ORIGINAL ARTICLE

Pyroptosis was occurs in the gingivitis due to bacterial triggers by expressing Gasdermin-D and inflammasome-NLRP-3 proteins

*Adi Prayitno[1], Widia Susanti[1], Aldissa Yova Elmanda[2]

[1] Oral and Dental Depatement, Universitas Sebelas Maret Hospital, Sebelas Maret University, Solo, Jalan Ir. Sutami 36 Kentingan, Jebres, Surakarta, Jawa Tengah. Indonesia 57126.
[2] Depatement of Oral Surgery, Universitas Gajah Mada, Oral and Dental Hospital, Gajah Mada University, Solo, Jl Sekip Utara. Bulaksumur. Jogjakarta, Indonesi 55281

ABSTRACT

Introduction: Gingivitis is inflammation that often attacks the gum tissue. Bacteria are the most important cause. Pyroptosis is a type of programmed cell death caused infection trough expressed pro-inflammatory cytokines. Objective of this study is to know that pyroptosis was occurs in the gingivitis due to bacterial triggers by expressing Gasdermin-D and inflammasome-NLRP-3 proteins. **Material and Methods:** The experimental is analytic research with the case and control groups design. Event gingivitis was triggered by Aggregatibacter actinomycetemcomitans. After secrified a biopsy was performed on the distal portion of teeth and fixed with 10% buffered formalin. Hematoxylin eosin are stained to make sure which is healthy or gingivitis. Immunohistochemical stain was done using anti Gasdermin-D and inflammasome-NLRP-3 monoclonal antibodies. The interval data from 0 to 4 is analyzed to determine the differences in expression of Gasdermin D and inflammasome-NLRP-3 proteins between healthy pericorona and pericoronitis tissue. **Results:** The median of expression Gasdermin-D reflected in healthy gum and gingivitis are 1.75 : 3.125, while for Inflammasome-NLPR-3 are 2 : 3.625. Found differences between healthy gum and gingivitis both in Gasdermin D (p=0.001) and inflammasoeme-NLRP-3 (p=0,009). **Conclusion:** Pyroptosis was occurs in the gingivitis due to bacterial triggers by expressing Gasdermin-D and inflammasome-NLRP-3 proteins.

Keywords: Gingivitis, pyroptosis, gasdermin-D, inflammasome-NLRP-3

Corresponding Author:
Adi prayitno
Email: adiprayitno@staff.uns.ac.id
Tel: +6287734941844 /+6282114135395

INTRODUCTION

Gingivitis is inflammation that often attacks the gum tissue. Gingivitis if untreated can damage the composition of the teeth and cause bad breath. This disease infects gum of teeth that grow abnormally, embedded, or grow sideways. Gingivitis symptoms are divided into two based on the condition of the disease, namely acute or chronic. Prevalence of gingivitis was found 4.92% and occur in 20 and 25 years old (72.41%). [1, 2] Chronic gingivitis emerges by 73.3%. The prevalence is 0.63%. Bilateral events were 36.4%. Women were more frequent (63.6%). [3] As a result of infection and inflammation in the gum tissue, cell death will occur either in the form of necrosis, apoptosis or pyroptosis. [4, 5]

Pyroptosis is programmed cell death coordinated by caspase-1 and released pro-inflammatory cytokines, including IL-1β and IL-18. Pathogenic Associated Molebular Pattern (PAMP) and/or Dangerous Associated Molecular Pattern (DAMP) are recognized by N-terminal Like Receptor (NLR), which assembles as inflammasome (NLRP-3: N terminal like receptors pyrin 3) to activate caspase-1 and trigger pi\yroptosis. [4, 6, 7, 8] Apoptosis morphologically characterized by caspase-3 activation, mitochondrial permeability, DNA fragmentation, cell shrinkage, and membrane blebbing. Bacteria are maintained in the body of apoptosis and are swallowed by phagocytic cells. Necrosis is triggered by the production of ROS or hazard signals, such as depletion of ATP, release of calpain, and destabilization of lysosomes, which is caused by bacterial infection or physical damage. Necrosis is characterized by nuclear swelling, membrane rupture and released cellular content and accompanied by independent inflammation of caspase. [4, 6]

Gasdermin-D (GSDMD) is a protein encoded by his gene

on chromosome 8. [9] Gasdermin-D mainly expressed from epithelial cells to play a role in the regulation of epithelial cells proliferation and differentiation. GSDMD has agreed to act as a tumor suppressor. Function of GSDMD is as a specific substrate of caspase-1 and as an effector programmed cell death pyroptosis. [10, 11] GSDMD is an important mediator of host defense against microbial infections and danger signals. pore formation activity of N-terminal cleavage products causes swelling of cells and lysis to prevent replication of intracellular pathogens and for release of cytoplasmic content like cytokines interleukin-1β (IL-1β) and Il-18 into extracellular space. [12]

