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Review

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Epidemiology and pathogenesis of the link between rheumatoid arthritis and periodontitis

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Abstract: Rheumatoid arthritis (RA), an autoimmune disease characterized by chronic inflammation of synovial tissue, is divided into two subtypes—anticitrullinated protein antibodies (ACPA)-positive and ACPA-negative RA. While the pathogenic mechanisms of ACPA-positive RA are well-understood, the etiology of ACPA-negative RA remains largely unknown. The association between RA and periodontitis (PD) has been observed since the early 1900s, with the two diseases sharing common genetic and environmental risk factors that lead to the progressive destruction of bone and connective tissue. However, the association between PD and the two subtypes of RA is different. This comprehensive review aims to provide an updated understanding of the epidemiological association between RA and PD, explore potential pathogenic mechanisms linking the two diseases, and highlight the key distinctions between the subtypes of RA and their respective associations with PD. We also discuss the possibility of early intervention or the treatment of the two diseases. Ultimately, this review aims to provide valuable insights for future research in this field.

Key words: Rheumatoid arthritis; Periodontitis; Pathogenesis; Citrullination; ACPA

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1 Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune rheumatic disease characterized by chronic and painful joint inflammation, leading to progressive disability and systemic complications. These complications contribute to increased mortality among patients and impose a significant economic burden on society (Sparks, 2019). The etiology of RA is known to involve a combination of genetic and environmental factors (Scherer et al., 2020). The major histocompatibility complex (MHC) class II Human leukocyte antigen, D related beta chain (HLA-DRB1) alleles such as *0401 have been identified as the most significant genetic risk factors for RA. Specifically, the shared epitope (SE) located in the third hypervariable region of the DRβ chain is associated with disease severity (Firestein, 2003; Firestein and Mcinnes, 2017). Environmental factors, such as smoking and pathogens, exert their influence on mucosal surfaces. In response, tissues activate various mechanisms that trigger post-translational modifications of peptides (Haro et al., 2022). This process involves the activation of autoimmune responses, including macrophages and dendritic cells, which release inflammatory factors and tissue-degrading enzymes. Additionally, the activation of T and B immune cells occurs (Firestein and Mcinnes, 2017; Potempa et al., 2017). Rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) are relatively specific autoantibodies associated with RA, and both

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autoantibodies are included in the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA (Aletaha et al., 2010; Laurent et al., 2015). RF is an antibody that specifically targets the denatured IgG Fc fragment and plays a significant role in autoantigens. More specific than RF, ACPA are detectable in approximately 70% of RA patients, and are generated by the immune system in response to the presence of citrullinated proteins that have undergone a post-translational modification due to the enzyme peptidylarginine deiminase (PAD) (Krutyholowa et al., 2022). Citrullination, also known as deimination, is a post-translational enzymatic modification and transfers a positively charged arginine residue into a neutral citrulline residue (Schellekens et al., 1998; Krutyholowa, et al., 2022). Cell damage in RA patients activates PADs, combined with the released intracellular protein that catalyzes the creation of citrullinated protein containing citrullinated epitopes. By binding to ACPAs, this citrullinated epitope intensifies the autoimmune reaction and leads to the breakdown of tolerance.

ACPA-positive and ACPA-negative RA are two subtypes of RA that differ based on the presence or absence of ACPAs. There are key distinctions between these two subtypes in terms of genetic associations, clinical presentation, disease progression, and response to treatment. ACPA-positive RA is strongly associated with the HLA-DRB1 gene, specifically with certain variants of the gene known as shared epitope alleles. These genetic associations are less pronounced in ACPA-negative RA, suggesting potentially different underlying genetic mechanisms (Smolen et al., 2016; Sparks, 2019). Conversely, research has indicated that the DR3 allotype is linked to ACPA-negative RA as opposed to ACPA-positive RA (Verpoort et al., 2005; Li et al., 2022a). Some studies suggest that ACPA-positive RA may be associated with more severe joint inflammation (Korkmaz et al., 2006), more frequent involvement of small joints, and higher levels of systemic inflammation markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). ACPA-positive patients had significantly lower bone density compared to ACPA-negative patients (Amkreutz et al., 2021). ACPA-positive RA tends to have a more aggressive disease course (Ronnelid et al., 2021). ACPA-positive RA has been found to be more responsive to disease-modifying anti-rheumatic drugs (DMARDs), including biologic DMARDs, such as tumor necrosis factor inhibitors (Willemze et al., 2012; Martin-Mola et al., 2016; Sokolove et al., 2016). On the other hand, ACPA-negative RA may have a relatively better response to conventional DMARDs. However, these distinctions are not absolute and there may be some overlaps between the two subtypes. Additionally, the presence or absence of ACPAs is just one aspect of the disease, and other factors, such as the overall disease activity and individual patient characteristics, also play critical roles in determining treatment strategies and outcomes for RA patients.

