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Review

Autopathogenic correlation of periodontitis and rheumatoid arthritis

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Abstract

Recently, a number of studies have pointed to a potential relationship between periodontitis (PO) and RA and vice versa. Both diseases are characterized by chronic inflammation, osseous destruction, damage of the supporting soft tissues, similar cellular immune responses and common immunogenetic findings. Although a definite, methodological report associating these diseases is missing from the literature, it is possible that both diseases share a common aetiopathogenic background. This background includes the post-translation modification citrullination, which guides the conversion of the amino acid arginine to citrulline in certain self-proteins, generating neo-epitope structures. This results in reduced self-tolerance, development of autoimmunity and the production of ACPAs. The current hypothesis suggests that certain oral bacteria induce the citrullination of proteins under the action of the enzyme peptidyl arginine deiminase (PAD), which exists in both *Porphyromonas gingivalis* and inflammatory cells. Antibodies against citrullinated proteins and peptides constitute a common serological finding in both RA and PO. The aim of this review is to map the immunological and serological profiles of PO, and to unveil the parameters that connect PO with the appearance of RA at clinical, prognostic and pathogenetic levels. Until now, there have been no reports sufficiently mapping the immunological profile of PO and defining its aetiopathogenic connection with RA, although a similarity between the immunological profile of PO and RA is highly expected.

Key words: Periodontitis, Rheumatoid arthritis, Anti-citrullinated protein antibodies, Peptidyl arginine deiminase, Antibodies to cyclic citrullinated peptides.

Introduction

Unlike RA, the immunological profile of periodontitis (PO) and a possible common aetiopathogenesis of the two entities have not been studied extensively in the literature. During recent years, there has been increasing evidence suggesting a correlation between RA and PO. A number of well-conducted studies have shown that patients with RA have an increased possibility of expressing mild to severe PO, compared with healthy people [1]. In this regard, certain studies have shown a 4-fold incidence of RA in patients with PO [2].

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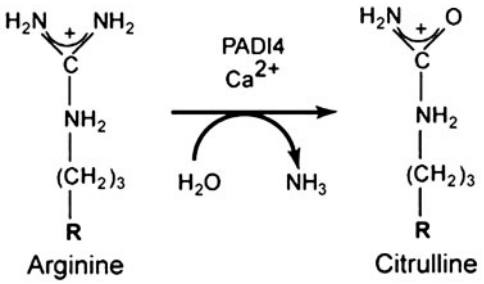
The clinical correlation (or comorbidity) of the two diseases possibly relies on a common aetiololgy and pathology. The fact that PO and RA have pathological and immunological resemblances supports the formulated hypothesis [3]. Both diseases are characterized by chronic inflammation, osseous erosions, periosteal soft tissue damage, similar humoral and cellular immune response and common immunogenetic background [3]. Nevertheless, more well-designed studies and randomized clinical trials are needed to elucidate this correlation.

The incidence of RA is ~1%, characterized by synovitis, fibrous deposition and damage of the cartilage, erosions of the subchodrial bone and periosteal soft tissue inflammation [4]. The laboratory findings include acute-phase reactants (i.e. elevated ESR and CRP) and specific autoantibodies (RF, anti-CCP and ANA). A similar serological profile in PO is under investigation.

PO is the most common infectious diseases affecting 10–60% of the adult population, according to different diagnostic criteria [5], consisting of inflammation of the

Fig. 1 Post-translational modification of arginine by PADI4.



gingiva (gingivitis) and bacterial infection of the periodontium (PO). In most cases, there is stimulation of immune cells, production of specific autoantibodies, participation of specific HLAs, mobilization of immune mediators and cytokines such as IL-1β, TNF-α and IL-6, resulting in tissue damage, which in turn produces enzymes such as collagenolytic matrix metalloproteinases (MMPs) [6, 7]. The above-mentioned molecules play an interventional role in the pathogenesis of RA [8]. Many studies today have focused on the immunological profile of PO, which is of particular interest.

The present hypothesis is that oral bacteria induce the citrullination of peptides that play a major role in the mechanism of autoimmunity [9]. More specifically, they contribute to the breakdown of self-tolerance and the production of specific anti-CCPs or ACPAs [10]. The term citrullination of a protein or peptide reflects the conversion of the amino acid arginine to citrulline, which takes place during inflammation, under the action of a specific enzyme, the peptidyl arginine deiminase (PAD) (Fig. 1). This post-translational process provides neo-antigenic properties to the protein molecule. In RA, antibodies to citrullinated proteins, such as filagrine, keratine, fibrine, vimentin, fibrinogen as well as antibodies to CCP (anti-CCP) have been reported and have been accepted as specific for the disease [10].

