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The Role of Immune-related NLR Pyrin Domain Containing 2 (*NLRP2*) Gene in the Development and Diseases

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Authors' contributions

This work was carried out in collaboration among all authors. Authors FB and AA designed the study, collect the literature, draw figures, tables and wrote the first draft of the manuscript. Authors SA, AA and MA managed the analyses of the study and revised the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

The Nucleotide-binding oligomerization domain, Leucine-rich Repeat, and Pyrin domain-containing (NLRP) family, including NLR Family Pyrin Domain-Containing 2 (*NLRP2)* gene, is defined as a critical element in regulating both apoptosis and inflammation. Although the NLRP2 protein involves in stimulating the production of inflammatory cytokines and chemokines in response to pathogens, the expression of *NLRP2* gene has been reported in many diseases. Some studies indicated that *NLRP2* as a Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB)-positive regulator resulted in the production of NF-κB-driven cytokines. Wherease other studies reported *NLRP2* as an NF-κB-negative regulator that limits IκB kinase, an enzyme involved in elucidating the cellular response to inflammation. This literature review has directly evaluated the relation of both the *NLRP2* gene and NLRP2 protein in the development and different diseases based on journal articles obtained from databases such as PubMed, Science direct and Medline. Scientific names and symbols of the gene were utilized as keywords for published data from 2003 until 2020. We

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propose that the overexpression of the *NLRP2* gene might result in an inflammatory microenvironment associated with localized or systematic diseases based on; the cells that express this particular gene and the location of the immune responses and the triggered signal transduction pathway.

Keywords: Immune response; Immune-related NLR pyrin domain containing 2 (NLRP2), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB).

1. INTRODUCTION

The Immune system recognizes and responds to pathogens through innate and adaptive immune responses. In innate immunity, immune cells express pattern-recognition receptors (PRRs) that interact with the pathogen-associated molecular patterns (PAMPs) expressed by pathogens. Many innate immune cells such as; neutrophils, monocytes, and macrophages express the PRRs, which directly allow the capture of pathogens at the infection site [1]. Among these PRRs, the Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) family is expressed in the cytoplasm and enables immune cells to detect intracellular pathogens damaged cells. Various studies have reported that NLRs have different and vital roles in several aspects of inflammatory responses and immunity. The function of NLRs can be categorized into four groups, as summarized in Fig. 1. [2].

The interaction between autophagy and NLRs is decisive for homeostasis. Besides, the association between proteins that form autophagic instruments and mutations of NLRs highlights the importance of these proteins in regulating inflammation [3]. The activation of NLRs family proteins during a bacterial invasion in mammalian cells induces inflammatory responses resulted in pathogens removal. Several signal transduction pathways are operated by NLRs proteins such as, MAPK pathway, canonical and alternative NF-kB, and inflammasome pathway [4]. The inflammasomes are natural multi-proteins that join together for the activation of inflammatory responses. For example, the secretion of interleukin-1β (IL-1β), a pro-inflammatory cytokine produced as a consequence of phagocytic activation, induces different hematologic, metabolic, and immunologic

