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Periodontal research contributions to basic sciences: From cell communication and host-parasite interactions to inflammation and bone biology

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Abstract: The periodontium comprises all structures surrounding the teeth, including gingiva, root cementum, periodontal ligament and alveolar bone. Those tissues aim to protect and support the teeth and are challenged by a residing microbiota that leads to subclinical inflammation even in physiological conditions. Periodontitis, a prevalent multicausal inflammatory and destructive disease, develops as a result from complex host-parasite interactions. This unique physiologic and pathologic scenario enables the development of research methods which allows conclusions beyond the simple understanding of periodontal homeostasis. The aim of this viewpoint was to explore potential contributions of periodontal research to a wide array of basic science specialties, such as cell and molecular biology, microbiology, immunology, endocrinology, rheumatology, among others.

Introduction

The tooth-surrounding structures (a.k.a., periodontium) are comprised of gingiva, root cementum, periodontal ligament and alveolar bone. Gingiva is formed of diverse–in location and features-epithelial layers (i.e., sulcular, junctional and oral epithelium) on top of an underlying connective tissue. Fibroblasts, epithelial cells, cementoblasts, cementocytes, osteoblasts, osteoclasts and osteocytes are some of the tissue-specific cell components of this great complex structure, which also includes blood vessels, nerves, and extracellular matrix (Nanci and Bosshardt, 2006).

Periodontal literature greatly contributes to dental research, with dedicated journals being ranked #1, #2 and #3 in Dentistry, Oral Surgery and Medicine Category of Journal Citations Report 2020. Over the recent years, the core periodontal journals have increased their impact factors approximately 50–100%, suggesting their contributions for both oral health care and medicine (Ahmad and Slots, 2021). Moreover, a recent study showed that from the 300 most cited articles published in periodontology, basic sciences including microbiology comprised more than 50% of the included articles (Faggion *et al.*, 2017). Therefore, not only periodontal knowledge may benefit from basic sciences development, but the opposite is also true.

The aim of this viewpoint was to explore potential contributions of periodontal research to a wide array of basic science specialties, such as cell and molecular biology, microbiology, immunology, endocrinology, rheumatology, among others.

Main text

Different cell types act together to dictate the homeostasis of periodontal tissues. Innate and adaptive immune cells contribute through the release of their molecules trying to maintain homeostasis in periodontal tissues, so the host immune response plays a pivotal role in protect against periodontal pathogens (Becerra-Ruiz *et al.*, 2021). Understanding specific cell response in physiological and 'challenged' conditions, as well as cell response to different potential treatments, has been the focus of several investigations. Also, co-culture has been used as a model to better characterize interaction between cell types in this scenario (Bedran *et al.*, 2014; Loomer *et al.*, 1998). Additionally, the periodontal ligament space harbors mesenchymal stem cells that can potentially regenerate biological structures and deserves special attention (Liu *et al.*, 2019).

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However, homeostasis of the periodontal tissues is frequently disturbed, since microbial accumulation on the tooth and gingival crevice occurs right after every attempt for plaque removal. As a consequence, subclinical inflammation characterized by histological neutrophil infiltrate, with some macrophages and very few plasma cells can be frequently observed in physiological conditions (Hajishengallis and Korostoff, 2017). In this scenario, potential periodontopathogens have been characterized and studied, such as *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia*, *Prevotella intermedia* and *Treponema denticola*. Some of those microorganisms have also been involved in other systemic diseases. For example, *P. gingivalis* and *A. actinomycetemcomitans* have been detected in coronary atheromatous plaque, suggesting systemic dissemination of oral pathogens (Joshi *et al.*, 2021). Additionally, *P. gingivalis* and *A. actinomycetemcomitans* have also been linked to the pathogenesis of rheumatoid arthritis (RA) throughout different mechanisms, as briefly described down below (de Molon *et al.*, 2019a). Hence, observations from host-parasite interactions in the periodontium may serve as basis for useful models to characterize other microbial-associated systemic diseases as well.

