Chapter 7
Inflammasome and Oral Diseases

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Abstract One of the main steps in the development of the life in the earth is multicellularity. It enables cell differentiation and the development of morphological structures within an organism and is an essential factor in how to recognize friendly cells that are part of the multicellular organism and which foreign organisms can be harmful. Recognition includes devices such as the major histocompatibility complex (MHC), and the pattern recognition receptors (PRRs). PRRs are a group of proteins expressed by cells of the innate immune system that identify two classes of products: pathogen-associated molecular patterns (PAMPs), related to microbial pathogens, and damage-associated molecular patterns (DAMPs), associated with cell components that are released during cell damage or death. All these activate the inflammasome, which is a multiprotein oligomer that includes caspase 1, PYCARD, NALP, and caspase 5 (also known as caspase 11 or ICH-3). It is responsible for

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activation of inflammatory processes and has been shown to induce cell pyroptosis, a programmed cell death distinct from apoptosis, and promotes the maturation of the inflammatory cytokines interleukin 1β (IL-1β) and interleukin 18 (IL-18). We review whether inflammasome is related to diseases that can occur in the oral cavity. The mouth is always a possible environment for the development of pathological conditions because of the wide variety of microorganisms. Small variations in the equilibrium of the oral flora can cause disorders that could affect the organism in a systemic form. We provide data on periodontal disease, candidiasis, herpes virus, oral cancer, caries, and other oral diseases. There are very few papers that study this issue; therefore, we need more investigation and publications about inflammatory molecular processes, and more specifically, related to the inflammasome complex.

Keywords Periodontal diseases · Inflammasome · Oral diseases · Cancer · Caries

7.1 Introduction

Life is the ability to utilize and control energy derived from the sun that distinguishes every unicellular or multicellular organism. One of the main steps in the development of lives on Earth is the multicellularity by which the concept of what an individual organism is has been redefined and involves the transition from the microscopic to the macroscopic domain. Multicellularity enables cell differentiation and development of morphological structures within an organism that require cell–cell adhesion and intercellular communications to coordinate various activities (Lyons and Kolter 2015). It is an essential factor in how to recognize friendly cells that are part of the multicellular organism and which foreign organisms can be harmful. It is named allorecognition, which is defined as the ability of an individual organism to distinguish its tissues from those of another. Also, the different levels of cell development in an organism assume various types of energy consumption, the production of molecules, and waste disposal. All of them involve the production of molecules or damaged cellular structures that need to be identified and eliminated. When the external or internal aggression has been identified, the immune system starts to work and the host defense system comprising many biological structures and processes within an organism is activated. Therefore, it is essential for a cell that is part of a superior multicellular organism to have a device to detect foreign aggression that eliminates all the harmful molecules or structures. These devices include the major histocompatibility complex (MHC) and the pattern recognition receptors (PRRs). The MHC is a type of cell surface protein indispensable for the acquired immune system to identify foreign molecules in vertebrates that determines histocompatibility. PRRs are a group of proteins expressed by cells of the innate immune system that identify two classes of products: pathogen-associated molecular patterns (PAMPs), related to microbial pathogens, and damage-associated molecular patterns (DAMPs), associated with cell components that are released during cell damage or death. These may be on the membrane surface, e.g., Toll-like receptors (TLRs) and C-type lectin receptors (CLRs), or within the cytoplasm, e.g., NOD-like

receptors (NLRs) and RIG-I-like receptors. All these activate the inflammasome, which is a multiprotein oligomer that includes caspase 1, PYCARD, NALP, and caspase 5 (also known as caspase 11 or ICH-3). It is responsible for activation of inflammatory processes and has been shown to induce cell pyroptosis, which is a programmed cell death distinct from apoptosis, and promotes the maturation of the inflammatory cytokines interleukin 1β (IL-1β) and interleukin 18 (IL-18) (Patel et al. 2017).

If life is energy, the main issue for all organisms is to obtain nutrients to keep the metabolic process active. In prokaryotic cells, the first step of nutrient intake consists of a break through the cell membrane with the mechanism of endocytosis. The main characteristic in the eukaryotic cells is the presence of membrane-bounded organelles that allow the energetic and metabolic advantage offered by the intracellular digestion of substrates (de Duve 2007). The multicellular organisms need more energy and have evolved a cell specialization by developing a gastrointestinal tract. It started as a simple blind sac-like structure and then became more heterogeneous, regionalized, and acquired a second opening, with a mouth and an anus (Soukup et al. 2013). The gastrointestinal tract takes in food, then digests it with the decomposition of highly insoluble food ingredients into small water-soluble food molecules, so that they can be absorbed into the blood plasma without any immunity reaction, and finally expels the remaining waste as feces. The oral cavity is the place in which the digestive process starts with chewing, salivation, and swallowing. Therefore, it is essential to keep it healthy and avoid diseases. However, the oral microbiota is abundant, diverse, and has high a capacity for producing pathological conditions. Oral diseases are among the most common human diseases. For instance, periodontal disease can affect up to 90% of the worldwide population and is an infectious disease related to some systemic conditions, such as cardiovascular disease and diabetes (Pihlstrom et al. 2005).

Our goal is to review whether the inflammasome is related to diseases that can occur in the oral cavity.

7.2 Periodontal Disease

Periodontal disease is a chronic inflammatory illness that affects many adults, and it is characterized by a chronic infection related to Gram-negative anaerobic bacteria in the dental biofilm. It leads to the irreversible destruction of tissues supporting the teeth and is clinically detectable by periodontal pockets and alveolar bone loss (Pihlstrom et al. 2005). Studies report how severe periodontitis affects 5–20% of adult populations worldwide, and it is one of the preeminent causes of tooth loss in both developed and developing countries (Pihlstrom et al. 2005; Petersen et al. 2005; Jin et al. 2011). It has been suggested that over 50% of the European population suffer from some form of periodontitis and over 10% have severe disease, with prevalence increasing to 70–85% of the population aged 60–65 years (König et al. 2010).

