Leptin's and antigen-presenting cells' functions in periodontitis – an overview

Leptin e as funções das células que apresentam antigénios na periodontite - uma visão geral

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ABSTRACT
Leptin is a hormone synthesized predominantly by white adipose tissue. Its production levels are directly proportional to the total mass of this tissue in an individual's body. Apart from its classic role in the regulation of hunger and satiety, it also plays an important part in scenarios involving innate and adaptive immune responses. It has been discovered that leptin levels are altered in a variety of inflammatory responses, such as periodontitis, a condition which derives from a persistent inflammatory immune response from a host facing bacterial infection. The initial trigger for this reaction is the recognition of the pathogens by antigen presenting cells, such as macrophages and dendritic cells, whose actions can be influenced by leptin. This review aims to present the relationship between leptin, dendritic cells and macrophages in the context of periodontal disease. Thus, we have assembled the most important findings related to leptin's role in the modulation of the immune response carried out by these cells in periodontitis.

Key-words: Leptin, periodontitis, innate immune system, macrophages, dendritic cells.

ABSTRACT
A leptina é uma hormona sintetizada predominantemente por tecido adiposo branco. Os seus níveis de produção são directamente proporcionais à massa total deste tecido no corpo de um indivíduo. Para além do seu papel clássico na regulação da fome e da saciedade, desempenha também um papel importante em cenários que envolvem respostas imunitárias inatas e adaptativas. Foi descoberto que os níveis de leptina são alterados numa variedade de respostas inflamatórias, tais como periodontite, uma condição que deriva de uma resposta imunitária inflamatória persistente de um hospedeiro que enfrenta uma infecção bacteriana. O desencadeador inicial desta reacção é o reconhecimento dos agentes patogénicos pelas células que apresentam antigenes, tais como macrófagos e células dendríticas, cujas acções podem ser influenciadas pela leptina. Esta revisão visa apresentar a relação entre leptina, células dendríticas e macrófagos no contexto da doença periodontal. Assim, reunimos as descobertas mais importantes relacionadas com o papel da leptina na modulação da resposta imunitária levada a cabo por estas células na periodontite.

Palavras-chave: leptina, periodontite, sistema imunitário inato, macrófagos, células dendríticas.

1 INTRODUCTION

Periodontitis is a highly prevalent chronic disease that affects a large portion of the population with a negative impact on the patients' quality of life (NASCIMIENTO et al., 2014). Current studies have demonstrated a relationship between periodontitis and systemic diseases such as obesity (MARTINEZ-HERRERA et al., 2019). Regarding its

association with obesity, it can be justified based on the low-grade inflammation caused by cytokines and adipocytokines released by adipose tissue in this condition, which may contribute to the inflammatory process associated with periodontal disease.

The inflammatory condition associated with this disease is characterized by progressive destruction of the tooth-supporting structures as a result of the failure to eradicate pathogenic microorganisms in the tissues surrounding the teeth (SIMA et al., 2019). There is great evidence for the participation of the innate immune response in the pathogenesis of periodontitis as well as of cytokines and adipocytokines produced during such responses (PAN et al., 2019). With respect to cytokines, TNF-□ and IL-6 have been reported to be related to periodontitis. Their production can be initiated when innate immune cells recognize pathogens involved in periodontitis. This recognition is mediated by pattern recognition receptors (PRRs) such as toll-like receptors (TLRs), present especially in phagocytes, which are able to detect pathogen-associated molecular patterns (PAMPs) in microorganisms. In addition, it has been demonstrated that TLRs are expressed in periodontal tissues (KIKKERT et al., 2007; PAN et al., 2019).

Leptin is an adipocytokine produced by adipose tissue, proportional to the mass of this tissue in the body. This hormone classically acts in weight regulation. In non-obese children, the leptin concentration level is of approximately 7.82 ng/mL, while in obese children, this level stands around 72.1 ng/mL (BOZAN et al, 2017). Moreover, it has been demonstrated that leptin is present not only in adipose tissue, but also in gingival tissues, both in conditions of health or marginal inflammation of such tissues.