Periodontal disease (PD) is a complex, high prevalent and multicausal chronic inflammatory disease associated with a dysbiotic biofilm and characterized by loss of gingival tissue, periodontal ligament, cement and alveolar bone (Papapanou *et al.*, 2018). It is considered a main cause of tooth loss in the adult population. Severe PD is the sixth most prevalent disease worldwide, with an overall prevalence of 11.2% and 734 million people affected (Richards, 2014). Various animal models have been used to mimic the observed features of periodontitis such as inflammatory infiltrate and bone loss around teeth. The development of PD through different animal models can be separated into different phases comprising the development of biofilm, invasion of periodontal pathogenic bacteria and their proinflammatory products, and the induction of a destructive host response (Marchesan *et al.*, 2018). Although no single animal model can replicate the complexity of PD (Hajishengallis *et al.*, 2015), distinctive phases of the disease can be addressed by three main animal models of PD, which include ligature placement, bacterial lipopolysaccharide (LPS) injections, and bacterial challenge in rodents. Briefly, the ligature-induced bone loss is one of the most utilized experimental PD model (da Ponte Leguizamon *et al.*, 2021). The rationale behind the ligature model is based on the accumulation of bacteria around the thread (silk or nylon) to sustain the inflammation and bone loss. It has been considered as an acute model of periodontal tissue breakdown resulting in two distinct phases: Acute (0–14 days), characterized by inflammation, increased gene expression of IL-6, IL-1β, TNF-α, RANKL, and OPG, and rapid alveolar bone destruction; and chronic (14–21 days) with no significant progression of bone loss (de Molon *et al.*, 2018). The major drawback of this model is the mechanical trauma caused during the ligature placement, especially in small rodents (de Molon *et al.*, 2013), which demands very high level of technical skills. Furthermore, the bacterial lipopolysaccharide (LPS) model is also highly employed in periodontal research due to the predictability of the bone resorption caused by the continuous injection of LPS into the gingival tissue (de Molon *et al.*, 2014; Graves *et al.*, 2008; Graves *et al.*, 2012). Finally, the oral inoculation model (oral gavage) with live bacteria (or consortium of bacterial species) is perhaps the model that best represents the PD in humans (de Molon *et al.*, 2013). The rationale behind it is to allow the adherence and colonization of the exogenous bacteria to grow into the animal mouth leading to an increase in pro-inflammatory mediators, inflammatory process and bone destruction. However, the disadvantage of this model is the increased time to consistently develop alveolar bone loss once bacteria need to colonize, grow, and then cause the disease (de Molon *et al.*, 2016).

It is noteworthy to mention the humanized mice models, which have been described as immuno-deficient mice engrafted with human hematopoietic cells and/or tissues capable of reconstituting a functional immune system. These models allow the study of human biological processes and affections. There are 3 main humanized mice models: the human stem cells (hu-HSC) model, the human peripheral blood lymphocytes (hu-PBL) model, and the human bone marrow/fetal liver/thymus (BLT) model. A complete description of the humanized mice models can be found in a review article (Rojas *et al.*, 2021). It is important to bear in mind that all experimental models of PD have their own limitation that are inherent of the model, and no one single model is able to replicate all aspects of human periodontitis.

Those models, apart from studying periodontal diseases, are also useful for 1) understanding systemic responses to low-grade inflammation; 2) characterizing bone biology and osteoimmunology in pathological scenarios; and 3) understanding the inflammatory and immunological processes (Cavagni *et al.*, 2016). For example, the role of sex hormones on periodontal health, inflammation and bone loss, and periodontal healing has been described and those findings can be extrapolated to different inflammatory diseases as well (Steffens *et al.*, 2015; Steffens *et al.*, 2018). Moreover, studies using experimental PD models have clarified the pivotal role of bacteria in starting the host inflammatory response that leads to periodontal tissue breakdown and have identified key mediators (IL-1, TNF, prostaglandins, complement, RANKL) that induce inflammatory breakdown (Hajishengallis *et al.*, 2015) and might affect other systemic diseases. In this context, it is well documented that diabetes mellitus increase the risk and severity of PD (Chapple *et al.*, 2013). PD models have recognized a mechanistic basis for this association through the increased formation of advanced glycation end products.

