RMD Open
Rheumatic & Musculoskeletal Diseases

EDITORIAL

Autoinflammation in psoriatic arthritis: time to better define the multifaceted enemy

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To cite: Bilgin E. Autoinflammation in psoriatic arthritis: time to better define the multifaceted enemy. *RMD Open* 2022;**8**:e002685. doi:10.1136/rmdopen-2022-002685

Received 12 September 2022
Accepted 26 September 2022

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Psoriatic arthritis (PsA) is a very heterogeneous disease involving the skin, joints, eyes, gastrointestinal and cardiometabolic systems.[1] In the perspective of 'psoriatic syndrome' or 'psoriatic disease', PsA is a distinct, important and complex entity.[1] PsA is a mysterious disease and still bears many aspects to explore. For instance, although we know many things about the relationship between psoriasis (PsO) and PsA—even though we have a long road to go—it took about 18 centuries for the literature to report this relationship after the papers published about PsO.[2] On the other hand, the mystery is being explored day by day, especially about pathogenesis. Till now, current literature has been focused on the autoimmune aspects of PsA pathogenesis, for example, human leucocyte antigens and clonal expansions of $CD8^+$ T cells.[3] Although a few genome-wide association studies and small studies found PsA and PsO susceptibility genes related to innate immunity,[4] no study has focused on the individual patient-level role of autoinflammatory disorder genes in PsA patients.

In this issue of *RMD Open*, Atschekzei *et al* have turned the spots on genes related to autoinflammatory disorders' clinical characteristics of a PsA cohort with their article entitled 'Identification of variants in genes associated with autoinflammatory disorders in a cohort of patients with PsA'. In their study, 120 consecutive, non-relative PsA patients were enrolled according to the CASPAR criteria. Targeted next-generation sequencing via a validated panel was performed to find rare genes associated with immune dysregulation or autoinflammatory disorders. Overall disease characteristics and treatment regimens of this cohort were similar to current literature. Of 37 (30.8%) patients among 120 patients had 45 rare, monoallelic germline variations. Among these variations, 25 autosomal dominant disorder (AID)-related variations were found in 20 (16.7%) patients. Five patients had AP1S3 variant, which is associated with pustular [5]PsO ; four patients with late-onset seronegative arthritis had PLCG2 variant, which encodes a signalling mediator and is associated with antibody deficiency and immune dysregulation syndrome[6] and two of the three patients with Crohn's disease had NOD2 variant, which is responsible from the production of an intracellular innate immune system receptor.[7] Other AID-related genes were TNFAIP3, COPA, TNFRSF1A, NFKB1, NLRP12, CARD14, IL1RN and DDX58. Pustular PsO and Crohn's disease were significantly more common in patients with any AID-related variant. Not surprisingly, but as confirmatory, patients with any AID-related variant had higher C reactive protein (CRP) levels at the last visit. Although not statistically significant, these patients had a higher rate of treatment escalation. This study is the next step in genetic studies to explore the heritability of PsA, as it used focused next-generation sequencing.

According to our current understanding of the immune system and disorders, PsA has autoimmunity and autoinflammatory features. Absence of female predominance (PsA frequency is similar in both sexes)[8]; activation of the innate immune system as a consequence of trauma and propagation of disease manifestations (deep Koebner phenomenon)[9 10]; episodic course in some patients[11]; extra-articular manifestations (gastrointestinal tract involvement and uveitis), which are mainly innate immune activation driven by IL-23 or Th-17[12]; overlapping features of several IL-1 driven autoinflammatory diseases such as hidradenitis suppurativa (HS), SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis), PsAPASH (PsA, pyoderma gangrenosum, acne and HS)

are all demonstrating the role of autoinflammation in the pathogenesis of PsA[13] clinically. From the cellular and molecular perspective, Toll-like receptor activation[13] via interferons and IL-1 and 6, IL-23 and Th-17-driven innate immune activation.[14 15] TNF-induced negative immune regulation of the innate immune system,[16] and NETosis[17] driven by polymorphonuclear cells can be counted as the components of autoinflammation in PsA pathogenesis.

As a clinician, I am very excited to see and read these kinds of studies. Although the authors clearly stated that they could not demonstrate the pathogenicity of the genetic variants, the results of this study will, hopefully, lead to more sophisticated studies, including functional and genetic studies. Eventually, this growing body of evidence will lead to drug development and clinical trials of already in-use drugs in PsA patients. Although anakinra had limited activity in PsA,[18] some candidate molecules (eg, IL-18 and IL-36) hypothesised by the authors need further evaluation for therapeutic evaluation. In daily practice, a subgroup of PsA patients is unresponsive to currently available biologics and/or has elevated inflammatory response (CRP level, etc) despite optimal therapy. Autoinflammatory aspects of PsA should be one of the future targets of PsA studies in this subgroup of patients.

Today, we know that PsA has several clinical subsets. It is still a highly relevant question whether these different clinical subtypes have clear-cut differences regarding clinical and genetic reflections of autoinflammation, specifically innate immunity. Future studies will hopefully focus on this aspect, besides the therapeutic interventions.

