Periodontitis and rheumatoid arthritis

de Smit, Menke

CHAPTER

06

General Discussion

Periodontitis and rheumatoid arthritis: what do we know?

Menke de Smit[1], Johanna Westra[2], Elisabeth Brouwer[2], Koen Janssen[3], Arjan Vissink[3] and Arie Jan van Winkelhoff[1, 4]

[1]Center for Dentistry and Oral Hygiene, University of Groningen, University Medical, Center Groningen, Groningen, The Netherlands

[2]Department of Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[3]Department of Oral and Maxillofacial Surgery, University of Groningen, University, Medical Center Groningen, Groningen, The Netherlands

[4]Department of Medical Microbiology, Center for Dentistry and Oral Hygiene, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Journal of Periodontology 2015 Sep;86(9):1013-9. doi: 10.1902/ jop.2015.150088. Epub 2015 May 13.

Introduction

In the field of rheumatology there is currently much attention for possible causality between periodontitis and rheumatoid arthritis (RA). Systemic inflammatory and infectious challenges have long been considered to be involved in triggering rheumatoid factor (RF), the first important biomarker for diagnosis and prediction of RA. Later, another auto-antibody system, anti-citrullined protein antibodies (ACPA), was found to be more specific for RA. These antibodies can be present before the disease becomes symptomatic [1]. Why ACPA and RF are induced as well as their role in RA development is still unclear. The relation between periodontitis and RA is not well understood. On one hand, systemic manifestation of increased 'total inflammatory burden' through periodontitis has been documented. On the other hand, infection with *Porphyromonas gingivalis* specifically has been suggested to play a role a because of its unique capacity of protein citrullination [2, 3].
Because causality is ultimately tested in longitudinal cohort studies that do currently not exist for periodontitis and RA, in this commentary the Bradford Hill [4] criteria are applied on existing literature to assess causality as most likely interpretation of this association.

1. Strength and consistency

Quantitative studies on the association between periodontitis and RA performed thus far are mostly case-control studies with a relatively low sample size. Nineteen of these studies, representing participants from different ethnic backgrounds, were included in a recent systematic review [5]. It was concluded that patients with RA, compared to those without RA, have a significantly higher incidence of periodontitis and a higher number of missing teeth. A recent case-control study explored the degree to which the association is affected by shared genetic and/or environmental factors [6]. After multivariable adjustments, including positivity for Human Leucocyte Antigen (HLA)-DRB1 shared epitope (SE) alleles, ever smoking, age, sex, race/ethnicity, body mass index, self-reported diabetes mellitus, marital status, presence of oral dryness, and education), the incidence of periodontitis remained significantly higher in ACPA seropositive RA patients than in controls (odds ratio 1.6). The association between periodontitis and RA is thus relatively consistent; however the strength of the association is uncertain.

2. Biological plausibility

Certain genetic, hormonal, infectious and environmental risk factors, such as smoking, can contribute to a susceptibility background against which RA can develop. In susceptible individuals, deregulation of the immune system occurs and can present itself with formation of autoantibodies such as RF and ACPA, which can be present before the disease becomes symptomatic [1]. Whether and why progression to the symptomatic phase occurs is unknown, but theoretically a 'second hit' could be necessary. In this 'two hit' model, the 'first hit' is the induction of ACPA formation, the 'second hit' is the induction of arthritis and expression of citrullinated antigens in the inflamed joint [7, 8] (Fig. 1, page 93).

ACPA production may be induced in inflamed periodontium

It has been hypothesized that initiation of ACPA production occurs at inflamed mucosal surfaces of lungs and periodontium [9]. Inflamed periodontium contains citrullinated proteins [10] and ACPA have been found in the inflammatory exudates [11]. Independent of smoking status, periodontitis patients and patients with lung mucosal inflammation (e.g., bronchiectasis) without RA have hi-