Also, new treatment modalities that benefit periodontal diseases can be understood as potential treatments for other inflammatory conditions. For instance, specialized proresolvin mediators (SPMs) are a novel family of oxylipids mediators including resolvins, maresins, lipoxins and protectins derived from omega-3 polyunsaturated fatty acid (PUFA), which regulate the inflammatory process without immunosuppression (Balta *et al.*, 2021). The SPMs function in the termination of inflammation by activating specific mechanisms to restore tissue homeostasis (Serhan, 2014; Serhan *et al.*, 2008). Briefly, they selectively inhibit leukocyte recruitment, activate macrophage phagocytosis of microorganisms, stimulate infiltration of monocytes, and stimulate expression of

molecules involved in antimicrobial defense (de Molon *et al.*, 2019b). Such SPMs promote tissue repair, elimination of bacteria, increase the host defense, and can impact the responses of adaptive immune cells (Mizraji *et al.*, 2018). Resolvins have been suggested as a potential treatment targeting the inflammatory process in periodontal diseases with promising results that could extrapolate its benefits from the local periodontal setting (Hamilton *et al.*, 2017). In this regard, Hasturk *et al.* demonstrated that topical application RvE1 was able to prevent initiation and progression of experimental PD, and even induce the regeneration of periodontal tissues (alveolar bone, periodontal ligament and cement) in a rabbit model of ligature-induced bone loss (Hasturk *et al.*, 2007; Hasturk *et al.*, 2006). RvE1 downregulated the progression of PD by decreasing proinflammatory mediators and reducing inflammatory bone loss. Studies investigating the effects of different SPMs, such as resolvin E1, maresins, and resolvin E2 treatment on other diseases have been described in the recent literature throughout different mechanisms. Most of them showed beneficial effects of SPMs on neuro-inflammation (Derada Troletti *et al.*, 2021), tuberculosis (Hayford *et al.*, 2021), wound healing, diabetes, (Shofler *et al.*, 2021), and chronic inflammation (Lamon-Fava *et al.*, 2021), just to cite a few.

Moreover, periodontitis has been epidemiologically associated with several other noncommunicable diseases (NCDs), such as diabetes mellitus, cardiovascular diseases,

