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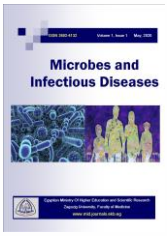

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Review article

Interactions between T-cells and B-cells in the microbiological and histopathological mechanisms of peri-implantitis development

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ABSTRACT

Background: Peri-implantitis is a pathological disease characterized by the presence of inflammatory osteolysis in the vicinity of dental implants. The comprehension of the microbiology and histopathology of the subject is crucial for its efficient management. This condition encompasses an intricate biofilm like the one seen in periodontal disease, yet with discernible bacteria profiles. Histopathological investigation at an advanced level provides significant insights into the shape of bones and the process of osseointegration, hence contributing valuable information about the course of diseases. **Aim:** The present review aims to consolidate existing literature on the identification of microorganisms and the histopathological characteristics associated with peri-implantitis. It elucidates the significant involvement of T-cells and B-cells in the immunological response to this condition. In this review, we examine the ramifications pertaining to the diagnostic, treatment, and public health domain, with a particular emphasis on the imperative nature of infection control measures and the development of novel therapeutic strategies that selectively target distinct immunological pathways. The significance of having a complete knowledge of peri-implantitis from several perspectives is emphasized in this review, as it has the potential to enhance clinical practice and improve patient care within the field of dentistry.

Introduction

Peri-implantitis is a pathological condition that affects the tissues surrounding dental implants. It is characterized by inflammatory osteolysis, which is the clinical hallmark of the disease. Understanding the microbiology and histopathology of peri-implantitis is crucial for effective diagnosis and treatment. Microbial profiles and detection techniques play a significant role in identifying the pathogens associated with peri-implant diseases [1]. Additionally, histological analysis of advanced peri-implantitis bone defects has revealed important insights into the morphology of the remaining peri-implant bone and the level of osseointegration, which are essential for understanding the disease progression [2]. Therefore, a comprehensive understanding of the microbiological and histopathological characteristics of peri-implantitis is essential for developing effective diagnostic and treatment strategies to address this significant issue in contemporary dentistry [3,4].

Description of peri-implant disease

Peri-implant diseases (PIDs) are inflammatory conditions that occur around dental

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implants. They are generally categorized into two types: peri-implant mucositis and peri-implantitis.

Peri-implant mucositis is characterized by specific clinical signs such as bleeding on probing (BOP), reddened soft tissues, swelling, and/or pus formation near the implant, notably without any loss of marginal alveolar bone. There may be increased probing depths (PD), but this is often attributed to swelling and reduced resistance to dental probing. Unlike periodontitis, these probing depth measurements may not be as diagnostic for peri-implant mucositis, and the standard depth ranges used for teeth (whether diseased or not) may not be directly applicable for assessing implant health. Early detection of peri-implant mucositis is crucial, as it can usually be effectively treated with debridement and antimicrobial therapies. Research by **Barootchi et al.** in 2020 even suggests that adding enamel matrix proteins to debridement can improve treatment outcomes for peri-implant mucositis [5].

In contrast, peri-implantitis is a more severe form of PID, presenting with similar inflammatory signs but typically with much deeper probing depths than those seen in periodontitis. This condition also includes other inflammation markers, such as pain during probing (occasionally spontaneous) and bleeding on probing, as noted by **Cosgarea et al.** in 2019 and **Berglundh et al.** in 2018. Furthermore, the loss of marginal bone in peri-implantitis is often much more extensive compared to the bone loss around teeth affected by periodontitis [6,7].

Current insights into the pathophysiological mechanisms of peri-implant diseases

Peri-implant diseases (PID), akin to periodontal diseases, are believed to originate from an overabundance of bacteria in biofilms, forming part of a dysbiotic microbiome. This microbial accumulation, along with associated virulence factors, triggers inflammatory responses in both the soft and hard tissues surrounding dental implants, as outlined by **Schwarz et al.** [8]. Initially, these inflammatory lesions affect the mucosa around the implant, but as the condition progresses or becomes chronic, it advances into the bone, leading to peri-implantitis and subsequent bone loss. This bone loss is critical since bone tissue is essential for the stabilization and anchoring of endosseous dental implants, as emphasized by **Albrektsson et al.** [9]. However, the specific pathophysiological pathways of PID, and particularly peri-implantitis, are not fully understood.