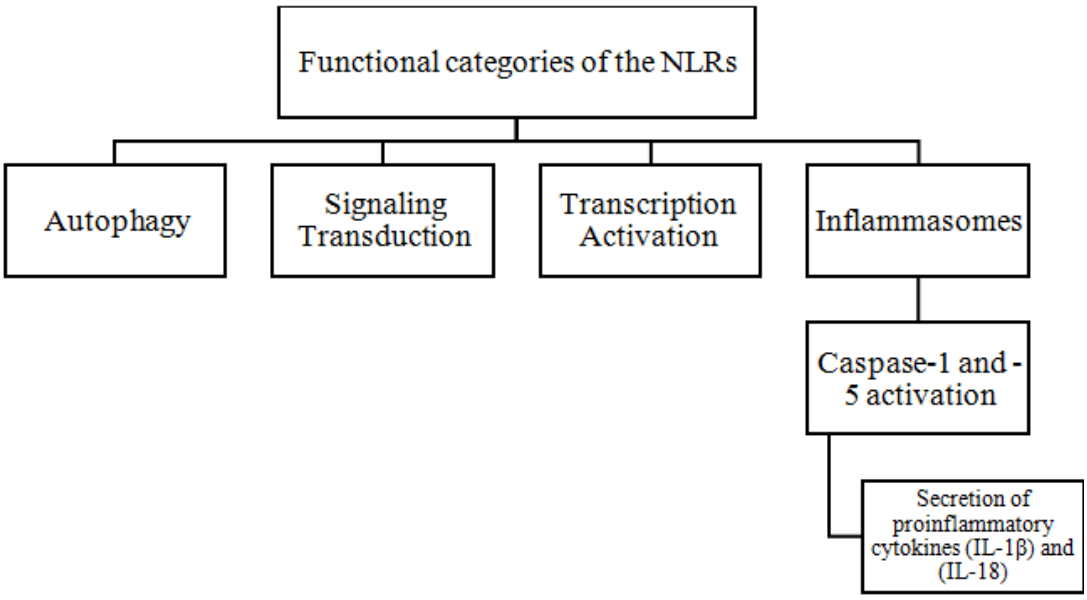

Fig. 1. Schematic diagram of the function of NLRs family divided into four categories

effects. The production of IL-1β is regulated by these inflammasomes. Other complexes of inflammasome have been identified in which most are specialized in recognizing the pathogens and inducing immune responses [5]. The NLRs family consists of four subfamilies: NLRA, NLRB, NLRC, and NLRP, according to the N-terminal domain, as shown in Fig. 2. [6].

The Nucleotide-binding oligomerization domain, Leucine-rich Repeat, and Pyrin domain-containing (NLRP) is a group of cytosolic proteins contains 14 members with the same structure. NLRP is placed in two groups in the human chromosome 11p15 (*NLRP6*, 10, and 14) and chromosome 19q 13.4 (*NLRP2, 4, 5, 7, 8, 9, 11, 12,* and *13*), which expressed in various tissues. NLRPs activate caspases, thus, contribute to both apoptosis and inflammation. NLRPs has also known as NACHT-LRR- and pyrin domain-containing proteins (NALPs), pyrin- and NACHT domain-containing proteins (PANs) or pyrin domain-containing Apaf1-like proteins (PYPAFs) [7]. Besides, most NLRP family members consist of; an adapter protein, an Apoptosis-associated Speck-like protein-containing Caspase recruitment domain (ASC), enzyme procaspases 1, and procaspases 5. Moreover, the most *NLRP* genes studied and reported are the *NLRP1*, *NLRP3*, *NLRP5*, *NLRP7,* and *NLRP12,* along with their functional proteins. However, fewer studies have focused on the functions and cellular distribution of the *NLRP2* gene and proteins. Therefore, this study aims to review all the literature of *NLRP2* since its discovery and its relation to both development and diseases. To our knowledge, there are no review articles published focused on this particular *NLRP2* gene.