Periodontitis (PD), a chronic inflammatory disease promoted by the dysbiosis of oral microbiota, is mainly characterized by the progressive destruction of the tooth-supporting apparatus. The primary manifestation is clinical attachment loss (CAL), periodontal pocket formation, and alveolar bone destruction. In severe cases, PD ultimately leads to tooth loss and has a negative impact on masticatory function (Papapanou et al., 2018). Multiple microorganisms colonize the surface of the tooth and tooth root, forming biofilms known as dental plaque, which play a role in preventing the colonization of exogenous species (Woelber et al., 2022). Normally, the composition of microorganisms in dental plaque remains relatively stable. However, certain conditions such as low pH, smoking, and an unhealthy lifestyle can disrupt this balance. Numerous studies have shown a shift in the microbial composition in PD, transitioning from predominantly Gram-positive organisms to mostly Gram-negative species (Marsh, 1994; Socransky and Haffajee, 1994). Among the recognized periodontal pathogens, *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* are commonly referred to as the "red complex," representing the most significant pathogens associated with periodontal disease (Suzuki et al., 2013; Kononen and Muller, 2014). Additionally, *Aggregatibacter actinomycetemcomitans*, *Filifactor alocis*, *Desulfobulbus*, and other microorganisms have also been linked to the disease (Griffen et al., 2012).

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Disruption of the microbiota homeostasis triggers an inflammatory response in the host, leading to the destruction of the periodontium and supporting tissues.

RA and PD share common genetic and environmental risk factors and both result in the progressive destruction of bone and connective tissue. The association between PD and the two subtypes of RA is different. There have been numerous studies dedicated to elucidating the mechanisms connecting RA to PD, which can significantly contribute to early intervention and treatment of the diseases. This comprehensive review seeks to update current knowledge regarding the epidemiological association between RA and PD, as well as the potential pathogenic mechanisms underlying the link, and contrast the key distinctions between the two subtypes of RA and their different associations with PD.

2 Clinical epidemiology

Since the late 19th century, the influence of PD on the occurrence and development of RA has been investigated in detail. Evidence suggests a bidirectional association between RA and PD (Tang et al., 2017). Both diseases share some similar characteristics and both have been linked to chronic inflammation. On the one hand, individuals with RA are more likely to develop PD. RA is an autoimmune disease that leads to chronic inflammation and joint damage. It is thought that the same inflammatory factors responsible for joint destruction in RA may also contribute to the destruction of periodontal tissues. Studies have shown that individuals with RA have a higher prevalence and severity of PD compared to those without RA (Gonzalez-Febles and Sanz, 2021).

On the other hand, PD has also been linked to an increased risk of developing RA. The chronic inflammation associated with PD may trigger an immune response that could contribute to the development of RA in susceptible individuals. A national survey demonstrated that patients with PD had an increased risk of developing RA (Demmer et al., 2011). Further research focused on the disease course of RA, indicating that PD played a crucial role in the risk of RA. A recent study detected a significantly higher prevalence of PD in individuals at-risk for developing RA compared with healthy controls (Mankia et al., 2019). Similarly, Bello-Gualtero et al. identified significantly elevated levels of plaque index, probing bleeding, and severity of PD in individuals with genetic susceptibility to RA, through assessing their periodontal conditions (Bello-Gualtero et al., 2016).

