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EDITORIAL

Periodontal disease, *Porphyromonas gingivalis*, and rheumatoid arthritis: what triggers autoimmunity and clinical disease?

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Abstract

Rheumatoid arthritis, currently regarded as a complex multifactorial disease, was initially characterized as such at the turn of the 19th century. Ever since, multiple lines of investigation have attempted to elucidate the etiological factor(s) involved in disease incidence. Genes – including those risk alleles within HLA-DR4 – have been implicated but are insufficient to explain the vast majority of cases. Several environmental factors, therefore, are being studied. Among them, the role of periodontal disease and *Porphyromonas gingivalis* in the pathogenesis of rheumatoid arthritis has attracted both clinical and bench interest given supportive epidemiologic and mechanistic data.

The notion that rheumatoid arthritis (RA) is a polygenic autoimmune disorder that requires environmental factors in order to become clinically apparent is not novel. Since the very beginning, infectious agents have been implicated. This includes early theories such as the 'oral sepsis' hypothesis, which supported the notion that periodontal infections were the true etiologic factors behind many chronic diseases. Soon after, dental extraction became a central part of the RA therapeutic armamentarium.

Over the last decade, an ever-increasing body of literature has been devoted to study the association between periodontal disease, *Porphyromonas gingivalis*, and RA. In this issue of *Arthritis Research & Therapy*, Arvikar and colleagues [1] demonstrate a positive correlation between *P. ginigivalis* antibody responses and presence/levels of anti-cyclic citrullinated peptide antibodies in a subset of patients with early RA. Moreover, subjects with serological reactivity toward *P. ginvgivalis* also tended to have higher RA disease activity as measured by Disease Activity Score in 28 Joints and Clinical Disease Activity Index. This occurred both at baseline – that is, in recently diagnosed patients who have not previously been treated with disease-modifying anti-rheumatic drugs (DMARDs) – and 12 months after initiation of therapy.

The study had several strengths. First, the authors enrolled early RA patients who were DMARD-naïve at the time of antibody measurements and clinical assessments. Second, patients were followed for a period of 1 year to address biologic and phenotypic alterations after initiation of therapy. This is of utmost importance since very few studies have addressed clinical and immunologic changes at the very onset of disease [2,3]. Too often, however, the natural history of RA is studied without considering the confounding effects of long-standing systemic inflammation or immunosuppressive therapies or both. It is almost certain that the use of DMARDs and biologics alters the quantification and behavior of multiple immune cells and proteins (including auto- and alloantibody responses), thus distorting the true understanding of disease pathogenesis. Efforts to elucidate the earliest changes in pre-clinical and clinical RA are underway [2,4].

An accumulating body of evidence suggests a role for clinical periodontal diseases in RA pathogenesis. Periodontitis was more common and severe in patients with RA compared with osteoarthritis [5], and subjects with RA had an increased likelihood of periodontitis compared with controls [6]. Multiple recent studies have specifically implicated *P. gingivalis*, a periodontopathic bacterium, as a possible triggering factor. This microorganism has gained scientific attention given its ability

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to citrullinate peptides via unique enzymatic properties conferred by peptydil arginine deiminase (*PAD*), which reportedly promotes the generation of neoantigens and the subsequent production of antibodies to citrullinated protein antigens (ACPAs). Experimentally, *P. gingivalis-PAD* is capable of citrullinating human peptides [7] and ACPAs have proven pathogenic in murine models of arthritis [8].

A decade ago, it was postulated that a specific humoral immune response to *P. gingivalis* was the actual stimulus for the development of RA [9]. Since then, multiple reports used serological methods [10,11] to correlate the generation of antibodies to *P. gingivalis* with autoimmunity (that is, ACPA antibodies) and clinical RA. Several lessons can be learned from these types of approaches. First, as in the case of reports by Arvikar and colleagues [1] and others [2,10,11], the methodology and antigens used to quantify anti-*P. gingivalis* antibodies have been heterogeneous. Prior studies used antibodies against whole-cell, bacterial lipopolysaccharide, or *P. gingivalis*-specific chaperone protein. The sensitivity and specificity of each one of these antibodies (and their measurements through different phases of disease) add to the complexity of correlating *P. gingivalis* serologic responses to RA pathogenesis. A concerted effort toward standardization is warranted in the interest of scientific validation and replication. Second, very few studies have reported the direct presence of *P. gingivalis* (or other periodontopathic bacteria) in subgingival biofilms of patients with RA. This can now be achieved without the need for laborious, classic microbiologic culture techniques. The advent of high-throughput, bacterial DNA sequencing has allowed taxonomic classification of multiple bacterial species within hundreds of samples (that is, microbiome analysis) in a matter of days.

Finally, and perhaps more importantly, virtually all studies consistently reported only a small fraction of RA patients as being exposed to *P. gingivalis* (serologically, microbiologically, or both). This can have several (and possibly complementary) explanations. It is conceivable that the overabundance of other, non-measured, periodontopathic bacteria (or the lack of protective flora or both) contributes to disease initiation. Moreover, exposure to bacterial antigenic burden at other body sites, such as the lung or the gut, may represent triggering factors for RA. The intestinal microbiome, for example, is vast and diverse. It contains 100 times more protein-coding genes than the human genome and harbors 100 trillion cells (10-fold the amount of total host human cells). Studies in animal models support the notion that the oral, lung, or intestinal microbiome (or a combination thereof) is required to develop inflammatory arthritis. This is based on the fact that rodents do not develop joint inflammation under germ-free conditions or when treated with antibiotics. It is plausible, therefore, that an alteration in the bacterial taxa of several mucosal sites (including oral, lung, and intestinal microbiomes) is required for the transition from a preclinical, autoimmune phase of RA into clinically classifiable disease.

