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Role of Innate Immune Response of Dental Hyperplastic Pulpitis: A Review

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Abstract

Immunity plays an important role in many areas, including dental health. Dental caries is the main and most common problem in dental and oral health fields. Dental caries was influenced by 4 important factors, among them was a bacterial infection. The bacterial infection can cause inflammation of the pulp. Chronic inflammation pulpitis can stimulate pulp polyps or hyperplastic pulpitis. This study aimed to identify the role of innate immune response to hyperplastic pulpitis process. Bacteria Streptococcus mutans was the most prevalent bacteria in dental caries. Its lipopolysaccharide could trigger an immune response by activating the cellular and humoral components in the pulp cavity. The cellular components include polymorphonuclear cells, monocyte and macrophage cells, dendritic cells, basophil cells, and mast cells. The humoral component was histamine and pro-inflammatory cytokines, such as IL-1β, IL-4, IL-6, and IL-12. The presence of bacterial infections or pathogens causes the body to stimulate defense mechanisms through innate immune cells and humoral components.

Keywords: Innate Immunity, Cytokine, Caries, Pulpitis Hyperplastic

1. Introduction

Immunity plays an important role in many areas, including dental health. Dental caries is the main and most common problem in dental and oral health fields. Based on Riskesdas 2018, the prevalence of dental caries in South Sumatra is 45.1%, and in Indonesia is 45.3%.[1] It is quite high when compared to the 2030 SDGs mission that Indonesia free dental caries.[2] Dental caries is a condition of cavities caused by four factors, namely substrate or food remains, bacterial invasion, tooth anatomy, and time.[3] Bacterial infections that have reached the deepest layers cause inflammation of the pulp. [4]

Dental pulp is the third and deepest layer of the tooth, often referred to as the pulp cavity. This pulp tissue is the softest tissue when compared to enamel, dentin, and cementum. The pulp contains many nerves, blood vessels, cellular components, and basic substances.[5-7] When the inflammation in the pulp has become chronic inflammation, it can cause the formation of granulation tissue found in the occlusal of open cavity teeth.[8] Generally, the condition of hyperplastic pulpitis is more often found in children and young adults than in the elderly because the body's immune response in the age group is felicitous.[8] This review will discuss and find out more about the innate immune response in the inflammatory condition of hyperplastic pulpitis or pulp polyps.

2. Antigen Invasion in Pulpa Tissue

Teeth are an important component of the body which consists of three important layers in the crown and root teeth. Corona layers, namely enamel, dentin, and pulp; while root layers of the tooth, namely cementum, dentin, and pulp.[5,6] Dental pulp is rich in blood vessels and dental nerves so it has formative, sensory, nutritional, and protective functions during the life of the

tooth. It also plays a very important role in tooth vitality.[5]

Dental pulp tissue is divided into 2 parts, the coronal pulp which is located at the crown of the tooth and the apical pulp which is located at the root of the tooth. The coronal pulp part resembles the shape of the original tooth with many sides, such as buccal, lingual, mesial, and distal. The inter-cups are connected and the top of the pulp is called the pulp horn. On the other hand, the apical pulp or root pulp is known as the root canal.[5] The pulp is a cell-rich zone of tooth tissue. The most common cells found are fibroblast cells. Apart from that, there are also other cells such as undifferentiated mesenchymal cells, macrophage cells, and mast cells.[5]

Fibroblast cells in the pulp secrete collagen types I, III, V, and VI and various non-collagenous extracellular matrix components, such as proteoglycans and fibronectin. The process of collagen synthesis and degradation occurs continuously in the pulp. However, as we age, these fibroblast cells will decrease in number.[5]

Undifferentiated mesenchymal cells are also often found in pulp tissue. These cells will proliferate into odontoblast cells, fibroblast cells, or macrophages if needed. These cells are found in areas near blood vessels.[5] Normal pulp, also has several defense cells, such as histiocyte cells, macrophage cells, dendritic cells, mast cells, plasma cells, PMN cells, eosinophil cells, basophil cells, monocyte cells, and lymphocyte cells are also visible. These immune cells are normal cells that reside in the pulp matrix and respond to situations that cause inflammation such as dental caries, mechanical and chemical irritation, occlusion trauma, etc.[5]

Dental caries is a chronic disease or condition caused by cariogenic bacteria attached to teeth.[3] The bacteria that commonly infect teeth are *Streptococcus mutans*. These bacteria can metabolize sugar and produce acidic conditions.[3] If the condition of the human oral cavity is at a low pH (acid), it will be easier for other bacteria to enter and colonize, thereby triggering a demineralization process over time.[4] The dental caries process is influenced by four important components, namely the substrate or food remains, bacteria, tooth anatomy, and time.[4] Thus, on an ongoing basis, this process will produce dental cavities which are often referred to as dental caries.