Treating PD may help improve RA symptoms, and numerous studies have investigated whether conventional treatment for PD can delay or improve the disease state of RA. It has been found that non-surgical periodontal therapy for RA patients with PD has a positive impact on RA disease activity (Silva et al., 2022). Additionally, the ESR, a marker of inflammation in RA patients, was significantly reduced following periodontal treatment (Kaur et al., 2014; Mariette et al., 2020). Similarly, the levels of anti-cyclic citrullinated peptide (anti-CCP) antibodies, a kind of ACPA, were dramatically decreased after nonsurgical periodontal therapy (Lappin et al., 2013; Cosgarea et al., 2019). When considering conventional treatment for RA, similar positive outcomes have been observed. Treatment with anti-tumor necrosis factor-α (TNF-α), interleukin (IL) receptor inhibitors, methotrexate (MTX), and monoclonal antibodies has been shown to improve the periodontal status of RA patients (Pers et al., 2008; Mayer et al., 2013; Kobayashi et al., 2014; Kobayashi et al., 2015; Zhang et al., 2015; Ziebolz et al., 2018). These findings highlight the importance of considering the clinical manifestations and examination indications of both RA and PD when preventing and treating these conditions, although further research is still needed to optimize management strategies and explore the mechanisms underlying the relationship between PD and RA.

3 Potential pathogenic mechanisms

3.1 Susceptibility gene

Genetic factors play a role in the susceptibility to both RA and PD. Studies have found that certain genetic variations can contribute to an increased likelihood of developing these conditions. ACPA-positive RA and PD share common risk factors, both genetic and environmental. Certain genes have been found to be associated with an

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increased risk of developing both ACPA-positive RA and PD. Variations in genes related to the immune system and inflammation, such as the HLA-DRB1 gene, have been associated with the development of both conditions (Lundstrom et al., 2009; Gehlot et al., 2016). Environmental factors also play a role in the development of ACPA-positive RA and PD. Smoking, for example, is a well-known risk factor for both conditions (Van Winkelhoff et al., 2001; Heasman et al., 2006; Detert et al., 2010). Smoking has been found to increase the production of ACPA, which play a major role in ACPA-positive RA (Linn-Rasker et al., 2006; Sakkas et al., 2014). Additionally, smoking can also worsen PD by affecting the immune response to oral bacteria. Other environmental factors, such as stress, hormonal changes, and certain infections, have also been implicated in the development of both ACPA-positive RA and PD (Detert, et al., 2010). However, the exact mechanisms by which these risk factors contribute to the development of each condition are not yet fully understood. Understanding these shared risk factors can provide insights into the possible relationships between these two conditions and may guide future research and treatment strategies. We found that, as yet, there have been no exploratory studies investigating the relationship between ACPA-negative RA and PD.

PAD, which plays a crucial role in triggering autoimmunity through the citrullination of self-proteins, is encoded by the PADI gene. The PADI gene has been implicated in the susceptibility to RA. There were four PADI genes, called PADI1, PADI2, PADI3, and PADI4. It has been demonstrated that the PADI4 haplotype is significantly associated with the susceptibility to RA and the production of antibodies with citrullinated peptides. Four new single nucleotide polymorphisms (SNPs) with significant associations with RA in the PADI4 gene have been reported (Suzuki et al., 2003). SNPs in PADI2 were also associated with the development of RA in both East Asian populations and Southern Mexican populations (Too et al., 2012; Guzman-Guzman et al., 2021). Specifically, SNPs in the PADI gene have been shown to interact with known risk factors for ACPA-positive RA. However, no association has been identified between PADI/SNP and PD (Massarenti et al., 2021). Interestingly, among a population of patients with pre-existing PD, individuals carrying minor alleles of the PADI2 SNPs locus—specifically rs2057094, rs2076616, or rs2235912—may have an elevated risk of developing anti-CCP-negative RA, regardless of their smoking status (Massarenti et al., 2022). This finding suggests that PD might have an unknown influence on the impact of PAD gene polymorphisms on the risk of developing RA.

