Editorial

Help Stop Tooth Decay...and Prevent RA?

Among his many astute medical observations, Sir William Osler is credited with noting that "The health of the mouth is the window to the health of the body." With more than a century elapsed, this statement now appears prophetic with a rapidly expanding body of contemporary literature linking oral health with both the risk and progression of systemic disease. Several studies have now shown associations of cardiovascular disease, obstructive lung disease, and diabetes, among others, with periodontitis (PD), a bacterially mediated chronic inflammatory disease involving the gums and surrounding connective tissues. More recently, PD has been implicated as a risk factor in systemic rheumatic illness, most notably in the development and progression of rheumatoid arthritis (RA).

Snyderman and McCarty were among the first to comment on the shared attributes of PD and RA, similarities that include "self-sustaining inflammation in a fluid-filled compartment adjacent to bone" — noting that inflammatory pathways in both diseases lead to pain, swelling, and tenderness in addition to erosive destruction of adjacent bone[1]. PD and RA also share similar cellular, enzymatic, and cytokine profiles including the "overexpression" of matrix metalloproteinases and tumor necrosis factor (TNF), and share common disease risk factors that include both HLA-DRB1 alleles and cigarette smoking. In addition, therapies used in RA treatment, both tetracyclines (metalloproteinase inhibitors) and biologic response modifiers, appear to be effective in the treatment of PD[2-4]. Kasser, *et al* found that patients with RA compared to healthy controls experienced more gingival bleeding, had more missing teeth, and had more than twice as much tooth detachment[5]. Mercado and colleagues reported that RA patients exhibited increased alveolar bone and tooth loss compared to controls, although these groups had comparable degrees of dental plaque and gingival bleeding[6]. In a recent study of US veterans, we found that patients with RA were almost twice as likely to have moderate to severe PD compared to patients with osteoarthritis[7]. Additional studies, including one by our group, have shown associations of PD with measures of disease severity in RA including higher acute-phase responses, higher swollen joint counts, and worse functional scores[6,8]. Given the small number of patients in these studies and the trial designs used (predominantly cross-sectional), there remains substantial uncertainty whether the association of PD with RA is causal.

In this issue of *The Journal*, Hitchon and colleagues report findings that add further support for a potential causal role of *Porphyromonas gingivalis* in RA[9]. In their investigation involving North American Native (NAN) populations, antibody responses to the lipopolysaccharide (LPS) component of *P. gingivalis* (a major bacterial pathogen in PD) were significantly higher in patients with RA than unaffected relatives (primarily first-degree relatives) or healthy controls. Antibody responses to *P. gingivalis* LPS were also substantially higher in RA patients with anti-citrullinated protein antibody (ACPA) than in seronegative patients with RA, confirming results from a previous study conducted by our group[8]. In our prior work involving patients with established RA, we found significant correlations of IgG antibody to *P. gingivalis* lysates with select ACPA isotypes including IgM and IgG-2[8]. Extending these observations, Hitchon and colleagues also found that *P. gingivalis* antibody concentrations were significantly higher among ACPA-positive unaffected relatives than in ACPA-negative relatives ($p < 0.001$), an association that was not evident for rheumatoid factor expression. This is important because it suggests that infection with *P. gingivalis* is specifically associated with ACPA expression in the preclinical period, which is noteworthy since ACPA expression is nearly exclusive to RA and has been shown to portend a high risk for future disease development in other disease-free populations[10]. The lack of correlation of *P. gingivalis* antibody responses in the present study with smoking and measures of oral hygiene sug-

See P. gingivalis antibodies are associated with ACPA in RA patients and relatives, *page 1105*

gest that these factors do not serve as a major source of confounding.

There are limitations to the study by Hitchon, *et al* that warrant discussion, many of which are inherent to its cross-sectional study design. Questions remain about the relationship of PD and *P. gingivalis* infection with RA risk and mechanisms underpinning this possible relationship: What is the direction of this association? Does infection with PD increase risk for autoantibody "seroconversion" in unaffected relatives, individuals initially negative for ACPA? Can results from the NAN population, a population "enriched" for RA risk, be extended to other populations with lower rates of HLA-DRB1 shared-epitope positivity and perhaps lower rates of smoking? What is the clinical and biologic relevance of the various ACPA isotypes examined — autoantibodies (e.g., IgA-, IgM-ACPA) with metric properties that remain poorly defined? Does positivity for these ACPA isotypes translate into increased RA risk over time? Does immunity to *P. gingivalis* simply serve as a surrogate for clinical PD or alternative bacterial pathogens that could play a more direct causal role in RA pathogenesis? Lastly, what is the biologic relationship of PD or *P. gingivalis* infection with RA? In other words, is this relationship supported by biologic plausibility?

Speculation that RA is somehow "triggered" by an infection is not new. It has long been speculated that select infections could lead to adaptive immune responses, eventual tolerance loss, and autoantibody responses through the phenomenon of molecular mimicry. Indeed, hypotheses regarding the role of *P. gingivalis* in RA follow numerous reports examining the pathogenic functions of other select microorganisms including Mycoplasma, parvovirus B19, enteropathogens, Epstein-Barr virus, and human herpesvirus, among others. Over time, reports conclusively linking these many different organisms to RA incidence have failed to materialize and, until recently, there have been no reports linking any of these infections with ACPA expression that appears to be nearly unique to RA.

Admittedly, the "case" being made in support of a role for *P. gingivalis* infection in RA pathogenesis is built largely on circumstantial evidence. *P. gingivalis* is the only known prokaryote to express peptidylarginine deiminase (PAD) as a virulence factor, an enzyme responsible for the post-translational citrullination of arginine residues. While not homologous with human PAD, it is still conceivable that bacterially expressed PAD could help to facilitate autoantigen presentation in RA, particularly in light of data supporting the existence of multiple different citrullinated autoantigens in RA[11]. In addition to PAD expression, *P. gingivalis* also expresses lysine- and arginine-specific proteinases (so-called gingipains), which cleave various host peptides including human fibrinogen/fibrin that lead to the bleeding tendency that characterizes PD[12]. This is noteworthy since autoantibody to citrullinated fibrinogen is among the various ACPA subtypes that have been identified in RA[11]. In addition, autoantibody to citrullinated enolase could also serve as a link between *P. gingivalis* infection and RA. In efforts led by Lundberg and Venables, human enolase shows marked homogeneity with enolase expressed by *P. gingivalis*, with a sequence identity of 82% across the immunodominant peptide and 100% sequence identity in a 9 amino acid span in this region[13]. Whether *P. gingivalis*-expressed PAD and gingipains act in concert to form neoantigens in RA remains to be seen, but the work presented by Hitchon and colleagues coupled with that of other groups suggests that this may be a fruitful avenue for future research. It is possible that such investigations could pave the way for future interventions targeting PD and the eradication of *P. gingivalis* infection as an effective means of treating or even preventing RA.

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