International Journal of Health Sciences and Research
Vol.13; Issue: 12; December 2023
Website: www.ijhsr.org
Review Article *ISSN: 2249-9571*

Role of Nod-like Receptor Protein 3 (NLRP3) in Acute Kidney Injury: A Review

Prayuda[1], Yenny Kandarini[2], I Gde Raka Widiana[2]

[1]Postgraduate Medical Study Programme, Faculty of Medicine Udayana University, Denpasar, Bali, Indonesia
[2]Nephrology and Hypertension Division, Department of Internal Medicine, Udayana University, Denpasar, Bali/Prof. Ngoerah General Hospital, Denpasar, Bali

Corresponding Author: Prayuda

DOI: https://doi.org/10.52403/ijhsr.20231216

ABSTRACT

Inflammasomes are multiprotein complexes that have a role in regulating inflammatory signaling and the innate immune system. One of these is Nod like-receptor protein 3 (NLRP3), the most studied inflammasome. Activation of NLRP3 is associated with various inflammatory diseases. Renal also have inflammatory response against an infectious or non-infectious activators. NLRP3 is yet another component of the inflammasome that is expressed in the tissue of the kidney, however the underlying mechanism is not completely known. The capacity to trigger cell death by activating caspase-1 and modifying the NLRP3 inflammasome component is possessed by renal mononuclear phagocytes such as macrophages and dendrites. According to the findings of a number of research, podocytes and renal tubular cells may be responsible for activating the NLRP3-ASC-caspase-1 pathway, which leads to the discharge of mature forms of IL-1 and IL-18. Acute kidney injury (also known as AKI) may be caused by a wide variety of conditions, such as ischemic damage, nephrotoxicity, and sepsis, amongst others. Damage to tubular epithelial cells can initiate an inflammatory response by activating immune cells such as macrophages and leukocyte. These immune cells infiltrate to the kidney, which then releases various inflammatory mediators. There are recent studies that suggest that mtDNA-related inflammatory responses are also involved in the AKI process.

Keywords: Inflammasome, Nod-like receptor protein 3 (NLRP3), acute kidney injury (AKI)

INTRODUCTION

Inflammatory mediators, also known as "inflammatory caspases," are released into the body whenever the body's innate immune system is activated. This may happen as a result of infections, dead cells, trauma, or chemical damage. Inflammation and the activation of the innate immune system are both necessary functions that are triggered when the multiprotein complex known as the Nod-like receptor protein 3 (NLRP3) inflammasome is activated. The defective activator circuitry of NLRP3 and its activation in a variety of inflammatory disorders have led to it being the inflammasome that has received the most attention to this day. NLRP3 oligomerizes and activates caspase-1 after being activated by damage- and pathogen-associated molecular patterns (DAMPs), which in turn promotes the processing and release of proinflammatory cytokines such as IL-1β and IL-18.[1]

Pattern recognition receptors, also known as PRRs, are what activate the body's innate immune system when it is confronted with potentially harmful stimuli such as viruses, dead cells, or irritants from the surrounding environment. The innate immune system is the body's first line of defense. PRRs contain either pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) as a result of endogenous stress. PAMPs and DAMPs both stimulate inflammatory

pathways, which in turn assists in the repair of damaged tissue and the elimination of microbial infections. Inflammation is caused mostly by the inflammasome, which is a collection of intracellular multimeric protein complexes that, when activated, cause the caspase-1 inflammasome to become active. In response to either DAMPs or PAMPs, the sensor protein (PRR) in the cell oligomerizes to form a pro-caspase-1 activation platform. This is how the cell determines the level of inflammation in the cell. The inflammasome is undoubtedly composed of the nucleotide-binding oligomerization domain (NOD), the leucine-rich repeat (LRR), and the NLRP1 family member containing protein (NLR). These are the five PRR components. The inflammasome contains a number of new PRR members in addition to those already present, such as NLRP2, NLRP6, NLRP7, NLRP12, and IFI16.[2]