Leptin's actions are mediated by its connection with the ObR receptor. Apart from its expression in the central nervous system, it has been demonstrated that the ObR receptor is also expressed in peripheral tissues, such as the hematopoietic and immune systems (WAUMAN et al., 2017). Through its receptor, leptin modulates the actions of macrophages and dendritic cells, as well as other immune cells. The ObR receptor is structurally similar to the IL-6 receptor's subunit gp130, which is a member of the group of class I cytokine receptors. It is known that 6 ObR isoforms (ObRa- ObRf) come from the codification of a single gene, and that the 3 most common kinds are the soluble form, the short form and the long form. The long form of ObR is known as LepRb and the short forms as LepRa, LepRc, LepRd and LepRf. The soluble form of the receptor is known as LepRe or sOb-R. The increase of the concentration levels of sOb-R inhibits the expression of ObR, which partially explains the variations in sensibility observed in leptin receptors in response to changes in sObR levels (GORSKA et al., 2010).

Leptin circulates through the blood either in its free form or bound to sOb-R and possibly other receptors not yet known. The binding of leptin with its soluble receptor can increase its biodisponibility in the blood and decrease the binding between leptin and its membrane receptors (SCHAAB et al., 2015).

Leptin induces an increase in T-cell proliferation, as well as the production of Th1-type cytokines by these cells. Using ObR as an intermediate, leptin also induces proliferative signals during hematopoiesis and lymphopoiesis (LAM et al., 2007).

When leptin connects with its receptor in these cells, the activation of the JAK/STAT signalization pathways are induced. All leptin receptors have an extracellular domain, but only the long form of the receptor (ObRb) possesses a big enough intracellular domain, which signals through the janus kinase (JAK/STAT) pathway, leading to the phosphorylation of STAT3 (VIOLA et al., 2019).

Recent research has demonstrated the role of leptin in different immune system cells, therefore disclosing that the hormone has very important immunomodulatory functions (NAYLOR et al., 2016). Moreover, studies have shown that mice who are transgenic to leptin (ob/ob) and leptin receptor (db/db) have reduced numbers of leukocytes in lymphoid tissues, as well as an impaired immune response. Leptin is also able to promote activation of monocytes and to induce the production of proinflammatory cytokines such as IL-1, TNF or IL-6 by these cells. Leptin also stimulates the oxidative burst, which is an important function of macrophages. In dendritic cells (DC) the hormone acts as a stimulator of maturation and migration (RAMIREZ et al, 2014).

Dendritic cells and macrophages are antigen-presenting cells (APCs), which capture, process and present antigens to lymphocytes. During these processes, both cells initiate and regulate the adaptive immune response. Langerhans cells are a subtype of DC in oral mucosal epithelium and in the skin epidermis, where it has a function of APC (DECKERS et al., 2018)

2 METODOLOGY

The electronic periodical database used for this review was PubMed – NCBI (National Center for Biotechnology Information). The key words searched included “leptin”, “antigen presenting cells”, “immune system”, “periodontitis”, “macrophages” and “dendritic cells”. Based on the results of this search, 20 articles in English published from 2007 to 2020 were selected.

3 RESULTS AND DISCUSSION

3.1 ANTIGEN-PRESENTING CELLS, LEPTIN AND PERIODONTITIS

3.1. Macrophages

Macrophages are known as professional mononuclear phagocytes, responsible for maintaining homeostasis in different tissues; they are able to do that due to their function of eliminating pathogens, senescent cells or dead cells. Circulating monocytes differentiate themselves into different types of resident macrophages found in almost every tissue. It has been found that macrophages at different stages of differentiation and activation are present in periodontal tissues. However, it has also been revealed that it is not possible to find an alteration in macrophage numbers or activation in this disease.

In each tissue, the macrophages are given a different name, such as Kupffer cells in the liver and spleen, alveolar macrophages in the lungs and adipose tissue macrophages. Moreover, macrophages within the same tissue can express different phenotypes, as can be seen in the adipose tissue. These phagocytes can be divided into 2 types: the ones with a pro-inflammatory profile (M1) and the anti-inflammatory/ pro-resolution type (M2). Based on this definition, M1 macrophages are capable of initiating and sustaining inflammatory responses by releasing pro-inflammatory cytokines, activating endothelial cells and recruiting other immune system cells to the inflamed tissue. On the other hand, M2 macrophages induce inflammation resolution, coordinate tissue integrity and release anti-inflammatory cytokines (VIOLA et al., 2019).

It has been established that mastocytes can indirectly influence on the polarization of macrophages in the adipose tissue in response to changes in leptin levels. Interestingly, it has been reported that in lean mice, the reduced quantity of leptin leads to an anti-inflammatory mastocyte response, consequently inducing the differentiation of adipose tissue macrophages into the M2 type (ZHOU et al., 2015).