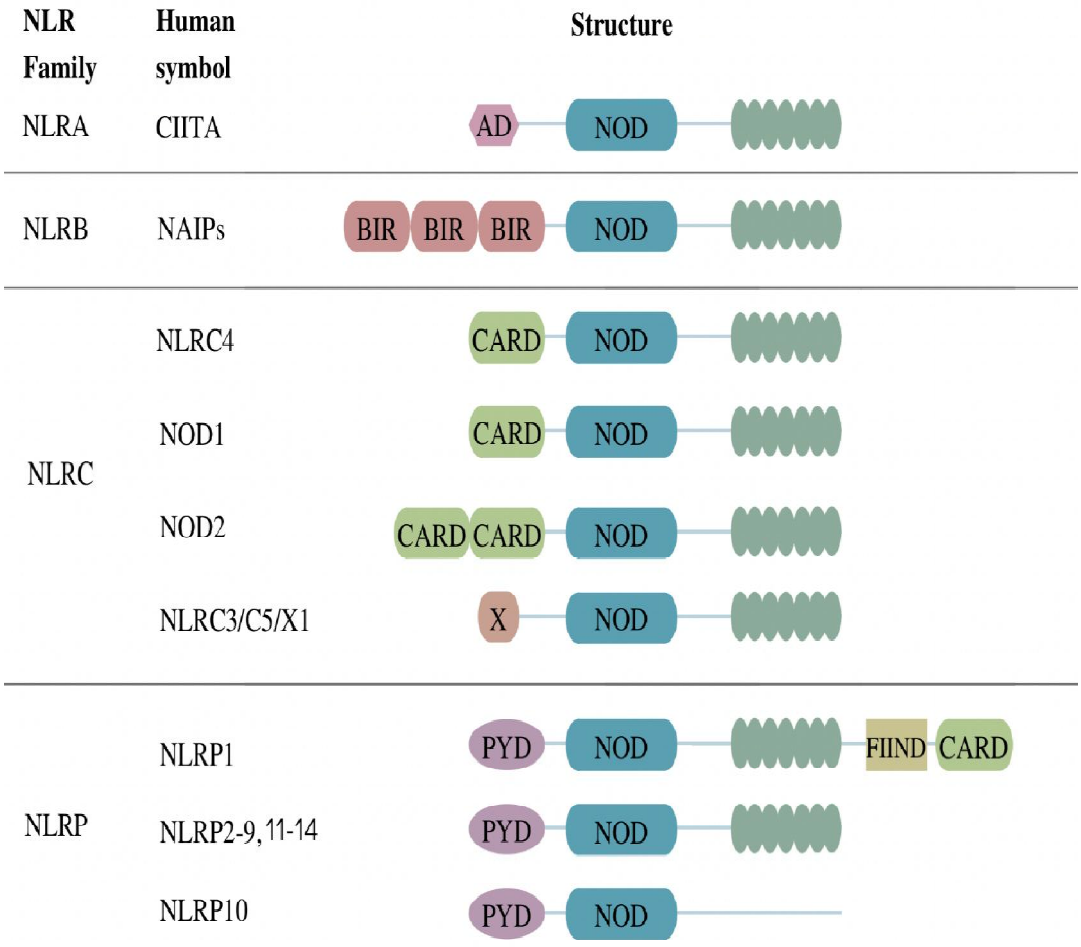

Fig. 2. Structural Comparison of the NLR family based on the N-terminal domain's nature

2. STUDY DESIGN

Information including; title, abstract, references, and full text of the scientific articles were obtained from virtual databases including PubMed, Science direct, and Medline. The selection was based on keywords for published data from 2003 until 2020. Keywords used are either scientific names of the gene or scientific symbols. The gene's scientific terms are; PYRIN-containing APAF1-like, Nucleotide-binding oligomerization domain leucine-rich repeat, and pyrin domain-containing 2, and NACHT-LRR-PYD containing protein, whereas scientific symbols for this gene are *NLRP2*, *CLR19.9*, *NALP2*, *NBS1*, *PAN1*, *PYPAF2*.

3. NLR FAMILY PYRIN DOMAIN CONTAINING 2 (*NLRP2*)

3.1 Structure of the NLR Family Pyrin Domain-Containing 2 (*NLRP2*)

NLRP2 gene is also known as PYRIN-containing APAF1-like, Nucleotide-binding oligomerization domain leucine-rich repeat and pyrin domain containing 2, and NACHT-LRR-PYD containing protein 2. The scientific synonym symbols for this gene are (*CLR19.9*, *NALP2*, *NBS1*, *PAN1*, *PYPAF2*). *NLRP2* gene is located at human chromosome 19 on the long arm (19q13.42) (Fig. 3). It contains 14 exons that generate a 3540 bps transcript which codes for 1062 amino acids. *NLRP2* is expressed in different human tissues, including the heart, placenta, thymus, and brain. In addition, many studies indicated that the NLRP2 protein structure consists of three parts. Starting from the N-terminal pyrin effector domain (PYD), a centrally-located nucleotide-binding and oligomerization domain (NACHT), and the C-terminal contains leucine-rich repeats (LRR) as shown in Fig. 4 [8]. The PYD protein involved in signal transduction results in the activation of pro-inflammatory pathways as a consequence of pathogen invasion. NALP proteins, including NALP2, contribute to the activation of the caspase-1 post the ligation of Toll-like receptors (TLRs). Besides, the *NLRP2* gene encodes proteins able to bind with the IkB kinase (IKK) complex and also regulate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB). It has also been shown that the production of NLRP2 protein is regulated by lipopolysaccharide (LPS) or interferons (IFN beta and IFN gamma) in the THP-1 macrophage cells [9].