In nature, the progression of periodontitis is inflammatory, with the main triggers of oral inflammation usually residing in the oral microbes and the balance of its components (Yilmaz and Lee 2015). Within the host's inflammatory response, various biochemicals are strongly associated with the severity and progression of periodontal disease, interleukins (IL-1, IL-18), prostaglandins (PGE2), and matrix metalloproteinases (MMPs) (Orozco et al. 2006). IL-1β has been found to be significantly increased in the periodontal tissues and gingival fluid from diseased sites, compared with healthy sites (Stashenko et al. 1991; Masada et al. 1990). IL-1β up-regulates MMPs and down-regulates tissue inhibitors of metalloproteinase production (Ohshima et al. 1994), and is also a powerful and potent bone-resorbing cytokine (Schwartz et al. 1997), which suggests that it plays a role in degrading the extracellular matrix in periodontitis (Bascones-Martínez et al. 2012).

Although inflammasome signaling is becoming well established in the progression of various diseases, there is intriguingly mounting evidence supporting the association of the oral microbiome with the same array of conditions (Han and Wang 2013). The oral cavity is essentially a diverse ecosystem, harboring vast numbers of oral microorganisms, and can serve as a reservoir for possible systemic dissemination of microorganisms or their components and the release of inflammatory signals, possibly leading to inflammation at distant body sites (Amodini Rajakaruna et al. 2012). With advances in technologies for microbial detection, a diverse group of oral species has additionally been directly detected in several systemic chronic diseases (Detert et al. 2010).

Inflammasomes are emerging as chief regulators of the host innate immune defense system in chronic inflammatory diseases, and their role against microbial pathogens is becoming critical in controlling and limiting invading microbes. On the other hand, increasing numbers of microorganisms and their virulence factors are found to function by targeting inflammasomes and modulating IL-1β and IL-18 processing, which, taken together, could be involved in the development and/or progression of various inflammatory diseases, including periodontal disease (Davis et al. 2011; Kim and Jo 2013).

7.2.1 NLRP3 in Periodontitis

Inflammasome complexes appear to assume a pivotal role in periodontal disease and the inflammasome-associated inflammatory mediators involved in the progression of the disease have been highlighted by several clinical studies. The relationship between the interleukin-1 cytokine family and the NLRP3 inflammasome complex has been revealed by Bostanci et al. (2009). The findings indicated that higher expression levels of NLRP3 and NLRP2, but not of apoptosis-associated speck-like protein containing a carboxyl-terminal caspase recruitment domain (ASC), were detected in gingival tissue samples from patients with three forms of the periodontal disease (gingivitis, chronic periodontitis [CP], and generalized aggressive periodontitis [G-AgP]) compared with healthy subjects. The mRNA expression of NLRP3, its

putative antagonist NLRP2, its effector molecule ASC, IL-1β, and IL-18 are detected by quantitative real-time polymerase chain reaction (qPCR) in gingival tissues from patients with gingivitis, CP, G-AgP, and healthy subjects. The data indicated that NLRP3 and NLRP2, but not ASC, were significantly expressed at higher levels in the three forms of the disease compared with healthy subjects. Park et al. (2014) had similar results in gingival crevicular fluid and gingival tissue samples from peritonitis sites compared with healthy sites. Examining the distribution and intensity of NLRP3, NLRP1, and AIM2 expression in gingival tissues with different types of periodontitis (patients with chronic and G-AgP compared with healthy subjects) by qPCR and immunohistochemistry, Xue et al. (2015) found that overall intensity of NLRP3 expression was significantly higher in CP or G-AgP than in healthy tissue, more considerably in the periodontal epithelium. NLRP1 was barely expressed in the samples, whereas absent in melanoma 2 (AIM2) was better represented in the CP group. In another study, gingival samples from patients with CP, and with CP and type 2 diabetes mellitus compared with healthy subjects, were analyzed using immunohistochemistry (Huang et al. 2015). Compared with control subjects, NLRP3 and IL-1β were significantly up-regulated in the gingival epithelium of patients with CP and/or type 2 diabetes mellitus, but the authors observed no differences between groups with periodontitis with or without type 2 diabetes mellitus. Recently, a study in NLRP3-deficient mice infected with *Porphyromonas gingivalis* showed that this bacterial challenge significantly increased the loss of alveolar bone; gingival expression of pro-IL-1β, pro-IL-18, and receptor activator of nuclear factor kappa-B ligand; production of IL-1β, IL-6, and IL-18; and caspase-1 activity in peritoneal macrophages of wild-type mice. In contrast, it did not affect NLRP3-deficient mice. Meanwhile, mRNA expression of OPG in gingival tissue and peritoneal IL-6 production were significantly higher in NLRP3 knock-out (KO) mice (Yamaguchi et al. 2017). This evidence suggests that different inflammasomes, such as NLRP1, NLRP2, NLRP3, and AIM2, and their products IL-1β and IL-18 are over-expressed in gingival tissues from patients with periodontal diseases compared with healthy controls, confirming that these complexes are involved in the pathogenesis of periodontitis to different degrees.

Inflammatory and immune mechanisms turned on by infectious agents are crucial in the development of atherosclerosis. Numerous epidemiological studies have demonstrated that host immune reactions against persistent infectious pathogens, including *Porphyromonas gingivalis*, may promote the development of atherosclerosis (Kurita-Ochiai et al. 2015). In 2015, Yamaguchi et al. challenged orally spontaneously hyperlipidemic mice with wild-type *P. gingivalis* significantly increasing the area of aorta covered with atherosclerotic plaque and alveolar bone loss, compared with gingipain-null mutant or FimA-deficient mutant strains (Yamaguchi et al. 2015). The challenge also increased IL-1β, IL-18 and TNF-α production in peritoneal macrophages, and gingival or aortic gene expression of NLRP3, pro-IL-1β, pro-IL-18, and pro-caspase-1. In another study performed by Velsko et al. (2015), the ability of a polymicrobial consortium of *P. gingivalis*, *Treponema denticola*, *Tannerella forsythia*, and *Fusibacterium nucleatum* to colonize the periodontium and induce local and systemic inflammatory responses was

investigated. The author's observations suggested that polybacterial infection with periodontal pathogens triggers aortic TLR and inflammasome signaling and increases aortic oxidative stress.