In damaged tissue, DAMPs are released, which trigger the flow of inflammatory mediators to the damaged area. PYHIN and proteins from the Nod-like receptor family are the two main components of the multiprotein complex that is referred to as the inflammasome. This complex is activated by two distinct molecular patterns and plays an essential role in the innate immune response. The three key components that make up the NLRP3 protein repeats are the N-terminal pyrin domain, also known as PYD, the central nucleotide-binding oligomerization domain, also known as NACHT, and the C-terminal leucine, also known as LRR. Following the recognition and integration by LRR of external microorganisms or chemicals connected to endogenous tissue damage, NACHT oligomerizes, and PYD subsequently recruits ASC and pro-Caspase-1 to form the NLRP3 inflammasome. Following the formation of caspase-1, pro-caspase-1 undergoes activation, which in turn causes the production of interleukin-1 beta and interleukin-18.[3]

Activation of the NLRP3 Inflammasome

Considering that the activation of the inflammasome is an inflammatory process, it is essential that it be carefully managed. It is common practice to think of inflammasome activation as a two-step process, with very few exceptions; preparations need to be made before activation can take place. Priming accomplishes a minimum of two different goals. The first objective was to increase the synthesis of pro-IL-1, caspase-1, and NLRP3, which are all components of the inflammatory response. This transcriptional upregulation can be caused by either the recognition of various damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) involving pattern recognition receptors (PRRs) like Toll (TLRs) or NOD2 or the recognition of cytokines like tumor necrosis factor (TNF) and IL-1, which activates nuclear factor-kappaB (NF-kB). In addition, priming with lipopolysaccharide (LPS), which is a TLR4 ligand, triggers a transition in macrophage metabolism from oxidative phosphorylation to glycolysis. This is because glycolysis is an alternative metabolic pathway for macrophages. The results of this include an increase in the transcription of the IL1 gene as well as the stability of the hypoxia-inducible factor 1 (HIF1) gene. The second priming function is the induction of post-translational changes (also known as PTMs) to the NLRP3 protein.[4]

It was only recently discovered that NLRP3 has a function that is not related to inflammation. For example, hypoxia in renal tubular epithelial cells of mice with unilateral ureteral obstruction may elevate NLRP3 independently of ASC, IL-1β and caspase-1. These animals also had ureteral blockage. The important inflammatory mediator known as IL-1β is in charge of many various cellular processes, including cell death, cell differentiation, and cell division. However, since it has an effect on the creation of podocyte proteins, IL-1β has the potential to jeopardize the structural

integrity of podocytes as well as their functional capabilities. In addition to this, it has the ability to dismantle the glomerular filtration barrier by dissolving the strong adherences and bonds that are present between the glomerular endothelial cells. Another important pro-inflammatory cytokine that may be found in the kidney is referred to by the acronym IL-18. Through the processes of activating and developing T cells, it plays a role in the adaptive immune system. In addition to stimulating the production of other inflammatory cytokines such as chemokines, nitric oxide, and cell adhesion molecules, IL-18 is also responsible for promoting the activation of inflammatory cells[3]

NLRP3 and Kidney Disease

The development of the NLRP3 inflammasome may be started in a variety of different ways by a large number of distinct stimuli, both endogenous and external. At the present time, there are currently three different methods in which the NLRP3 inflammasome may be activated. Opening and efflux of potassium channels, secretion of cathepsin-B resulting from lysosome rupture and damage, and production of reactive oxygen species (ROS) are these three pathways. The ATP-P2X7 receptor can be activated by various types of microbial toxins, enzymes, and extracellular ATP. Potassium ions may also be released, which activates the NLRP3 inflammasome. Inflammation is activated by ROS and cathepsin-B by crystalline substances such as silicon dioxide, antibiotics, and antifungal drugs.[5]

Renal immunity responds to infectious and non-infectious activators in the renal inflammatory response. It is unclear how the NLRP3 inflammasome component occurs in kidney tissue. Several studies have shown that renal mononuclear phagocytes, including macrophages and dendrites, can express the inflammasome component NLRP3 and activate caspase-1, which triggers cell death. On the other hand, mature forms of IL-1β and IL-18 may be generated and secreted by renal tubular epithelial cells, podocytes, and the NLRP3-ASC-caspase-1 pathway. The NLRP3 inflammasome serves as an intracellular pattern recognition receptor, and it plays a critical role in both the promotion and regulation of inflammation within the immune system. Through inducing the production of pro-inflammatory cytokines like IL-1β and IL-18, activation of the NLRP3 inflammasome leads to both acute and chronic inflammation of the kidneys. These cytokines stimulate inflammatory responses as well as self-defense mechanisms.[5,6]

