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Gingiva as immunological protection of the periodontium (Minireview)

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Abstract

OBJECTIVES: The anti-infective, predominantly antibacterial protection of the periodontium has been well-mapped in its various inflammatory diseases, especially in different clinical forms of gingivitis and periodontitis. In various inflammatory periodontal diseases, many immunocompetent cells and substances have been identified in periodontal structures, including the gingiva, which implement and ensure this anti-inflammatory response. There is ample evidence that in many clinical forms of gingivitis and periodontitis, these immunological-defensive reactions occur in the gingival tissue. Our small review study aims to demonstrate that gingival tissue acts as a small immunological-defensive organ localized in the tissue of healthy gingiva at the necks of the teeth throughout the lifetime of our patients. Furthermore, through a literature search, we investigated whether the anti-inflammatory and defensive equipment and responses are identical in differently inflamed and clinically healthy gingiva.

MATERIAL AND METHODS: We compiled a small review study that illuminates the knowledge on the gingiva as an immunocompetent organ through a focused search and retrieval of currently available literature sources. Our small review study aims to demonstrate that gingival tissue acts as a small defensive-immunological organ localized in the healthy gingival tissue at the dental necks throughout the lifetime of our patients. Furthermore, through a literature search, we investigated whether the anti-inflammatory and defensive equipment and responses are identical in differently inflamed and clinically healthy gingiva.

CONCLUSION: Our findings confirm ongoing anti-inflammatory, immunological, and regenerative responses and processes in healthy gingival tissue that prevent bacterial and viral microorganisms from crossing into deeper periodontal tissues. From these results, we can further conclude that the healthy human gingiva performs an essential function as a relatively independent and small anti-inflammatory and lymphatic organ.

MINIREVIEW

INTRODUCTION

Healthy periodontal tissues provide an adequately solid yet flexible connection between the tooth roots and the jaw bones' alveolar processes, which is crucial requirement for adequate transmission of masticatory pressure and provision of masticatory function. As is generally known, the periodontium consists of four basic components: the gingiva, periodontal ligaments, alveolar bone, and dental cement. Each component differs in its typical localization, tissue structure, biochemical and cellular composition. Nevertheless, all these components work together in its immunological protection as a single unit (Kayal, 2013). Despite the considerable accumulation of oral and periodontal microbial pathogens in the oral cavity and on the surface of oral tissues, including gingival structures, the gingival tissue remains free of significant inflammatory changes almost throughout the lifetime of our patients, even though the gingival third of the hard dental tissues is an exposed and predilection site for the formation of oral biofilms or plaques. Recognizing this fact, the following question arises: What is the anti-inflammatory and immunological competency of the gingiva that enables to maintain its relatively healthy condition despite continuous microbial and other infectious attacks? The answer to the above question will be sought in the immunological competency of the gingival structures and the temporal sequence of attacks by oral pathogens.

SUMMARY OF THE MOST IMPORTANT FACTS

In our short study, we summarize the facts that confirm anti-infective and immunological protection in gingival structures in different types of defensive inflammation during some clinical forms of gingivitis and periodontitis. It is now accepted that the action of oral and periodontal microbial pathogens begins through the presentation of their antigens to gingival structures (O'Brien *et al.* 2004). The epithelial surface of the oral gingiva, as well as the human epidermis, contains highly specialized cells of the dendritic superfamily called **Langerhans cells**. Their primary function is to identify and present bacterial antigens of oral commensal and pathogenic bacteria. They were first described by Paul Langerhans in 1868 and 100 years later, Ralph Steinman discovered the presentation of antigens by dendritic cells (Deckers *et al.* 2018). Their function has been investigated and studied mainly in the epidermis of the human skin. Langerhans cells represent a unique population of tissue-resident macrophages that form a functional network in the dermal epidermis and oral mucosa and can migrate to the respective draining lymph nodes. Despite decades of research, their exact function and role are not precisely identified but if removed from the superficial layers of the skin, they are subject to fatal infections (West, Bennett, 2018). Langerhans cells (LCs) do not contain desmosomes or tonofibrils, and their dendritic morphology may associate certain relationships with melanocytes, with LCs containing melanin-like granules. In contrast, these may be modified melanocytes that have lost their ability to produce melanin (Waterhouse, Squier, 1967). In healthy human oral mucosa and gingiva, Langerhans cells are localized in the oral and sulcular epithelium, where they are found predominantly in its basal layers. They are not found in the connective epithelium at the base of the sulcus gingivalis. The presence of LCs in gingival tissue is linked to the presence of infection or inflammation in this tissue, as confirmed by experimental studies in mice living in a sterile environment, in which LCs were not present at all or in very low numbers but increased in number as infection or gingivitis progressed (Jaitley *et al.* 2014). Increased accumulation of LCs has been confirmed in patients with chronic periodontitis (Wilensky *et al.* 2014). However, in severely inflammatory damaged periodontal pocket surface epithelial tissue, they were not present at all (Newcomb, Powel, 1986). This fact may be associated with their disappearance during a long-lasting destructive inflammation in the periodontal pocket environment. The research of LCs belonging to the group of dendritic cells (DCs) has received much attention in the etiopathogenesis of periodontitis. Different groups of dendritic cells in the epithelial and subepithelial layers of the oral mucosa check oral microorganisms and, through their specific mechanisms, control different components of innate and acquired immunity by their connection to different subpopulations of Th cells (Randolph *et al.* 2008; Aramaki *et al.* 2011). Several studies confirm the facts that LCs take samples from supragingival and subgingival biofilms as well as from the biofilm in the periodontal pocket and transmit immunological information to CD4+ Th cells or even to other Th cell subpopulations (Bittner-Edy *et al.* 2016). However, the precise roles of individual Th cell subpopulations in the pathogenesis of periodontitis currently need to be better defined (Moutsopolous *et al.* 2012; Bittner-Edy *et al.* 2016). The presence of LCs in healthy gingiva and oral mucosa is common and standard but does not protect the patient from severe periodontal infection by the G-negative anaerobic bacterium *Porphyromonas gingivalis*, which stimulates the differentiation of a TH17-specific immune response and stimulates the development of new osteoclasts through the pro-inflammatory mediators IL-1, IL-6, TNF-alpha and the activation of RANKL (Bittner-Edy *et al.* 2016; Moutsopolous *et al.* 2012; Cardoso *et al.* 2009).