7.2.2 Porphyromonas gingivalis

Porphyromonas gingivalis is the bacterium most frequently associated with CP and can be detected in up to 85% of the disease sites (Yang et al. 2004), whereas in healthy sites, it is rarely found or only in small numbers (Bostanci and Belibasakis 2012). The presence of *P. gingivalis* in periodontal pockets may be a predictor of disease progression (van Winkelhoff et al. 2002) and a positive correlation is found between the quantity of *P. gingivalis* and pocket depth (Kawada et al. 2004). *P. gingivalis*, like all Gram-negative bacterial species, is covered by a lipopolysaccharide (LPS), which is a component of the outer membrane recognized by the host that can trigger intracellular signaling events. The affinity of LPS to its PRRs, such as the TLRs and CD14, enables discernment between commensal and pathogenic species. The *P. gingivalis* LPS is a stimulator of proinflammatory responses and bone resorption, as demonstrated in experimental animal models. Owing to the importance of this bacterium in periodontal diseases, several in vitro studies have investigated its effects on different cell populations of the periodontium.

One of the strategies for observing the effects of *P. gingivalis* on the tissues is to challenge a certain cell line with live cultures of this bacterium, an approach that several studies have followed. Bostanci et al. (2009) challenged the human myelomonocytic cell line, Mono-Mac-6, with *P. gingivalis*, and observed that although the untreated cells showed low levels of expression of NLRP3, the infected cells showed a high concentration of expression of NLRP3, IL-1β, and IL-18 (Yamaguchi et al. 2015). Park et al. in a recent in vitro study, examined the mechanisms of activation of NLRP3 and IL-1β secretion in a human acute monocytic leukemia cell type (THP-1) differentiated to macrophages. It has been discovered that activation of both NLRP3 and AIM2 is necessary for the secretion of *P. gingivalis*-induced caspase-1-dependent IL-1β via TLRs 2 and 4. Some studies have added DAMPs to their methodology. Yilmaz et al. found that *P. gingivalis* down-regulated NLRP3 expression and induced production of pro-IL-1β, but only promoted the secretion of mature IL-1β upon stimulation with danger signal extracellular ATP in a primary gingival epithelial cell model (Yilmaz et al. 2010). Moreover, *P. gingivalis* may induce the production of DAMPs itself. Jun et al. observed that *P. gingivalis* induced activation of caspase-1, caspase-4, and induced pyroptotic cell death in THP-1-derived macrophages, but only at low concentrations. These results suggest that *P. gingivalis* might modulate the host immune responses, in favor of pathogen survival and persistence. *P. gingivalis* induced the release of ATP, too, which ultimately leads to caspase-1 activation (Jun et al. 2017).

Another strategy for studying *P. gingivalis* in vitro has been to use culture supernatants or the bacterial LPS as PAMPs. Hamedi et al. reported that

P. gingivalis supernatants differentially regulated IL-1β and IL-18 from human monocytes. *P. gingivalis* enhanced IL-1β and IL-18 mRNA expression, the former being induced earlier, but transiently. IL-18 up-regulation was not affected by heat inactivation or chemical inhibition of gingipains, whereas both treatments resulted in a 50% reduction of IL-1β expression. Purified *P. gingivalis* LPS enhanced both IL-1β and IL-18 expression. However, only IL-1β, but not IL-18, secretion was detected and was up-regulated by *P. gingivalis*. Therefore, cytokines of the IL-1 family may participate via different pathways in the pathogenesis of periodontitis (Hamedi et al. 2009). Champaiboon et al. (2014) challenged primary human monocyte-derived macrophages (M1 and M2 macrophages) and human coronary artery endothelial cells (HCAECs) with *P. gingivalis* LPS as PAMPs and cholesterol crystals (CCs) as DAMPs. The authors found a marked release of IL-1β from LPS-primed M1 and M2 macrophages treated with CCs. On the other hand, HCAECs showed no release of IL-1β in response to *P. gingivalis* LPS priming and treatment with either CCs or extracellular danger molecule ATP. The authors conclude that the mechanistic role of periodontal infection in inflammasome activation as a cause of atherosclerotic vascular disease requires further investigation (Champaiboon et al. 2014).

Some authors have studied strategies to reduce the expression of NLRP3 and its products. Li et al. induced the production of heme oxygenase-1 (HO-1), a ubiquitous inducible cellular stress protein and an endogenous cytoprotective enzyme, by hemin on gingival epithelial cells (GECs) and compared the results when cells were challenged with LPS, with or without hemin. The cells cultivated with LPS + hemin demonstrated less NLRP3 formation and overexpression and lower production of IL-1β, leading to the conclusion that the activation of HO-1 protects LPS-induced inflammatory damage in GECs and that it may be used as a target for the prevention and treatment of CP (Li et al. 2014).

Some researchers suggest that *P. gingivalis* might modulate specific inflammasome components and successfully colonize and persist in host cells. Belisakis et al. challenged gingival fibroblasts with a 10-species and a 9-species biofilm model, the second without *P. gingivalis*. The authors observed that the exclusion of *P. gingivalis* from the biofilm partially rescued NLRP3 and IL-1β expression, concluding that subgingival biofilms down-regulate NLRP3 and IL-1β expression, partly because of *P. gingivalis* (Belibasakis et al. 2013). Another study by Taxman et al. (2012) performed in an in vitro mouse macrophage model, demonstrated that *P. gingivalis* could synergistically regulate the invasion of host cells by *F. nucleatum* by inhibiting both *F. nucleatum*-induced IL-1β and IL-18 processing and *F. nucleatum*-promoted cell death (Taxman et al. 2012).

