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REVIEW PAPER

Correlation between rheumatoid arthritis and periodontitis

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ABSTRACT

Introduction and aim. The association between periodontitis (PD) and rheumatoid arthritis (RA) has been analyzed and described in literature. Periodontal pathogens, such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* are pointed as the common factors for both diseases. In this work we demonstrate that treatment of dental and oral diseases is an unconditional requirement for patients with RA.

Material and methods. PubMed was searched with the keyword "rheumatoid arthritis" and "periodontitis" from May 1999 to January 2022, showed 181 articles. Ultimately 72 articles were included in the review.

Analysis of the literature. The above mentioned pathogens exhibit multiple mechanisms that disturb immune and inflammatory responses of the human organism. Those mechanisms lead to the periodontal disease (PD) that may activate the systematic reactions which in turn lead to intensification of systematic diseases such as rheumatoid arthritis (RA). *P. gingivalis* has the ability to expresses PAD enzyme (peptidylarginine deiminase) and activates the citrullization process. Moreover, the bacterium produces gingipain cysteine proteinases, which degrade the mechanisms of immunological system. The latter pathogen, *A. actinomycetemcomitans,* expresses hypercitrullization in neutrophils.

Conclusion. Both pathogens influence inflammatory response of the organism, through the common pro-inflammatory mediators for periodontitis and rheumatoid arthritis, intensify the clinical manifestations of both diseases.

Keywords. *Aggregatibacter actinomycetemcomitans*, periodontitis, *Porphyromonas gingivalis,* rheumatoid arthritis, risk factors

Introduction

The association between periodontitis (PD) and rheumatoid arthritis (RA) has been analyzed and described in literature.[1-3] Periodontal pathogens, such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* are pointed as the common factors for both diseases. The above mentioned pathogens exhibit multiple mechanisms that disturb immune and inflammatory responses of the human organism. Those mechanisms lead to the periodontal disease (PD) that may activate the systematic reactions which in turn lead to intensification of systematic diseases such as rheumatoid arthritis (RA).[4,5] *P. gingivalis* has the ability to expresses PAD enzyme (peptidylarginine deiminase) and activates the citrullization process. Moreover, the bacterium produces gingipain cysteine proteinases, which degrade the mechanisms of immunological system.[6] The latter pathogen, *A. actinomycetemcomitans,* expresses hypercitrullization in neutrophils.[7] Both pathogens influence inflammatory response of the organism, through the common pro-inflammatory mediators for periodontitis and rheumatoid arthritis, intensify the clinical manifes-

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tations of both diseases.[5] In this work we demonstrate that treatment of dental and oral diseases is an unconditional requirement for patients with RA.[8]

Rheumatoid arthritis (RA) is a chronic, systematic disease with an inflammatory and autoimmunological background of unclear etiology. The pathogenesis of RA consists of not only genetic, but also environmental factors such as smoking. The disease can cause symmetrical cartilage and bone damage mainly in hands and feet. The clinical manifestations include pain, swollen and inflammatory exudate in joints and periarticular tissues. Additionally, patients complain about morning stiffness and limited range of motion. The course of illness is variable with remission and exacerbation periods. RA appears more frequently in females than males, especially in the elderly. It can lead to systematic extra-articular changes, disability, premature death and socioeconomic burdens.[9,10]

Periodontitis (PD) is a chronic, inflammatory disease which is associated with dysbiosis of the oral microbiota (dental plaque). It relates to the supporting structures of the teeth – the gingiva, bone and periodontal ligament. The potential results include tooth loss and systemic inflammation. To the risk factors, which promote the development of the disease are: inappropriate oral hygiene, interaction with the immune defense of the host, dysbiosis of oral microbiota, environmental risk factors (smoking) and genetic susceptibility.[11-14]

Many authors who in their studies indicate a possibility of simultaneous occurrence of RA and PD emphasize the existence of the association between these diseases.[1-3] They indicate common features such as: pathogenesis, inflammatory mediators profile, environmental factors (smoking, low socioeconomic status), genetic factors (*HLA-DRB1* allele of the MHC class II molecules), clinical manifestations (Figure 1).

We could say, that PD is a risk factor for RA.[15] The risk is especially pronounced within patients with a severe and seropositive RA where a stronger clinical course of PD has been observed. Coexistence of RA and PD can lead to intensification of either or both of the diseases. Active periodontal disease is associated with higher RA disease symptoms. Consequently, the treatment of one disease may have influence on the other.[16]

Aim

The aim of the study was to analysis of the currently available literature related to periodontitis and rheumatoid arthritis. In this work, we focus on the periodontal pathogens such as *Porphyromonas gingivalis* and *Aggregatibacter actimomycetemcomitans* which are pointed out as the comman factors for both diseases.