3.2 Inflammatory mediator

Given that RA and PD are both chronic inflammatory conditions, Golub et al. proposed a "two-hit" model, providing a possible explanation for the link between RA and PD (Golub et al., 2006). This model suggests that the first hit of ACPA production due to PD is followed by a second hit in the joint that induces RA.

Nesse et al. highlighted the role of citrullination, which is dependent on inflammatory responses in the periodontal stroma. The source of citrullination is thought to be related to various factors, including inflammatory processes, genetic factors, environmental triggers, and age-related changes. Citrullination is often associated with inflammation and autoimmune diseases. Inflammatory cells, such as neutrophils, macrophages, and lymphocytes, are known to express PAD enzymes and can contribute to citrullination. The citrullinated proteins formed in PD stroma bear significant similarities to those formed in the synovium of RA patients, suggesting a potential role of PD-induced citrullination in the pathogenesis of RA (Nesse et al., 2012). In the initial defense against oral pathogenic microorganisms, the innate immune system plays a critical role. Pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), and antimicrobial peptides (AMPs) can induce the secretion of inflammatory factors (De Molon et al., 2019). AMPs, including alpha-defensins, beta-defensins, and the inflammation-related antimicrobial peptide LL-37, are secreted into the oral cavity by salivary gland epithelial cells, neutrophils, monocytes, and other immune cells. These AMPs can simultaneously inhibit the invasion of pathogenic bacteria and promote wound healing (Di Benedetto et al., 2013; Lobognon and Alard, 2022).

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Among the AMPs, LL-37, a cathelicidin peptide, is of particular interest in PD. It exhibits antimicrobial properties, inhibiting the growth of various microorganisms. Additionally, LL-37 can neutralize the effects of lipopolysaccharide (LPS) produced by gram-negative bacteria, which contribute to the inflammatory response. LL-37 expression is positively associated with inflammatory markers and is particularly expressed by neutrophils in both PD and RA patients (Gorr and Abdolhosseini, 2011; Li et al., 2018; Cheah et al., 2020). Cheah et al. found that the levels of LL-37 in the saliva were significantly increased in RA patients with PD. Moreover, they observed a correlation between LL-37 levels and the titer of ACPA (Cheah et al., 2022).

In the development of RA, there is an accumulation of inflammatory cells in the synovium and joint cavity, leading to synovial intimal hyperplasia and the excessive production of pro-inflammatory cytokines and proteases, which stimulate synovial fibroblasts and chondrocytes. Several pro-inflammatory cytokines play significant roles in the inflammatory processes of RA, including TNF-α, IL-1β, IL-6, IL-17, granulocyte macrophage colony-stimulating factor (GM-CSF), and the receptor activator of nuclear factor kappa-B ligand (RANKL) (Feldmann et al., 1996). The dysregulation of these pro-inflammatory cytokines and the subsequent inflammatory cascades contribute to the destructive nature of RA, resulting in joint damage and functional impairment. Targeting these cytokines has been an effective therapeutic approach to manage RA and reduce disease activity (Araujo et al., 2015; Roeleveld and Koenders, 2015). In PD, oral microbiota dysbiosis causes toll-like receptors (TLRs) activation on immune cells, and gingival epithelial cells and phagocytes recognize PAMPs, inducing the secretion of pro-inflammatory cytokines such as IL-1β, TNF, IL-6, and IL-8 (Di Benedetto, et al., 2013; Potempa, et al., 2017). TWEAK/TNFSF12, IL-35, IFN-α2, pentroxin-3, gp130/sIL6Rb, sIL-6Ra, IL-19, and sTNF-R1 were significantly increased in the saliva of PD patients with RA compared with those without RA (Eriksson et al., 2022). In addition, IL-33 was positively correlated with both periodontal parameters and RA disease parameters (Correa et al., 2019; Eriksson et al., 2019), which suggests a possible role of pro-inflammatory cytokines in the relationship between these two diseases.