NLRs (N-terminal like receptors) located in the cytoplasm, which is responsible for recognizing PAMPs and.or DAMPs that enter the cell including DNA/RNA viruses, LPS, endogenous pro-inflammatory cytokines, components of gram-negative bacteria and so on. NLRs are divided into two major groups based on their N-terminal arrangement, namely NLRP and NLRC. NLRP is a group of NLRs that have an N-terminal pyrin domain and NLRC that contains a CARD domain. Several NLRs have been identified. Each of the NLRs is different in terms of the types of DAMPs and PAMPs components that can be identified the type of adapter protein. However, all NLRs in the inflammasome complex will basically activate the pro-caspase 1 protein which is tasked with changing the pro IL-1β and pro IL-18 into active forms. [10, 13]

Pathogenic Associated Molecular Pattern (PAMP) and/or Dangerous Associated Molecular Pattern (DAMP) are recognized by N-terminal Like Receptor (NLR), which assembles as inflammasome (NLRP-3: N terminal like receptors pyrin 3) to activate caspase-1. In the other side PAMP/DAMP also trigger GSDMD proteins expression that have 2 side, name N-terminal and C-terminal. The active caspase-1 then to cut that GSDMD into 2 segmen (N-terminal side and C-terminal side). Then N-terminal molecules will vulid pore in membrane of the cell and trigger pi\yroptosis programe cells death. [4, 6, 7, 8]

MATERIALS AND METHODS

The type of research is laboratory experimental with pre and post test only design. Using Wistar rats divided inato 2 groups namely the healthy gum as control group and gimgivitis as treated group.

Subjects needed 4 Wistar rat. Group I as control (pre test) and Group II as treated (post test). Event gingivitis was triggered by Aggregatibacter actinomycetemcomitans in hole form by injecting into the distal portion of the lower gum as much as 108gr/ml in a row in 2-3 weeks. The injection method is carried out until clinical signs of gingivitis are seen and then sacrificed by decapitation [13]. Furthermore, rat was sacrificed by the method of decapitation. A biopsy was performed on the distal and mesial portion of the lower posterior teeth and fixed with 10% buffered formalin. After softening, the specimen is planted in paraffin and cut serially with a thickness of 5μm. Hematoxylin eosin are stained to make sure which is healthy or gingivitis.

Immunohistochemical stain was done using anti Gasdermin-D and NLRP-3 monoclonal antibodies. Data is analyzed with the Test to determine the differences in expression of Gasdermin-D and NLRP-3 proteins between healthy gum and gingivitis tissue. Cut paraffin block tissue affixed to an object glass that has been coated with 1% poly elysine. The next step is de-parafinisation using xylene and rehydration with multilevel alcohol concentration and distilled water. Rehydrated tissue is heated in a citrate buffer using a microwave for five minutes, continued washed with phosphate buffered saline tween 20 (PBST 20) three times in five minutes for retrieval antigen purposes. The process was followed by blocking endogenouse peroxidase using 3% H2O2 for 30 minutes, then washed with PBST three times. Blocking nonspecific binding is done by dripping tissue using 1% fetal bovine serum (FBS) for 30 minutes then washing with PBST three times each for five minutes, then the tissue is dripped with primary antibodies and incubated for one night at 40C and then washed again with PBST three times each for five minutes. The tissue was dropped with secondary antibodies for 30 minutes after washing, and continued with washing using PBST three times each for five minutes. Subsequently the tissue was dripped with HRP streptavidin for 30 minutes, then washed again with PBST three times each for five minutes. Chromogen 3,3′-diaminobenzidine (DAB) dropped on the tissue and left for 15 seconds. After administration of DAB, immersion was carried out in distilled water and continued with counterstain Hematoxylin Eosin for 25 seconds. Then followed by a dehydration process using multilevel alcohol and clearing with xylol. The tissue in the object glass is then mounted with permount and given a glass cover.

The assessment of staining results is based on: Value 0 expression looks none positive per 100 cells, value 1 expression looks 25% positive per 100 cells, value 2 looks 50% positive per 100 cells, value 3 looks 75% positive per 100 cells and value 4 looks 100% positive per 100 cell. The collected semi-quantitative data (8 point : 4 rats and mesial-distal portiom) is analyse using Test. The significance level used is $p<0.05$. Thus the value is significant if $p<0.05$.