P. gingivalis is not an aggressor of the inflammatory response, but rather an opportunist that can cross-talk with the host and subvert its defense mechanisms. Using this strategy, *P. gingivalis* prolongs its survival and becomes established in the periodontal pocket (Hajishengallis et al. 2011). Preferably, it deregulates the innate immunity, which may, in turn, impair adaptive immunity (Pathirana et al. 2010). Major representative examples of these abilities are its capacity to degrade human defensins (Carlisle et al. 2009), its resistance to oxidative burst killing by

polymorphonuclear neutrophils (PMNs) (Mydel et al. 2006) and its ability to inhibit "at will" the production of critical proinflammatory cytokines (Bostanci et al. 2007).

7.2.3 Aggregatibacter actinomycetemcomitans

Aggregatibacter actinomycetemcomitans is a gram-negative capnophilic coccobacillus, which is commonly isolated from the oral cavity of adolescents and young adults afflicted by aggressive periodontal disease states (Slots et al. 1980). In localized juvenile periodontitis, it was described as affecting first molars and then incisors preferentially (Armitage 1999). *A. actinomycetemcomitans* possesses different well-studied virulence factors, among which leukotoxin is suggested to play a significant role in the pathogenicity. Leukotoxin belongs to the repeats-in-toxin (RTX) family, which is produced by many other Gram-negative pathogens such as *Actinobacillus pleuropneumoniae*, *Escherichia coli*, *Bordetella pertussis*, and *Mannheimia haemolytica*. The toxins of the RTX family selectively kill human leukocytes by inducing apoptosis and lysis (Kelk et al. 2011).

As with *P. gingivalis*, some studies have researched the effects of *A. actinomycetemcomitans*, using live strains of the bacteria. Zhao et al. infected human osteoblastic cells with *A. actinomycetemcomitans* and observed that the apoptosis of the cells was significantly enhanced. Expression levels of both NLRP3 and ASC were increased dramatically after exposure to the bacteria. The secretion of mature IL-1β and IL-18 was extensively induced in infected cells compared with the non-invasion group (Zhao et al. 2014). In another in vitro study, leukotoxin and cytolethal distending toxin gene KO mutant strains of *A. actinomycetemcomitans* were used to challenge human mononuclear leukocytes. Only up-regulation of NLRP3, IL-1β, IL-18, and reduction of NLRP6 were observed, but no other inflammasome components, such as ASC, were affected (Belibasakis and Johansson 2012).

As for studies using leukotoxin to challenge different cell strains in vitro, Kelk et al. (2005) tested human macrophages with leukotoxin or LPS from *A. actinomycetemcomitans* or LPS from *Escherichia coli*. Leukotoxin induced abundant production of IL-1β and caspase 1 compared with controls, proving that leukotoxin from *A. actinomycetemcomitans* can trigger inflammatory reactions on other cells, not only on leucocytes (Kelk et al. 2005).

The common pathway usually described for the induction of IL-1β is through the NLRP3/caspase-1 pathway, but Okinaga et al. (2015), in an in vitro study on mouse macrophages, described periodontopathic invasion with *A. actinomycetemcomitans* inducing the production of ROS and the release of cathepsin B. Moreover, IL-1β processing was down-regulated by inhibition of these molecules, but not caspase-1 or NLRP3, suggesting that *A. actinomycetemcomitans* invasion in mouse macrophages might induce IL-1β production, which is dependent upon ROS and cathepsin B, but not NLRP3/caspase-1 activity (Okinaga et al. 2015).

Xylitol is a well-known anti-caries and anti-inflammatory agent, but its effect on the inflammasome had not been researched. Kim et al. (2016) studied the effects of inflammasome activation, by supplementing xylitol to macrophages infected with *A. actinomycetemcomitans*. The authors observed that xylitol inhibited the production of IL-1β and AIM2 inflammasome, seen in the control group, by suppressing the internalization of *A. actinomycetemcomitans* into cells (Kim et al. 2016). Xylitol may be used as a therapeutic weapon for the prevention of periodontal inflammation caused by *A. actinomycetemcomitans*.

7.2.4 Treponema denticola, Tannerella forsythia, *and* Mycoplasma salivarium

Treponema denticola is a spirochete that is identified in several gingivitis cases, especially its presence in necrotizing ulcer gingivitis, root canal infection, and acute apical abscesses. *T. denticola* is a relevant pathogen in periodontal and pulpal processes, its aggressiveness is due to a diversity of virulence factors, emphasizing its dentilisin, mobility and its ability to modulate the defensive response of the host (Dashper et al. 2011). *T. forsythia* is an anaerobic Gram-negative member of the *Cytophaga-Bacteroides* family, which was initially described as *Bacteroides forsythus* by Tanner and Stillman (1993) and later reclassified as *Tannerella forsythia* by Sakamoto et al. (2002) based on 16S rRNA phylogenetic analysis. *T. forsythia* is associated more frequently and/or at higher levels with various forms of the disease, including gingivitis and chronic and aggressive periodontitis, than with health. Several studies have also implicated *T. forsythia* in the progression of clinical attachment loss associated with periodontitis (Sharma 2010).

Jun et al. (2008, 2012) in two in vitro studies, described a pathway of how *T. denticola* activates the NLRP3 inflammasome through Td92, a protein present on its surface. The direct interaction of Td92 with the cell membrane integrin α5β1 resulted in ATP release and K+ efflux, which are the main events in NLRP3 activation (Jun et al. 2008, 2012). Jun et al. also studied how macrophages reacted to the infection with *T. denticola* and *T. forsythia*. Both *T. denticola* and *T. forsythia*, induced pyroptotic cell death and the activation of caspase-1 and caspase-4 in macrophages (Jun et al. 2017).