Activated synovial fibroblasts and chondrocytes contribute to the pathogenesis by secreting collagen-degrading enzymes, known as matrix metalloproteinases (MMPs), and inducing osteoclast differentiation. MMP-8, a crucial subtype of protease involved in joint destruction in RA, has been found to be significantly increased in the saliva of both early and chronic RA patients. This elevation in MMP-8 levels is accompanied by increased levels of the tissue inhibitor of MMPs (TIMP)-1 and IL-6 (Cheah, et al., 2022). TIMPs serve as cytokine-like signaling molecules that protect healthy tissues from the excessive activity of MMPs. In the context of inflamed periodontal tissue, an imbalance between MMP-8 and TIMP-1 has been observed, leading to irreversible tissue deterioration (Ries, 2014; Ayravainen et al., 2018). MMP-9, another subtype of matrix metalloproteinase, has also demonstrated a similar pattern in RA patients with PD (Silosi et al., 2015). However, Javed et al. found that RA patients exhibited higher levels of inflammatory factors, including IL-1, IL-4, IL-10, MMP-8, MMP-13, and TNF-α, compared to a healthy group without PD (Javed et al., 2014). Therefore, further research is needed to elucidate the specific mechanisms underlying the potential connection between inflammatory factors in the oral cavity and joints.

3.3 Oral microbial dysbiosis

The association between PD and RA is primarily reflected in the dysregulation of the oral microbiome. Substantial evidence has demonstrated that oral microbial dysbiosis can increase individuals' susceptibility to RA. Studies have revealed significant alterations in the composition of the oral microbiota of early RA patients and individuals at high risk for developing RA (Zhang, et al., 2015; Kroese et al., 2021). To further identify the specific microbial species that may be related to RA, researchers have utilized next-generation segueing to analyze the microbiome of oral samples. In saliva, *Veillonella sp.*, *Prevotlla sp.*, and *Tannerella sp.* were discovered with higher abundance in RA patients (Kroese, et al., 2021; Eriksson, et al., 2022). *Defluviitaleaceae UCG-011* and *Neisseria oralis* were found to be significantly lower in early RA

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patients and high-risk individuals compared to healthy controls. Moreover, the serum concentration of ACPA in the high-risk groups was positively correlated with the relative abundance of *Eubacterium nodatum*, *Peptostreptococcus*, *Tannerella*, and *Absconditabacteriales SR1* (Tong et al., 2019).

Similar findings have been observed in the tongue coating and dental plaque of individuals with RA or those at high risk of developing RA. In the tongue coating, *Veillonella sp.* was found to be present in a high abundance in RA patients and high-risk individuals. In the dental plaque, *Actinomyces meyeri*, *Prevotella nigrescens*, *Treponema socranskii*, and other 10 species were significantly enriched (Kroese, et al., 2021).

P.gingivalis infection has been consistently identified as a specific bridge connecting RA and PD (Gabarrini et al., 2015). *P.gingivalis*, the keystone pathogen accumulating in the plaque of PD patients, produces numerous virulence factors that can directly or indirectly modify the host's inflammatory response, leading to the destruction of periodontal tissue (Holt et al., 1999; How et al., 2016). In addition to *P.gingivalis*, *A.actinomycetemcomitans* was associated with RA by detecting antibodies in serum (Konig et al., 2016; Mukherjee et al., 2018). A significant difference in *A.actinomycetemcomitans* infection was found between RA and non-RA controls using oral samples (Laugisch et al., 2016). As a crucial pathogen involved in the process of hypercitrullination in PD, the role of *A.actinomycetemcomitans* in the pathogenesis of RA has been suggested, which we will further discuss below.

3.4 Citrullination mediated by PAD and *P.gingivalis* peptidylarginine deiminase (PPAD)

PAD, a member of the amidino-transferase superfamily, originated from various sources, including mammalian PADs such as PAD2 and PAD4. PADs, which are expressed in inflammatory tissue cells, are responsible for the hydrolysis of guanidinium side chains of peptidyl arginine to peptidyl citrulline and ammonia (Kwon and Ju, 2021). Human PAD4 has been shown to undergo auto-citrullination; this modification renders the enzyme inactive but enhances its detection by human anti-PAD4 autoantibodies (Andrade et al., 2010).