RESULTS

Immunohistochemistry staining results using monoclonal antibodies anti-Gasdermin-D (A and B) and anti- NLRP-3 monoclonal antibodies (C and D). There is a difference in the strength of expression of Gasdermin-D protein between healthy gum tissue (A:arrow) and gingivitis (B:arrow), healthy gum is ligher than gingivitis. And

seen difference in the strength expression of NLPR-3 proteins expression between healthy gum (C:arrow) and gingivitis (D:arrow), healthy gum is ligher than gingivitis. This perceptions showed in figure 1.

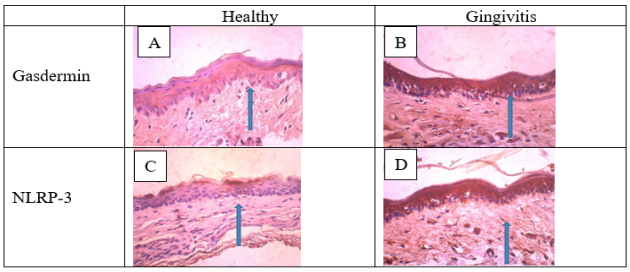

Fig. 1: Immunohistochemistry staining results using monoclonal antibodies anti-Gasdermin-D (A and B) and anti-NLRP-3 (C and D). There had difference in the strength of expression of Gasdermin-D proteins between healthy gum (A:arrow) which is lighter (brown) than gingivitis (B:arrow). And seen difference in the strength expression of Inflammasome-NLRP-3 proteins between healthy gum (C:arrow) which is lighter than gingivitis (D: arrow)

The results of the assessment of IHC staining recorded a median for Gasdermin-D expression reflected in gingivitis higher than in healthy gum tissue (healthy=1.75 vs gingivitis=3.125), while for inflammmasome-NLRP-3 expression reflected in gingivitis is higher than in healthy gum (healthy=2 vs gingivitis=3,625). All data showed in table I. Difference in the strength expression also showed in figure 2.

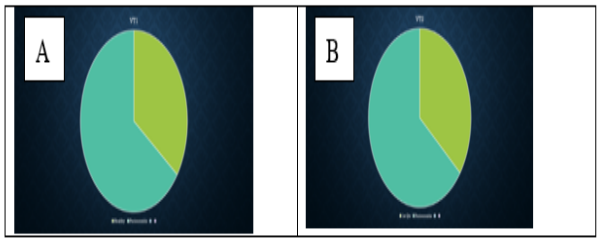

Fig. 2: A. Difference in the strength of Gasdermin D expression between healthy gum (yellow) and gingivitis (green). B. Difference in the strength of NLRP-3 expression between healthy gum (yellow) and gingivitis (green).

From statistic analyzis obtained a significance difference between healthy gum and gimgivitis in Gasdermin-D protein (p=0.001) and Inflammasome-NLRP-3 (p=0.009) (note table 1). The other statistical analyzis to determine differences in expression of Gasdermin-D with inflammasome-NLRP-3 both in healthy gum and gingivitis were recorded differently at p=0.806 that showed in note table 1.

DISCUSSION

Inflammasomes have been shown to be involved in the inflammatory response and death cells of pyroptosic. Inflammatory structure consists of intracellular ASC adapter protein that binds pro-caspase-1 to the inflammatory complex and NLR sensors protein that acts as triggers for the activation of pro-caspase-1 to

Table I: The data count for Gasdermin-D and inflammasome-NLRP-3 expression in healthy gum and gingivitis

Variable	Gasdermin	Everage (X)	sd	Inflammasome-NLRP-3	Everage (X)	sd
Healthy Gum	2.00 2.00 2.00 1.00 2.00 2.00 2.00 1.00	1.75	0.375	2.00 2.00 2.00 2.00 2.00 2.00 2.00 2.00	2.00	0,00
Gingivitis	4.00 3.00 3.00 3.00 3.00 2.00 4.00 3.00	3.125	0.437	4.00 4.00 2.00 4.00 4.00 3.00 4.00 4.00	3.625	0.562

Chi Square Test
1. Gasdermin (healthy gum vs Gingivitis) : p=0.001
2. NLRP-3 healthy gum vs Gingivitis) : p=0.009
3. Gasdermin vs NLRP-3 : p=0.800

caspase-1 which finally activates pro IL-1β and IL- 18 to IL-1β and IL-18. Some types of inflammation contain different sensor proteins such as NLRP-1, NLRP-3, NLRP-6, NLRP-12. NLRP-3 (the nucleotide-binding domain of leucine-rich repeat containing families, pyrin domain containing 3) is the most widely studied. NLRP-3 is activated by endogenous danger signaling tissue injury molecules, such as hyaluronan, uric acid crystals and amyloid-β fibrils, industrial particles, extracellular ATP, and nanoparticles such as alum, asbestos, silica and titanium Dioxide. NLRP-3, has been extensively studied, regulates insulin signaling, plaque formation in atherosclerosis, myocardial ischemia reperfusion injury and neurodegeneration. [14, 15]