3.2 Timeline of the *NLRP2*

NLRP2 was first isolated during a study of the immune system in zebrafish. It is believed that the *NLRP2* gene has derived from a mutation in the NLR gene family, such as *NLRP7.* Previous studies have reported NLRP2 protein functions as a regulator of the immune response in the NF-κB-dependent manner [9]. According to Fontalba, the expression of *NLRP2* resulted in the suppression of the NF-κB signaling pathway without reporting much analysis in this pathway [11]. The role of the expression of NLRP group expression in preimplantation in various phases of embryos has been explored by comparing expression stages between abnormal and normal embryos via real-time PCR technique in a human embryo. Results show a decrease in the expression of *NLRP2* from oocytes by day three and increased again by day five [7]. Studies have also indicated the association of *NLRP2* with different diseases. For example, a frameshift mutation in *NLRP2* was detected in Beckwith-Wiedemann Syndrome (BWS), excessive fetal growth, and familial imprinting disorder [12]. While some studies indicated that the *NLRP2* has a role in the development of mice at embryonic stages [13], others found that *NLRP2* acts as a critical element in the development of diseases as arsenic-induced skin lesions in human [14]. In 2013, the first detection of NLRP2 inflammasome in human Astrocytes was reported leading to the conversion of procaspase-1 to its active form resulted in IL-18 and IL-1β pro-inflammatory cytokines production [8]. Although there are many studies on the NLRPs family, *NLRP1*, *NLRP3* and *NLRP6*, fewer studies were conducted on *NLRP2* in which the focus was on its functions at embryonic development and reproduction [15]. Furthermore, several studies have reported *NLRP2* in immune pathways and inflammation. For example, in human trophoblasts, *NLRP2* was involved in blocking anti-fetal responses by suppressing NF-κB and major histocompatibility complex (MHC) class I and II [16]. In addition, NLRP2 protein could act as a negative activation of kinase 1 (TBK1) in response to viral infection [17]. This role of NLRP2 protein as a regulator of pro-inflammatory signaling was observed in the lung [18]. Another study showed that kynurenine (Kyn), an immune dysfunction biomarker in depression, increased by the NLRP2 inflammasome upregulation in an NF-κB-dependent manner [19]. Recently investigators have examined the *NLRP2* as a risk factor out of the six genes affecting tumor prognosis in

patients with neck and head carcinoma and found a positive correlation between the gene and this type of cancer [20]. Fig. 5. presents a timeline of the *NLRP2* gene. Based on this, *NLRP2* is a potential candidate for further studies in human developments and diseases.

3.3 Functions of the NLRP2

Based on the literature here, we grouped the functions of *NLRP2* into three significant sections. First, *NLRP2* contribution to signal transduction. Then, the role of *NLRP2* in the development and last *NLRP2* in different diseases. However, it is important to mention that some of the *NLRP2* functions are still controversial.

3.3.1 NLRP2 in signal transduction

Various studies have looked at the signal pathways of *NLRP2*. Table 1. summarized all studies of NLRP2 at gene or protein levels in signal pathways.