To elucidate the etiopathogenesis of destructive periodontitis, various periodontopathogenic bacteria and their effect on immunocompetent cells, the range of which in gingival tissue is extensive and contains multiple populations of antigen-presenting

cells, including the already mentioned resident Lcs, have been intensively investigated. This group can also include **monocytes** circulating in the blood, representing mononuclear phagocytes with differentiation potential to convert them into phagocytic cells (Randolph *et al.* 2008). There is no consensus on the importance and role of monocytes as possible precursors for DCs or LCs in different studies despite the facts that they belong to the vital antigen-presenting mechanisms of the T-cell-mediated immune responses (Randolph *et al.* 2008; Guilliams *et al.* 2014; Capucha *et al.* 2015). The connective structures of the gingiva contain or are infiltrated by different subpopulations of **lymphocytes**. The localization of B-lymphocytes by CD20 immunohistochemical staining in healthy gingiva and inflammation-affected gingiva diagnosed with gingivitis and periodontitis was investigated by Amanulla *et al.* (2008). Maturing B-lymphocytes with CD20 antigen were diffusely dispersed in all layers of healthy and gingivitis-affected gingiva, and clusters were identified in the layer just below the epithelium in samples with periodontitis (Amanulla *et al.* 2008). Various subpopulations of **T cells** are equally present in gingival tissue, and their important role in periodontal protection against periodontal bacteria is well documented (Guyodo *et al.* 2012). The presence of blood mononuclear cells (PBMCs) and neutrophil granulocytes of inflammatory origin has been confirmed in several studies by CD68+ monoclonal antibodies in many inflammatory diseases, such as Crohn's disease and colitis ulcerosa. CD68+ is a specific marker for **monocytes-macrophages** and neutrophil granulocytes (Amanzada *et al.* 2013). In biopsies from gingival tissue infected with the aggressive periodontopathic bacterium *Porphyromonas gingivalis*, the presence of immunocompetent Th2-type immunological response cells, including cells with the epitope CD20+, mature B lymphocytes and CD138+ plasma cells has been identified (Guyodo *et al.* 2012). The presence of activated or mature B-lymphocytes generates numerous but relatively well-identifiable **plasma cells** in the gingival tissue. When they accumulate excessively and unchecked in the gingival tissue – a well-defined clinical entity called "plasma cell gingivitis" characterized by benign diffuse edematous swelling of the gingiva of varying extent develops (Joshi, Shukla, 2015). Elevated levels of **nuclear proliferation factor Ki-67** have been found in the gingiva in various forms of gingivitis and periodontitis, in drug-induced gingival enlargement, and in some oral neoplastic diseases (Preethi *et al.* 2014; Pilmane *et al.* 2019; Nagappa *et al.* 2016; Chandrakanta *et al.* 2021). The proliferation marker Ki-67 is a non-histone protein of the cell nucleus that is produced during all phases of cell division, and its positive levels in gingival tissues demonstrate high mitotic activity, growth, and proliferation of cellular elements (Straka, Varga, 2017). Ki-67 protein is present during all active and dividing cell cycles, including G_1, G_2, S cycles, and mitosis (Bruno *et al.* 1992). The proliferation factor Ki-67 has received much attention in lung cancer, where it is used as an essential tissue marker for the further development and prognosis of this severe disease (Davey *et al.* 2021). Its extensive research began in 1983 with the discovery of murine monoclonal antibodies that recognize it as a proliferation factor present in the nucleus of proliferating cells in many solid tumors and invasive lung cancer neoplasms (Brian *et al.* 2023).

CONCLUSION

In the briefly outlined review, the presence of many types of anti-inflammatory and immunocompetent cells and their components in the gingival tissue during inflammatory diseases of the gingiva and periodontium in various clinical forms of gingivitis and periodontitis is mentioned and presented in several studies. Their identification in gingival tissue has been and is performed by immunohistochemical methods. However, gingival tissue is subject to constant attacks by periodontopathic bacteria throughout the lifetime of our patients. **Despite this, gingival and periodontal tissues show no signs of clinical gingival inflammation, and the immunologic-defensive reactions mentioned above take place covertly under the image of clinically healthy gingiva. The various clinical forms of gingivitis and periodontitis are present only after their defensive thresholds and capacity are overcome by highly virulent bacteria or by the failure of anti-inflammatory mechanisms.**

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