Mechanisms of action of the two diseases

The role of infections in PO

PO is caused by bacteria affecting the peridental membrane, i.e. *Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, Bacteroides forsythus, Prevotella melaninogenica, Prevotella intermedia* and *Eubacterium nodatum*. Increased levels of immunoglobulin G and A (IgG and IgA) against certain bacteria colonizing the oral mucosa are found in the synovium of patients with RA. This fact may suggest that these bacteria and their antibodies act as a possible aetiopathogenic mechanism in RA [10–12].

In particular, *P. gingivalis* is a Gram-negative anaerobic immobile bacterium with a possible involvement in the development of PO in adults. In experimental models, implantation of *P. gingivalis* in the oral cavity seems to play a crucial role in the pathogenesis of PO [13] and it is recognized as the main pathogenic organism for the development of the disease. *Porphyromonas gingivalis* is the only known bacterium expressing the PAD enzyme [14]. Although it is not a complete homologue of the human PAD, this enzyme is responsible for the post-translation and conversion of arginine to citrulline, leading to the production of anti-CCP antibodies [15]. These antibody reactions seem to be specific almost exclusively to RA patients [16]. The ability of *P. gingivalis* to express the PAD enzyme, as shown by recent data [9, 12], is probably indicative of the concept that infection by this organism may induce and accelerate RA, facilitating the presence of neo-antigens and the production of disease-specific autoantibodies to citrullinated epitopes.

Anti-CCP antibodies

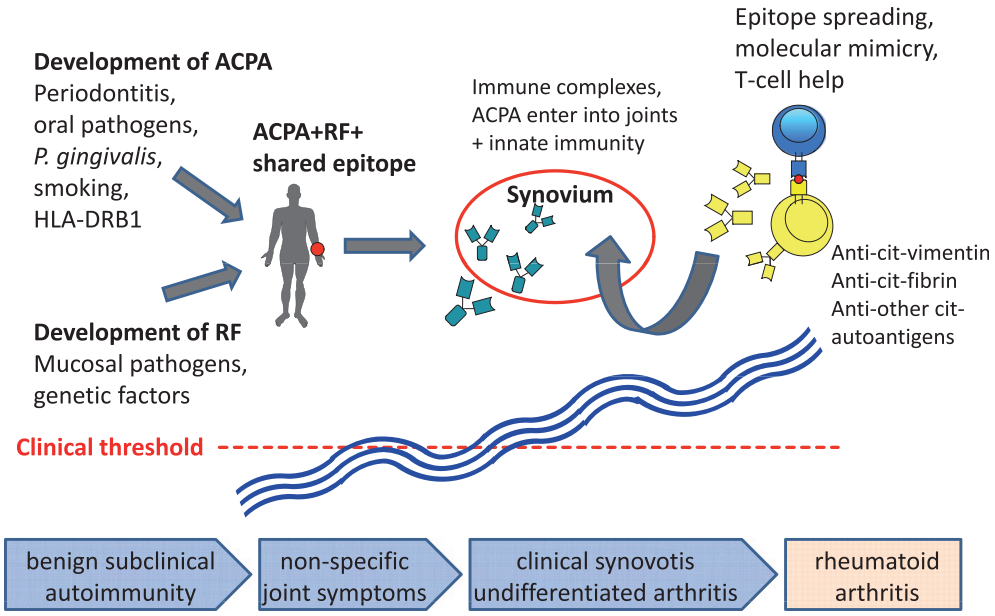
Anti-CCP antibodies are specific markers for RA, originally described as antibodies targeting post-translationally modified filaggrin [17, 18]. They represent the most specific autoantibodies of RA, since they are found in ~80% of the sera of patients with RA, with a 99% specificity [19]. They are also found in early RA and can predict the severity of the disease. They are produced in the inflammatory synovium, denoting their role in the local inflammation and possibly in the systemic appearance of the disease. In animals with induced collagen arthritis, anti-CCP antibodies and antibodies to Type II collagen are found early after immunization. They bind to citrullinated fillagrin and fibrinogen leading to inflammatory arthritis [9]. The intracellular and extracellular deposition of fibrin in synovitis in RA patients is well documented [20]. A recent proteomic study showed that fibrinogen was the main citrullinated autoantibody target in the synovium of patients with RA [21].

Correlation between anti-CCP and *P. gingivalis* antibodies

As mentioned above, infection with *P. gingivalis* is of main importance in PO. Recent studies have shown that increased titres of anti-*P. gingivalis* antibodies in RA patients are correlated with certain anti-CCP antibody isotypes (mainly anti-CCP IgM and IgG2-specific subtypes for RA) [22]. *Porphyromonas gingivalis* infection in these patients, accompanied by elevated CRP levels, could possibly affect inflammation pathways of native and specific immunity in RA patients [22]. This correlation could be of particular interest, since anti-CCP IgG2 antibodies are predominantly elevated in *P. gingivalis* infection [23].

