# Correspondence to 'Bacterial citrullinated epitopes generated by *Porphyromonas gingivalis* infection—a missing link for ACPA production'

With great interest, we read the work by Jenning *et al*, which proposed a mechanism by which *Porphyromonas gingivalis (P.g.)* is involved in rheumatoid arthritis (RA) progression by citrullinating and producing exogenously citrullinated human and bacterial epitopes.[1] This commendable work elucidated the mechanism by which autocitrullinated prokaryotic peptidyl arginine deiminase (PPAD) mediates the inflammatory pathogenesis of RA. In particular, the authors demonstrated a correlation between anti-RA-PPAD and both anticitrullinated peptide/protein antibody (ACPA) levels and interstitial lung disease autoantigen reactivity. The study also provided evidence regarding how PPAD citrullinates the internal arginines of RA autoantigens.[1] Moreover, the findings of this study suggested that the failure to clear *P.g.* induces bacterial citrullinated epitope-specific ACPAs, which might trigger ACPA-mediated autoimmunity.[1] *P.g.* is the main pathogen responsible for periodontitis and has been proposed to be involved in stimulating self-reactive immune responses,[2 3] which underlie the association between RA and periodontitis.[4] We are highly interested in the upstream and downstream cellular mechanisms of ACPA development in patients with RA.

We compared the transcriptome profiles of human blood samples from patients with RA and human gingival tissues from periodontitis patients registered in the National Center for Biotechnology Information-Gene Expression Omnibus database. Overall, we identified 14 periodontitis-associated pathways that were significantly expressed during RA pathogenesis using p-value and Z-score visualisation. As shown in figures 1, eight pathways were upregulated with positive Z-scores. Among the eight periodontitis-associated pathways upregulated during RA pathogenesis, we found host responses against bacterial infections that were associated with ACPA development, including oxidative stress responses in macrophages,[5–7] B cell receptor signalling,[8–10] and lipopolysaccharides/interleukin (IL)-1-mediated pathways. These findings are consistent with previous studies reporting that inducible nitric oxide synthase (iNOS)-producing inflammatory M1 macrophages are responsible for autoimmunity, including that of RA,[11] and that glycosylated ACPA IgG molecules[8] are extensively expressed by autoreactive memory B cells.[8–10] Likewise, IL-8, a proinflammatory CXC chemokine responsible for recruiting leukocytes,[12] was also upregulated during RA onset. Thus, it is possible that the initiation of RA onset following *P.g.* infection involves these immune responses. Since signalling pathways associated with both IL-8 and leucocyte extravasation were upregulated, it can be inferred that infiltrating leucocytes may contribute to or be associated with ACPA development.

Among the four downregulated pathways that were during RA pathogenesis, PKC-θ signalling in T lymphocytes, the Th1 pathway, and calcium-induced T lymphocyte apoptosis were significantly inhibited in patients with RA and those with periodontitis, suggesting decreased activity of certain T cells during RA pathogenesis. These findings are interesting because the maturation of autoreactive memory B cells is driven by T cells,[13] although the specific T cell subtypes involved in the induction of ACPA have not been elaborated. Because studies have suggested that Th1/Th2 homeostasis[14] plays a role in inflammatory arthritis, it is likely that the interaction between different types of T cells may regulate the production of ACPA. Moreover, PKC-θ signalling has been shown to promote the activity of regulatory T cells, effector T cells and Th2 cells.[15] This observation further indicates a complex interplay between these presenting pathways and supports the need for further studies on the infection-based induction of ACPAs.

In conclusion, our data suggest that infection-driven activation of macrophages and B cells is involved in RA pathogenesis. This activation primarily occurs through increased cellular activities involving iNOS-producing macrophages and B cell receptor signalling, and these processes may be associated with ACPA production, which underlies the pathogenesis of *P.g.*-triggered RA.