Material and methods

In this work we analyzed literature, related to the connection between periodontitis and rheumatoid arthritis. We focused on the latest available literature by searching electronic database – PubMed (NCBI). 181 articles were found from the period of May 1999 until January 2022. Finally, 72 titles were considered for analysis. We selected the articles on periodontitis and rheumatoid arthritis in which two periodontal pathogens (*P. gingivalis, A. actinomycetemcomitans)* were described together with their influence on rheumatoid arthritis.

Analysis of the literature

Porphyromonas gingivalis

As described in the literature, *P. gingivalis* – a gram-negative, anaerobic bacterium involved in periodontal disease, could be also predisposing factor for RA development or exacerbation. The bacterium disturbs the immune and inflammatory responses of the human organism and causes inflammation in the dental pockets. This inflammation in turn could affect systematic reactions which intensify the systematic diseases such as RA.[4,14,17-19]

Citrullination is a physiological process in healthy tissues that regulates apoptosis and inflammatory processes through the human enzyme PAD (peptidylarginine deiminase (PAD).[17] *P. gingivalis* is a pathogen, which has the ability to express its own PAD enzyme and causes citrullization process.[6,20] Liao et al. formulate a hypothesis that *P. gingivalis*, the major pathogen in PD and only pathogen which expresses PAD enzyme, could be involved in the pathogenesis of RA through citrullination of RA autoantigen (i.e. fibrin in synovium).[21]Additionally, it has the ability to change free arginine in the way independent on calcium. Citrullination, that is stimulated by *P. gingivalis* PAD enzyme, increas-

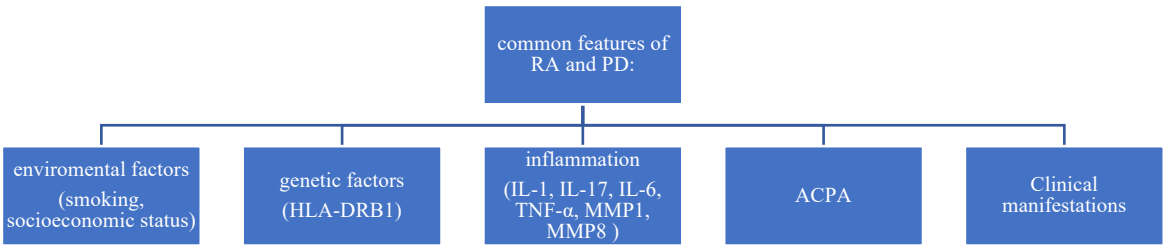

Fig. 1. Common features of rheumatoid arthritis and periodontitis

es the adaptation and ability for survival of the pathogen in humans.[22] The immune system recognizes the generated citrullinated peptides as foreign antigens. As a result, it stimulates the production of anti-citrullinated protein antibodies which could initiate inflammatory process in RA patients.[23-25] Citrullinated proteins generate the epitopes which break immunological tolerance in genetically predisposed patients. Several authors, including Makrygiannakis et al., have demonstrated the presence of some anti-citrullinated protein antibodies in synovial fluid in RA patients as compared to the healthy ones.[26] The antibodies are a highly specific diagnostic tool towards RA. Many studies show that a higher level of positive anti-cyclic citrullinated peptide antibodies (anti-CCP) is associated with a more aggressive course of RA and the bone destruction. The increasing level of anti-CCP appears also in an aggressive PD. Wagner et al. have observed similar relations. They suggest a "two-hit" model of RA. Citrullinated peptides provided by *P. gingivalis in inflamed gingival tissues spread epitopes* to the citrullinated proteins in the inflamed synovial joint. This could lead to an aggressive and chronic reaction, characteristic for RA.[27-30] Smit et al. showed an increased activity of RA within the patients with severe periodontitis which corresponded to a higher level of antibodies against *P. gingivalis* as compared to severe periodontitis patients without RA.[31]

P. gingivalis produces virulent factors, i.e. gingipain cysteine proteinases, specific for arginine or lysine. Some factors, such as cytokines, chemokines, immunoglobulins, complement proteins and host cell receptors, involve the destruction of host proteins. They also degrade periodontal tissues (collagen and proteins of basement membrane). Stathopoulou et al. demonstrated that the lack of secondary cytokine response is caused by *P. gingivalis* protease degradation process. The authors conclude that *P. gingivalis* could change protective immune response to pathogenic one, because of changing cytokine profile to unfavorable by lysine gingipains associated degradation of cytokines.[32]

Recent researches showed that *P. gingivalis* could change the adaptive immune response through the interaction with dendritic cells. This response in turn promotes a cytokine release, that stimulates development of T helper 17 cells (Th17) with simultaneous downregulation of Th1 cells. Moreover, *P. gingivalis* stops gingival epithelial cells production of Th1 stimulating chemokines. As a result the pathogen influences balance between Th1 and Th17 lymphocytes, supporting the line Th17 responsible for inflammation.[33-37]

