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Anti-Porphyromonas gingivalis antibodies in rheumatoid arthritis: Comment on the article by Seror *et al*

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Disclosures:

Professor Paul Emery has undertaken clinical trials and provided expert advice to Pfizer,MSD,Abbvie,BMS,UCB,Roche,Novartis,Samsung,Lilly and Takeda.

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Anti-Porphyromonas gingivalis antibodies in rheumatoid arthritis: Comment on the article by Seror *et al*

We read with interest the article by Seror et al (1) which showed no difference between anti-P gingivalis antibody titers in rheumatoid arthritis (RA) patients in a large early arthritis cohort and those measured in controls. From this they concluded that the well documented association between periodontal disease (PD) and RA could be linked to bacterial species other than P Gingivalis or to a mechanism other than citrillunation.

Several studies have reported on anti-P gingivalis antibodies in relation to RA. While some have described higher anti-P gingivalis levels in individuals at risk of RA compared to controls (2-4), others have found no difference in those with established RA compared to controls (1, 5, 6). As Seror et al point out, methods for measuring anti-P gingivalis are not yet standardised and different assays detect antibodies to different protein targets. Comparing the results of antibody assays across different studies must therefore be done with some caution. While we acknowledge these data suggest RA patients cannot be distinguished from controls by anti-P gingivalis serology, we do not agree that this undermines an aetiological model involving P gingivalis and citrillunation in RA.

P Gingivalis is a key component of the 'red complex' bacteria that are synonymous with PD (7). It expresses a bacterial peptidyl-arginine deaminase (PPAD) that is able to citrillunate arginine residues in a distinct way to human PADs. Firstly, P gingivalis expresses arginine-specific gingipains (RGPs) which cleave host proteins, exposing C-terminal arginines that are then citrillunated by PPAD (8). In contrast, endogenous human PADs cannot generate C-terminal citrullines. Secondly, there is evidence that PPAD undergoes autocitrullination in RA patients (9). Both these features highlight the unique ability of P gingivalis to generate novel citrillunated peptides that could potentially break immune tolerance at the oral mucosa.

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Work using 16S ribosomal RNA pyrosequencing, including in RA patients, confirms that the oral microbiome is distinct in PD compared to controls, with P gingivalis significantly more prevalent and abundant in patients with PD (5). In line with the results from Seror et al, there was no difference in anti-P gingivalis antibody levels between these groups. As P gingivalis is a ubiquitous oral microorganism, it is not surprising that antibodies, a measure of past exposure, are found in individuals regardless of periodontal disease state. It is instead the abundance and prevalence of P gingivalis at the oral mucosa that is heightened in PD. Seror et al used DNA-DNA hybridization to detect P gingivalis in the periodontal tissue of their periodontitis controls. They found that those with detectable P gingivalis had higher levels of anti-P gingivalis antibodies and concluded that a higher titre of anti-P gingivalis is a good marker for chronic P gingivalis infection. However, this implies that their healthy control group, of whom only 16% were ever smokers, had a similar prevalence of active P gingivalis to the periodontitis patients. This would be out of keeping with previous studies (7, 10) and is difficult to accept particularly as a similar analysis in the healthy controls and RA patients was not performed.

When considering the aetiological role of P gingivalis in RA, anti-P gingivalis antibodies alone are unlikely to be informative. Simple exposure to this ubiquitous bacterium is unlikely to be sufficient to trigger autoimmunity. Instead, an increased abundance of P gingivalis in the context of active periodontal inflammation is likely to be required to generate the local citrillulination that breaks immune tolerance. As such, periodontal examination and microbiome characterisation must be important inclusions in future prospective work in this area.

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