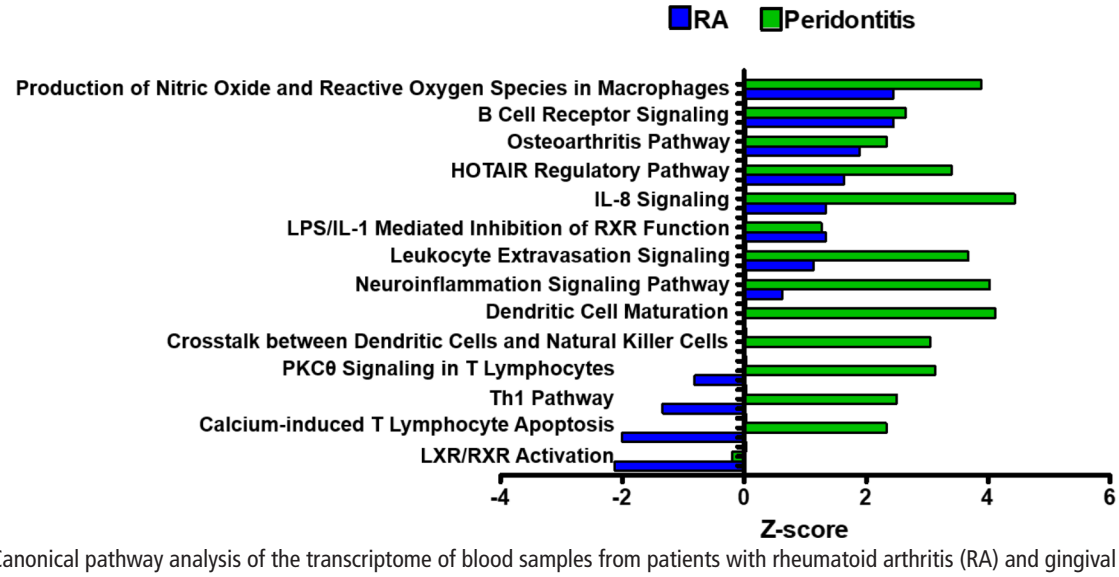


**Figure 1** Canonical pathway analysis of the transcriptome of blood samples from patients with rheumatoid arthritis (RA) and gingival tissues from patients with periodontitis. Cellular mechanisms for RA pathogenesis are labelled in blue. Among these mechanisms, pathways associated with periodontitis are labelled in green. Positive Z scores represent upregulation. Negative Z scores represent downregulation. HOTAIR, HOX transcript antisense RNA; IL, interleukin; LPS, lipopolysaccharide; RXR, retinoid X receptor; PKC, protein kinase C; Th, T helper; LXR, liver X receptor.

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## REFERENCES

1 Jenning M, Marklein B, Ytterberg J, *et al*. Bacterial citrullinated epitopes generated by *Porphyromonas gingivalis* infection-a missing link for ACPA production. *Ann Rheum Dis* 2020;79:1194–202.
2 de Pablo P, Chapple ILC, Buckley CD, *et al*. Periodontitis in systemic rheumatic diseases. *Nat Rev Rheumatol* 2009;5:218–24.
3 Li S, Yu Y, Yue Y, *et al*. Microbial infection and rheumatoid arthritis. *J Clin Cell Immunol* 2013;4.
4 Chen H-H, Huang N, Chen Y-M, *et al*. Association between a history of periodontitis and the risk of rheumatoid arthritis: a nationwide, population-based, case-control study. *Ann Rheum Dis* 2013;72:1206–11.
5 Fang FC, Frawley ER, Tapscott T, *et al*. Bacterial stress responses during host infection. *Cell Host Microbe* 2016;20:133–43.
6 Wang P, Geng J, Gao J, *et al*. Macrophage achieves self-protection against oxidative stress-induced ageing through the Mst-Nrf2 axis. *Nat Commun* 2019;10:755.
7 Chirivi RGS, van Rosmalen JWG, van der Linden M, *et al*. Therapeutic AcpA inhibits net formation: a potential therapy for neutrophil-mediated inflammatory diseases. *Cell Mol Immunol* 2020. doi:10.1038/s41423-020-0381-3. [Epub ahead of print: 20 Mar 2020].
8 Scherer HU, Huizinga TWJ, Krönke G, *et al*. The B cell response to citrullinated antigens in the development of rheumatoid arthritis. *Nat Rev Rheumatol* 2018;14:157–69.
9 Titcombe PJ, Wigerblad G, Sippl N, *et al*. Pathogenic Citrulline-Multispecific B cell receptor clades in rheumatoid arthritis. *Arthritis Rheumatol* 2018;70:1933–45.
10 Germar K, Fehres CM, Scherer HU, *et al*. Generation and characterization of Anti-Citrullinated protein antibody-producing B cell clones from rheumatoid arthritis patients. *Arthritis Rheumatol* 2019;71:340–50.
11 Tardito S, Martinelli G, Soldano S, *et al*. Macrophage M1/M2 polarization and rheumatoid arthritis: a systematic review. *Autoimmun Rev* 2019;18:102397.
12 Taub DD, Anver M, Oppenheim JJ, *et al*. T lymphocyte recruitment by interleukin-8 (IL-8). IL-8-induced degranulation of neutrophils releases potent chemoattractants for human T lymphocytes both in vitro and in vivo. *J Clin Invest* 1996;97:1931–41.
13 Lu DR, McDavid AN, Kongpachith S, *et al*. T cell-dependent affinity maturation and innate immune pathways differentially drive autoreactive B cell responses in rheumatoid arthritis. *Arthritis Rheumatol* 2018;70:1732–44.
14 Chen Z, Andreev D, Oeser K, *et al*. Th2 and eosinophil responses suppress inflammatory arthritis. *Nat Commun* 2016;7:11596.
15 Zanin-Zhorov A, Ding Y, Kumari S, *et al*. Protein kinase C-theta mediates negative feedback on regulatory T cell function. *Science* 2010;328:372–6.