3.3.1.1 Positive regulation of NF-κB transcriptional activity

NF-kB is a crucial transcription factor in regulating inflammation and controlling the expression levels of several genes involved in the immune and stress responses, cell survival, and cell adhesion. The Transcription factor NF-κB is regulated by the inhibitor of nuclear factor kappa B (IκBα), a complex consists of IKKα, IKKβ, and IKKγ subunits. The role of kinase complex is to phosphorylate IκBα, which then degrade leading to the activation of NF-κB. A study has been conducted in Cystinosis patients, which is a disorder characterized by the accumulation of the amino acid cystine within cells that resulted in many organs and tissues damages, has found a high expression of *NLRP2* in these patients in the (PTEC) in the kidney [21]. Moreover, exogenous expression of NLRP2 protein in a healthy control PTEC resulted in an increase in the production of IL-6 and IL-8 in an NF-kB-dependent manner. Furthermore, DNA-binding activities through p65 and p50 are also regulated by NF-kB proteins by the upregulation of NLRP2. However, the evidence for this positive regulation in the *NLRP2* gene needs to be more studied.

3.3.1.2 Negative regulation of NF-κB transcriptional activity

In 2004, a first study indicated that NLRP2 regulates NF-κB activity by binding to the IKK complex components [9]. The properties of NLRP2 in regulating NF-κB are identical

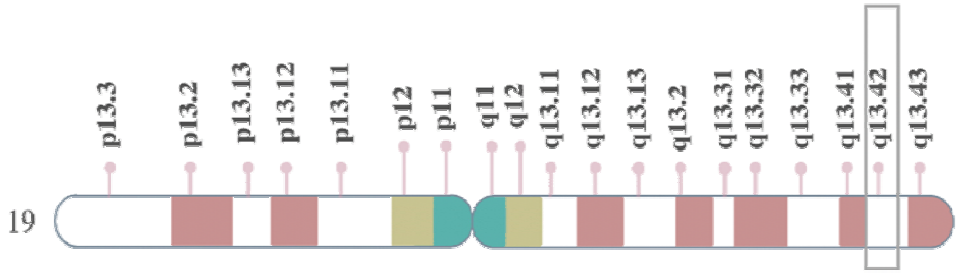

Fig. 3. Cytogenetic Location of NLRP2 in human: 19q13.42, which is the long (q) arm of chromosome 19 at position 13, Band 4, sub-band 2, with molecular Size: 48,013 bases (NCBI, [10])

Fig. 4. NLRP2 domain structure, showing the location of the N-terminal pyrin effector domain (PYD), centrally-located nucleotide-binding and oligomerization domain (NACHT,) and C-terminal leucine-rich repeats (LRR)