Many authors emphasize the effect of *P. gingivalis* on the complement. The bacterium provides both activating as well as inhibiting influence. This pathogen generates gingipains, which degrade complement components such as the C3, C4 and C5, what leads to the inhibition of the complement activation (regardless of the pathway of its activation) and compromises the immune response of the organism. It is suggested that *P. gingivalis* has the ability to inactivate the complement in order to protect the other periodontal bacteria. On the other hand, the capacity of activation of the complement, provided by *P. gingivalis,* cause the local inflammatory response ensuring necessary nutrients for the whole microbiome. Consequently, periodontal bacteria create own mechanism managing the inflammation to reach crucial benefits. Periodontitis is the disorder between homeostasis of the organism and microbiome which strongly affects etiology and modulation of other systematic diseases, such as RA.[38-41]

According to many studies, complement and toll-like receptors (TLR) form an important link between the infection and the local or systematic inflammatory/autoimmunological reactions such as RA or PD.[42] Literature has described, that *P. gingivalis* is able to avoid recognition by the TLRs particularly TRL2.[43,46] *P. gingivalis* with complement C5 convertase-like activity, increases cyclic adenosine monophosphate (cAMP) concentrations, resulting in suppression of macrophage function and enhanced pathogen survival. This synergy is orchestrated by TLR2 signaling, a pertussis toxin – and thapsigargin-sensitive C5a receptor pathway, with protein kinase A and glycogen synthase kinase-3b as downstream effectors. The blockade of the C5a receptor could have therapeutic implications for periodontitis and atherosclerosis.[47]

Abe et al. in their original studies performed with the use of mouse model demonstrated that *P. gingivalis* abolishes C5a receptor inactivating the immune system. In the process it releases an inflammatory response which depends on the immune complement system. The response leads to the destruction of the alveolar bone.[48] Curtis et al. presented the results of investigation showing that increased temperature at the site of inflammation in the periodontium may alter the modification of *P. gingivalis* lipid A and its interaction with TLR4, which influences the interaction of this pathogen with the innate host defense (Figure 2).[49]

Studies indicate that RA and PD express a similar profile of inflammatory mediators. RA is represents the inflammation of the synovial membrane and the destruction of bones and cartilage. In PD we can observe the destruction of the periodontal ligament and the alveolar bone. *P. gingivalis* deregulate the inflammation reactions leading to the above-mentioned processes.

Notably, *P. gingivalis* induces increased level of IL-17 in serum of periodontitis patients. A chronic activation of the IL-17R could potentially switch the acute inflammatory process into a chronic one, associated with RA.[34,50-52] In the same studies, IL-17 is demonstrated to be a significant mediator regulating immune response, produced by subset of T cells and has a strong impli-