gher serum ACPA levels compared to healthy controls, although lower than in RA patients [12-15].
In addition, it has been suggested that ACPA production is induced by the periodontal pathogen *Porphyromonas gingivalis (P. gingivalis)*, being unique in expressing a variant of the deiminating enzyme necessary for protein citrullination, peptidyl arginine deiminase (PAD) [2, 3]. *P. gingivalis* PAD (PPAD) is able to citrullinate endogenous as well as human proteins, thereby creating antigens that have been presumed to initiate the ACPA response in RA [16].
ACPA in RA include antibodies against citrullinated histones [17]. Histone citrullination is a common event during neutrophil activation and neutrophil death induced by different pathways, including apoptosis and neutrophil extracellular trap (NET) formation. NETs are increased in RA and are a source of citrullinated autoantigens [18]. Neutrophils from patients with periodontitis have been shown to be hyperreactive in terms of baseline, unstimulated generation and release of extracellular reactive oxygen [19]. As NET release is known to be dependent upon production of extracellular reactive oxygen, periodontal disease may be associated with excessive production of NETs, i.e., in a process triggered initially by the response of neutrophils to plaque bacteria. High and concentrated levels of NET associated molecules could lead to a localized chronic inflammatory response, potentially followed by an autoimmune response in genetically prone persons [20].
Recently, Romero et al. [21] identified a different citrullination pattern in PAD expressing RA synovial fluid cells (neutrophils and monocytes), which they termed cellular hypercitrullination because of the broad spectrum of citrullination across the entire range of proteins. Cellular hypercitrullination is induced by two immune-mediated membranolytic pathways, mediated by perforin and the membrane attack complex both leading to calcium influx. These data are supported by Neeli et al. [22], who showed that in human neutrophils PAD4 induces histone citrullination in the presence of calcium ionophore. Up to now, it is unknown whether cellular hypercitrullination is present in inflamed periodontium.

Mutual exacerbation of inflammatory responses

Another interpretation of the 'two-hit' model is that of mutual exacerbation: periodontitis serves as 'first hit', while an (unknown) arthritrogenic hit induces RA ('second hit') that leads, in susceptible individuals, to mutual exacerbation of the inflammatory responses mediating self-perpetuating tissue destruction in both the joint and the periodontium [8] (Fig. 1, page 93).
Neutrophils are the major cell type involved in periodontal inflammatory responses [20]. Besides providing a source of citrullinated autoantigens, neutrophils can cause tissue destruction through release of degradative enzymes (e.g., matrix metalloproteinases) and cytotoxic substances such as extracellular reactive oxygen. Neutrophils indirectly mediate destructive effects by chemotactic recruitment of T-helper 17 (Th17) cells. Th17 cells selectively produce the pro-inflammatory cytokine IL-17 which is crucial for host defense against extracellular pathogens [23]. Uncontrolled Th17 activity has been implicated in joint inflammation and bone destruction in RA, both at onset and in established disease [24, 25]. Presence of IL-17 and Th17 cells in human periodontitis may be associated with disease severity, possibly after activation of innate immune cells by *P. gingivalis* [26]. How this response regulates inflammation-mediated bone destruction has not been fully elucidated (see for illustration of possible mechanisms Hajishengallis et al. [27]).
In both periodontitis and RA, osteoclasts are predominantly activated by mechanisms dependent on upregulation of receptor activator of nuclear factor κB ligand (RANKL), a member of the tumor necrosis factor (TNF)

cytokine family that is also implicated in RA [28]. Mechanisms that underlie chronic joint inflammation in RA have not been clarified, although there is some evidence for both a T-cell dependent autoimmune mechanism and a more progressive fibroblast mediated chronic inflammation [29]. Th17 cells are recognized as effective B-cell helpers for antibody responses in inflammatory conditions [27]. B-cells constitute, along with T-cells, a major source of membrane-bound and secreted RANKL in the periodontal lesions (see for illustration Hajishengallis et al. [27]).

3. Temporal relationship

In both interpretations of the 'two-hit model', periodontitis precedes RA. Commonly, more advanced forms of periodontitis are present at disease onset in patients with new-onset RA [30, 31]. A recent nationwide, population-based case-control study using longitudinal administrative data found an association between a history of periodontitis and newly diagnosed RA in Taiwan (odds ratio 1.2) [32].

4. Specificity regarding *Porphyromonas gingivalis*

The PPAD gene is highly conserved, ubiquitous in *P. gingivalis* and absent in *P. gingivalis* related species (chapter 5). We found no indications that RA patients carry a different PPAD *P. gingivalis* variant than patients without RA (chapter 5). Studies on oral colonization by *P. gingivalis* have shown no difference in subgingival *P. gingivalis* distribution in patients with or without RA independent of periodontal status, detection techniques and RA disease duration [6, 30, 31, 33]. However, DNA of periodontal pathogens has been detected in synovial fluid of RA patients [34]. Of five different periodontal pathogens assessed, only DNA of *P. gingivalis* was more frequently detected in synovial fluid of RA patients than in synovial fluid of non-RA controls [35].