Additionally, it is known that NLRP3 contributes to diabetic nephropathy, a kidney disease. Hyperglycemia is a sign of a metabolic disease known as diabetes mellitus (DM). With DM, it often causes permanent damage to blood vessels, kidneys, eyes, and legs. The most common end-stage renal disease (ESRD) is a complication known as diabetic nephropathy. The inflammatory response is the main component causing diabetic nephropathy. Both monocyte chemoattractant protein-1 (MCP-1) and C-reactive protein (CRP) contribute to the fibrosis of the renal tubules and the infiltration of macrophages, which in turn speeds up the progression of glomerulosclerosis. The activation of inflammasomes is what starts these processes in motion.[7]

Patients suffering from diabetic nephropathy, as well as diabetic mice, have an active NLRP3 inflammasome. Podocytes, which are glomerular visceral epithelial cells, are responsible for the glomerular filtration barrier, the control of the ultrafiltration coefficient K/f, the maintenance of the normal architecture of the glomerular basement membrane (GBM), and the stability of glomerular capillaries. Podocytes also play a role in the ultrafiltration coefficient K/f. According to the findings of research, podocyte destruction is a significant contributor to the progression of diabetic nephropathy. The

NLRP3 inflammasome is activated in mouse podocytes when blood glucose levels are high, since this indicates that there are increased levels of the proteins NLRP3, ASC, and caspase-1. In addition to this, there was a rise in the activity of the caspase-1 enzyme. There was a reduction in the synthesis of caspase-1 and IL-1 after transfecting podocytes with NLRP3 small interfering RNA siRNA, and there was an increase in the expression of the podocyte functional protein nephrin. It is not known how the NLRP3 inflammasome operates when it is present in podocytes at this time. According to the findings of the study, the activation of the NLRP3 inflammasome led to a worsening of podocyte autophagy and a reduction in nephrin expression. On the other hand, NLRP3 inhibition improved podocyte autophagy and reduced podocyte damage caused by hyperglycemia. The conclusion that can be drawn from this is that autophagy may play a role in the regulation of the podocyte NLRP3 inflammasome. [5]

Damage to the tubules of the kidney is one of the primary contributors to the progression of renal failure seen in diabetic nephropathy. There was an uptick in the level of NLRP3 expression, as well as an increase in the amount of IL-1, IL-18, and ATP that were produced in HK-2 cells that were subjected to hyperglycemia in vitro. The tubular epithelial-mesenchymal transition (EMT) that is caused by hyperglycemia may be stopped by inhibiting the NLRP3 gene. This is achieved by blocking the production of reactive oxygen species (ROS) and activating signaling pathways ERK1/2, p38MAPK, and Smad3. A significant factor in the development of inflammation is the overproduction of reactive oxygen species (ROS), also known as mtROS. In response to treatment with the antioxidant mtROS given by MitoQ for HK-2 cells, thioredoxin (TRX) is shown to detach from its corresponding protein complex, TXNIP. Furthermore, it blocks the association between TXNIP and NLRP3, leading to inactivated NLRP3 inflammasome and inhibited IL-1β maturation. Another study showed that ATP-P2X4 signaling controls NLRP3 inflammasome activation caused by hyperglycemia, controls IL-1β secretion, and causes tubulointerstitial inflammation in diabetic nephropathy. In general, hyperglycemia stimulation can activate the NLRP3 inflammasome through various pathways, resulting in changes in intrinsic renal cells. Current research shows that NLRP3 activation is found in many cases of diabetic nephropathy. In addition, therapies targeting NLRP3 play a significant role in improving diabetic nephropathy.[5]

Inflammatory and immune responses may be the main factors causing chronic kidney disease. Albuminuria, which gradually damages kidney tissue, is a symptom of systemic lupus erythematous (SLE) mice. Activation of the NLRP3 inflammasome can cause kidney damage. n addition to having shrunken tubules, patients who have a condition known as mesangial proliferative glomerulonephritis have renal tubular epithelial cells that have an abnormally high level of the protein NLRP3. These findings suggest that there is a link between the activation of inflammatory pathways and SLE. In SLE patients who had lupus nephritis, researchers found a correlation between elevated urine protein levels and an increase of NLRP3 in glomerular podocytes. The renal interstitium also has these accumulations. When compared with healthy subjects, hemodialysis CKD patients had higher blood mononuclear cell NLRP3 mRNA levels. Therefore, uremic patients receiving dialysis treatment activate inflammasomes. Mitochondrial dysfunction, which is critical for the activation of the NLRP3 inflammasome, may be the cause of this non-physiological condition.[3]