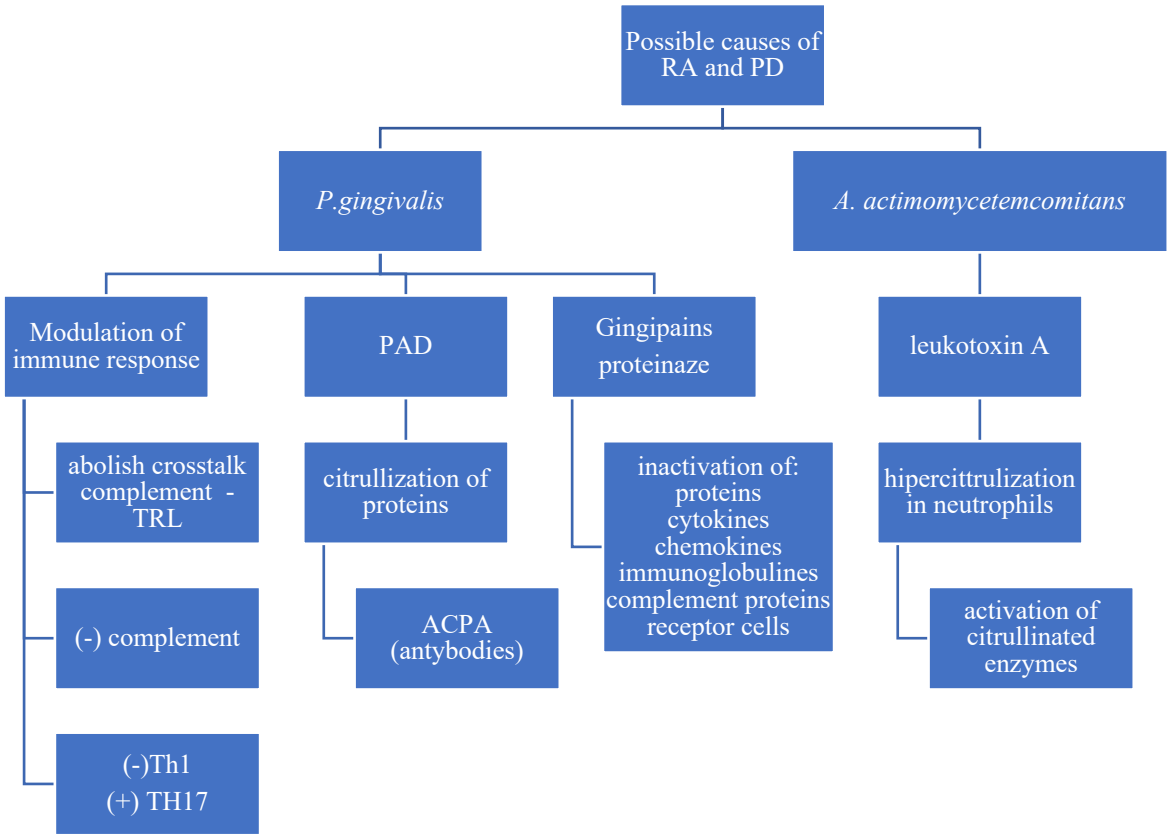

Fig. 2. Possible causes of rheumatoid arthritis and periodontitis

cation in autoimmunity and inflammation.[53] Increasing expression of the IL-17 is observed in autoimmune diseases, such as RA. Moreover, in case of periodontitis, its growth induces inflammation of gingival tissue and alveolar bone loss.[53-55]

TNF-α plays a key role in inflammatory reactions in RA and PD. This cytokine is locally produced by neutrophils as a result of innate immune response.[56,57] Kato et al. presented that, T*NF-α* increases the activity of *P. gingivalis* in human gingival epithelial cells. This situation causes a persistent infection of *P. ginigvalis* and a continuation of immune responses in periodontal tissues.[58] In other studies Palm et al. showed that *P. gingivalis* induces apoptosis of fibroblasts, that is a characteristic feature of periodontitis and periodontitis is associated with a decreased number of fibroblasts. A variety of fibroblast-derived inflammatory mediators including TNF- α are inactivated by *P. gingivalis* due to proteolytic activities of gingipains. Because of this, bacteria can create a more favorable microenvironment where it can evade the host immune response and promote its own growth and establishment.[59]

While analyzing inflammatory mediators the IL-6 should be mentioned. It is produced mainly by macrophages. However, fibroblasts, monocytes, T lymphocytes and endothelial cells also contribute to the production of IL-6. The main functions of this mediator include: removing of infection factors and regeneration of damaged tissues. What is important, IL-1 and T*NF-α stimulate the production of this interleukin.*[60] *An increased level of IL-6 is found in synovial fluid and serum of RA patients. It has been proven, that IL-6 is associated with a risk and pathogenesis of PD. It plays a significant role in the initiation of the acute phase of PD.*[61,62] According to some authors, significant increase the IL-6 production in human gingival fibroblasts is caused by lipopolysaccharide, produced by *P. gingivalis*.[63-65.]

Recent studies suggest that neutrophils play an increasingly significant role in chronic inflammatory diseases, such as rheumatoid arthritis or periodontitis. Accumulation of neutrophils can be found in inflamed and osteolytic lesions in PD. LPS generated by *P. gingivalis* could have the ability to activate osteoclastogenesis through the interaction between neutrophils and osteoclasts.[33,72]

Aggregatibacter actinomycetemcomitans

In addition to *P. gingivalis, A. actinomycetemcomitans* is mentioned as a common risk factor for RA and PD. It is a gram-negative, anaerobic bacterium, involved in the chronic and aggressive periodontitis.[66,67] This pathogen induces hypercitrullization in neutrophils through toxin leukotoxin A (LtxA) which could change the morphology of neutrophils, mimicking extracellular trap forma-

tion and this process results in the hypercitrullinated autoantigen release, triggering autoimmune response in rheumatoid arthritis patients.[5] Leukotoxin A disturbs citrullination by human PAD enzymes in host neutrophils. Hipercitrullinated proteins resemble citrullinated proteins in joints. They are also observed in gingival crevicular fluid (GCF) of patients with periodontal disease.[68] Konig et al. demonstrated that *A. actinomycetemcomitans* has the ability to deregulate protein citrullization in host's immune cells and acts as a potential inducer of cellular hypercitrullination as it expresses a potent inducer of cellular hypercitrullination as well as citrullinated RA autoantigens. In comparison to another periodontal pathogens *A. actinomycetemcomitans* might stimulate the release of citrullinated autoantigens without the participation of citrullinated enzymes.[37,67] New insights into this matter were provided by a recent study showing that *A. actinomycetemcomitans* could express a production of ACPA in individuals genetically predisposed to RA. The presence of anti-LtxA antibodies was significantly correlated with ACPA and RF positivity (Figure 2).[7,68]