When bacteria penetrate and reach the pulp, antigen invasion in pulp tissue takes place. When odontoblasts and immune cells in the pulp identify the antigens, they release inflammatory mediators such as prostaglandins and cytokines, which sets off an immunological reaction. To combat the infection, these signals enlist immune cells such as lymphocytes, neutrophils, and macrophages. [4]

Early carious conditions can still be restored with minimally invasive treatment.[4] However, if a tooth with caries is left until the infection reaches the deepest layer, namely the dental pulp, then the treatment and the body's response to fighting the infection will become more advanced. [4] When the *S. mutans* bacteria enter and infect the tooth, the immune cells found in normal pulp tissue will be active. In this condition of infection, the teeth also experience degradation of collagen and extracellular matrix so that the hard tissue of the teeth becomes more brittle.[7]

3. Role of Innate Immune Cells

Neutrophil Cells

Neutrophil cells also often known as PMN cells are the first leukocytes to reach areas of inflammation.[9] These cells have an important function in killing bacteria, namely by phagocytosing these pathogens. The cell compartment that traps the bacteria is the phagosome.[10] In the cytoplasm of the

neutrophil cell, the phagosome will fuse with another cellular compartment, namely the lysosome, and cause the pathogenic bacteria to lyse.[10] Apart from that, the neutrophil cell can also degranulate the pathogenic cell. Its life span is around 6 hours to several days.[11]

Monocyte and Macrophage cells

The second most common white blood cell to kill bacteria is monocytes. Monocyte cells have 2 important roles in killing bacteria. First, just like neutrophil cells, namely by phagocytosis, monocyte cells can act as antigen-presenting cells (APC) to adaptive immune cells.[12] The monocyte cells can differentiate into macrophage cells. Monocyte cells in circulation have a half-life of between 10-72 hours.[11] Then, they enter the tissue to become macrophage cells. The average life in tissue is around 3 months.[13] If there is a tissue infection or inflammation, the monocyte cells will migrate to the infected location.[13] Initially the number of monocyte cells is less than the number of neutrophil cells. However, in ongoing inflammation (more than 12 hours), monocyte cells are more numerous than neutrophil cells.[13] In addition, in chronic inflammatory conditions, macrophage cells can change shape into multinucleated giant cells.[9]

Basophil Cells

Basophil cells are one of leukocyte cells that have granules, similar to neutrophil cells/PMN.[9] These cells are very few in number, around 0-1% of the total leukocytes.[14] Their function is to release histamine and serotonin in the overall inflammatory response.[14] The cells These basophils also have a short life span, around a few hours to a few days.[11]

Mast Cells

Mast cells are one of the major effector cells in the innate immune system because these cells contain several vasoactive substances, such as histamine and arachidonic acid metabolites.[15] Freitas et al., in their research, revealed that mast cells were found in teeth with pulp polyps or hyperplastic pulpitis.[16] There is a significant difference between the number of mast cells found in the coronal pulp and root pulp.[16] These mast cells are spread throughout the connective tissue, especially around dental nerve fibers, newly formed blood vessels, and other inflammatory cells.[16] The presence of mast cells in the chronic phase of inflammation can be influenced by the initiation of a specific immune response and the progress of pulp pathology. In this case, mast cells migrate to inflammatory tissue to release specific chemokines in the chronic inflammatory response.[16]

Dendritic Cells

Monocyte cells in capillary blood vessels, apart from transforming into macrophage cells in tissues, can also transform into specialized mononuclear cells.[9] These cells are known as dendritic cells. When compared with PMN cells, monocytes, and macrophages, these dendritic cells have weaker phagocytic properties. The main function of these cells is as APC (Antigen Presenting Cells) which play an important role in processing antigens from the *S. mutans* bacteria and bringing them to be recognized by T lymphocyte cells.[3,9] When antigens from these bacteria enter the dentin-pulp tissue of the tooth, the dendritic cells will recognize them and take them to the specific immune system for processing.

