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RESEARCH ARTICLE

HYPERCITRULLINATION- THE PATHOLOGIC LINK BETWEEN PERIODONTITIS AND RHEUMATOID ARTHRITIS

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ABSTRACT

Periodontitis is one of the most prevalent chronic inflammatory diseases across the globe. The link between periodontitis and rheumatoid arthritis has been well established by various biologically plausible mechanisms in the past decade, however periodontitis being a polymicrobial disease has recently been found to initiate and maintain the auto-inflammatory response that occurs in rheumatoid arthritis.This article focuses on the role of hypercitrullination, as one of the pathologic link between the two forms of chronic diseases.

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INTRODUCTION

Periodontitis (PD) is a chronic inflammatory disease of tooth supporting structures, leading to progressive bone loss thereby resulting in loss of tooth. Various epidemiologic and clinical studies suggest a strong relationship between rheumatoid arthritis (RA) and periodontitis and that the extent and severity of one condition affects the other. (Kaur *et al*., 2013) Though the autoimmune inflammatory response remains the underlying pathology for both the conditions; periodontal disease is of microbial origin as opposed to rheumatoid arthritis. However exposure to common genetic and environmental factors might contribute to a non-causal association between both conditions. There are emerging evidence supporting the fact that periodontal disease could be a causal factor in the initiation and maintenance of the autoimmune inflammatory response that occurs in RA; and PD could be a modifiable risk factor for RA (Koziel *et al*., 2014; Mercado *et al*., 2003; Wegner *et al*., 2010)

Periodontitis and rheumatoid arthritis-The established link

RA is an autoimmune chronic inflammatory disease characterised by painful inflammation of the joints resulting in disability and dysfunction, with an increased morbidity. Regardless of the differing aetiologies, both RA and PD are characterized by localised chronic inflammation resulting in higher concentrations of pro-inflammatory cytokines, connective tissue breakdown and bone erosion. Studies have shown higher levels of inflammatory markers such as CRP in the circulation of both PD and RA patients. (Abou-Raya *et al*., 2008) Various clinical studies have indicated a potential positive association between the occurrence of periodontitis and RA. (Xiao *et al*., 2017; Calderaro *et al*., 2017) The virulence factors from the periopathogens are immunomodulatory in nature that might have many systemic influence, one such being the probability of occurrence of Rheumatoid arthritis (RA) in susceptible individuals.

Citrullination

Citrullination is the post-translational modification of protein bound arginine into the nonstandard amino acid *citrulline*, catalyzed by Ca^{2+} dependent peptidyl arginine deiminases (PAD) enzymes. Physiological processes in which citrullination commonly occurs are epithelial terminal differentiation, gene expression, regulation, and apoptosis. (György *et al*., 2006) To date, five isoforms of PAD enzyme have been identified with different tissue expression and consequently different functions. (Nachat *et al*., 2005) PAD catalyzed protein citrullination also occurs under pathological inflammatory conditions like necrosis and been associated to the breakdown of immune tolerance to citrullinated proteins leading to initiation of RA in susceptible individuals. (Wang and Wang, 2013)

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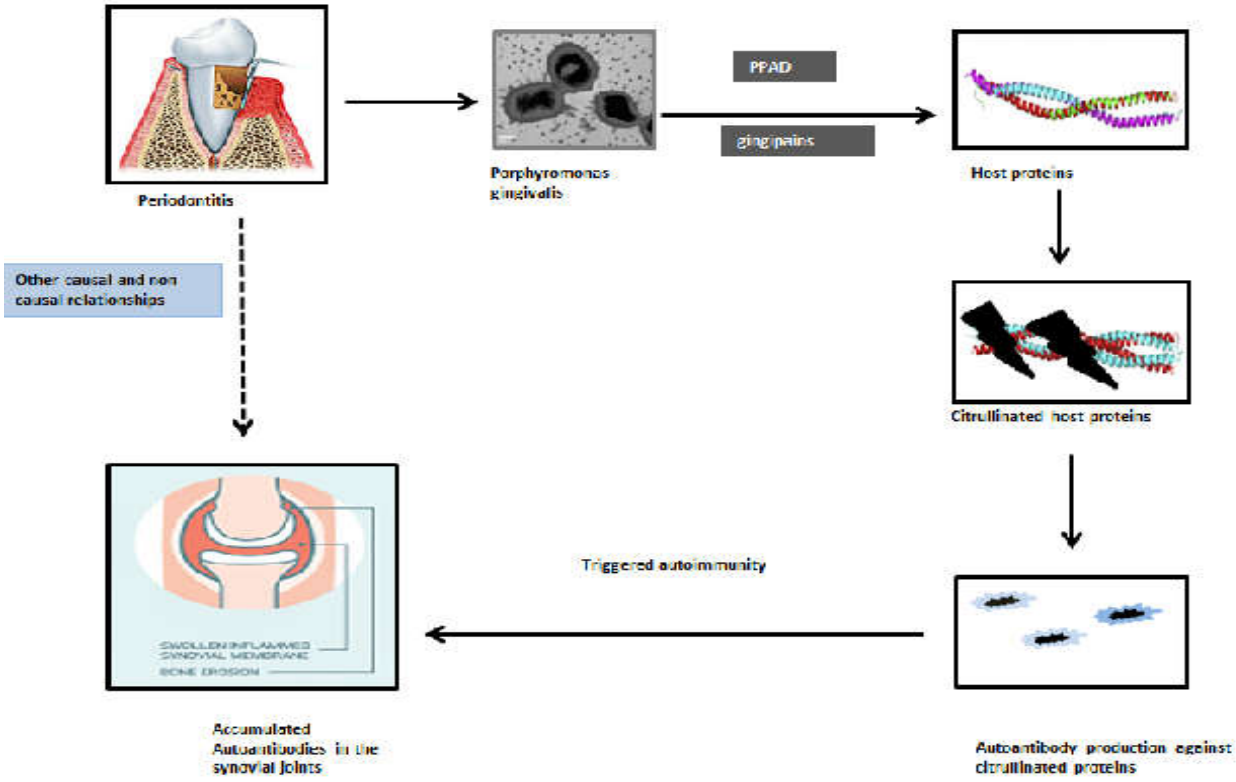