Leukotoxin A produced by *A. actinomycetemcomitans*, activates the secretion of IL-1β from human macrophages, which stimulate the bone loss process in the periodontal disease and RA.[69,70] IL-1 plays an important role in the inflammation processes and stimulates the autoimmune reactions which lead to the destruction of tissues in RA and PD. Higher level of this cytokine is observed in synovial and gingival fluid in RA patients.[71]

Conclusion

Because of many clinical and experimental studies, which have suggested a connection between periodontal disease (PD) and rheumatoid arthritis (RA), there is a significant need of cooperation between physicians, dentists and dental hygienists. Local control of periodontal diseases and inflammation processes, followed by non-surgical periodontal treatment, decrease the systematic inflammation and may prove beneficial in reducing the severity of RA .The non-surgical treatment is the essential therapy in the case of periodontal disease, which may improve the oral condition in patients with RA. It consists of dental plaque control, supragingival scaling and root planning. As a result, the systematic level of inflammatory mediators and periodontal pathogens is decreased. This decrease leads to the reduction of RA activity. A routine oral examination should be conducted in patients diagnosed with RA. Within patients with active PD the basic periodontal treatment should be applied. Many studies highlight the need for complex and adequate dental care for the RA patients aiming to improve the oral health. The necessity of an interdisciplinary collaboration between doctors and dentists is undeniable, so as to the RA patients have the possibility of an interdisciplinary treatment.

Declarations

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Author contributions

Conceptualization, A.Z; Methodology, A.Z.; Investigation, A.Z.; Writing – Original Draft Preparation, A.Z.; Writing – Review & Editing, J.T.

Conflicts of interest

The authors declare no competing interests.

References

1. Renvert S, Berglund JS, Persson GR, Söderlin MK. The association between rheumatoid arthritis and periodontal disease in a population-based cross-sectional case-control study. *BMC Rheumatol.* 2020;4:31. doi: 10.1186/s41927-020-00129-4
2. Varshney S, Sharma M, Kapoor S, Siddharth M. Association between rheumatoid arthritis and periodontitis in an adult population – A cross sectional study. *J Clin Exp Dent.* 2021;13:10. doi: 10.4317/jced.57562
3. Moura MF, Cota LOM, Costa AM, Silva TA, Costa FO. Rheumatoid arthritis associated with the occurance, severity and extension of periodontitis: A case control study. *J Clin Exp Dent.* 2021;13(4):e389-e396. doi: 10.4317/jced.57540
4. De Luca F, Shoenfeld Y. The microbiome in autoimmune diseases. *Clin Exp Immunol.* 2019;195(1):74-85. doi: 10.1111/cei.13158
5. Ceccarelli F, Saccucci M, Di Carlo G, et al. Periodontitis and Rheumatoid Arthritis: The Same Inflammatory Mediators? *Mediators Inflamm.* 2019;2019:6034546. doi: 10.1155/2019/6034546
6. Mei F, Xie M, Huang X, et al. Porphyromonas gingivalis and Its Systemic Impact: Current Status. *Pathogens.* 2020;9(11):944. doi: 10.3390/pathogens9110944
7. Darrah E, Andrade F. Rheumatoid arthritis and citrullination. *Curr Opin Rheumatol.* 2018;30(1):72-78. doi: 10.1097/bor.0000000000000452
8. Ding N, Luo M, Wen YH, Li RY, Bao QY. The Effects of Non-Surgical Periodontitis Therapy on the Clinical Features and Serological Parameters of Patients Suffering from Rheumatoid Arthritis as Well as Chronic Periodontitis. *J Inflamm Res.* 2022;15:177-185. doi: 10.2147/jir.s326896
9. Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. *Bone Res.* 2018;6:15. doi: 10.1038/s41413-018-0016-9
10. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet.* 2016;388(10055):2023-2038. doi: 10.1016/s0140-6736(16)30173-8
11. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. *Lancet.* 2005;366(9499):1809-1820. doi: 10.1016/s0140-6736(05)67728-8