Ischemia reperfusion nephropathy is also caused by NLRP3 inflammasome. The kidneys are highly susceptible to ischemic injury which can damage the renal tubules. For tissue to survive, blood circulation is required. On the other side, it might make

the damage to the kidney tissue worse and intensify the inflammatory response. Following renal ischemia-reperfusion damage in wild-type mice, there was a significant increase in the expression of genes associated with inflammation. This increase included NLRP3, ASC, and a number of other genes. This resulted in injury to the kidneys as well as an invasion of neutrophils. On the other hand, following a 24-hour period of reperfusion, renal function was significantly improved in NLRP3-depleted mice, yet there was a significant reduction in the levels of pro-inflammatory cytokines and neutrophil infiltration. The NLRP3 and ASC proteins were found to be present in the renal tubular epithelial cells of both mice and humans that were examined in vitro.[3,8,9]

During the process of renal ischemia reperfusion injury, the NLRP3 mutant animals demonstrated an extremely low rate of apoptosis and necrosis in the renal tubular epithelial cells. On the other hand, renal function and tubular damage were not improved in mice missing ASC and caspase-1, which suggests that NLRP3 makes a contribution to the inflammatory pathway on its own. Necrosis and apoptosis of renal tubular epithelial cells were significantly reduced in mice that were free of leukocytes. In contrast, repair of renal tubular epithelial cells is increased by the presence of leukocytes. These experiments demonstrate that leukocyte-derived NLRP3 inflammasome correlates with renal tubular epithelial cell death, and renal tubular epithelial repair after ischemia reperfusion correlates with each other. [3]

The Role of NLRP3 in Acute Kidney Injury

There are abundant numbers of NLRP3-like receptors present in each and every kind of inflammatory response that is brought on by injury to the kidneys. They increase the expression of Caspase-1, interleukin-1 beta (IL-1 beta), and interleukin-18 (IL-18), amongst other genes. Gene expression of the NLRP3 protein may attenuate the degree of renal tubular injury due to the signaling pathway that it uses. [10] According to study conducted on mice with AKI, activation of NLRP3 inflammatory cells may increase the risk of AKI. On the other hand, kidney injury may also lead to the production of mROS, which stands for mitochondria-derived reactive oxygen species. This might trigger TXNIP to bind to NLRP3, which in turn can cause more kidney damage. A study showed that thioredoxin-interacting protein (TXNIP) has the ability to control the level of inflammation in NLRP3 cells.[11]

A study conducted by Zheng et al. in 2012 looked at renal NLRP3 expression in mice that experienced ischemia reperfusion injury (IRI) in both short-term and long-term phases.[12] This study examined the association of NLRP3 with tubular maladaptive repair after AKI and the transition of AKI to CKD. In this study, it was found that after severe kidney injury, NLRP3 expression increased in the kidney. NLRP3 expression is also increased in mild AKI. Renal NLRP3 expression increased in mild and severe AKI mice after two days, and simultaneously at the early stage after IRI, renal NLRP3 expression increased in mild and severe AKI mice. However, 28 days later, renal NLRP3 remained unregulated in mild AKI mice. After AKI, similar results are also found in serum or urine. During the first week, mice with mild AKI showed transient increases in NLRP3 in serum or urine, but by the second day, levels remained high. Mice with severe AKI still expressed high levels of NLRP3. In addition, There is a correlation between the overexpression of NLRP3 and maladaptive tubular repair, which is associated to the presence of fibrosis and inflammatory infiltration. As indicated by double immunofluorescence labeling, NLRP3 is predominantly regulated by the negative cell polarity marker E-cadherin in atypical tubular epithelial cells. This was discovered by studying the interaction between the two proteins. NLRP3 positive tubules were found in samples with and without the presence of lotus tetragonolobus lectin

(LTL), a marker that is characteristic of proximal tubules. By using HE staining, it was shown that the area surrounding these tubules exhibited fibrosis, atrophy, dedifferentiation, and maladaptive repair. More expression of NLRP3 in tubules was shown to be associated with maladaptive repair. According to this study, overexpression of tubular NLRP3 is associated with maladaptive repair and is associated with renal inflammatory infiltration and fibrosis.[12]