As already noted, *P. gingivalis* is the only infectious prokaryotic organism producing PAD, causing deimination of arginine of the fibrin that is present in PO [24]. Respectively, human PAD has the same action in joints. These modified antigens of the synovium could be the target of autoantibody production, triggered by oral infections initiated by *P. gingivalis*. This is of interest, since α- and β-citrullinated chains of fibrin are considered targets for pathogenic autoantibodies in RA [25].

FIG. 2 Proposed model for the pathogenesis of RA. In a asymptomatic pre-clinical stage, people with the appropriate genetic background develop ACPAs under the action of *P. gingivalis*. These antibodies trigger the breakdown of immune tolerance leading to the appearance of RA.



PAD

Post-translation citrullination of arginine is achieved through the action of PAD, which is an important common enzyme of human cells and the *P. gingivalis* bacterium. In humans PAD exists in five isoforms, with Isoform 4 (PADI4) being the most important for autoimmunity. PADI4 has been mapped in the locus 1p36 of the human chromosome, sharing 17 single nucleotide polymorphisms and has a strong association with susceptibility to RA in the Japanese population [26]. PADI4 is expressed in many cells, such as T and B lymphocytes, neutrophils, eosinophils, monocytes and NK cells. It is also present (as a protein) in macrophages of the synovia. Normally, PADI4 enzyme is inactive but in case of oxidative stress or during apoptosis, calcium enters the cells activating this enzyme, inducing the citrullination of vimentin, fibrin, collagen and α-enolase, and therefore increasing their antigenicity. These modified proteins are recognized by ACPAs, which are found in >80% of RA patients [9, 27]. Moreover, the IgG autoantibodies produced can recognize this enzyme itself [28–30].

Substantial genetic basis (immunogenetic characteristics)

Risk factors in RA and PO are strongly associated with certain histocompatibility antigens, especially HLA-DR4 [31, 32]. The most prominent correlation of RA and PO is associated with Region 70–74 of the third hypervariable region of HLA-DRB1 gene [32, 33]. The so-called shared epitope of RA contains the amino acids Q/R,K/R,R,A,A in the peptide binding pocket P4 of the MHC class II molecule and appears mainly in alleles 0401, 0404, 0408 in the Caucasian population and allele 0405 in Asian people. The same genetic loci (0401, 0404, 0405 and 0408) have been previously correlated with rapidly progressing PO, indicating that the two disease states may share common immunogenetic characteristics [33]. Due to the positively charged amino acids that exist in the common epitope, pocket P4 has the potential to interact with neutral or negatively charged amino acid side chains of the antigenic peptide that binds MHC class II. On the other hand, binding of positively charged side chains (like that of arginine) in pocket P4 is strongly inhibited. The conversion of the positively charged amino acid arginine to the polar—but uncharged—amino acid citrulline in the antigenic peptide, adds the ability for this residue to bind pocket P4 and therefore to interact efficiently with MHC class II. A recent study with transgenic HLA-DRB1*0401 mice revealed that the conversion of arginine to citrulline in antigenic peptides activates $CD4^+$ T cells, indicating that there is an important pathogenetic mechanism, in which the common epitope of RA can recognize the citrullinated autoantigens in complex with HLA-DRB1 molecules of RA patients [34].

A pathogenetic model of RA

The combination of all remarks made above can lead us to a realistic model for the pathogenesis of RA (Fig. 2). Based on these observations, in an asymptomatic pre-clinical state, infection with *P. gingivalis* triggers the production of autoantibodies (ACPA and RF) in genetically predisposed people. There is also evidence that ACPAs

are detected before the presence of RF and may be of diagnostic value in relation to the appearance of RF [35]. These antibodies can be detected even 2.5–4 years before the clinical onset of RA, in the majority (2/3) of patients [35]. Consequently, RF favours the creation of immune complexes that contain ACPAs that can enter the inflammatory joint through the joint micro-vessels [36]. In the joint, the specificity of ACPAs is enhanced through epitope spreading to other citrullinated auto-antigens, such as fibrinogen and vimentin [37]. The presence of the latter coincides with the clinical manifestations of the disease.

Conclusions

Taking together the above presented data, it appears that there are common mechanisms in the immunopathogenesis, immunopathology and immunogenetics of RA and PO. *Porphyromonas gingivalis* (the aetiological agent of PO) seems to be capable of inducing citrullination of host proteins, converting them to autoantigens. These modified proteins, under a common immunogenetic background, can be recognized by the immune system, triggering an inflammatory process, associated with the clinical manifestations of the two diseases. The immunopathogenic mechanisms connecting PO with RA and vice versa, as well as the immunological and inflammatory profile of PO, need to be further elucidated.

Rheumatology key messages

- Common mechanisms are implicated in the pathogenesis of RA and PO.
- *Porphyromonas gingivalis* may play a crucial role in the breakdown of immune tolerance via citrullination and neo-epitope formation.

Disclosure statement: The authors have declared no conflicts of interest.

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