According to the hypothesis that *P. gingivalis* contributes to ACPA production, the association of *P. gingivalis* presence and serum ACPA levels has been assessed. In new-onset RA patients, subgingival presence of *P. gingivalis* was not correlated with ACPA levels as determined using the diagnostic anti-cyclic citrullinated peptide 2 (anti-CCP2) test [30]. In established RA patients, presence of subgingival *P. gingivalis* was not of influence on ACPA levels, but increased reactivity against several citrullinated peptides of fibrinogen, fillagrin, clusterin, histone 2B and apolipoprotein was found when subgingival *P. gingivalis* was present [6, 33].
In periodontitis patients without RA, we found no differences in ACPA levels between *P. gingivalis* positive and –negative periodontitis patients [15], in contrast to Lappin et al. [12] who found that serum ACPA levels in periodontitis patients carrying subgingival *P. gingivalis* were higher compared to periodontitis patients without subgingival *P. gingivalis*. The relatively low patient numbers in both studies and different detection techniques of *P. gingivalis* and ACPA may account for this discrepancy.
Levels of serum anti-*P. gingivalis* antibodies showed no differences in a large cohort of RA patients and a cohort of osteoarthritis control patients [6]. A study in Japanese patients with RA showed higher anti-*P. gingivalis* antibody levels compared to age-, sex-, smoking status-, and periodontal condition-balanced healthy controls [36]. Independent of *P. gingivalis* distribution, we observed a more robust antibody response against *P. gingivalis* in established RA patients with severe periodontitis than in non-RA controls with the same periodontal status [33]. The role of the antibody response in periodontitis is not fully understood, but it may be not protective [27]. No differences in anti-*P. gingivalis* antibody levels were found between ACPA and/or RF seropositive arthralgia patients, who developed or did not develop RA within 2 years follow-up [37].
In established RA patients a weak correlation

between ACPA levels and anti-*P. gingivalis* antibody levels has been found [6, 33]. Nevertheless, anti-*P. gingivalis* antibody levels were found to be significantly higher in children with ACPA positive juvenile idiopathic arthritis compared to children with ACPA negative juvenile idiopathic arthritis, while no differences were noted for anti-*Prevotella intermedia* anti-*Fusobacterium nucleatum* antibody levels [38].

5. Dose–response relationship

A dose–response pattern in the association between severity of periodontitis and RA development was found in a Taiwanese population based on longitudinal administrative data [32]. Also, a large case-control study by Mikuls et al. [6] revealed that presence of periodontitis was associated with increased swollen joint counts, greater RA disease-activity according to the 28-joint Disease-activity Score (DAS28). We showed an association between severity of periodontitis and severity of RA [33]; RA patients with severe periodontitis had significantly higher DAS28 scores than RA patients with no or moderate periodontitis.

Experimental evidence in humans on the effect of periodontal treatment on RA disease-activity is limited. Only four studies met the inclusion criteria according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and were included in the recent meta-analysis of Kaur et al. [39] on the effect of non-surgical periodontal therapy on RA disease activity measured by clinical (DAS28) and laboratory parameters (ESR, TNF-α and CRP levels). These studies generally had a small sample size and a relatively short follow up period (up to 6 months). Microbiology was not assessed; except for one study that measured serum anti-*P. gingivalis* antibodies. Although these studies are considered preliminary and indicate the need for further large-scale intervention studies, they reported a beneficial effect of periodontal therapy on laboratory RA parameters and clinical symptoms of RA.

6. Experimental evidence

The most widely studied model of RA is collagen-induced arthritis (CIA) in genetically susceptible mice. Balb/c mice with pre-existing periodontitis, induced by oral inoculations of *P. gingivalis*, developed more severe CIA at a faster rate compared to CIA mice without periodontitis [40]. Micro-CT analysis of joint and periodontal bone loss provided evidence for a bidirectional relationship between periodontitis and arthritis; mice with CIA only showed alveolar bone loss, whereas mice with periodontitis only showed bone loss within radiocarpal joints [40]. The severity of adjuvant arthritis in Dark Agouti rats was increased when there was a pre-existing extra-synovial chronic inflammatory lesion induced by subcutaneous sponges impregnated with heat-killed *P. gingivalis* [41]. No evidence of arthritis development occurred in Dark Agouti rats with a *P. gingivalis* extra synovial inflammatory lesion only, however, using computer assisted morphometric analysis, periodontal bone loss after adjuvant arthritis induction was seen in Lewis rats as measured on defleshed jaws [42].