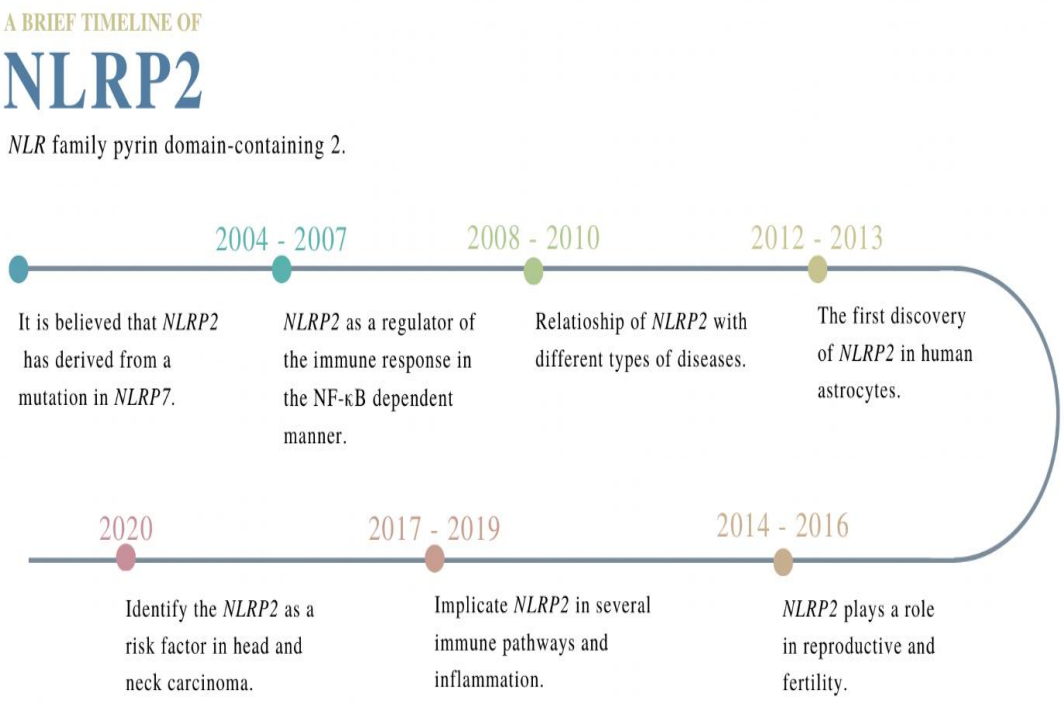

Fig. 5. A simplified timeline of some key events and discoveries in the NLRP2 gene and its protein

to NLRP4. Like NLRP4, the PYRIN domain (PYD) of NLRP2 was found to be sufficient for the inhibition of NF-κB activity. It is also found that the overexpression of NLRP2 inhibited tumor necrosis factor-alpha (TNFα), which induces IκBα degradation. Interfering with NLRP2 expression by siRNA positively correlated with the increased lipopolysaccharide -an inducible expression of an NF-κB target gene in (THP-1) macrophages cells differentiated from human monocytes. These results indicate that the endogenous NLRP2 protein can inhibit NF-kB activation and participate as a negative regulator of NF-kB activation by limiting the duration of IKK activity. Further studies on the NLRP2-dependent NF-κB regulation in different contexts physiologically and pathologically are still in need to solidify the functions of NLRP2. Moreover, the expression of *NLRP2* decreased restrained signals on the NF-κB, thus reducing inflammation [11]. Another study has shown that *NLRP2* could inhibit NF-kB p65 phosphorylation and suppress IκBα degeneration in fetal extravillous trophoblasts in humans [16].

3.3.1.3 NLRP2 inflammasome in Astrocyte

The inflammasome complex in the central nervous system (CNS) involves in inducing an innate immune inflammatory response due to IL-1β cytokine release and apoptosis. However, the NLRP2 inflammasome has shown to be expressed in human neural Astrocytes and is activated by extracellular adenosine 5′-triphosphate (ATP). The structure of the NLRP2 inflammasome differs in Astrocytes but mainly consists of three parts; NLRP2, adaptor protein (ASC), and caspase 1, as shown in Fig. 6. Additionally, the activation of astrocytes with ATP resulted in the activation of NLRP2, which is essential to processing the caspase-1 and IL-1β. Results suggest that the NLRP2 inflammasome might be a crucial part of the CNS inflammatory response and could be used as a curative target to impede inflammation due to CNS injury [8]. Moreover, NLRP2 inflammasome in neural Astrocytes has shown to be involved in depression. Also, the effect of Kynurenine (Kyn) on NLRP2 inflammasome in astrocytes and its

implication in the pathophysiology of depression has been studied in mice models [19].

3.3.2 The role of NLRP2 in the Development of Embryonic

The maternal genes encode proteins that formed during oogenesis, which have roles in early embryogenesis. The NLRP2 protein is expressed in different types of cells such as oocytes and granulosa cells. Moreover, a study investigates that *NLRP2* acts as a maternal effect gene desired for the development of early embryonic in the mouse. The reduction of NLRP2 protein in zygotes leads to an early embryonic arrest. While on the other hand, the high expression of *NLRP2* in zygotes leads to normal development but raises apoptosis rate in blastocysts [13]. This function of this gene is still not understood, and the exact effects on the embryo need further studies. Furthermore, previous studies have reported the expression role of *NLRP2* in preimplantation in different stages of embryos in humans [7]. However, Kuchmiy et al. explored a role for oocytes that expressed NLRP2 protein in early embryogenesis, and their findings exhibited that NLRP2 could contribute to *in vivo* fertility with advanced maternal age. Therefore, the *NLRP2* could act as a regulator marker of oocyte features in mice [15].