Current research is focusing on the pathogenic bacteria implicated in PIDs and their interaction with the immune system, which results in inflammatory disease and the destruction of peri-implant connective tissues. There's a growing interest in exploring the distinctive aspects of the inflammatory processes in peri-implantitis compared to periodontitis. A study like the one by **Oliveira et al.** [10]. have identified uniquely higher levels of certain pro-inflammatory cytokines (such as interleukins) and osteoclastogenic cytokines (RANKL) in the peri-implant crevicular fluid during peri-implantitis. This suggests that while PIDs may have clinical manifestations similar to periodontitis, they are likely driven by a distinct microbial profile and inflammatory response, as proposed by **Viafara-García et al.** [11].

Understanding these unique microbial and immunoinflammatory markers could provide deeper insights into the pathophysiology of PID, particularly peri-implantitis, and potentially lead to better diagnostic and treatment approaches. This is essential for the ongoing investigation into PIDs, as it could pave the way for more effective management of these conditions [10,11]. **(Figure 1)** [12].

Oral microbiome of peri-implantitis

Peri-implantitis is a complex disease that involves a mixed microbial flora, which resembles that of periodontal infections, with some notable differences [13]. The microbial profiles of peri-implantitis have been studied using various methods, including bacterial culture, PCR-based assessment, hybridization techniques, pyrosequencing, and transcriptomic analyses [14]. However, after analyzing several studies, no microbial species were found to be specific for peri-implantitis [3,4]. The microbial etiology of peri-implantitis is due to the accumulation of a complex biofilm community along the implant surface, which triggers the inflammatory destruction of the peri-implant tissues [3]. The predominant genera in the peri-implant microbiota include *Butyrivibrio*, *Campylobacter*, *Eubacterium*, *Prevotella*, *Selenomonas*, *Streptococcus*, and others [4]. The differences between periodontal and peri-implant health and disease are not consistent across all

studies, possibly due to the bias introduced by the microbial detection technique **(Figure 2)** [14].

Histopathological Changes in peri-implant tissues

The tissue responses to microbial invasion in peri-implantitis involve non-specific changes in the peri-implant mucosa, including inflammatory lesions, accumulation of bacterial plaque, and microbial contamination, leading to inflammation and exudation of inflammatory cells [15]. Mast cells are also actively involved in the pathogenesis of peri-implant inflammation [15]. Furthermore, histopathology plays a crucial role in diagnosing and understanding peri-implantitis. A study on advanced peri-implantitis bone defects revealed that inflammatory osteolysis is the clinical hallmark of peri-implantitis, and the morphology of the remaining peri-implant bone and the level of osseointegration are essential for understanding the disease progression [16].

Supporting this, **Baus-Domínguez et al.** in 2023, have contributed valuable insights into the histopathological changes in peri-implant tissues in contact with different implant materials **(Figure 3)** [17]. Their use of Masson's Trichrome technique revealed how different materials can influence the inflammatory response in the soft tissue surrounding dental implants [17]. These findings align with observations of inflammatory osteolysis as a clinical hallmark of peri-implantitis and underscore the importance of material selection in managing the transmucosal barrier around dental implants [16].

Additionally, the microbial profiles of peri-implant diseases have been studied using various methods, and the mixed microbial flora of peri-implant infections resembles that of periodontal infections, with some notable differences [18].

T-cell and B-cell responses in peri-implantitis

T-cells and B-cells are essential components of the immune system that play specific roles in peri-implantitis. T-cells are involved in the regulation of the immune response, and their activation is essential for the clearance of bacterial infections. In peri-implantitis, the inflammatory milieu contains higher levels of RANKL-expressing CD4+ T-cells, which are involved in the pathogenesis of the disease. B-cells, on the other hand, are responsible for the production of antibodies that recognize and neutralize specific pathogens [18]. In peri-implantitis, the presence of bacterial plaque and microbial contamination of peri-implant soft tissue causes inflammation and large exudation of inflammatory cells, including B-cells [2,3]. Histopathological and immunohistochemical analysis of peri-implant soft and hard tissues in patients with peri-implantitis has revealed the presence of mast cells, vascularization, and the process of angiogenesis, which are involved in the pathogenesis of the disease [4].