PPAD, a unique peptidyl-arginine deiminase generated by *P.gingivalis*, directly citrullinate host proteins including fibrinogen, vimentin, hnRNP-A2/B1, histone H1, and multiple peptides that contain a common RG/RGG consensus motif (Jenning et al., 2020). This process of protein citrullination is depicted in Fig. 1a. In contrast to human PAD enzymes, PPAD exhibits unique characteristics. It is catalytically independent of calcium ion concentration and can be activated at higher pH levels. PPAD shows a preference for substrates containing a C-terminal arginine residue (Quirke et al., 2014; Kwon and Ju, 2021). Arginine gingipains, derived from *P.gingivalis*, are enzymes responsible for cleaving polypeptides into short peptide fragments with a C-terminal arginine residue. These peptide fragments are then specifically citrullinated by PPAD (Wegner et al., 2010; Quirke, et al., 2014; Shimada et al., 2016). The collaboration between arginine gingipains and PPAD in *P. gingivalis* facilitates the specific citrullination of endogenous proteins. This enzymatic process contributes to the generation of citrullinated autoantigens that may play a role in the pathogenesis of RA.

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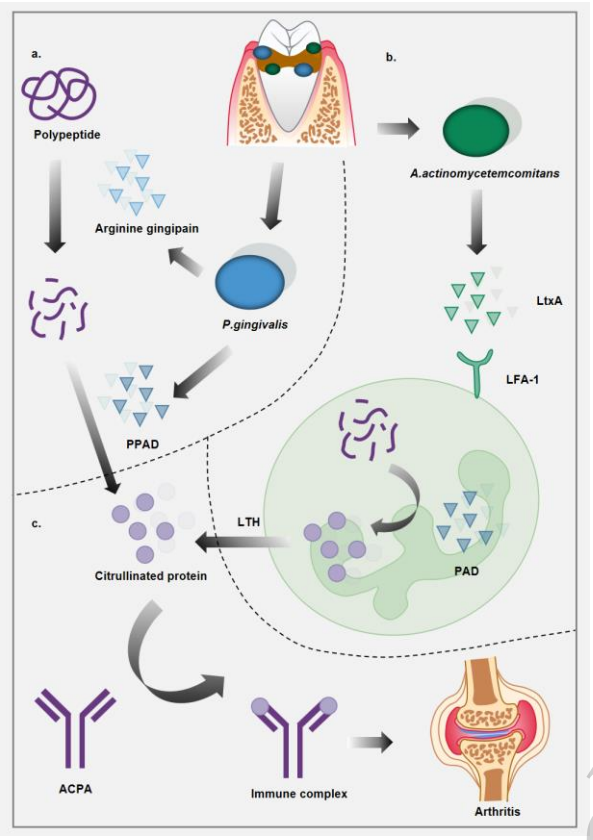

Fig. 1 Possible connection between periodontitis and rheumatoid arthritis involving *P.gingivalis* and *A.actinomycetemcomitans*. a. *P.gingivalis* releases arginine gingipains, which cleave polypeptides into short peptide fragments with C-terminal arginine. These fragments are then catalyzed by the peptidylarginine deiminase (PPAD) derived from *P.gingivalis*, leading to endogenous protein citrullination. b. *A.actinomycetemcomitans* releases Leukotoxin A (LtxA), which specifically binds to the leukocyte receptor (LFA-1) on the surface of neutrophils. This binding induces PADs to catalyze the production of autoantigens, which are released by lysing cells in the form of leukocyte toxicity hypercitrullination (LTH). c. Hypercitrullinated proteins, produced through both pathways, trigger the generation of anti-citrullinated protein antibodies (ACPA), leading to the accumulation of immune complexes. This accumulation ultimately results in the tissue damage in patients with RA.