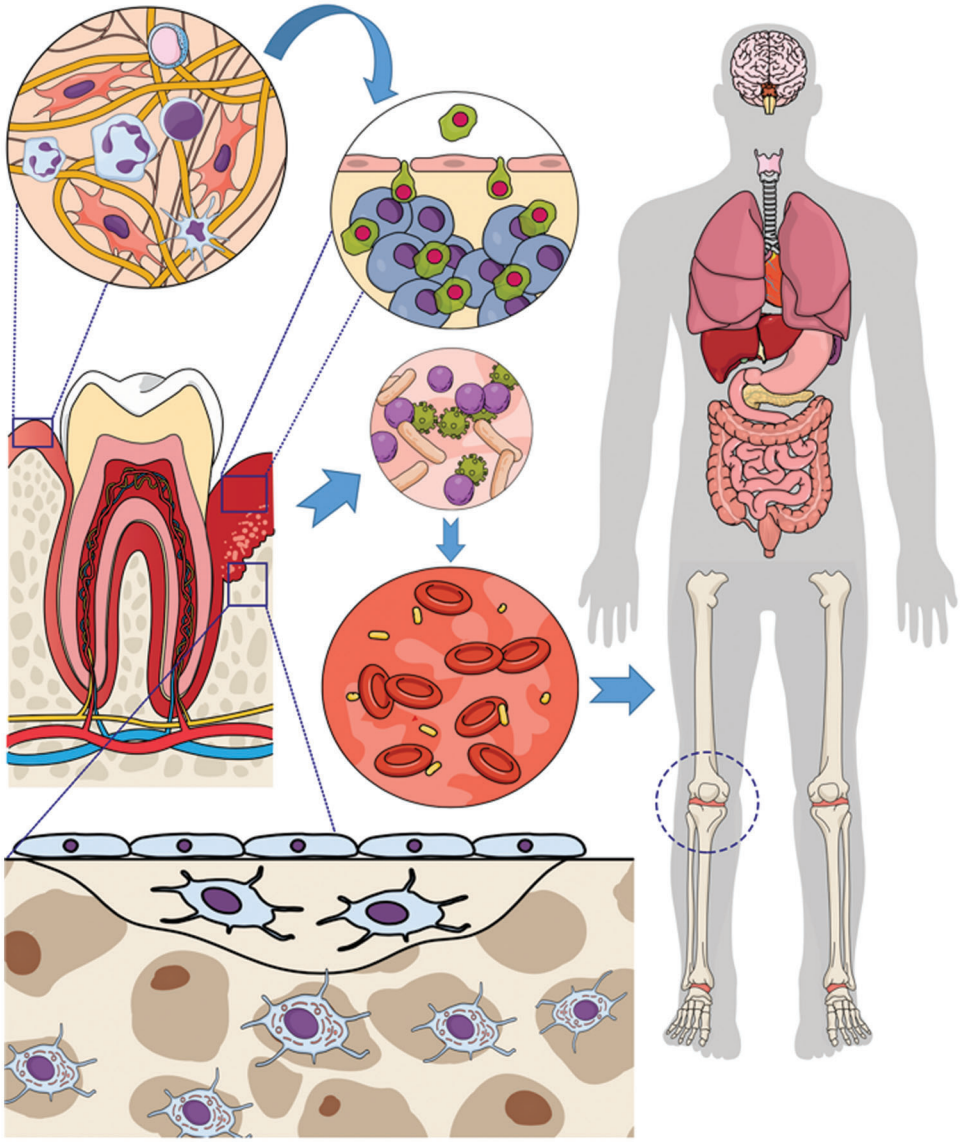

FIGURE 1. An overview of periodontal disease characteristics and how it affects other systemic diseases. PD is initiated by a dysbiotic biofilm in intimate contact with the gingival tissue. In a homeostatic situation (upper left circle) there is predominance of fibroblast and few inflammatory cells (neutrophils, macrophages, and T cells) in the connective tissue. With the progression of PD (represented by the circle in the upper center) there is predominance of B cells (plasma cells) and T cells due to the activation of the host adaptive immune response trying to eliminate the bacteria antigens. The adaptive host response is responsible for the majority of tissue destruction observed during the PD progression, which leads to the activation of osteoclasts, the cells accountable for the resorption of the alveolar bone, leading to the clinical signs of periodontitis (represented by the rectangle). One of the biologically plausible mechanisms linking PD to other non-communicable diseases rely on the translocation of bacteria from the ulcerated epithelium to the blood stream (represented by the central and inferior circles), which can reach other tissues from the host, such as heart, lung, intestine, pancreas, and joints) and is represented in Fig. 1 by the human body in the right of the panel.

obesity and RA (Beck *et al.*, 2019; Hajishengallis and Chavakis, 2021; Marcantonio *et al.*, 2021). Recent data on interventional studies indicates that PD treatment ameliorates surrogate-markers of inflammation-driven disorders (D'Aiuto *et al.*, 2018; Teles and Wang, 2011; Moura *et al.*, 2021). Potential causal mechanisms involve periodontal-related microbial (or their byproducts) and inflammatory pathways that contribute to the development of the systemic conditions (Winning *et al.*, 2015). For instance, the most described biologic plausibility linking PD and other systemic conditions rely on the translocation of microorganisms and/or their products through the ulcerated epithelium of the periodontal pocket to the bloodstream. This might lead to systemic alteration in consequence to the increased immunological response of the host to the virulent factors of the bacterial species, as shown in Fig. 1. On the other hand, it is also possible that the observed associations derive from shared risk factors to NCDs, such as smoking, genetic background, gut microbiota, physical inactivity, unhealthy diet and harmful use of alcohol (Tonetti *et al.*, 2017).