Interactions between microbial agents and immune cells

T-cells and B-cells interact with microbial agents in peri-implantitis through various mechanisms. In peri-implantitis, the inflammatory milieu contains higher levels of RANKL-expressing CD4+ T and B cells, which contribute to the pathogenesis of the disease [18]. The interactions between T-cells, B-cells, and microbial agents in peri-implantitis can be summarized as follows:

1. Recognition of microbial antigens:

T-cells and B-cells recognize microbial antigens presented by antigen-presenting cells (APCs), such as dendritic cells and macrophages. This recognition triggers an immune response, leading to the production of cytokines and other inflammatory mediators [17,18].

2. Activation and differentiation:

Activated T-cells differentiate into effector cells, such as Th1, Th2, Th17, and Th9 cells, which produce cytokines like IFN-γ, IL-4, IL-17, and IL-9, respectively. These cytokines further influence the immune response and the production of antibodies by B-cells [17].

3. B-cell activation:

B-cells are activated by microbial antigens and differentiate into plasma cells, which secrete antibodies that neutralize specific pathogens [17].

4. Inflammatory response:

The interactions between T-cells, B-cells, and microbial agents in peri-implantitis lead to an excessive inflammatory response, characterized by the infiltration of neutrophils, monocytes, lymphocytes, and RANKL-expressing CD4+ T and B cells [16,17]. This inflammatory response contributes to the progression of peri-implantitis, causing bone resorption and implant dysfunction **(Figure 4)** [14,17].

Clinical implications and public health perspectives

Implications for infection control and public health.

1. Infection control:

Peri-implantitis is a significant issue in contemporary dentistry, and understanding the interactions between T-cells, B-cells, and microbial agents is crucial for developing effective infection control strategies [17,18]. This knowledge can help dental professionals identify and manage patients at risk for peri-implantitis, leading to better patient outcomes and reduced morbidity.

2. Public health:

The excessive inflammatory response to infection in peri-implantitis can have significant public health implications, as it may lead to increased healthcare costs, reduced quality of life for affected individuals, and increased burden on healthcare systems [18]. By identifying risk factors and implementing preventive measures, public health interventions can help reduce the prevalence of peri-implantitis and improve overall oral health.

Potential therapeutic strategies targeting T-cell and B-cell responses

1.Immune modulation:

Developing therapies that modulate T-cell and B-cell responses in peri-implantitis may help reduce the inflammatory response and prevent bone resorption around dental implants [18]. This could involve using biologics, such as cytokine inhibitors or monoclonal antibodies, to target specific immune cells and pathways.

2.Resolvin D2:

Resolvin D2 (RvD2) has been shown to resolve inflammation in experimental peri-implantitis by reducing the infiltration of neutrophils, monocytes, lymphocytes, and RANKL-expressing CD4+ T and B cells [17,18]. Further research is needed to determine the potential therapeutic applications of RvD2 in treating peri-implantitis.

3.Microbiome manipulation:

Manipulating the microbiome around dental implants may help prevent the development of peri-implantitis by promoting a more favorable balance of oral microflora [18]. This could involve the use of probiotics, antibiotics, or other interventions to alter the bacterial community around dental implants [19,20].

Figure 1. Diagrammatic representation of the immune response in peri-implantitis and resulting osteoclastic activity [12].

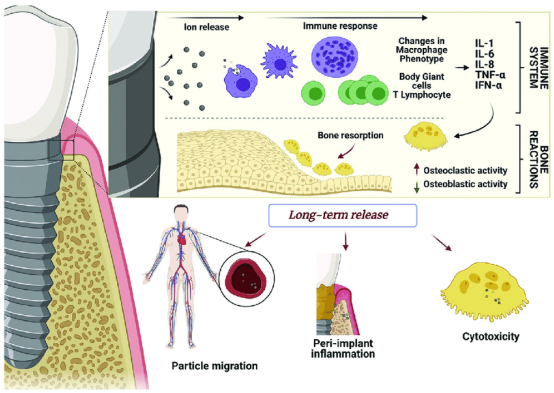


Figure 2. The role of bacterial biofilm and inflammation in peri-implant diseases [14].