Macrophages or circulating monocytes can recognize living microorganisms through their pattern- recognizing receptors, such as Toll-like receptors (TLRs). The expression of TLRs on these cell's membranes can be influenced by leptin treatment. In a study carried out by Jaedicke et al., (2013), it was revealed that leptin increases the expression of TLR-2 in human monocytes. Therefore, according to this research, leptin can potentialize innate immunity and inflammation in conditions such as obesity and type II diabetes.

Leptin also enhances the phagocytic function in macrophages and monocytes, as well as the production of pro-inflammatory cytokines (such as TNF- α) and the expression of adhesion molecules. Studies made with circulating leptin- deficient or ObR- deficient mice prove that such mice present a downregulation of their phagocytic role and a decrease in the production of cytokines. On the other hand, a recent published study has shown that obese children (with visceral obesity) present higher blood leptin levels, which possibly affects in a negative way the phagocytic functions of their cells (TOAIMA et al., 2019). Macrophages express both the long and the short forms of leptin receptor (LEPR), which favors the chemotaxis and cytokine synthesis.

Cytokines produced in response to macrophage polarization play important roles in the development and progression of periodontitis (ALMUBARAK et al., 2020). Current evidence suggests that periodontitis has also been associated with enhanced activity of the M1/M2 macrophage phenotypes (YU et al., 2016).

Zhou et al. (2019) reported that M1-type macrophages were more prevalent in the gingival tissue in patients with periodontitis, which was not observed in patients with gingivitis. In this last condition, M2-type macrophages were more prominent. In this study, authors also concluded that M1 macrophages release pro-inflammatory cytokines TNF-α, IFN-γ, IL-6 and IL-12, which probably aggravate the degree of inflammation in the gingival tissue of periodontitic teeth.

Considering the stages of the periodontal inflammatory process, transformation of macrophages from the M1 to the M2 phenotype might be a potential therapeutic target for the management of chronic periodontitis.

3.1.2 Dendritic cells

Dendritic cells are potent and heterogeneous antigen-presenting cells, divided into the myeloid and plasmacytoid subgroups. The myeloid population represents the conventional dendritic cells, which are mostly present in the skin and mucous membranes and are specialized in uptaking antigens and presenting them to naive T-cells in lymph nodes. During this presentation, dendritic cells produce cytokines that induce TCD4+ differentiation, especially into Th1, Th2 or Th17 (VILLADANGOS et al, 2008).

In the oral epithelium, Langerhans cells are a predominant subtype of DC, which express CD207. Langerhans cells are characterized by the expression of CD1a and langerin, as well as the by the presence of Birbeck granules in the cytoplasm, which are responsible for internalizing viruses (BIGLEY et al., 2015).

It is known that leptin plays an important role in the maturation of dendritic cells. It has also been demonstrated that CD11c+ cells in the spleen and lymph nodes express the long form of the receptor (ObRb) and that ob/ob mice present a reduced number of these cells, when compared with mice from the control group (MORAES-VIEIRA et al., 2014).

Dendritic cells from ob/ob mice express a reduced quantity of co-stimulatory molecules (CD40, CD80 and CD86) as well as class II MHC. These animals also produce decreased quantities of IL-12, TNF and IL-6. The reduced production of these cytokines can be related to the increased levels of IκB-α, an inhibitor of NFκB. Research made by Mattioli et al. has shown that leptin is capable of activating NFκB, thus stimulating an inflammatory response. In the absence of leptin, dendritic cells produce Th2-type cytokines. However, the treatment of these cells with leptin stimulates the production of Th1-type cytokines, which is already characteristic of this APC (LAM et al., 2007).

In human dendritic cells, leptin is able to promote differentiation, survival and to control IL-10 production. This control favors Th1 immune response. It has been demonstrated that during periodontitis, an increased number of Langerhans cells were found in the epithelium. However, this increase was not observed in the conditions of gingivitis or in healthy epithelium. It has been suggested that these cells are able to stimulate Treg cells, which controls exacerbated inflammation. Interestingly, it is known that leptin deficiency impairs maturation of dendritic cells and enhances induction of Treg and Th17 cells (MORAES-VIEIRA et al., 2014).

4 CONCLUSIONS

Leptin is a hormone produced by adipose tissue that influences the functions of immune cells such as macrophages and dendritic cells. In the condition of increased leptin levels, which can be associated with obesity, these cells increase the production of pro-inflammatory cytokines, which can contribute to the progression of periodontal disease. In this way, leptin may represent a new therapeutic target for the treatment of the disease, taking into consideration the knowledge of molecular processes in this exact context.

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