3.3.3 The involvement of *NLRP2* in different diseases

NLRP2 gene has been detected in different diseases, as summarized in Table 2. The inflammasome dysregulation drives pathology in a wide variation of human diseases (e.g., diabetes, various cancers, and neurodegenerative tive diseases). Numerous studies tried to recognize the mechanisms by which these inflammasomes drive human diseases and evolve new inflammasome inhibitors [2]. There has been an increasing interest in some inflammasomes defined in human diseases, including NLRP1, NLRP3, NLRP7, and AIM2. One of the inflammasomes mentioned earlier is the NLRP3 inflammasome, concerned with a range of human diseases, including Type 2 diabetes, Alzheimer's disease, and several infectious diseases [22]. Moreover, the initial statement of NLRP2 alteration in human disease emerged in 2009. Meyer et al. establish an extensive homozygous region within chromosome 19q13.4 (including *NLRP7* and *NLRP2* genes) in a mother with two children affected by Beckwith Wiedemann syndrome (BWS) [12]. Additionally, Results show that 20 gene transcripts have been implicated in immune-inflammatory response in individuals with Axial spondyloarthropathy (SpA) disease. They found high regulation in IL-1 receptors and a reduced level in the *NLRP2* [23]. Recently, the importance of inflammasomes has been shown by the high existence of inflammasomes in the post-mortem brain specimens in different neural disorders such as bipolar disorder, Alzheimer's and stroke [24]. Moreover, a previous study has reported that the various significant expressed genes were the NLRP2 inflammasome in bipolar patients using RNA sequencing in both pluripotent stem cells and neural stem cells [25]. In 2016, Xia Sun et al. investigate the expression of NLRP2 protein in the CNS in both ischemic strokes and under normal conditions in mice. The result showed that NLRP2 protein had an expression in CNS, mostly in Astrocytes, and higher in the ischemic brains *in vivo* [26]. However, whether *NLRP2* was related to such neurological diseases and whether it is shown in CNS *in vivo* still needs to be explored. Furthermore, Out of 47 variant genes that were detected in 15 autism spectrum disorder (ASD) patients, 2 of these genes are related to immune responses; Mannosyl-Oligosaccharide Glucosidase (*MOGS*) and NLR family pyrin domain containing 2 (*NLRP2*). *NLRP2* has been detected as an autosomal recessive (AR) in one male ASD patient [27]. Therefore, the presence, absence, or even a variation in the expression of such immune-related genes may shed light on the immune system's role in ASD. Recent evidence suggests the role of *NLRP2* as a regulator of pro-inflammatory signaling in lung inflammation due to an increase in the IL-8 cytokines after silencing *NLRP2* in the bronchial epithelial cells in humans [18].