Experimental evidence for involvement of periodontitis in pathogenesis of RA via cellular immunity comes from a murine model of T-cell–dependent experimental arthritis. Periodontitis induced by oral inoculations with *P. gingivalis* and *Prevotella nigrescens* significantly aggravated severity of CIA characterized by increased arthritic bone erosion in DBA/1 mice via induction of an antigen specific Th17 response [43]. A model in which experimental periodontitis and arthritis were co-induced in an inflammation-prone mouse strain using oral inoculations with *Aggregatibacter actinomycetemcomitans* and *P. gingivalis* in pristane-induced arthritis showed that co-induction in control mice did not alter the course of both periodontitis and arthritis. It was concluded that the interaction between periodontitis and arthritis in

mice involves a shared hyper-inflammatory genotype and functional interferences in innate and adaptive immune responses [44]. Experimental evidence for PPAD as key player in the link between periodontitis and RA comes from aggravation of CIA in DBA/1 mice, which appeared dependent on the expression of PPAD [45]. Increased serum ACPA levels were measured after infection with wild type *P. gingivalis* W83 as compared to mice infected with *P. gingivalis* W83 with PPAD deletion. Moreover, at the site of infection with wild type strain higher levels of citrullinated proteins were found as compared to the site of infection with the PPAD knock-out strain. These results were confirmed by Gully et al. [46] using another murine model for experimental periodontitis and another *P. gingivalis* strain (W50); in BALB/c mice, the extent of CIA was significantly reduced in animals exposed to prior induction of periodontal disease through oral inoculation of a PPAD knock-out *P. gingivalis* W50 strain versus prior periodontal infection with the *P. gingivalis* W50 wild type stain. Furthermore, serum ACPA tended to be lower in mice prior infected with PPAD-deficient *P. gingivalis* compared to ACPA levels in CIA mice with periodontitis induced by the wild type strain.

7. Coherence

Animal models have shown that pre-existing periodontal infection (first hit) leads to exacerbation of arthritis after an arthritogenic hit (second hit) [40, 41]. In the same animal models, a bidirectional relationship between experimental periodontitis and experimental arthritis existed, e.g., experimental arthritis leads to alveolar bone loss, and experimental periodontitis leads to joint inflammation [40-42]. This is in concordance with observations that newly diagnosed and early RA patients have more frequently periodontitis and more periodontal attachment loss compared to controls [30-32]. In human periodontitis patients joint inflammation has not been systematically assessed.

Mutual exacerbation of the inflammatory responses in animal experiments, where both diseases co-existed, was shown to involve Th17 mediated immunity and to be dependent on a shared hyperinflammatory genotype [43, 44]. The correlation of RA disease-activity with the severity of periodontitis in humans [33] can probably be contributed to mutual exacerbation of inflammatory responses of both diseases. The importance of Th17 mediated immunity is increasingly acknowledged in human RA and periodontitis [24, 26] while gene polymorphisms within the IL-1 gene cluster are associated with cytokine levels in patients with periodontitis and in patients with RA, but not in healthy controls [47]. The latter supports the hypothesis of a shared genetic background for cytokine profiles [47]. IL-10 gene polymorphisms are also suggested to contribute to susceptibility for both RA and periodontitis. Three of several polymorphisms of IL-10 have been studied in some detail regarding to RA susceptibility. Meta-analysis of twenty-two relevant studies on these IL-10 polymorphisms, all located in putative regulatory regions of the gene promoter, suggest that these IL-10 polymorphisms contribute to susceptibility of RA in European, Asian, and Black populations [48]. Recently, an IL-10 polymorphism, also located in the genetic region upstream of IL-10, was validated as a candidate gene in aggressive periodontitis in European patients [49].