The role of mitochondrial DNA in acute kidney injury

Mitochondria and their integrity and function influence the normal function of the kidneys. Issues with aerobic respiration, malfunctioning of cells, and even death of cells may be caused by mutations in the mitochondrial DNA (mtDNA). Abnormalities in the mtDNA copy number have also been linked to the development of acute and chronic forms of renal disease. mtDNA that has been released into the cytoplasm as a result of cellular stress can be recognized by a wide variety of DNA recognition mechanisms, including Toll-like receptor 9 (TLR9), cGAS-stimulator of cytosolic interferon gene (STING) signaling, and activation of the inflammasome, which subsequently mediates the inflammatory cascade. These mechanisms can do this by identifying the sequence of the mtDNA.[13] After mitochondria are injured, some parts of mitochondria will be released into the cytoplasm or extracellular environment via PRR by DAMPs. Furthermore, this will cause a downstream inflammatory response, which includes mtDNA, which is a component of mitochondria.[14]

Ischemic injury, nephrotoxicity, and sepsis are some of the conditions that can cause AKI. The infiltration of immune cells such as macrophages and leukocytes into the kidney might be triggered into an inflammatory response if tubular epithelial cells are damaged when the kidney is still in the process of developing. After then, a number of inflammatory mediators are discharged into the body. Recent studies suggest that acute kidney injury (AKI) may be associated with inflammatory responses that are related to mtDNA.[15]

MtDNA is more susceptible to oxidative damage than nuclear DNA due to its subcellular location close to the electron transport chain, which is the location where reactive oxygen species (ROS) are produced, as well as the absence of histones that may protect it. The mitochondrial genome is susceptible to damage and mutations, which may lead to problems with aerobic respiration, cellular dysfunction, or even death of the cell. According to the findings of several studies, mtDNA could play a part in the process of activating the innate immune response, which is essential for the progression of a great number of diseases[13,16] As a result, even in the event that the cells are damaged, mtDNA and the cells will remain in a state of balance. The activation of the innate immune response will be triggered upon the detection of the released mtDNA from mitochondria by the major three sensors. To begin, mtDNA will bind to TLR-9 and myeloid differentiation factor 88 (MyD88) inside of endosomes, which will then activate both of these proteins. Next, this makes it possible for NF- κB to get activated, which then results in an increase in the production of inflammatory cytokines such as TNF- and IL-6. In addition, the movement of STING from the endoplasmic reticulum to the Golgi apparatus causes TBK1-IRF3 to become active, which in turn increases the production of type I interferon. Furthermore, PRRs such as NLRP-3 are activated by mtDNA, and this attracts ASC and procaspase 1 to produce inflammasomes, which assists in the production of IL-1β and IL-18. [13] The number thirteen It is possible that circulating mtDNA assists the p38-MAPK pathway. Circulating mtDNA also activates TLR-9 in polymorphonuclear neutrophils, which results in increased neutrophil secretion.[17]

It is possible that the release of mtDNA into the cytoplasm, in concert with other triggers such as K+ efflux and mitochondrial ROS production, is what kickstarts the inflammatory cascade that is associated with NLRP3. To be more precise, cytosolic mtDNA binds the NLRP3 inflammasome when it is in an oxidized condition, which then activates the inflammasome. In addition, the findings reveal that mtDNA is released from mitochondria by means of a process that is dependent on the NLRP3 inflammasome. This results in the formation of a positive feedback loop between the release of mtDNA and the activation of the NLRP3 inflammasome.[13]

CONCLUSION

An innate immune system sensor known as the NLRP3 inflammasome is responsible for initiating inflammatory responses in response to various inputs from the environment. In addition to causing damage to the kidneys, it may also lead to the development of other metabolic disorders. The activation of the NLRP3 inflammasome in the kidney may be triggered by a number of metabolic disorders. The activation of the NLRP3 inflammasome leads to an increase in renal tissue damage as well as inflammatory infiltration via a variety of different processes, including autophagy, the generation of inflammatory chemicals, and the destruction of extracellular matrix. Mitochondria and their integrity and function influence the normal function of the kidneys. The NLRP3 inflammatory cascade may be initiated by the release of mtDNA into the cytoplasm along with other stimuli such as K + efflux and mitochondrial ROS production. The binding of oxidized cytosolic mtDNA to the NLRP3 inflammasome is the primary mechanism by which this inflammasome is activated. In addition to this, there is evidence to suggest that the process that is reliant on the NLRP3 inflammasome releases mitochondrial mtDNA. This suggests that mtDNA release and NLRP3 activation are positively correlated.