Of importance, RA has been linked to PD in several translational and clinical studies (de Molon *et al.*, 2019a; de Aquino *et al.*, 2017; de Aquino *et al.*, 2014). Despite its common pathological features between RA and PD (increased infiltration of inflammatory and immune cells, increased expression of pro-inflammatory mediators and degrading enzymes, and osteoclast activation), *P. gingivalis* and *A. actinomycetemcomitans* have also been associated to the RA pathogenesis. *P. gingivalis* is the only known microorganism that is able to express the peptidylarginine deiminase (PAD), an enzyme that mediate the post-translational modification of the amino acid arginine into citrulline, a process called citrullination (Mangat *et al.*, 2010). Increased formation of citrullinated proteins can act as autoantigens, leading to the production of auto-antibodies favoring the RA pathogenesis. Thus, resulting in the generation of an immune response to citrullinated self-antigens (Rosenstein *et al.*, 2004). Furthermore, *A. actinomycetemcomitans* leads to the hypercitrullination of neutrophils and, as a result, there is activation of citrulline enzymes, which are also involved in the breakdown of the immune tolerance to the host molecules (Konig *et al.*, 2016). PD has also been linked with other rheumatic diseases such as, psoriatic arthritis (Ustun *et al.*, 2013; Sezer *et al.*, 2016), ankylosing spondylitis (Enginar *et al.*, 2021; Pandey *et al.*, 2020), systemic lupus erythematosus (Bolstad *et al.*, 2021; Sojod *et al.*, 2021), and osteoarthritis (Kim *et al.*, 2020).

Taken together, periodontal research can contribute to the understanding of pathogenic mechanisms of several inflammatory diseases.

Vision of the future

There is growing body of evidence demonstrating that PD negatively impacts systemic health and several inflammatory conditions, such as diabetes, cardiovascular diseases, RA, pregnancy outcomes, pulmonary diseases, and others, through different mechanisms (Hajishengallis and Chavakis, 2021). On the other hand, clinical, interventional and experimental studies suggest that different NCDs also affect PD initiation and progression. It is important to bear in mind that the development of research methods of experimental periodontitis might contribute significantly to study potential biological mechanisms of a wide range of NCDs and their association with PD. Furthermore, basic science can also contribute to the understanding of PD pathogenesis and its effects on systemic conditions. Future translational research should target the mechanism, understanding the potential link among periodontitis and other inflammatory conditions.

Emerging evidence on the field of mechanobiology have been described recently (Jang *et al.*, 2018; Dieterle *et al.*, 2021; Gauthier *et al.*, 2021). The periodontium, made of tissues of different natures, shows a complicated biomechanical environment. It is known that the activity of the different cell types are greatly influenced by this biomechanical environment, that is studied in the field of mechanobiology. Investigating this mechanical environment to understand how the mechanical cues are transmitted to the osteocytes of the alveolar bone, to the cementoblasts of the cementum, or to the fibroblasts of the periodontal ligament might be of great interest for those who are interested in general cell mechanobiology. More specifically, the periodontal ligament being a soft tissue, understanding what occurs in terms of biomechanics, at the interface between the ligament and the bone is relevant to understanding how bone cells respond to a very specific biomechanical cue. The issue of interface between bone and other type of tissues, such as other ligaments or cartilage, is still a great challenge. Indeed, understanding periodontium biomechanics and mechanobiology can contribute to better understanding other joints' biomechanics and mechanobiology and osteoarticular pathologies.

Availability of Data Material: Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Author Contribution: The authors confirm contribution to the paper as follows: study conception and design: RSM, EDA, JAC, and JPS; draft manuscript preparation: RSM, EDA, JAC, and JPS. All authors reviewed the article text and approved the final version of the manuscript.

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