Mycoplasmas, the smallest self-replicating microorganisms without cell walls, cause various infectious diseases in humans and animals, such as atypical pneumonia, nongonococcal urethritis, and arthritis. *Mycoplasma salivarium* is a non-fermenting species and is part of the human oral microbial flora and inhabits the level of gums and dental plaque. This microorganism is isolated more frequently from the periodontal cavity of the subjects with this disease (Engel and Kenny 1970). The antibody response to this mycoplasma is significantly high in patients compared with healthy subjects (Watanabe et al. 1986). *Mycoplasma salivarium* induces the production of IL-6 and IL-8 in gingival fibroblasts (Shibata et al. 1997).

Sugiyama et al. (2015) studied the association between *M. salivarium* and periodontitis and elucidated the etiological roles of *M. salivarium* in periodontal diseases. Their study determined whether *M. salivarium* can activate the inflammasome to induce IL-1β production by innate immune cells such as dendritic cells or macrophages and, if so, what kinds of inflammasomes are activated by *M. salivarium*, *M. pneumoniae*, and their heat-killed cells. The authors observed that live and heat-killed *M. salivarium* and *M. pneumoniae* cells induced the production of IL-1β by dendritic cells and pyroptosis. Live *M. salivarium* and *M. pneumoniae* lost the ability to induce IL-1β production by macrophages from ASC- and caspase-1-deficient mice almost completely, but not entirely on macrophages from NLRP3-deficient mice. These results suggest that live *M. salivarium* and *M. pneumoniae* might be capable of activating several types of inflammasomes including the NLRP3 inflammasome (Sugiyama et al. 2015).

7.3 Other Oral Infectious Diseases

7.3.1 Candidiasis

Humans need to be protected from the damage a huge variety of microorganisms can cause. When we talk about the fungi kingdom we need to highlight the *Candida* family and especially the *Candida albicans* species. *Candida* is an ascomycete (Arendorf and Walker 1979), opportunistic (Repetto et al. 2012), polymorphic fungi. Fungal infections are becoming increasingly prevalent (Richardson and Moyes 2015). *Candida* species are the fourth most common pathogens in nosocomial bloodstream infections in the USA and Europe (Chen et al. 2013). *Candida albicans* colonizes in an asymptomatic way 65% of healthy people (Joly and Sutterwala 2010). Its overgrowth is limited by competing commensal bacteria and host defense (Tomalka et al. 2011). Alterations in the normal flora cause *Candida* overgrowth. It is usually produced by antibiotic treatment or immunocompromised states such as AIDS, during chemotherapy or following allogenic transplantation (Joly and Sutterwala 2010). *Candida* overgrowth results on oropharyngeal candidiasis (OPC, also recognized as thrush) or denture stomatitis (Abu-Elteen and Abu-Alteen 1998).

Candida albicans can grow in several forms: unicellular yeast, pseudo hyphae and hyphae. *Candida* is capable of changing the morphological and physical structure during growth and this development is reversible, which helps to potentiate its pathogenicity. Multiple forms are often found simultaneously. On the one hand, *Candida* as unicellular yeasts is typically associated with widespread dissemination (commensalism), controlled by neutrophils and macrophages. On the other hand, growth of pseudohyphae and hyphae is commonly shown in infections of the mucosal surfaces, controlled by T-cells (Repetto et al. 2012).

There are very few papers that directly relate inflammasome to *Candida albicans* and oral diseases, none of them in humans, some in vivo using murine models, and

others in vitro. The experiments carried out in mice used the same strain. All were female C57BL/6 mice. The method used to infect the mice was very similar in all the studies presented. After a brief period with antibiotic coverage, mice were infected with the fungus. Small scratches were made on the dorsal surface of the tongue, limited to the stratum corneum (Hise et al. 2009).

In one of the publications the authors compared wild-type (WT) mice with interleukin 1 (IL-1) receptor-deficient mice (IL-1r1−/−). They studied the effect of *Candida albicans* infection depending on the time since inoculation. Mice were divided into groups according to the moment of the sacrifice. Three, 7, 14, and 21 days after infection the animals were euthanized and scored clinically. Samples from tongue and kidney were removed to determine local and systemic grades of infection. Results show how IL-1r1−/− mice had higher levels of local colonization and systemic dissemination. This group also showed lower survival rates compared with WT mice. The same findings were observed comparing WT mice with caspase 1 (casp-1)-, NLRP3-, and ASC-deficient mice (Hise et al. 2009).

In another study, the periods of time when the mice were euthanized were the same as in the study explained above. In this case, WT mice were compared with NLRP3-, NLRC4-, and ASC-deficient mice. Tongues were removed after sacrifice and evaluated with a microscope. Comparing two inflammasome complexes of the NLR family, it is shown how genetic knock-down of a single NLR inflammasome could have an important effect on the expression of other NLR proteins. NLRC4-deficient mice responded worst to Candida infection than NLRP3 KO mice (NLRP3−/−) and WT mice measuring the same parameters described above. These data reveal that NLRP3 and NLRC4 play different roles in immunity against *Candida*, NLRC4 being more important in the last period of the fungal infection (Tomalka et al. 2011).

It is also important to mention that we have seen a relationship between the results found from studies that discuss oral and vulvovaginal candidiasis. Similar environmental conditions and characteristics are described. There is a paper where the authors used mice of the same strain, but in this case, the inoculation was intravaginal, concentrating their efforts on studying the role of IL-22. It has been demonstrated that IL-22 controls the process by which NLRP3 recruits neutrophils and promotes inflammation when it is activated. IL-22 also activates NLRC4 so that it can produce IL-1 receptor antagonist (IL-1Ra). WT mice were compared with NLRP3- and NLRC4-deficient mice. Interestingly, NLRP3 inhibition matches NLRC4 activation. NLRP3 is associated with casp-1 activation, polymorphonuclear activation, and inflammatory damage in vulvovaginal candidiasis. NLRC4 is suggested to be part of a process that limits inflammation. Continuing with the study, they used human samples of vulvovaginal candidiasis to examine results in vitro. The results found were the same as in the murine model. They conclude that a lower production of IL-1Ra and IL-22 might be a risk factor for recurrent vulvovaginal candidiasis (Borghi et al. 2015).