Animal experiments have shown that there is an important role for PPAD in protein citrullination, ACPA formation and development and aggravation of experimental arthritis [45, 46]. There are, however, no differences in PPAD gene and endogenous citrullination patterns of *P. gingivalis* isolated from patients with or without RA (chapter 5). Also, oral colonization by *P. gingivalis* is not different in RA patients compared to patients without RA, independent of periodontal status, detection techniques and RA disease duration [6, 30, 31, 33]. At this moment the relevance of PPAD in priming autoimmunity and RA development in humans is not clear.

8. Analogy

Infections have been shown to be highly associated with the onset of systemic lupus erythematosus (SLE), a chronic destructive autoimmune disease characterized by immune dysregulation and hyperproduction of different autoantibodies. Particularly Epstein-Barr virus (EBV), parvovirus B19, retrovirus, and cytomegalovirus (CMV) infections might play a pathogenetic role, however, the etiopathogenesis of SLE is far from being completely elucidated [50]. Viral (e.g., parvovirus B19, EBV and CMV) and microbial (e.g., *Campylobacter*) infections play a role in acute arthritis, but the role of infection in the development of RA needs further prospective controlled studies [51]. Approximately 10–20% of patients with early RA have serological evidence of recent infection, however, no single infectious agent is predominant, which indicates that total infectious exposure can represent a risk factor that could trigger RA [51].

Summary

From an epidemiological point of view, RA patients have a higher incidence of periodontal disease than subjects without RA. In addition, there is a dose–response pattern in the association between the severity of periodontitis and RA disease-activity.
There are indications that periodontitis precedes RA, but there is yet no evidence available to show that *P. gingivalis* plays a direct role in this temporal relationship. The role of the unique characteristic of citrullination by *P. gingivalis* remains unexplained. In animal models however, periodontal pathogens and PPAD play a distinct role in development and aggravation of experimental arthritis.
Although the role of periodontal pathogens in RA remains speculative, a causative role for periodontitis as a chronic inflammatory disease caused by infectious agents in RA seems biologically plausible. Considering the great variety in disease manifestation of both periodontitis and RA, a causal relationship, if existing, may only be present between certain forms of periodontitis and RA.

Future perspectives

More evidence in humans is needed to rate the association between periodontitis and RA in susceptible individuals. It has to be mentioned that when systemic effects are subtle, determining cause-and-effect mechanisms is complicated. Therefore, it is worthwhile to assess the influence of periodontitis on arthritis development in prospective follow-up studies with distinct and well described patient groups with a minimum of confounding factors. Given the complex etiology of periodontitis and RA, periodontitis patients and patients at risk for developing RA should be assessed at the microbiological level, based on the presence of oral dysbiotic microbial communities [52], and should be assessed for genetic factors that may predispose to or protect from disease.

References

(1) Nielen MM, van Schaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, Habibuw MR, Vandenbroucke JP, Dijkmans BA: Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum 2004, 50:380-386.

(2) 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.

(3) McGraw WT, Potempa J, Farley D, Travis J: Purification, characterization, and sequence analysis of a potential virulence factor from Porphyromonas gingivalis, peptidylarginine deiminase. Infect Immun 1999, 67:3248-3256.

(4) Hill AB: The environment and disease: association or causation? Proc R Soc Med 1965, 58:295-300.

(5) Kaur S, White S, Bartold PM: Periodontal disease and rheumatoid arthritis: a systematic review. J Dent Res 2013, 92:399-408.

(6) Mikuls TR, Payne JB, Yu F, Thiele GM, Reynolds RJ, Cannon GW, Markt J, McGowan D, Kerr GS, Redman RS, Reimold A, Griffiths G, Beatty M, Gonzalez SM, Bergman DA, Hamilton BC,3rd, Erickson AR, Sokolove J, Robinson WH, Walker C, Chandad F, O'Dell JR: Periodontitis and Porphyromonas gingivalis in patients with rheumatoid arthritis. Arthritis Rheumatol 2014, 66:1090-1100.

(7) de Vries RR, Huizinga TW, Toes RE: HLA and RA revisited: citrullinated food for the SE hypothesis, the DR6 effect, and NIMA. Hum Immunol 2006, 67:454-459.

(8) Golub LM, Payne JB, Reinhardt RA, Nieman G: Can systemic diseases co-induce (not just exacerbate) periodontitis? A hypothetical "two-hit" model. J Dent Res 2006, 85:102-105.