Table 1. The role and lifespan of innate immune cells in hyperplastic pulpitis

Cells	Role	Lifespan
Macrophage	Pathogenic phagocytes, also known as APCs to T lymphocyte cells	Months-years
Monocytes	Pathogenic phagocytes in blood circulation	10 – 72 hours
Neutrophil	Pathogenic phagocytes and cell degranulation	6 hours – days
Basophil	Cell degranulation, Release of histamine, enzymes, cytokines	unknown: around hours-days
Mast cells	Cell degranulation, Release of histamine, enzymes, cytokines	Months-years
Dendritic	As APC to T lymphocyte cells stimulate the release of cytokines.	Weeks-months
Fibroblast	Release of pro-inflammatory cytokines and proliferate to form granulation tissue.	Months-years

4. Role of Pro-Inflammatory Molecules

Response immune to bacterial invasion and inflammation, macrophages and monocytes cells will release cytokines, that mediated the inflammatory process.[7] Innate immune cells secrete interleukins, such as IL-1, IL-6, IL-10, IL -12 and IL-18 in multifunctions.[7] For example IL-1 can stimulated macrophage cells and lymphocyte cells, IL-6 can activated B cells and IL-10 inhibits the function of macrophage cells and dendritic cells.[7] Criticou et al., explained the presence of these cytokines in their research as follows[7]:

Interleukin-1β (IL-1β)

IL-1β is an important cellular mediator, such as in the processes of proliferation, differentiation and apoptosis. The comparison of the levels is significant between healthy pulp and those experiencing inflammation, especially chronic inflammation.[7]

Interleukin-4 (IL-4)

IL-4 encourage IgE production and stimulate mast cells.[7,17] Abd-Elmeguid et al., explained that IL-1rα, IL-4 and IL-12 are inflammatory mediators which are significantly increased in pulpitis conditions, especially chronic pulpitis compared to pulp that healthy.[18]

Interleukin-6 (IL-6)

IL-6 will stimulate tissue degradation by increasing MMPs levels, and will induce the differentiation of mature B lymphocyte cells into plasma cells.[7] Study of Abd-Elmeguid et al., also explains that there is a significant difference in IL-6 levels in healthy pulp and pulp that is chronically inflamed.[18]

Interleukin-12 (IL-12)

IL-12 levels in chronically inflamed pulp also increase compared to normal pulp, but not significant.[7,17]

Histamine

The presence of histamine in pulpitis hyperplastic is also influenced by immunoglobulin E.[17] Study by Sattari et al., shows that IgE is an important factor of releasing histamine from mast cells.[17] In hyperplastic pulpitis, the release of vasoactive substances, such as histamine, will damage the pulp and lead to a very large increase in tissue pressure. This is because the dental

pulp is surrounded by dentin tissue which is a rigid mineralized tissue structure.[17] Shoji et al., found that bacterial LPS present in the process of developing pulpitis or gingivitis will induce an increase in histidine decarboxylase (a histamine-forming enzyme) so that histamine concentrations will also increase.[19]

5. Pathogenesis

Pulpitis or pulp inflammation is a condition when a bacterial infection enters the tooth and affects the pulp. The bacteria commonly found in dental caries are *S. mutans* bacteria. This bacterial LPS can stimulate immune response by activating cellular and humoral components in the pulp cavity. Immune cells such as PMN cells and macrophages will carry out their function in phagocytosing pathogens. On the other hand, bacterial LPS will induce an increase in histidine decarboxylase (a histamine-forming enzyme), as well as induce basophil cells and mast cells to release histamine.

Other cells in the pulp tissue, such as dendritic cells, macrophage cells and fibroblast cells will stimulate the release of pro-inflammatory cytokines. These cytokines will induce the proliferation of fibroblast cells in the pulp so that granulation tissue and a proliferative mass are formed which are rich in connective tissue and new blood vessels. This is supported because in children to young adults, the number of fibroblast cells and undifferentiated mesenchymal cells is still large compared to older people. Thus, this condition influences the age predilection for cases of hyperplastic pulpitis because it is still rich in cells and the body's immune response in the age group is felicitous.

Hyperplastic pulpitis or pulp polyp is a chronic condition of teeth affected by caries and involving the pulp tissue. The teeth most frequently involved are molars.[20] Hyperplastic pulpitis is a condition where the pulp is still vital and is caused by mechanical irritation and bacterial invasion into the dental pulp. Exposed pulp tissue will produce a chronic inflammatory response and stimulate many granulation tissue reactions.[8,21] The pulp will experience hyperplasia and a reddish proliferative mass will form in the occlusal part of the tooth. The formation of granulation tissue occurs because young pulp teeth have a rich blood supply and a good immune response, making them more resistant to bacterial infections.[8]

Histologically, this hyperplastic pulpitis condition contains a lot of connective tissue and new blood vessels. The presence of neuropeptides such as substance P and peptides that are tightly bound to the calcitonin gene, will regulate blood flow and permeability of micro blood vessels in the pulp.[7]

6. Conclusions

When bacterial or pathogenic infection enters the tooth and penetrates the pulp, the body will provide immune and inflammatory response by activating the innate immune system through both cellular and humoral components. However, hyperplastic pulpitis is a condition of chronic infection and inflammation, so further discussion regarding specific immune responses is needed to determine the roles of cellular and humoral components, such as T lymphocyte cells, B lymphocyte cells and antibodies.

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