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-carbamylated 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.[9-11] The presence of anti-carbamylated LL-37 antibodies has also

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001228

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Chinese Medical Journal 2020;133(24)
Received: 06-08-2020 **Edited by:** Li-Shao Guo

been linked to PsA.[9] 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.[11] 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.[9]

ADAMTS-L5 belongs to the ADAMTS superfamily, which binds and modulates microfibril function.[12] Autoantibodies to ADAMTS-L5 have also been reported in patients with psoriasis and PsA. Similar to anti-LL-37, anti-ADAMTS-L5 titers were reported to be significantly higher in patients with PsA than in patients with psoriasis without PsA.[11]

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.[13] 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[14] 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)[15]; this has been considered an early event in the development of psoriasis. Recently, Herster *et al*[16] 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.[17] 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,[9,18] and LL-37 is overexpressed in the joint synovium of patients with PsA. However, the overexpression of ADAMTS-L5 in the synovium of patients with PsA is yet to be investigated.

LL-37 and ADAMTS-L5 have been reported to be involved in the pathogenesis of psoriasis and increasing evidence suggests that LL-37 plays a role in PsA. However, further studies are required to investigate whether and how autoantibodies to LL-37 and ADAMTS-L5 participate in the pathogenesis of PsA. LL-37 and ADAMTS-L5 are neither skin- nor joint-specific antigens; however, they are overexpressed in psoriatic skin and PsA synovium. The reason behind this remains unclear. Are they expressed in response to inflammation? The overexpression of LL-37 and the autoantibodies against LL-37 have been observed in the skin of patients with lupus. $CD4^+$ T cells assist in the production of anti-LL-37 autoantibodies.[19,20] In psoriasis, LL-37 may be presented by neutrophils and are found in abundance in the early stage PsA. Hence, further investigations are required to address these questions. The findings reported by Yuan *et al*[11] are promising; nonetheless, more prospective studies are required to determine whether these autoantibodies against LL-37 and ADAMTS-L5 would be useful in predicting whether subpopulations of patients with psoriasis will develop PsA.

In recent studies wherein antigen array assays were employed, autoantibodies against gliadin were found in patients with psoriasis but not in healthy participants.[11,21] However, whether these autoantibodies can distinguish PsA from psoriasis has not yet been determined.

Other novel autoantigens, including phospholipase A2 group IVID (PLA2G4D), keratin-17, and heterogeneous nuclear ribonucleoprotein A1 (hnRNP-A1) have been reported to be linked to psoriasis.[22] PLA2G4D is overexpressed in the psoriatic epidermis and is presented to T cells by $CD1a^+$ Langerhans cells; lipid-specific T cells produce a large amount of IL-22 and IL-17A.[23] However, whether PLA2G4D is a B cell antigen and whether it is expressed in joint tissues with PsA remains unknown. Keratin-17 is another T cell autoantigen that is overexpressed in psoriatic skin[24]; its expression is upregulated by IL-22 and IL-17A. Moreover, keratin-17 can stimulate $CD8^+$ T cells to produce interferon-γ. Autoantibodies against keratin-17 have not been described in patients with psoriasis. Autoantibodies to hnRNP-A1[25] have been reported in patients with psoriasis, but whether these autoantibodies are more prevalent in patients with PsA remains unclear.

In summary, there is a large knowledge gap regarding autoimmunity in psoriasis. The antigen array assay reported by Yuan *et al*[11] offers an advantage in finding novel autoantibodies that are specific to a variety of antigens. In contrast, in a study by Dolcino *et al*,[26] 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[27]; a similar mechanism by anti-LL-37 is yet to be demonstrated in the pathogenesis of PsA.

Conflicts of interest

None.

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How to cite this article: Zhu J, Shi XF, Chu CQ. Autoantibodies in psoriatic arthritis: are they of pathogenic relevance? Chin Med J 2020;133:2899–2901. doi: 10.1097/CM9.0000000000001228