Expressed Gasdermin-D (GSDMD) caused by releasing caspase-1 from the super protein inflammasome-NLRP-3 which further triggers pyroptosis, a form of cell death that important for immune defense and disease. GSDMD contains important functional domains Gasdermin-N that are divided in the Gasdermin family. The functional mechanism of action of gasdermin protein is unknown. Gasdermin-N domains from the GSDMD, GSDMA3 and GSDMA gasdermin proteins can bind to membrane lipids, phosphoinositide and cardiolipin, and show membrane cytotoxicity, disturbing in mammalian cells and artificially altered bacteria. Gasdermin-N moves to the plasma membrane during pyroptosis. Purified gasdermin-N efficiently inhibits phosphoinositide / cardiolipin liposomes and forms pores on membranes made from artificial or natural phospholipid mixtures. Most gasdermin pores have an inner diameter of 10-14 nm and contain 16 symmetrical protomers. The crystalline structure of GSDMA3 shows the architecture of two eternal autoinhibited domains in the gasdermin family. Pyroptosis is driven by non-selective gasdermin-D pores and the morphology is different from the channel in necroptosis. [9] Although there is intensive research on inflammasomes, the mechanism of

IL-1β / IL-18 production and pyroptosis after caspase-1 activation is unknown. The interference between pyroptosis and other types of programmed cell death has not been explained. Gasdermin D (GSDMD) as a new component of inflammasomes. This is necessary for pyroptosis and IL-1β secretion but does not play a role in the processing of IL-1β. GSDMD was recruited for the formation of inflammasome NLRP3 with kinetics similar to caspase-1 after LPS stimulation. GSDMD is cleaved by pro-caspase-1 and most likely also by caspase-1 in inflammasomes, and proteolytic cleavage of GSDMD released N-terminal fragments to mediate pyroptosis and IL-1β secretion. [10]

The inflammatory process is initiated by cells found in all tissues, especially macrophages, dendritic cells, histiocytes, buffer cells, and mastocytes. These cells on the surface have receptors called pattern recognition receptors (PRRs) which can widely recognize molecules derived from pathogens called pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) that are induced from endogenous stress. PRRs consist of at least four classes based on genetics and functions, namely Toll-like receptors (TLRs) and C-type lectin receptors (CLRs) found on the surface of cell membranes as well as retinoic acid-inducible gene-Ilike receptors (RLRs)) and nucleotide-binding oligomerization domain-like receptors (NLRs) in the cytoplasm. [12, 17] Some PRRs in the cytoplasm are important components of the inflammatory complex, including NLRs. Activation of inflammation is known to be an important part of the inflammatory process where inflammation regulates activation of caspase-1. Caspase-1 functions to break down IL-1β cytokines into active forms namely IL-1β and IL-18 and cause pyroptosis. IL-1β contributes to the occurrence of fever and activates lymphocytes by causing leukocyte infiltration in the area of infection or injury while IL-18 induces IFN-production production and contributes to the polarization of T-helper 1 (Th1) cells. [9, 12]

Pyroptosis is the most common form of programmed cell death in infections with intracellular pathogens as in the form of antimicrobial responses. In this process, immune cells recognize foreign danger signals and release pro-inflammatory cytokines from within the cells themselves, so they swell, explode and die. The cytokines that are released will attract other immune cells to fight infection and contribute to inflammation in the tissues. [18, 19] Pyroptosis promotes rapid clearance of various bacterial and viral infections by removing intracellular niches and increasing the host's defensive response. However, in chronic pathogenic diseases, the inflammatory response does not eradicate the primary stimulus, as would normally occur in most cases of infection or injury, and thus in chronic inflammation will ultimately contribute to tissue damage. In contrast to apoptosis or necrosis, pyroptosis requires the function of the enzyme caspase-1. [20] Caspase-1 is activated during pyroptosis by a large supramolecular complex called inflammasome. [21] Large inflammodes are formed in each macrophage, within minutes of infection. Unlike apoptosis and necrosis, dead cells result from pyroptosis in plasma-membrane rupture and release DAMP1 molecules such as ATP, DNA and ASC oligomers into the extracellular environment, including cytokines that recruit more immune cells and subsequently cause an inflammatory cascade in tissue. [18, 22, 23]

CONCLUSION

Pyroptosis was occurs in the gingivitis due to bacterial triggers by expressing Gasdermin-D and inflammasome-NLRP-3 proteins.

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