Fig.1. Schematic representation of Hypercitrullination as the link between Periodontitis and Rheumatoid arthritis

Hypercitrullination- causal route to RA

It was reported in 1998 by Schellekens and colleagues that many RA autoantibodies detect citrulline on peptides, that many of these were specific for RA, and that the antibodies are present early in disease. (Schellekens *et al*., 2000) The anti-citrullinated protein antibodies are the most specific autoantibodies present in the RA sera. (Vossenaar and van Venrooij, 2004) Citrullination of specific proteins, including filaggrin, vimentin, fibrin, fibrinogen, α-enolase, and collagen II, produces new epitopes that give rise to autoantibodies produced in synovial fluid of the inflammatory joints. (Van Steendam *et al*., 2011) The presence of citrulline residues in these proteins sends the immune cells a wrong signal and initiates immune responses to generate anticitrulline antibodies against these proteins. (Kuhn *et al*., 2006) Thus there is autoantibody production resulting in host tissue destruction.

Periodontal pathogens and Rheumatoid arthritis

Pg (Porphyromonas Gingivalis) recognised as one of the keystone pathogen in periodontitis, even when present in low abundance could modify the microbiota into a dysbiotic one thereby instigating periodontal inflammation. It was hypothesized that *P. gingivalis* impairs innate immunity that alter the growth and development of the entire biofilm, triggering a destructive change in the normally homeostatic host-microbial relationship in the periodontium. (Olsen *et al*., 2017) P. Gingivalis is the only prokaryote that expresses peptidylargininedeaiminase (PPAD) that differs from human PADs in that it is not a Ca^{2+} dependent enzyme. Furthermore, it is active at higher pH and preferentially citrullinates C-terminal arginines, both the peptide-bound and the free ones. (Wegner *et al*., 2010; Maresz *et al*., 2013) The citrullinated peptides generated by P. *Gingivalis* are produced by the combined action of arginine gingipains cleaving polypeptides in short peptides with C-terminal arginines followed by rapid citrullination by PPAD. This citrullinated protein found in periodontal tissue, then act as systemic immunogen. Auto antigens modified by citrullination through exposure to periodontal pathogens might sustain synovial inflammation in the context of untreated periodontitis. (Corrêa *et al*., 2017) Rosenstein *et al* hypothesised that PPAD-mediated protein citrullination at inflamed periodontal sites can initiate a cascade of events that culminate in the production of anti-citrullinated protein antibodies (ACPAs) and, eventually, in the clinical manifestation of RA. (Rosenstein *et al*., 2004) Mikuls *et al* compared the levels of antibodies against *P. gingivalis*correlating with levels of ACPA in patients with RA, and proved that antibody to *P. gingivalis* is associated with the presence of RA-related autoantibody (a combination of rheumatoid factor (RF) and/or ACPA) among individuals at increased risk for disease but who have not yet developed RA symptoms, underscoring the potential role of this pathogen in RA development. (Mikuls *et al*., 2014)

A. Actinomycetemcomitans and citrullinated proteins:

Konig *et al* in 2016 have identified leukotoxin A (LtxA) as the molecular mechanism by which Aggregati bacter Actinomycetemcomitans (Aa) triggers activation of citrullinating enzymes in neutrophils, inducing changes in neutrophil morphology resulting in extracellular trap formation and releasing hypercitrullinated proteins. (Konig *et al*., 2016) Thus it could be speculated that a can also have an indirect role in increasing the risk of occurrence of RA in Periodontitis patients.

Conclusion

Emerging evidence suggests that the PPAD mediated citrullination resulting in citrullinated epitopes at inflamed periodontal sites results in the production of ACPA's which could possibly contribute to the initiation of RA. Hence it is understood that the periodontal pathogens, apart from initiating periodontal disease could trigger a loss of tolerance to host proteins leading to the production of citrullinated proteins and thus stimulating autoantibody production which can aggravate RA-associated pathologies.

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