12. Kwon T, Lamster IB, Levin L. Current Concepts in the Management of Periodontitis. *Int Dent J.* 2021;71(6):462-476. doi: 10.1111/idj.12630
13. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. *Nat Rev Dis Primers.* 2017;3:17038. doi: 10.1038/nrdp.2017.38
14. How KY, Song KP, Chan KG. Porphyromonas gingivalis: An Overview of Periodontopathic Pathogen below the Gum Line. *Front Microbiol.* 2016;7:53. doi: 10.3389/fmicb.2016.00053
15. Kumar PS. From focal sepsis to periodontal medicine: a century of exploring the role of the oral microbiome in systemic disease. *J Physiol.* 2017;595(2):465-476. doi:10.1113/jp272427
16. Rahajoe PS, Smit MJ, Kertia N, Westra J, Vissink A. Cytokines in gingivocrevicular fluid of rheumatoid arthritis patients: A review of the literature. *Oral Dis.* 2019;25(6):1423-1434. doi: 10.1111/odi.13145
17. Gabarrini G, Grasso S, van Winkelhoff A, van Dijl J. Gingimaps: Protein Localization in the Oral Pathogen Porphyromonas gingivalis. Review. *Microbiol Mol Biol Rev.* 2020;84(1):e00032-19. doi: 10.1128/MMBR.00032-19
18. Bostanci N, Belibasakis GN. Porphyromonas gingivalis: an invasive and evasive opportunistic oral pathogen. *FEMS Microbiol Lett.* 2012;333(1):1-9. doi: 10.1111/j.1574-6968.2012.02579.x
19. Schmidt J, Jentsch H, Stingu CS, Sack U. General immune status and oral microbiology in patients with different forms of periodontitis and healthy control subjects. *PLoS One.* 2014;9(10):e109187. doi: 10.1371/journal.pone.0109187
20. Rovas A, Puriene A, Punceviciene E, Butrimiene I, Stuopelyte K, Jarmalaite S. Associations of periodontal statis in periodontitis and rheumatorid arthritis patients. *J Periodontal Implant Sci.* 2021;51;2.
21. Liao F, Li Z, Wang Y, Shi B, Gong Z, Cheng X. Porphyromonas gingivalis may play an important role in the pathogenesis of periodontitis-associated rheumatoid arthritis. *Med Hypotheses.* 2009;72(6):732-735. doi: 10.1016/j.mehy.2008.12.040
22. Gabarrini G, de Smit M, Westra J, et al. The peptidylarginine deiminase gene is a conserved feature of Porphyromonas gingivalis. *Sci Rep.* 2015;5:13936. doi: 10.1038/srep13936
23. Gómez-Bañuelos E, Mukherjee A, Darrah E, Andrade F. Rheumatoid Arthritis-Associated Mechanisms of Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans. *J Clin Med.* 2019;8(9):1309. doi: 10.3390/jcm8091309
24. Mikuls TR, Payne JB, Reinhardt RA, et al. Antibody responses to Porphyromonas gingivalis (P. gingivalis) in subjects with rheumatoid arthritis and periodontitis. *Int Immunopharmacol.* 2009;9(1):38-42. doi: 10.1016/j.intimp.2008.09.008
25. Mikuls TR, Payne JB, Yu F, et al. Periodontitis and Porphyromonas gingivalis in patients with rheumatoid arthritis. *Arthritis Rheumatol.* 2014;66(5):1090-100. doi: 10.1002/art.38348
26. Makrygiannakis D, af Klint E, Lundberg IE, et al. Citrullination is an inflammation-dependent process. *Ann Rheum Dis.* 2006;65(9):1219-1222. doi: 10.1136/ard.2005.049403
27. Snir O, Widhe M, Hermansson M, et al. Antibodies to several citrullinated antigens are enriched in the joints of rheumatoid arthritis patients. *Arthritis Rheum.* 2010;62(1):44-52. doi: 10.1002/art.25036
28. Kinloch A, Lundberg K, Wait R, et al. Synovial fluid is a site of citrullination of autoantigens in inflammatory arthritis. *Arthritis Rheum.* 2008;58(8):2287-2295. doi: 10.1002/art.23618
29. Fuggle NR, Smith TO, Kaul A, Sofat N. Hand to Mouth: A Systematic Review and Meta-Analysis of the Association between Rheumatoid Arthritis and Periodontitis. *Front Immunol.* 2016;7:80. doi:10.3389/fimmu.2016.00080
30. Wegner N, Wait R, Sroka A, et al. Peptidylarginine deiminase from Porphyromonas gingivalis citrullinates human fibrinogen and α-enolase: implications for autoimmunity in rheumatoid arthritis. *Arthritis Rheum.* 2010;62(9):2662-2672. doi: 10.1002/art.27552
31. de Smit M, 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(5):R222. doi: 10.1186/ar4061
32. Stathopoulou PG, Benakanakere MR, Galicia JC, Kinane DF. The host cytokine response to Porphyromonas gingivalis is modified by gingipains. *Oral Microbiol Immunol.* 2009;24(1):11-17. doi: 10.1111/j.1399-302X.2008.00467.x
33. Hajishengallis G. Immunomicrobial pathogenesis of periodontitis: keystones, pathobionts, and host response. *Trends Immunol.* 2014;35(1):3-11. doi: 10.1016/j.it.2013.09.001
34. Moutsopoulos NM, Kling HM, Angelov N, et al. Porphyromonas gingivalis promotes Th17 inducing pathways in chronic periodontitis. *J Autoimmun.* 2012;39(4):294-303. doi: 10.1016/j.jaut.2012.03.003
35. Jauregui CE, Wang Q, Wright CJ, Takeuchi H, Uriarte SM, Lamont RJ. Suppression of T-cell chemokines by Porphyromonas gingivalis. *Infect Immun.* 2013;81(7):2288-2295. doi: 10.1128/iai.00264-13
36. Gaddis DE, Maynard CL, Weaver CT, Michalek SM, Katz J. Role of TLR2-dependent IL-10 production in the inhibition of the initial IFN-γ T cell response to Porphyromonas gingivalis. *J Leukoc Biol.* 2013;93(1):21-31. doi: 10.1189/jlb.0512220
37. Firestein GS, McInnes IB. Immunopathogenesis of Rheumatoid Arthritis. Immunity. 2017;46(2):183-196. doi: 10.1016/j.immuni.2017.02.006
38. Hajishengallis G, Abe T, Maekawa T, Hajishengallis E, Lambris JD. Role of complement in host-microbe homeostasis of the periodontium. *Semin Immunol.* 2013;25(1):65-72. doi: 10.1016/j.smim.2013.04.004