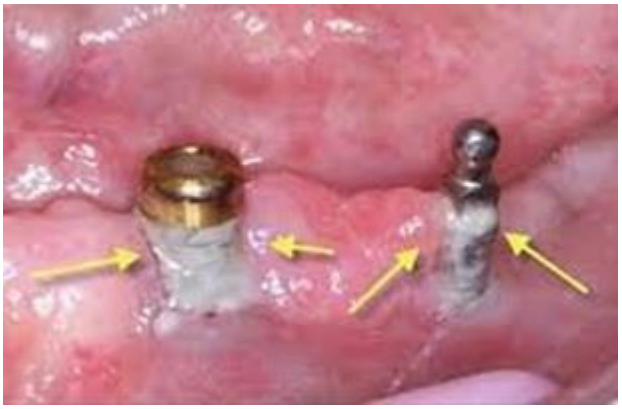


Figure 3. Histology with Masson's Trichrome technique of soft tissue in contact with BRILLIANT Crios. (a) 4× image showing proliferation of connective tissue bundles without alterations in their arrangement in the submucosal space. (b) 10× image showing increased vascular proliferation [17].

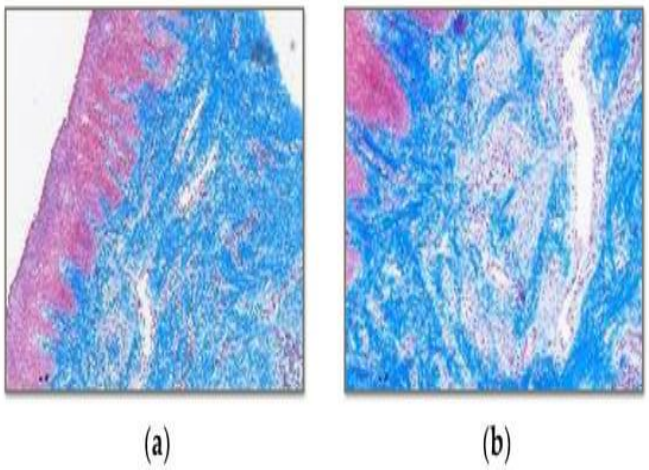
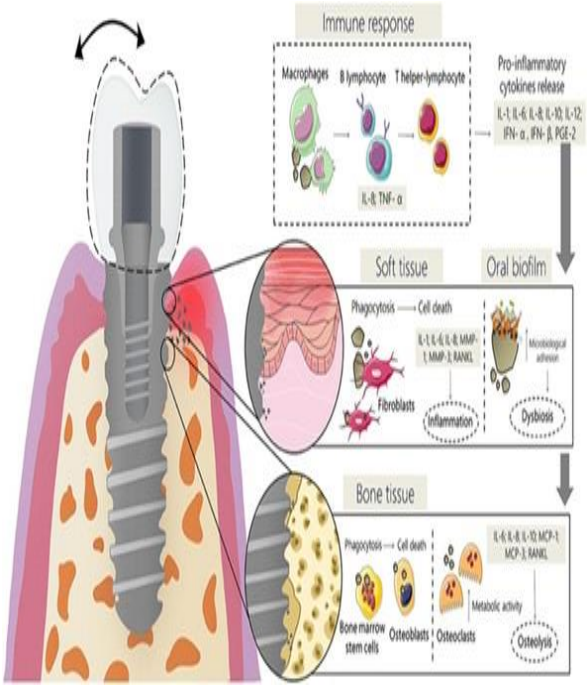


Figure 4. The role of bacterial biofilm and inflammation in peri-implant diseases [14].



Conclusion

Peri-implantitis is a complex dental issue where microbial infection and immune responses, particularly from T-cells and B-cells, interact closely. Understanding these interactions is vital for better diagnosis and treatment. Addressing the disease involves innovative treatments, emphasizing infection control for public health, and patient education. Future research should investigate regenerative therapies and targeted immunomodulatory treatments, alongside the influence of oral hygiene on disease risk. A holistic understanding of the disease's microbiological, histopathological, and immunological aspects is key to enhancing dental care and patient health.

Conflict of interest

The authors declared any conflict of interest.

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