Macrophages from WT in addition to NLRP3- and ASC-deficient mice were evaluated in the presence of *Candida albicans* to investigate the NLRP3–ASC–caspase-1 axis and IL-1β production. An active form of IL-1β was only located in

supernatants of WT macrophages. The induction and processing of IL-1β are controlled and mediated by the NLRP3–ASC–caspase1 axis (Hise et al. 2009).

7.3.2 *Herpes Virus*

Many species of virus can affect the oral tissues. We are going to look for information about the herpes virus (HV) family. We can find the herpes simplex virus (HSV), human cytomegalovirus (HCMV), varicella zoster virus (VZV), and Epstein–Barr virus (EBV). HSV is the most frequently studied, particularly type 1 (HSV-1). HSV-1 is frequently associated with facial and oral lesions. HSV-2 is related to genital and neonatal infections. We briefly explained some of the characteristics of HSV-1.

HSV-1 is a ubiquitous (Xu et al. 2006), common and highly contagious pathogen that infects most people (90%) (Smith and Robinson 2002). It is an icosahedral, enveloped, nuclear-replicating, double-stranded DNA virus belonging to the neurotropic *Alphaherpesvirinae* subfamily. Primary infection occurs during childhood and usually affects the oral mucosa. In most cases, with very few symptoms, making it very difficult to diagnose correctly at an early stage. A lifelong infection takes place in the trigeminal ganglia, keeping the virus latent. It periodically activates to a lytic state producing recurrent lesions at the site of primary infection. HSV can cause fatal infections such as encephalitis, blindness, or even the death in immunocompromised patients.

Breast cancer tumor suppressor protein (BRCA1) and interferon inducible protein 16 (IFI16) were studied in human microvascular dermal endothelial cells (HMVECs) and human fibroblasts. BCRA1 is a DNA damage repair sensor and transcription regulator. IFI16 is a restriction factor for HCMV and HSV-1 (Johnson et al. 2014). IFI16 is a sequence-independent nuclear innate sensor recognizing nuclear replication of herpes virus such as Kaposi's sarcoma-associated herpes virus (KSHV), EBV or HSV-1. The recognition takes place in the infected cell nucleus, then forming an inflammasome complex with ASC and pro-caspase-1 (Johnson et al. 2013). It finally produces IL-1β. BCRA1 works together with the IFI16 inflammasome, increasing expression levels during de novo KSHV, EBV, and HSV-1 infection, and in latent KSHV or EBV infection (Dutta et al. 2015a). In a similar paper, Johnson et al. (2013) demonstrate that IFI16 and NLRP3 inflammasomes were activated by HSV-1 infection, promoting IL-1β maturation. Although the host immune system responds to the virus, the authors explained that HSV-1 has evolved defense mechanisms to evade host reaction (Johnson et al. 2013).

The interaction of HVS1 infection with TLR2 is critical, modulating the production of proinflammatory cytokines, for example, IL-6. Excessive signaling can cause too much inflammation and tissue damage (Wang et al. 2012). The balance between proinflammation and down-regulation mechanisms is important. CD200R1 is a protein expressed on myeloid and glial cells, which interacts with CD200 expressed

on neurons, epithelial cells, endothelial cells, and lymphocytes. Their junction occurs to initiate inhibitory signaling (Mihrshahi and Brown 2010). CD200R1-deficient mice generated lower levels of IL-1β and IL-6. They are also protected from intracranial HSV-1 infection, increasing the survival rates (Soberman et al. 2012).

Herpes virus infection causes NLRP3 redistribution to the nucleus. Mice and human corneal tissues were used to study keratitis and how NLRP3 was expressed with HSV-1 infection. NLRP3, Casp-1, and IL-1β levels were higher in mice infected with HSV-1, presenting a partial redistribution of NLRP3 to the nucleus. The same results were found in human tissues (Wang et al. 2015). In contrast, Miettinen et al. (2012) published a paper experimenting with human macrophages in which they affirmed that the inflammasome is not activated in response to HSV-1 infection. HSV-1 infection can activate a wide variety of proteins in the absence of inflammasome activation (Miettinen et al. 2012).

HSV-1 infection was studied in KO and normal NLRP3 mice in facial infection and keratitis. Deficient mice had more severe and earlier keratitis, and higher levels of IL-1β and IL-18 in the early stages of infection. Elevated recruitment of neutrophils and elevated levels of CD4+ T cells occurred at advanced stages of infection. To conclude, the NLRP3 inflammasome plays a specific role against keratitis pathogenesis and acts as a regulator and a beneficial support (Gimenez et al. 2016).

We finish describing the HV family by speaking of VZV. VZV induces formation of the NLRP3 inflammasome and consequently the production of IL-1β. This was shown in human T helper-1 (TH-1) cells, fibroblasts, and melanoma cells. NLRP3 recruitment is independent of AIM2, revealing different pathways. VZV triggers formation of the NLRP3 inflammasome complex with activated caspase-1 in the absence of AIM2 (Nour et al. 2011).

7.4 Cancer

Oral cancer is the most common cancer of epithelial origin in the head and neck and the sixth most common cancer overall. Nowadays, oral cancer represents 3% of all new cancers diagnosed and this is rapidly increasing (Parkin et al. 2005; Reid et al. 2000). Most oral cancers are oral cavity squamous cell carcinomas (OSCCs). They are usually locally aggressive with moderate recurrence (Funk et al. 2002). The 5-year survival after treatment (surgery, radiotherapy, and chemotherapy) is only 50% because the diagnosis is often made in the late stages (Siegel et al. 2016; Ferlay et al. 2015). The most frequent locations are the tongue, buccal area, gingiva, lips, floor of the mouth, and hard palate. It is important to clarify that most of the cases start from a potentially malignant disorder that is important to detect and treat as soon as possible. The continuous exposure of this lesion to carcinogens such as tobacco, alcohol or chronic inflammation (25% of malignancies are associated with chronic inflammation and/or infection) (Mantovani et al. 2008) may force it evolve to malignization by a process called carcinogenesis (Lippman et al. 2005).

