KL, Jarrett R, Subramaniam S, Salimi M, Gutoski-Owsiak D, Chen YL. Neutrophil extracellular trap-associated RNA and LL37 enable inflammation in psoriasis. J Exp Med 2015;212:2203–2212. doi: 10.1084/jem.20151093.

13. Lande R, Chamilos G, Ganguly D, Demaria O, Frasca L, Durr S, et al. Cytotoxic antinuclear antibodies in psoriatic skin cooperate to break innate tolerance to self-DNA. Eur J Immunol 2015;45:203–213. doi: 10.1007/ej.2013.44277.

14. Lande R, Botti E, Jandus C, Dojcinovic D, Fanelli G, Conrad C, et al. The antinuclear peptide LL37 is a T-cell autoantigen in psoriasis. Nat Commun 2014;5:5621. doi: 10.1038/ncomms6621.

15. Lande R, Chamilos G, Ganguly D, Demaria O, Frasca L, Durr S, et al. Cytotoxic antinuclear antibodies in psoriatic skin cooperate to break innate tolerance to self-DNA. Eur J Immunol 2015;45:203–213. doi: 10.1007/ej.2013.44277.

16. Herster F, Bittner Z, Archer NK, Dickhofer S, Eisel D, Eigenbrod T, et al. Neutrophil extracellular trap-associated RNA and LL37 enable self-amplifying inflammation in psoriasis. Nat Commun 2020;11:105. doi: 10.1038/s41467-019-13756-4.

17. Arakawa A, Siewert K, Stohr J, Begon P, Kim SM, Ruhl G, et al. Melanocyte antigen triggers autoimmunity in human psoriasis. J Exp Med 2015;212:2203–2212. doi: 10.1084/jem.20151093.

18. Canete JD, Santiago B, Cantaert T, Sanmarti R, Palacin A, Celis R, et al. Neutrophils activate plasmacytoid dendritic cells by releasing self-DNA-peptide complexes in systemic lupus erythematosus. Sci Transl Med 2011;3:73ra19. doi: 10.1126/scitranslmed.3001180.

19. Lande R, Palazzo R, Gestermann N, Jandus C, Falchi M, Spadaro F, et al. Native/citrullinated LL37-specific T-cells help autoantibody production in Systemic Lupus Erythematosus. Sci Rep 2020;10:5858. doi: 10.1038/s41598-020-62480-3.

20. Qiu J, Yuan Y, Li Y, Haley C, Mui UN, Swali R, et al. Autoantigens ADAMTSL5 and LL37 are significantly upregulated in active psoriasis and localized with keratinocytes, dendritic cells and other leukocytes. Exp Dermatol 2017;26:1075–1082. doi: 10.1111/exd.13378.

21. Yunusbayev B, Palavecino B. Psoriasis patients demonstrate HLA-Cw∗06:02 allele dosage-dependent T cell proliferation when treated with hair follicle-derived keratin 17 protein. Sci Rep 2018;8:6098. doi: 10.1038/s41598-018-24991-2.

22. Canete JD, Santiago B, Cantaert T, Sanmarti R, Palacin A, Celis R, et al. Autoantigens ADAMTSL5 and LL37 are significantly upregulated in active psoriasis and localized with keratinocytes, dendritic cells and other leukocytes. Exp Dermatol 2017;26:1075–1082. doi: 10.1111/exd.13378.

23. De Santis M, Iaslovic N, Generali E, Ceribelli A, Altamore L, Real Fernandez F, et al. Humoral response against LL37 in psoriatic arthritis: comment on the article by Yuan et al. Arthritis Rheumatol 2019;71:1964–1965. doi: 10.1002/art.41010.

24. Yuan Y, Qiu J, Lin ZZ, Li W, Haley C, Mui UN, et al. Identification of novel autoantibodies associated with psoriatic arthritis. Arthritis Rheumatol 2019;71:941–951. doi: 10.1002/art.40830.

25. De Santis M, Iaslovic N, Generali E, Ceribelli A, Altamore L, Real Fernandez F, et al. Humoral response against LL37 in psoriatic arthritis: comment on the article by Yuan et al. Arthritis Rheumatol 2019;71:1964–1965. doi: 10.1002/art.41010.

26. Bader HL, Wang LW, Ho JC, Tran T, Holden P, Fitzgerald J, et al. A dipeptidyl-like and metalloprotease domain-containing thrombospondin type 1 motif-like 5 (ADAMTSL5) is a novel fibrillin-1, fibrillin-2, and heparin-binding member of the ADAMTS superfamily containing a netrin-like module. Matrix Biol 2012;31:398–411. doi: 10.1016/j.mxb.2012.09.003.

27. Fuentes-Duculan J, Bonifaco KM, Hawkes JE, Kunyavzla N, Cuevo I, Li X, et al. Autoantibodies ADAMTSL5 and LL37 are significantly upregulated in active psoriasis and localized with keratinocytes, dendritic cells and other leukocytes. Exp Dermatol 2017;26:1075–1082. doi: 10.1111/exd.13378.

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