39. Potempa J, Pike RN. Corruption of innate immunity by bacterial proteases. *J Innate Immun.* 2009;1(2):70-87. doi: 10.1159/000181144
40. Slaney JM, Gallagher A, Aduse-Opoku J, Pell K, Curtis MA. Mechanisms of resistance of Porphyromonas gingivalis to killing by serum complement. *Infect Immun.* 2006;74(9):5352-5361. doi: 10.1128/iai.00304-06
41. Hajishengallis G, Lamont RJ. Breaking bad: manipulation of the host response by Porphyromonas gingivalis. *Eur J Immunol.* 2014;44(2):328-338. doi: 10.1002/eji.201344202
42. Krauss JL, Potempa J, Lambris JD, Hajishengallis G. Complementary Tolls in the periodontium: how periodontal bacteria modify complement and Toll-like receptor responses to prevail in the host. *Periodontol.* 2010;52(1):141-162. doi: 10.1111/j.1600-0757.2009.00324.x
43. Maekawa T, Krauss JL, Abe T, et al. Porphyromonas gingivalis manipulates complement and TLR signaling to uncouple bacterial clearance from inflammation and promote dysbiosis. *Cell Host & Microbe.* 2014;15:6.
44. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. *Nat Rev Immunol.* 2015;15(1):30-44. doi: 10.1038/nri3785
45. Jia L, Han N, Du J, Guo L, Luo Z, Liu Y. Pathogenesis of Important Virulence Factors of Porphyromonas gingivalis via Toll-Like Receptors. *Front Cell Infect Microbiol.* 2019;9:262. doi: 10.3389/fcimb.2019.00262
46. Mysak J, Podzimek S, Sommerova P, et al. Porphyromonas gingivalis: Major Periodontopathic Pathogen Overview. *J Immunol Res.* 2014;2014:476068. doi: 10.1155/2014/476068
47. Wang M, Krauss JL, Domon H, et al. Microbial hijacking of complement-toll-like receptor crosstalk. *Sci Signal.* 2010;3(109):ra11. doi:10.1126/scisignal.2000697
48. Abe T, Hosur KB, Hajishengallis E, et al. Local complement-targeted intervention in periodontitis: proof-of-concept using a C5a receptor (CD88) antagonist. *J Immunol.* 2012;189(11):5442-5448. doi: 10.4049/jimmunol.1202339
49. Curtis MA, Percival RS, Devine D, et al. Temperature-dependent modulation of Porphyromonas gingivalis lipid A structure and interaction with the innate host defenses. *Infect Immun.* 2011;79(3):1187-1193. doi:10.1128/iai.00900-10
50. Zenobia C, Hajishengallis G. Basic biology and role of interleukin-17 in immunity and inflammation. *Periodontol.* 2015;69(1):142-159. doi: 10.1111/prd.12083
51. Shaker OG, Ghallab NA. IL-17 and IL-11 GCF levels in aggressive and chronic periodontitis patients: relation to PCR bacterial detection. *Mediators Inflamm.* 2012;2012:174764. doi: 10.1155/2012/174764
52. Cheng WC, van Asten SD, Burns LA, et al. Periodontitis-associated pathogens P. gingivalis and A. actinomycetemcomitans activate human CD14(+) monocytes leading to enhanced Th17/IL-17 responses. *Eur J Immunol.* 2016;46(9):2211-2221. doi: 10.1002/eji.201545871
53. Behfarnia P, Birang R, Pishva SS, Hakemi MG, Khorasani MM. Expression levels of th-2 and th-17 characteristic genes in healthy tissue versus periodontitis. *J Dent (Tehran).* 2013;10(1):23-31.
54. Chabaud M, Lubberts E, Joosten L, van Den Berg W, Miossec P. IL-17 derived from juxta-articular bone and synovium contributes to joint degradation in rheumatoid arthritis. *Arthritis Res.* 2001;3(3):168-177. doi: 10.1186/ar294
55. Kotake S, Udagawa N, Takahashi N, et al. IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. *J Clin Invest.* 1999;103(9):1345-1352. doi: 10.1172/jci5703
56. Di Benedetto A, Gigante I, Colucci S, Grano M. Periodontal disease: linking the primary inflammation to bone loss. *Clin Dev Immunol.* 2013;2013:503754. doi: 10.1155/2013/503754
57. Graves D. Cytokines that promote periodontal tissue destruction. *J Periodontol.* 2008;79(8):1585-1591. doi:10.1902/jop.2008.080183
58. Kato Y, Hagiwara M, Ishihara Y, et al. TNF-α augmented Porphyromonas gingivalis invasion in human gingival epithelial cells through Rab5 and ICAM-1. *BMC Microbiol.* 2014;14:229. doi: 10.1186/s12866-014-0229-z
59. Palm E, Khalaf H, Bengtsson T. Porphyromonas gingivalis downregulates the immune response of fibroblasts. *BMC Microbiol.* 2013;13:155. doi: 10.1186/1471-2180-13-155
60. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol.* 2014;6(10):a016295. doi: 10.1101/cshperspect.a016295
61. Pan W, Wang Q, Chen Q. The cytokine network involved in the host immune response to periodontitis. *Int J Oral Sci.* 2019;11(3):30. doi: 10.1038/s41368-019-0064-z
62. Srirangan S, Choy EH. The role of interleukin 6 in the pathophysiology of rheumatoid arthritis. *Ther Adv Musculoskelet Dis.* 2010;2(5):247-56. doi: 10.1177/1759720x10378372
63. Naruishi K, Nagata T. Biological effects of interleukin-6 on Gingival Fibroblasts: Cytokine regulation in periodontitis. *J Cell Physiol.* 2018;233(9):6393-6400. doi:10.1002/jcp.26521
64. Herath TD, Wang Y, Seneviratne CJ, et al. Porphyromonas gingivalis lipopolysaccharide lipid A heterogeneity differentially modulates the expression of IL-6 and IL-8 in human gingival fibroblasts. *J Clin Periodontol.* 2011;38(8):694-701. doi: 10.1111/j.1600-051X.2011.01741.x
65. Ridwan RD, Sidarningsih, Kusumaningsih T, Salim S. Effect of lipopolysaccharide derived from surabaya isolates of Actinobacillus actinomycetemcomitans on alveolar bone destruction. *Vet World.* 2018;11(2):161-166. doi: 10.14202/vetworld.2018.161-166
66. Pahumunto N, Ruangsri P, Wongsuwanlert M, Piwat S, Dahlen G, Teanpaisan R. Aggregatibacter actinomycetemcomitans serotypes and DGGE subtypes in Thai adults with chronic periodontitis. *Arch Oral Biol.* 2015;60(12):1789-1796. doi: 10.1016/j.archoralbio.2015.09.003
67. Konig MF, Abusleme L, Reinholdt J, et al. Aggregatibacter actinomycetemcomitans-induced hypercitrullination