(9) Perry E, Kelly C, Eggleton P, De Soyza A, Hutchinson D: The lung in ACPA-positive rheumatoid arthritis: an initiating site of injury? Rheumatology 2014, 53:1940-1950.

(10) Nesse W, Westra J, van der Wal JE, Abbas F, Nicholas AP, Vissink A, Brouwer E: The periodontium of periodontitis patients contains citrullinated proteins which may play a role in ACPA (anti-citrullinated protein antibody) formation. J Clin Periodontol 2012, 39:599-607.

(11) Harvey GP, Fitzsimmons TR, Dhamarpatni AA, Marchant C, Haynes DR, Bartold PM: Expression of peptidylarginine deiminase-2 and -4, citrullinated proteins and anti-citrullinated protein antibodies in human gingiva. J Periodontal Res 2013, 48:252-261.

(12) Lappin DF, Apatzidou D, Quirke AM, Oliver-Bell J, Butcher JP, Kinane DF, Riggio MP, Venables P, McInnes IB, Culshaw S: Influence of periodontal disease, Porphyromonas gingivalis and cigarette smoking on systemic anti-citrullinated peptide antibody titres. J Clin Periodontol 2013, 40:907-915.

(13) de Pablo P, Dietrich T, Chapple IL, Milward M, Chowdhury M, Charles PJ, Buckley CD, Venables PJ: The autoantibody repertoire in periodontitis: a role in the induction of autoimmunity to citrullinated proteins in rheumatoid arthritis? Ann Rheum Dis 2014, 73:580-586.

(14) Perry E, Stenton C, Kelly C, Eggleton P, Hutchinson D, De Soyza A: RA autoantibodies as predictors of rheumatoid arthritis in non-CF bronchiectasis patients. Eur Respir J 2014, 44:1082-1085.

(15) Janssen KM, de Smit MJ, Brouwer E, de Kok FA, Kraan J, Altenburg J, Verheul MK, Trouw LA, van Winkelhoff AJ, Vissink A, Westra J: Rheumatoid arthritis-associated autoantibodies in non-rheumatoid arthritis patients with mucosal inflammation: a case-control study. Arthritis Res Ther 2015, 17:174-184.

(16) 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.

(17) Pratesi F, Dioni I, Tommasi C, Alcaro MC, Paolini I, Barbetti F, Boscaro F, Panza F, Puxeddu I, Rovero P, Migliorini P: Antibodies from patients with rheumatoid arthritis target citrullinated histone 4 contained in neutrophils extracellular traps. Ann Rheum Dis 2014, 73:1414-1422.

(18) Sakkas LI, Bogdanos DP, Katsiari C, Platsoucas CD: Anti-citrullinated peptides as autoantigens in rheumatoid arthritis-relevance to treatment. Autoimmun Rev 2014, 13:1114-1120.

(19) Matthews JB, Wright HJ, Roberts A, Ling-Mountford N, Cooper PR, Chapple IL: Neutrophil hyper-responsiveness in periodontitis. J Dent Res 2007, 86:718-722.

(20) Cooper PR, Palmer LJ, Chapple IL: Neutrophil extracellular traps as a new paradigm in innate immunity: friend or foe? Periodontol 2000 2013, 63:165-197.

(21) Romero V, Fert-Bober J, Nigrovic PA, Darrah E, Haque UJ, Lee DM, van Eyk J, Rosen A, Andrade F: Immune-mediated pore-forming pathways induce cellular hypercitrullination and generate citrullinated autoantigens in rheumatoid arthritis. Sci Transl Med 2013, 5:209ra150.

(22) Neeli I, Radic M: Opposition between PKC isoforms regulates histone deimination and neutrophil extracellular chromatin release. Front Immunol 2013, 4:38.

(23) Annunziato F, Cosmi L, Liotta F, Maggi E, Romag nani S: Defining the human T helper 17 cell phenotype. Trends Immunol 2012, 33:505-512.

(24) Leipe J, Grunke M, Dechant C, Reindl C, Kerzendorf U, Schulze-Koops H, Skapenko A: Role of Th17 cells in human autoimmune arthritis. Arthritis Rheum 2010, 62:2876-2885.

(25) van Hamburg JP, Asmawidjaja PS, Davelaar N, Mus AM, Colin EM, Hazes JM, Dolhain RJ, Lubberts E: Th17 cells, but not Th1 cells, from patients with early rheumatoid arthritis are potent inducers of matrix metalloproteinases and proinflammatory cytokines upon synovial fibroblast interaction, including autocrine interleukin-17A production. Arthritis Rheum 2011, 63:73-83.