PPAD can undergo auto-citrullination. Artificially overexpressed full-length PPAD in *Escherichia coli*, localized to the bacterial outer membrane, can facilitate auto-citrullination. Interestingly, the site of citrullination in PPAD was found to be within the internal part of the peptide chain, rather than at the C-terminus (Quirke, et al., 2014). PPAD and citrullinated PPAD peptide (CPP) have emerged as potential targets for antibody reactivity in RA. These targets elicit signals specific to α-citrulline antibodies (α-cit), which have been found to be positively correlated with α-CCP2 antibody levels (Jenning, et al., 2020). The presence of these neoepitopes can disrupt the immune tolerance to citrullinated proteins and trigger a specific antigen response (Bartold and Lopez-Oliva, 2020).

In PD patients, *P.gingivalis* infection may contribute to shaping the autoimmune response underlying RA (Lappin, et al., 2013; Mikuls et al., 2014; Kharlamova et al., 2016), and promote the development of ACPA in circulating plasma cells (Li et al., 2016). Johansson et al. found that the concentration of antibodies against *P.gingivalis* was significantly increased in RA patients compared to controls, and those antibodies were detectable years before the onset of RA symptoms (Johansson et al., 2016). The significance of *P.gingivalis* in the pathophysiology of RA was further established by the strong association between *P.gingivalis* and positive titers of anti-CCP antibodies in early RA patients (Mankia, et al., 2019). Speculatively, PAD and PPAD play an important role in the association between RA and PD.

The mechanism of auto-citrullination in PPAD is still a subject of debate. In contrast to artificially expressed PPAD in *Escherichia coli*, studies have shown that native PPAD derived from *P.gingivalis* undergoes truncation in the N-terminal and C-terminal domains rather than auto-citrullination. These truncations do not involve citrullination of the enzyme itself (Konig et al., 2015). Moreover, it has been observed that serum IgG antibodies from early RA patients, whether positive or negative for ACPA, did not show a preferential targeting of auto-citrullinated proteins from *P.gingivalis*, suggesting that the enzymatic activity of PPAD may not be a significant pathogenic mechanism in the early stages of RA (Munoz-Atienza et al., 2020). A recent clinical study demonstrated that PPAD antibodies are not related to citrullination in RA (Castellar-Mendoza et al., 2023).

3.5 NETosis and leukotoxic hypercitrullination

NETosis is a specific type of cell death process,

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usually carried out by neutrophils. During NETosis, neutrophils release web-like structures called neutrophil extracellular traps (NETs), which can capture and kill bacteria, viruses, and other pathogens. The process of NETosis also releases autoantigens and certain enzymes, including PADs, involved in the citrullination. NETosis holds significant research value in understanding the pathogenesis of RA. The study conducted by Oliveira et al. demonstrated that concentrations of NETs were higher in the saliva and plasma of patients with early RA compared to those with established RA or without RA. Furthermore, PD was found to increase the concentration of NETs in both non-RA and early RA patients (Oliveira et al., 2021). These findings suggest a potential involvement of NETosis in the development of RA. Furthermore, Bacteria (including *P.gingivalis* and *A.actinomycetemcomitans*), viruses, and endogenous factors can stimulate neutrophils to undergo NETosis, thereby releasing PADs and citrullinated extracellular proteins. This process leads to neutrophil death and is associated with the activation of PADs and the involvement of perforin and the membrane attack complex (Romero et al., 2013). As a consequence, hypercitrullination of proteins is induced.

Leukotoxic hypercitrullination refers to the excessive citrullination of proteins, particularly occurring in the context of neutrophil-mediated inflammation. Leukotoxin A (LtxA), a member of the Repeat in Toxin (RTX) family, is a pore-forming protein that specifically binds to the leukocyte receptor (LFA-1). This interaction leads to neutrophil apoptosis and the rapid release of lysosomal enzymes and MMPs (Linhartova et al., 2010; Johansson, 2011). Konig and Andrade found that *A.actinomycetemcomitans* induces hypercitrullination of host neutrophils by releasing LtxA, with the effect being dependent on extracellular calcium concentration (Konig, et al., 2016) (Fig. 1b). In their study, they proposed an alternative mechanism where LtxA induces the production of PAD autoantigens in neutrophils, leading to cell lysis resembling NETosis, which they termed leukocyte toxicity hypercitrullination (LTH). A clinical case involving a 59-year-old male with *A.actinomycetemcomitans* endocarditis and positive for ACPA demonstrated a significant increase in bacterial expression of LtxA. This patient also exhibited high levels of anti-LtxA antibodies and elevated Th1 and Th17-associated cytokines, which are associated with RA (De Aquino et al., 2017). Remarkably, after one year of anti-*A.actinomycetemcomitans* therapy, the arthritis symptoms and anti-CCP antibodies appeared to resolve (Mukherjee, et al., 2018). During LTH, hyper-citrullinated proteins are released along with DNA (Konig, et al., 2016) (Fig. 1c). LTH is indeed an immune escape mechanism employed by bacteria, which is triggered by pore-forming pathways and equivalent signals (Konig and Andrade, 2016). However, inhibitors of the NET formation have no effect on LtxA-induced hypercitrullination (Looh et al., 2022). However, the specific mechanism by which LtxA contributes to the pathogenesis of PD and RA requires further investigation.