Novel and comprehensive approaches for the study of the microbiome and the initiation of RA are now possible. Immunologic and microbiome analyses in prospective cohorts of subjects with periodontal disease and other risk factors for the development of RA (for example, first-degree relatives, discordant twins, or asymptomatic individuals with circulating autoantibodies or a combination thereof) may help elucidate some of these questions and ultimately target these organisms (or their components) as a diagnostic or even preventive strategy for RA.

Abbreviations

ACPA: Antibody to citrullinated protein antigens; DMARD: Disease-modifying anti-rheumatic drug; PAD: Peptydil arginine deiminase; RA: Rheumatoid arthritis.

Competing interests

The authors declare that they have no competing interests.

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References

1. Arvikar SL, Collier DS, Fisher MC, Unizony S, Cohen GL, McHugh G, Kawai T, Strle K, Steere AC: **Clinical correlations with *Porphyromonas gingivalis* antibody responses in patients with early rheumatoid arthritis.** *Arthritis Res Ther* 2013, **15:**R109.
2. Scher JU, Ubeda C, Equinda M, Khanin R, Buischi Y, Viale A, Lipuma L, Attur M, Pillinger MH, Weissmann G, Littman DR, Pamer EG, Bretz WA, Abramson SB: **Periodontal disease and the oral microbiota in new-onset rheumatoid arthritis.** *Arthritis Rheum* 2012, **64:**3083–3094.
3. Colin EM, Asmawidjaja PS, van Hamburg JP, Mus AM, van Driel M, Hazes JM, van Leeuwen JP, Lubberts E: **1,25-dihydroxyvitamin D3 modulates Th17 polarization and interleukin-22 expression by memory T cells from patients with early rheumatoid arthritis.** *Arthritis Rheum* 2010, **62:**132–142.
4. Demoruelle MK, Parish MC, Derber LA, Kolfenbach JR, Hughes-Austin JM, Weisman MH, Gilliland W, Edison JD, Buckner JH, Mikuls TR, O'Dell JR, Keating RM, Gregersen PK, Norris JM, Holers VM, Deane KD: **Anti-cyclic citrullinated peptide assays differ in subjects at elevated risk for rheumatoid arthritis and subjects with established disease.** *Arthritis Rheum* 2013, **65:**2243–2252.
5. Dissick A, Redman RS, Jones M, Rangan BV, Reimold A, Griffiths GR, Mikuls TR, Amdur RL, Richards JS, Kerr GS: **Association of periodontitis with rheumatoid arthritis: a pilot study.** *J Periodontol* 2010, **81:**223–230.
6. Pischon N, Pischon T, Kröger J, Gülmez E, Kleber BM, Bernimoulin JP, Landau H, Brinkmann PG, Schlattmann P, Zernicke J, Buttgereit F, Detert J: **Association among rheumatoid arthritis, oral hygiene, and periodontitis.** *J Periodontol* 2008, **79:**979–986.
7. Wegner N, Wait R, Sroka A, Eick S, Nguyen KA, Lundberg K, Kinloch A, Culshaw S, Potempa J, Venables PJ: **Peptidylarginine deiminase from *Porphyromonas gingivalis* citrullinates human fibrinogen and alpha-enolase: implications for autoimmunity in rheumatoid arthritis.** *Arthritis Rheum* 2010, **62:**2662–2672.
8. Kinloch AJ, Alzabin S, Brintnell W, Wilson E, Barra L, Wegner N, Bell DA, Cairns E, Venables PJ: **Immunization with *Porphyromonas gingivalis* enolase induces autoimmunity to mammalian alpha-enolase and arthritis in DR4-IE-transgenic mice.** *Arthritis Rheum* 2011, **63:**3818–3823.

9. Rosenstein ED, Greenwald RA, Kushner LJ, Weissmann G: **Hypothesis: the humoral immune response to oral bacteria provides a stimulus for the development of rheumatoid arthritis.** *Inflammation* 2004, **28:**311–318.
10. Mikuls TR, Thiele GM, Deane KD, Payne JB, O'Dell JR, Yu F, Sayles H, Weisman MH, Gregersen PK, Buckner JH, Keating RM, Derber LA, Robinson WH, Holers VM, Norris JM: ***Porphyromonas gingivalis*** **and disease-related autoantibodies in individuals at increased risk of rheumatoid arthritis.** *Arthritis Rheum* 2012, **64:**3522–3530.
11. Hitchon CA, Chandad F, Ferucci ED, Willemze A, Ioan-Facsinay A, van der Woude D, Markland J, Robinson D, Elias B, Newkirk M, Toes RM, Huizinga TW, El-Gabalawy HS: **Antibodies to** ***Porphyromonas gingivalis*** **are associated with anticitrullinated protein antibodies in patients with rheumatoid arthritis and their relatives.** *J Rheumatol* 2010, **37:**1105–1112.

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