(26) Cheng WC, Hughes FJ, Taams LS: The presence, function and regulation of IL-17 and Th17 cells in periodontitis. J Clin Periodontol 2014, 41:541-549.

(27) Hajishengallis G: Immunomicrobial pathogene sis of periodontitis: keystones, pathobionts, and host response. Trends Immunol 2014, 35:3-11.

(28) Bartold PM, Marshall RI, Haynes DR: Periodontitis and rheumatoid arthritis: a review. J Periodontol 2005, 76:2066-2074.

(29) Holmdahl R, Malmstrom V, Burkhardt H: Autoimmune priming, tissue attack and chronic inflammation - the three stages of rheumatoid arthritis. Eur J Immunol 2014, 44:1593-1599.

(30) 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.

(31) Wolff B, Berger T, Frese C, Max R, Blank N, Lorenz HM, Wolff D: Oral status in patients with early rheumatoid arthritis: a prospective, case-control study. Rheumatology (Oxford) 2014, 53:526-531.
(32) Chen HH, Huang N, Chen YM, Chen TJ, Chou P, Lee YL, Chou YJ, Lan JL, Lai KL, Lin CH, Chen DY: Association between a history of periodontitis and the risk of rheumatoid arthritis: a nationwide, population-based, case-control study. Ann Rheum Dis 2013, 72:1206-1211.

(33) Smit MJ., Westra J, Vissink A, Doornbos-van der Meer B, Brouwer E, van Winkelhoff AJ: Periodontitis in established rheumatoid arthritis patients: a cross-sectional clinical, microbiological and serological study. Arthritis Res Ther 2012, 14:R222.

(34) Moen K, Brun JG, Valen M, Skartveit L, Eribe EK, Olsen I, Jonsson R: Synovial inflammation in active rheumatoid arthritis and psoriatic arthritis facilitates trapping of a variety of oral bacterial DNAs. Clin Exp Rheumatol 2006, 24:656-663.

(35) Reichert S, Haffner M, Keysser G, Schafer C, Stein JM, Schaller HG, Wienke A, Strauss H, Heide S, Schulz S: Detection of oral bacterial DNA in synovial fluid. J Clin Periodontol 2013, 40:591-598.

(36) Okada M, Kobayashi T, Ito S, Yokoyama T, Komatsu Y, Abe A, Murasawa A, Yoshie H: Antibody responses to periodontopathic bacteria in relation to rheumatoid arthritis in Japanese adults. J Periodontol 2011, 82:1433-1441.

(37) de Smit MJ., van de Stadt LA, Janssen KM, Doornbos-van der Meer B, Vissink A, van Winkelhoff AJ, Brouwer E, Westra J, van Schaardenburg D: Antibodies against Porphyromonas gingivalis in seropositive arthralgia patients do not predict development of rheumatoid arthritis. Ann Rheum Dis 2014, 73:1277-1279.

(38) Lange L, Thiele GM, Pichavant M, Wang G, Ponder L, Stevens KR, Angeles-Han ST, Kennedy C, Vogler LB, Mikuls TR, Prahalad S: Abstract 116: increased antibody responses to Porphyromonas gingivalis in children with anticyclic citrullinated Peptide antibody-positive juvenile idiopathic arthritis. Arthritis Rheumatol 2014, 66 Suppl 11:S153.

(39) Kaur S, Bright R, Proudman SM, Bartold PM: Does periodontal treatment influence clinical and biochemical measures for rheumatoid arthritis? A systematic review and meta-analysis. Semin Arthritis Rheum 2014, 44:113-122.

(40) Cantley MD, Haynes DR, Marino V, Bartold PM: Pre-existing periodontitis exacerbates experimental arthritis in a mouse model. J Clin Periodontol 2011, 38:532-541.

(41) Bartold PM, Marino V, Cantley M, Haynes DR: Effect of Porphyromonas gingivalis-induced inflamma-

tion on the development of rheumatoid arthritis. J Clin Periodontol 2010, 37:405-411.

(42) Ramamurthy NS, Greenwald RA, Celiker MY, Shi EY: Experimental arthritis in rats induces biomarkers of periodontitis which are ameliorated by gene therapy with tissue inhibitor of matrix metalloproteinases. J Periodontol 2005, 76:229-233.

