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The association between rheumatoid arthritis and periodontitis

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The relationship between rheumatoid arthritis and poor oral health has been recognised for many decades. The association between periodontal infection and the risk of developing RA has been the subject of epidemiological, clinical and basic science research in recent times. Converging and reproducible evidence now makes a clear case for the role of specific periodontal infective pathogens in initiating, amplifying and perpetuating rheumatoid arthritis. The unique enzymatic properties of the periodontal pathogen *Porphyromonas gingivalis* and its contribution to the burden of citrullinated peptides is now well established. The impact of localized infection such as periodontitis in shaping specific anti-citrullinated peptide immune responses highlights a key area for treatment, prevention and risk assessment in rheumatoid arthritis.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease leading to synovial inflammation and destruction of cartilage and bone. RA, like many autoimmune diseases, is proposed to occur in genetically at risk individuals, in response to a trigger or triggers. Viral or bacterial infections have long

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been considered as putative triggers for this disease. Periodontitis (PD), is also a chronic inflammatory condition initiated by bacterial accumulation on the interface between the teeth and gingiva and modified by genetic, environments (eg smoking) and the host inflammatory reaction. The similarities between RA and PD were first recognized by Snyderman and McCarty [1] and since then considerable evidence has accumulated to support the concept of a strong interrelationship between these two inflammatory conditions.

The association between RA and periodontitis (PD) and the relationship of smoking to both conditions has become contextually relevant with the knowledge that immune responses to citrullinated peptides are associated RA with and likely to be pathogenic. Smoking is known to increase levels of citrullination via increases in the enzyme peptidylarginine deiminase (PAD). The opportunistic infection that characterizes PD has become particularly relevant in this context. *Porphyromonas gingivalis* (*P. gingivalis*), the major pathogen in PD is the only bacterium known to express a PAD enzyme (PPAD), and has been reported to be significantly associated with RA [2,3]. The role of PPAD in generating citrullinated bacterial and host proteins, the potential for these to interact with the host immune system in genetically at-risk individuals, and the implications for treatment will be the main focus of this review.

The link between rheumatoid arthritis and periodontitis

Rheumatoid arthritis (RA) is an autoimmune inflammatory arthritis characterised by evidence of serological autoimmunity and persistent synovial inflammation. It has a prevalence of approximately 1% with a peak incidence in pre-menopausal women. Inflammation of the synovial lining of joints results in destruction of cartilage and erosion of bone, which, if unchecked, will lead to loss of function, deformity and chronic pain. Periodontitis (PD) is the commonest described oral disease with highly variable estimated prevalence rates of up to 50–60% in most populations [4]. Opportunistic infection with bacteria within the sub-gingival biofilm is associated with periodontal destruction, which can lead to tooth loss and importantly create a significant systemic inflammatory burden. Virulence of the colonizing bacteria as well as the intensity of the host immune response is thought to contribute to the severity of the disease [5,6].

The increasing recognition of an epidemiological association between PD and RA must be considered in the context of the very high prevalence of PD in particular, the chronic nature of both conditions and shared genetic and environmental risk factors [7]. Evidence supporting a causal link has emerged from subsequent understanding of the pathogenic mechanisms underpinning both diseases, which will be discussed in later in this review. Nevertheless a range of epidemiological data examining presence and severity of both diseases as well as temporal relationships between the onset of RA and PD has driven deeper inquiry into pathogenic links. Although PD is common, patients with long-standing active RA were shown to have increased incidence of PD compared with healthy non-RA subjects [8,9]. Correspondingly RA prevalence is increased in patients with PD [10]. Indeed an increase in all systemic conditions including RA was reported in PD patients [11,12] In a study examining shared risk factors for PD and RA, Mikuls et al., recently confirmed higher prevalence of PD in 277 RA patients compared with 330 osteoarthritis controls using standardised periodontal examination [13].

The recent OSARA study examined oral health over time in outpatients with rheumatoid arthritis and found that 94% of RA patients had PD. In 46 percent of RA patients PD was described as severe [14]. Odds ratio's of having both conditions are variably estimated as being between 2:1 and 8:1 [9] depending on the criteria used to define periodontitis. These odds ratios must be considered in the context that RA has low but stable prevalence estimates whereas periodontitis prevalence estimates are highly divergent. However it is compelling that in the large US population study NHANES III, more than 50% of RA patients were edentulous [10].

Evidence supporting the association between periodontitis and RA

In addition to epidemiological data that supports the association between RA and PD, the shared environmental associations as well as the underlying biology and local pathological outcomes is striking. More than 100 genetic susceptibility loci have now been identified for RA [15]. The association