Metabolic comorbidities in patients with PsA are well described in current literature. Besides, a high CRP level, as a marker of inflammation, is a well-known risk factor for cardiovascular diseases (CVD).[19] It is an interesting question whether these genetic alterations of innate immunity have a role in the presence of metabolic disturbances in PsA patients and if they can be used as a predictor of metabolic comorbidities and CVD.

Autoinflammation seems a vital part of the PsA pathogenesis, especially in the presence of pustular PsO and Crohn's disease. Therapeutic application of this growing body of evidence is expected by clinicians dealing with PsA.

Acknowledgements I thank all authors for their contribution to the current understanding of PsA. Also, I thank the Editor and Editorial office staff very much for the invitation and their guidance.

Contributors Design, writing and proofing were done by EB.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

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REFERENCES

1 FitzGerald O, Ogdie A, Chandran V, *et al*. Psoriatic arthritis. *Nat Rev Dis Primers* 2021;7:59.
2 Benedek TG. Psoriasis and psoriatic arthropathy, historical aspects: Part I. *J Clin Rheumatol* 2013;19:193–8.
3 Haroon M, Winchester R, Giles JT, *et al*. Certain class I HLA alleles and haplotypes implicated in susceptibility play a role in determining specific features of the psoriatic arthritis phenotype. *Ann Rheum Dis* 2016;75:155–62.
4 Stuart PE, Nair RP, Tsoi LC, *et al*. Genome-Wide association analysis of psoriatic arthritis and cutaneous psoriasis reveals differences in their genetic architecture. *Am J Hum Genet* 2015;97:816–36.
5 Zhou J, Luo Q, Cheng Y, *et al*. An update on genetic basis of generalized pustular psoriasis (review). *Int J Mol Med* 2021;47.
6 Welzel T, Oefelein L, Holzer U, *et al*. Variant in the *PLCG2* Gene May Cause a Phenotypic Overlap of APLAID/PLAID: Case Series and Literature Review. *J Clin Med* 2022;11. doi:10.3390/jcm11154369. [Epub ahead of print: 27 07 2022].
7 Ashton JJ, Seaby EG, Beattie RM, *et al*. Nod2 in Crohn's disease-unfinished business. *J Crohns Colitis* 2022. doi:10.1093/ecco-jcc/jjac124. [Epub ahead of print: 25 Aug 2022].
8 Ogdie A, Langan S, Love T, *et al*. Prevalence and treatment patterns of psoriatic arthritis in the UK. *Rheumatology* 2013;52:568–75.
9 Tinazzi I, McGonagle D, Aydin SZ, *et al*. 'Deep Koebner' phenomenon of the flexor tendon-associated accessory pulleys as a novel factor in Tenosynovitis and dactylitis in psoriatic arthritis. *Ann Rheum Dis* 2018;77:922–5.
10 Generali E, Bose T, Selmi C, *et al*. Nature versus nurture in the spectrum of rheumatic diseases: classification of spondyloarthritis as autoimmune or autoinflammatory. *Autoimmun Rev* 2018;17:935–41.
11 Fornaro M, Righetti G, Abbruzzese A, *et al*. High disease relapse after bDMARD spacing in psoriatic arthritis compared to rheumatoid arthritis and axial spondyloarthritis patients: real-life data from biopure registry. *Clin Rheumatol* 2021;40:3659–65.
12 Rehaume LM, Matigian N, Mehdi AM, *et al*. Il-23 favours outgrowth of spondyloarthritis-associated pathobionts and suppresses host support for homeostatic microbiota. *Ann Rheum Dis* 2019;78:494–503.
13 Smith RL, Hébert HL, Massey J, *et al*. Association of Toll-like receptor 4 (TLR4) with chronic plaque type psoriasis and psoriatic arthritis. *Arch Dermatol Res* 2016;308:201–5.
14 Khader SA, Gaffen SL, Kolls JK. Th17 cells at the crossroads of innate and adaptive immunity against infectious diseases at the mucosa. *Mucosal Immunol* 2009;2:403–11.
15 Schett G, Rahman P, Ritchlin C, *et al*. Psoriatic arthritis from a mechanistic perspective. *Nat Rev Rheumatol* 2022;18:311–25.
16 Jiang Y, Wang W, Zheng X, *et al*. Immune regulation of TNFAIP3 in psoriasis through its association with Th1 and Th17 cell differentiation and p38 activation. *J Immunol Res* 2020;2020:1–9.
17 Herster F, Bittner Z, Archer NK, *et al*. Neutrophil extracellular trap-associated RNA and LL37 enable self-amplifying inflammation in psoriasis. *Nat Commun* 2020;11:105.
18 Jung N, Hellmann M, Hoheisel R, *et al*. An open-label pilot study of the efficacy and safety of anakinra in patients with psoriatic arthritis refractory to or intolerant of methotrexate (MTX). *Clin Rheumatol* 2010;29:1169–73.
19 Badimon L, Peña E, Arderiu G, *et al*. C-Reactive protein in atherothrombosis and angiogenesis. *Front Immunol* 2018;9:430.