(43) de Aquino SG, Abdollahi-Roodsaz S, Koenders MI, van de Loo FA, Pruijn GJ, Marijnissen RJ, Walgreen B, Helsen MM, van den Bersselaar LA, de Molon RS, Avila Campos MJ, Cunha FQ, Cirelli JA, van den Berg WB: Periodontal pathogens directly promote autoimmune experimental arthritis by inducing a TLR2- and IL-1-driven Th17 response. J Immunol 2014, 192:4103-4111.

(44) Trombone AP, Claudino M, Colavite P, de Assis GF, Avila-Campos MJ, Silva JS, Campanelli AP, Ibanez OM, De Franco M, Garlet GP: Periodontitis and arthritis interaction in mice involves a shared hyper-inflammatory genotype and functional immunological interferences. Genes Immun 2010, 11:479-489.

(45) Maresz KJ, Hellvard A, Sroka A, Adamowicz K, Bielecka E, Koziel J, Gawron K, Mizgalska D, Marcinska KA, Benedyk M, Pyrc K, Quirke AM, Jonsson R, Alzabin S, Venables PJ, Nguyen KA, Mydel P, Potempa J: Porphyromonas gingivalis facilitates the development and progression of destructive arthritis through its unique bacterial peptidylarginine deiminase (PAD). PLoS Pathog 2013, 9:e1003627.

(46) Gully N, Bright R, Marino V, Marchant C, Cantley M, Haynes D, Butler C, Dashper S, Reynolds E, Bartold M: Porphyromonas gingivalis peptidylarginine deiminase, a key contributor in the pathogenesis of experimental periodontal disease and experimental arthritis. PLoS One 2014, 9:e100838.

(47) Havemose-Poulsen A, Sorensen LK, Bendtzen K, Holmstrup P: Polymorphisms within the IL-1 gene cluster: effects on cytokine profiles in peripheral blood and whole blood cell cultures of patients with aggressive periodontitis, juvenile idiopathic arthritis, and rheumatoid arthritis. J Periodontol 2007, 78:475-492.

(48) Lee YH, Bae SC, Choi SJ, Ji JD, Song GG: Associations between interleukin-10 polymorphisms and susceptibility to rheumatoid arthritis: a meta-analysis. Mol Biol Rep 2012, 39:81-87.

(49) Schaefer AS, Bochenek G, Manke T, Nothnagel M, Graetz C, Thien A, Jockel-Schneider Y, Harks I, Staufenbiel I, Wijmenga C, Eberhard J, Guzeldemir-Akcakanat E, Cine N, Folwaczny M, Noack B, Meyle J, Eickholz P, Trombelli L, Scapoli C, Nohutcu R, Bruckmann C, Doerfer C, Jepsen S, Loos BG, Schreiber S: Validation of reported genetic risk factors for periodontitis in a large-scale replication study. J Clin Periodontol 2013, 40:563-572.

(50) Esposito S, Bosis S, Semino M, Rigante D: Infections and systemic lupus erythematosus. Eur J Clin Microbiol Infect Dis 2014, 33:1467-1475.

(51) Leirisalo-Repo M: Early arthritis and infection. Curr Opin Rheumatol 2005, 17:433-439.

(52) Hajishengallis G: Periodontitis: from microbial immune subversion to systemic inflammation. Nat Rev Immunol 2014, 15:30-44.

Figures

Fig. 1 Hypothetical two hit model proposed for contribution of periodontitis to RA.

Periodontitis and RA share certain genetic and environmental risk factors including smoking and infection with P. gingivalis. The named risk factors contribute to a susceptibility background against which periodontitis and/or RA can develop. In this 'two hit' model, the 'first hit' is induction of anti-citrullinated protein antibodies (ACPA), possibly in the inflamed periodontium, and the 'second hit' is induction of arthritis and expression of citrullinated antigens in the inflamed joint [7]. Another possible sequence regarding the 'two-hit' model is that of mutual exacerbation: periodontitis as a chronic inflammation serves as 'first hit', while an (unknown) arthritogenic hit ('second hit') induces RA, which leads, in susceptible individuals, to mutual exacerbation of inflammatory responses mediating self-perpetuating tissue destruction (including bone loss) in both joints and periodontium [8] (white arrow).