NLRP3 inflammasome was studied in 20 biopsied cases of OSCCs including the malignant tumor and the adjacent nonpathological tissues. It was revealed that the expression levels of NLRP3 inflammasome-associated genes (ASC, casp-1, Il-1β , and NLRP3) were higher in the tumor tissues, in addition to the protein expression levels, using immunohistochemical (IHC) techniques. These levels are related to clinical and pathological characteristics of OSCCs. The authors asked themselves how these levels could influence the overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS), showing that the up-regulation of ASC was the only independent predictor. Finally, they also added to their paper an experiment in vitro where they concluded that ASC facilitates migration and invasion of OSCC cell lines, promoting metastasis (Wu et al. 2016).

There are many publications related to cancer from South Asia, more precisely Taiwan. One of these papers shows the consequences of a high prevalence of a traditional custom, such as betel nut chewing. The total number of patients (all of them men) were divided into four groups: young control, middle-aged control, betel nut chewing, and oral cancer. An ELISA technique was used to measure cytokines and hormones: IL-1β, IL-6, IL-15, tumor necrosis factor α (TNF-α), cortisol, and testosterone in plasma. The results published show elevation of cortisol, lower levels of IL-1β, Il-15, and TNF-α, and lower testosterone concentrations in the betel nut chewing group (Hu et al. 2016).

Seven OSCC-related salivary biomarkers of periodontitis were studied in several groups: smokers, nonsmoker patients, patients without periodontal disease but with OSCC, and control patients (a total of 105 patients). The only biomarker that showed significant differences between the OSCC patient group and the rest was S100 calcium binding protein P (S100P) being much higher in the OSCC group. Cytokines that promote inflammation such as IL-1β and Il-8 did not show statistically differences between the groups (Cheng et al. 2017).

There are several papers that focus on IL-18, particularly the Il-18 polymorphism −607 A/C. Nilkaeo and Bhuvanath (2006) suggested that IL-18 might be a proinflammatory cytokine produced by cancer cells. On the one hand, Tsai et al. (2013) concluded in their paper that the IL-18 −137 G/C gene polymorphism could be considered an important factor that increases the susceptibility to OSCC, although they also suggested that it could be proposed as a protective factor for OSCC progression (Tsai et al. 2013). On the other hand, Eleftherios et al. tell us that IL-18 −607 A/C polymorphism gene expression is not a contributing factor in oral carcinogenesis or risk of cancer (Vairaktaris et al. 2007).

Interleukin-18 plays an important role in the regulation of OSCCs, specifically when it is localized in the tongue. It promotes the growth inhibition of OSCCs and helps in the regulation of cell apoptosis and gene expression. It could be used in the future after further investigations as a potential clinical and therapeutic target (Liu et al. 2012).

Interleukin-1β is also a very well recognized proinflammatory cytokine that can regulate cancer growth and metastasis in a secondary position. This is possible because it interacts by controlling the expression of CXCR4, a specific chemokine that regulates processes in cancer development. It is also suggested that CXCR4 may

be a link between inflammation and cancer (Sun et al. 2015). In addition, this cytokine may be used as a marker of malignant transformation in oral leukoplakia, one of the most frequently studied potentially malignant disorders (Dutta et al. 2015b).

In brief, we have just discussed IL-1β and IL-18, suggesting that an important relationship might exist among inflammation, the inflammasome, and cancer. High levels of IL-1β and IL-18 are associated with cancer. Likewise, activation of the autophagic process or mitochondrial oxidative stress are related to cancer. All this information is important in continuing to investigate cancer genesis and prognosis (Zhiyu et al. 2016).

7.5 Caries

Pulp lesions can be caused by many factors. Dental caries is the most prevalent cause. It is a chronic infectious disease. It provokes the demineralization of the most superficial tissue the teeth have, the enamel, and the subsequent interior tissue, called dentin, causing pulp injury (Akira et al. 2006; Bolwell 1999). We are not aware of the prevalence of dental pulp lesions. Clinically, we can classify them as pulp (dentin hypersensitivity, pulpitis, and necrosis) and periapical diseases (apical periodontitis and others with no endodontic etiology) (Moller et al. 1981). Experimental studies demonstrate that the presence of bacteria is essential for the development and progression of pulp inflammation (Kakehashi et al. 1965).

Dental pulp reacts to caries infection with inflammation. It has some peculiarities, such as its location in a hard chamber or the exclusive blood and lymphatic circulation. These facts make pulp inflammation processes difficult to control and resolve. Pulpitis is the most common inflammatory disease in mammals. We describe pulpitis as a nonspecific inflammation of the dental pulp. If it remains untreated, it can lead to the patient's death, but it is commonly solved with soft dental tissue removal and root canal treatment (Akira et al. 2006). Pulpitis occurs when caries infection has contact with dentine tubules, which are connected to the pulp tissues (Bortoluci and Medzhitov 2010). The first line of defense the teeth have against caries progression is the activation of the innate immune system components located in the pulp (Chang et al. 1998).

Apical periodontitis is also an inflammatory lesion that occurs in the most apical zone of the teeth because of bacterial infection of endodontic–periodontic origin. It is characterized by bone resorption in this location (Hong et al. 2004).

The relationship between pulpitis and the presence of the AIM2 inflammasome was an unknown fact. The authors exposed only the dental pulp of the right maxillary molars of male Sprague–Dawley rats and compared the levels of expression of AIM2 in both sides. In the in vitro study they cultivate the cells of the mandibular incisors of those rats. AIM2 inflammasome expression was higher in damaged tissues. IL-1β and caspase-1 levels increased whereas AIM2 levels were

higher. A direct relationship between AIM2 inflammasome and inflammatory processes such as pulpitis was affirmed (Wang et al. 2013).