links periodontal infection to autoimmunity in rheumatoid arthritis. *Sci Transl Med.* 2016;8(369):369ra176. doi: 10.1126/scitranslmed.aaj1921

68. Derksen V, Huizinga TWJ, van der Woude D. The role of autoantibodies in the pathophysiology of rheumatoid arthritis. *Semin Immunopathol.* 2017;39(4):437-446. doi: 10.1007/s00281-017-0627-z
69. Kelk P, Claesson R, Chen C, Sjöstedt A, Johansson A. IL-1beta secretion induced by Aggregatibacter (Actinobacillus) actinomycetemcomitans is mainly caused by the leukotoxin. *Int J Med Microbiol.* 2008;298(5-6):529-541. doi: 10.1016/j.ijmm.2007.06.005
70. Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. *Blood.* 2011;117(14):3720-3732. doi: 10.1182/blood-2010-07-273417
71. Barksby HE, Lea SR, Preshaw PM, Taylor JJ. The expanding family of interleukin-1 cytokines and their role in destructive inflammatory disorders. *Clin Exp Immunol.* 2007;149(2):217-225. doi: 10.1111/j.1365-2249.2007.03441.x
72. Caielli S, Banchereau J, Pascual V. Neutrophils come of age in chronic inflammation. *Curr Opin Immunol.* 2012;24(6):671-677. doi: 10.1016/j.coi.2012.09.008