3.6 Maladaptive innate immune training

The understanding of the role of innate immune cells in inflammatory comorbidities has been steadily growing. These cells possess the ability to remember foreign antigens or previous inflammation, resulting in an enhanced protective response upon encountering subsequent challenges. This phenomenon is known as trained innate immunity (TII). Li et al. claimed that the inflammatory response induced by experimental PD could trigger inflammatory adaptability and significant proliferation of hematopoietic stem and progenitor cells (HSPCs), leading to the epigenetic differentiation bias of myeloid cells, thereby resulting in TII (Li et al., 2022b).

The inflammatory response in PD induces a myeloid bias through the production of serum granulocyte colony-stimulating factor (G-CSF). This factor enters the bone marrow and stimulates the secretion of IL-1 by mature neutrophils, thereby facilitating trained myelopoiesis and exacerbating the systemic inflammatory response. Consequently, this process increases susceptibility to RA in experimental PD. Conversely, alterations in HSPCs in the bone marrow of experimental RA lead to maladaptive inflammatory phenotypes that can further worsen PD susceptibility, indicating a bidirectional correlation. These findings provide a

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novel explanation for the association between PD and RA from an immune cell perspective. Researchers have suggested that the maladaptive training of bone marrow hematopoietic progenitor cells can be blocked by systematically inhibiting IL-1-induced signaling. This intervention could potentially halt the bidirectional progression of inflammatory comorbidities (Hajishengallis et al., 2022). However, additional studies are needed to substantiate this idea.

4 Conclusions

There has been increasing research on the relationship between PD and RA. This article comprehensively summarized the findings from the perspectives of clinical epidemiology, etiology, and pathogenesis over the past decade. It has been observed that the oral health of RA patients worsens as the disease progresses. Conversely, individuals diagnosed with PD at an early stage are at a higher risk of developing RA, regardless of whether they test positive or negative for anti-ACPA antibodies. However, the exact causal relationship between these two diseases remains unclear.

Most recent studies have primarily focused on individuals with anti-ACPA-positive RA, while paying less attention to those who are anti-ACPA-negative. Recently, anti-Pentraxin 3 and anti-Dual Specificity Phosphatase 11 (DUSP11) autoantibodies have also been found to be biomarkers for the diagnosis of ACPA-negative RA, which will help to promote research into ACPA-negative RA (Li et al., 2021). For individuals in the preclinical stage of RA, the best preventive approach is to target susceptibility and risk factors before the onset of obvious clinical symptoms and serum antibody indicators, in order to prevent the development and progression of the disease. Therefore, it is important for future studies to also focus on early-stage RA patients and individuals who are anti-ACPA-negative, thus further enhancing our understanding of its pathogenesis as well as disease prevention.

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Author contributions

Zijian CHENG and Weiqian CHEN conducted and revised this review. Huiya FANG, Jin LIN, and Yiwu QIU wrote the manuscript and edited the figure. All authors read and approved the final manuscript and, therefore, had full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Huiya FANG, Jin LIN, Yiwu QIU, Zijian CHENG, and Weiqian CHEN declare that they have no conflict of interest. This article does not contain any studies with human or animal subjects performed by any of the authors.

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