The NLRP3 inflammasome complex has been studied related to pulpitis in humans. The third molars of 27 people were extracted: 9 of them had no pathological condition, 9 had reversible pulpitis, and the remaining 9 had irreversible pulpitis. Dental pulp fibroblasts were cultivated for experimentation. Depending on the grade of pulpitis, NLRP3 expression varies. Wisdom teeth with irreversible pulpitis showed significant differences in the levels of IL-1β, caspase-1, and of course, NLRP3. Only in irreversible pulpitis was caspase-1 present in an active form. In this study and the one before the analysis of the cells, the same results are revealed as those seen in the in vivo studies (Jiang et al. 2015).

A similar experiment was reported by Oliveira et al. (2009). Ten healthy wisdom teeth and another ten with pulpectomies. Pulp fibroblasts were analyzed with or without stimulation of *Escherichia coli* LPS. The purpose was to study the role that IL-1β and IL-8 play in a healthy state and in dental infections. As we assumed before reading, damaged pulp tissues presented higher levels of IL-1β and IL-8 (Oliveira et al. 2009).

A very important microorganism is found in infected dental pulp, even after canal treatment. *Enterococcus faecalis* plays an important role in inflammasome activation. Macrophages were infected with this bacterium. The results were that *Enterococcus faecalis* released ATP as a danger signal, making it higher in the extracellular space, which promoted the activation of the NLRP3 inflammasome, and consequently caspase-1 activation and IL-1β secretion (Yang et al. 2014). Wang et al. (2016) also studied the role of *Enterococcus faecalis* in inducing apical periodontitis in rats and the relationship it has with the NLRP3 inflammasome. Both papers reached the same results, but this latter experiment also studied the effect of the lipoteichoic acid (derived from *Enterococcus faecalis*) on the expression of the NLRP3 inflammasome, suggesting that it might act as a directly stimulating factor of this inflammasome complex (Wang et al. 2016).

There are higher levels of proinflammatory cytokines in dental periapical lesions (granulomas and cysts). The cytokine levels vary depending on the apical lesion size (larger or smaller than 5 mm) and the symptomatology. Symptomatic lesions produce higher levels of IL-1β, IL-6, and IL-8. On the one hand, the smaller apical lesions were related to higher numbers of mononuclear phagocytes; on the other hand, higher levels of TNF-α, IL-6, and IL-10, in addition to a higher concentration of CD8+ T cells, were found in large apical lesions (Gazivoda et al. 2009).

On the whole, these papers demonstrate that dental tissue damage is related to inflammation, the activation of some inflammasome complexes, and the secretion of proinflammatory cytokines.

7.6 Other Oral Diseases

Idiopathic burning mouth syndrome (iBMS) is considered by the International Association for the Study of Pain to be a chronic distinctive nosological entity in which patients perceive spontaneous burning sensations and/or other dysesthesias (tingling or itching) (Braud et al. 2013). Normally associated with xerostomia and dysgeusia (de Moraes et al. 2012). It commonly appears in the lips, hard palate, tongue and/or other oral mucosal surfaces with no clinical or laboratory signs that could demonstrate abnormalities (Suh et al. 2009; Kim et al. 2012). Mostly post-menopausal, stressed women are affected by iBMS, where it can rise up to 12% (Bergdahl and Bergdahl 1999). The origin and the way in which the pain is produced in the patient are still unknown (Forssell et al. 2015).

Liquen planus is a chronic inflammatory disease that can affect the mucous membranes of squamous cell origin and the skin (Qiu et al. 2017). Oral liquen planus (OLP) affects the oral mucosa, but skin alterations may not always be found. It appears more frequently in women than in men (Mozaffari et al. 2016). Comparing clinical characteristics, we can distinguish six types: reticular, papular, plaque-like, atrophic, erosive, and bullous (Shen et al. 2012). We can also classify them as non-erosive OLP and erosive OLP subtypes. This subdivision is important to differentiate the potential risks of malignization (Jun et al. 2008). The prevalence of OLP lesions is 0.5–2% (Setterfield et al. 2000), increasing if the patient smokes or has a high consumption of alcohol (Torrente-Castells et al. 2010).

Rare levels of expression of a variety of proinflammatory cytokines have been found in OLP lesions, and in the serum and saliva of those patients (Lu et al. 2015), suggesting a direct relationship between inflammation and OLP. The etiology of OLP is still unknown, but it is clear that immune dysregulation plays a superlative role (Lodi et al. 2005). Several treatments using different methods have been proposed. Topical and systemic products such as corticosteroids or immunosuppressants are the first ones most frequently used (Canter et al. 2007).

Kho et al. (2013) studied two different markers associated with the mucosal defense system, mucin 1 (MUC1) and TLR-2, in patients with iBMS or OLP, compared with control subjects . MUC1 is the membrane-bound mucin expressed by the salivary glands and oral epithelial cells (Hori et al. 2007). TLR-2 is an associated protein expressed in cell membranes that belongs to a family of proteins called PRRs, which recognize PAMPs. NLRP3 inflammasome needs two signals for its activation. MUC1 and TLR-2 play important roles during the priming or first signal. Levels of MUC1 were increased in patients with iBMS in comparison with patients with OLP or controls. These data may be important for confirming in further studies that an increase in the levels of subclinical inflammation could be involved in the intensity and perception of burning symptoms (Lopez-Jornet et al. 2011).

7.7 Conclusions

The mouth is always a possible environment for developing pathological conditions owing to the wide variety of microorganisms that exist there. Small variations in the equilibrium of the oral flora cause disorders that could affect the organism in a systemic form. Many publications have been written about oral diseases, but very few of them try to relate this information to the inflammasome complex. Therefore, further investigation and publications on inflammatory molecular processes are needed, in particular, those more specifically related to the inflammasome complex.

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