Declaration by Authors

Ethical Approval: Not applicable

Acknowledgement: None

Source of Funding: None

Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Blevins HM, Xu Y, Biby S, Zhang S. The NLRP3 Inflammasome Pathway: A Review of Mechanisms and Inhibitors for the Treatment of Inflammatory Diseases. *Front Aging Neurosci* 2022; 14. doi:10.3389/FNAGI.2022.879021.
2. Kelley N, Jeltema D, Duan Y, He Y. The NLRP3 Inflammasome: An Overview of Mechanisms of Activation and Regulation. *Int J Mol Sci* 2019; 20. doi:10.3390/IJMS20133328.
3. Huang G, Zhang Y, Zhang Y, Ma Y. Chronic kidney disease and NLRP3 inflammasome: Pathogenesis, development and targeted therapeutic strategies. *Biochem Biophys reports* 2023; 33: 101417.
4. Swanson K V, Deng M, Ting JP-Y. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. *Nat Rev Immunol* 2019; 19: 477–489.
5. Xiong W, Meng XF, Zhang C. NLRP3 Inflammasome in Metabolic-Associated Kidney Diseases: An Update. *Front Immunol* 2021; 12. doi:10.3389/FIMMU.2021.714340.
6. Chang A, Ko K, Clark MR. The emerging role of the inflammasome in kidney diseases. *Curr Opin Nephrol Hypertens* 2014; 23: 204–210.
7. Duran-Salgado MB, Rubio-Guerra AF. Diabetic nephropathy and inflammation. *World J Diabetes* 2014; 5: 393–398.
8. Karaba AH, Figueroa A, Massaccesi G, Botto S, DeFilippis VR, Cox AL. Herpes simplex virus type 1 inflammasome activation in proinflammatory human macrophages is dependent on NLRP3, ASC, and caspase-1. *PLoS One* 2020; 15: e0229570.
9. Zahran R, Ghozy A, Elkholy SS, El-Taweel F, El-Magd MA. Combination therapy with melatonin, stem cells and extracellular vesicles is effective in limiting renal ischemia-reperfusion injury in a rat model.

Int J Urol Off J Japanese Urol Assoc 2020; 27: 1039–1049.
10. McCullough PA. Contrast-induced acute kidney injury. *J Am Coll Cardiol* 2008; 51: 1419–1428.
11. Deng H, Chen F, Wang Y, Jiang H, Dong Z, Yuan B *et al*. The role of activated NLRP3 inflammatory body in acute kidney injury in rats caused by sepsis and NLRP3-TXNIP signaling pathway. *Saudi J Biol Sci* 2020; 27: 1251–1259.
12. Zheng Z, Xu K, Li C, Qi C, Fang Y, Zhu N *et al.* NLRP3 associated with chronic kidney disease progression after ischemia/reperfusion-induced acute kidney injury. *Cell Death Discov 2021 71* 2021; 7: 1–9.
13. Jin L, Yu B, Armando I, Han F. Mitochondrial DNA-Mediated Inflammation in Acute Kidney Injury and Chronic Kidney Disease. *Oxid Med Cell Longev* 2021; 2021. doi:10.1155/2021/9985603.
14. Banoth B, Cassel SL. Mitochondria in innate immune signaling. *Transl Res* 2018; 202: 52–68.
15. Tsuji N, Tsuji T, Ohashi N, Kato A, Fujigaki Y, Yasuda H. Role of Mitochondrial DNA in Septic AKI via Toll-Like Receptor 9. *J Am Soc Nephrol* 2016; 27: 2009–2020.
16. Collins LV, Hajizadeh S, Holme E, Jonsson I-M, Tarkowski A. Endogenously oxidized mitochondrial DNA induces in vivo and in vitro inflammatory responses. *J Leukoc Biol* 2004; 75: 995–1000.
17. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W *et al.* Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nat 2010 4647285* 2010; 464: 104–107.

How to cite this article: Prayuda, Yenny Kandarini, I Gde Raka Widiana. Role of nod-like receptor protein 3 (NLRP3) in acute kidney injury: a review. *Int J Health Sci Res.* 2023; 13(12):132-139. DOI: *10.52403/ijhsr.20231216*

******