Fig. 6. Structure of the NLRP2 inflammasomes in human astrocytes

Table 1. List of studies that indicate NLRP2 in biological pathways

References	Biological pathways	Type of study	Research Contribution
(Bruey et al. 2004)	Activation of NF-κB and Caspase-1	The function of NLRP2 protein in regulating NF-KB and pro-caspase-1 in macrophage cells.	The expression of NLRP2 protein is inducible through the lipopolysaccharide and other cytokines . NLRP2 protein plays a role in inflammation. NLRP2 binds to the IKK complex and control NF-κB activity.
(Fontalba et al. 2007)	Suppress the activation of NF-κB	The expression of *NLRP2* by NF-κB and how it contributes to inflammation due to the decrease of the NF-κB restrained signals.	*NLRP2* was upregulated following the differentiation of mesenchymal stem cells to adipocytes. Overexpress of the p65 subunit of the NF-κB resulting in upregulation of the *NLRP2*.
(Ji et al. 2009)	inducement of Human Beta-Defensins (HBD).	Characterize the *NLRP2* as an intercede in the induction of both human beta-defensin 2 and 3 by *Fusobacterium nucleatum* bacterium in gingival epithelial cells [30].	Decrease the induction of HBD-3 due to knockdown of *NLRP2* by RNA interference.
(Minkiewicz et al. 2013)	Regulatory in human astrocytes.	Investigate NLRP2 inflammasome express in the human neural Astrocytes.	Activation of NLRP2 resulted in converting procaspase-1 to its active form and maturation interleukins of IL-18 and IL-1β.
(Tilburgs et al. 2017)	NF-κB and Caspase-1 activation.	The role for *NLRP2* in inflammation through the regulation of major histocompatibility complex expression	*NLRP2* can inhibit HLA-C expression and also the NF-ƙB pathway. *NLRP2* helps to balance the anti and pro-inflammatory reactions in fetal extravillous trophoblasts.
(Mahadevan et al. 2017)	Development of early embryonic.	Investigate the link between expressed NLRP2 protein at fertility in a mouse lacking NLRP2 protein and the consequence on their offspring [32].	The female mice that lose NLRP2 protein are crucially compromised fertility.
(Peng et al. 2017)	Arrest an at an early embryonic stage.	Explore FAF1 expression of a protein in mice tissues detect evidence of an interplay between FAF1and NLRP2 proteins within early embryos and oocytes [35].	NLRP2 protein reacts to FAF1 protein under usual conditions, resulting in developing the mouse embryos' division stage. A Possible role for NLRP2 in modulating the development of an early embryo.

References	Biological pathways	Type of study	Research Contribution
(Li et al. 2018)	Inflammation and mechanism of oxidative stress.	Accelerates the hepatic steatosis is due to the inhibition of the *NLRP2* expression in non-alcoholic fatty liver disease in mice [31].	*NLRP2* was a noticeable reduction in the liver tissues of mice . The potential role of NLRP2 protein as a curative strategy to prevent NAFLD development. Oxidative stress was promoted by NLRP2 loss.
(Yang et al. 2018)	Regulation the antiviral immunity.	NLRP2 protein interaction with TANK-binding kinase 1 (TBK1) in viral infection preserve the immune homeostasis	NLRP2 protein serves as a negative activation of TBK1.
(Cheon et al. 2018)	Apoptosis signal-activating kinase.	Estimate the function of (ASK1) in controlling the NLRP2 inflammasome in murine neural Astrocytes post cerebral ischemia [28].	The level of NLRP2 inflammasome has been increased in the cortex of the mouse model after the ischemic injury. Suppressing of (ASK1) resulting in a decrease in the NLRP2 inflammasome in mice and Astrocyte cell lines.
(Rossi et al. 2019)	Pro-inflammatory.	Identified the role of *NLRP2* in controlling the antiapoptotic reaction and pro-inflammatory in proximal tubular epithelial cells in the kidney.	*NLRP2* is overexpressed in cystinosis PTEC. NLRP2 protein has a positive regulation of NF-κB through the production of several cytokines . The highly expressed NLRP2 protein result in reducing apoptotic cell rate.
(Zhang et al. 2019)	The MAPK signaling pathway.	The *NLRP2* has a significant role in preserve cell viability and motility in human umbilical vein endothelial cells by contributing to the MAPK pathway.	Silencing the *NLRP2* suppressed the (MAPK) pathway.

Table 2. List of studies that indicate NLRP2 related to different diseases

References	Diseases	Type of study	Research Contribution
(Zhang et al. 2008)	Preimplantation Development in human	The expression role of NLRP family in preimplantation in different stages of embryos.	Decrease the expression of *NLRP2* from oocytes on day 3, and rise once more in day 5.
(Meyer et al. 2009)	Beckwith-Wiedemann Syndrome (BWS)	Identified mutation in *NLRP2* gene that extracted from lymphocytes in the mother of two children with BWS.	A frameshift mutation in *NLRP2*. Role of *NLRP2* in the establishment of genomic imprinting in humans.
(Sharma et al. 2009)	Axial spondyloarthropathy (SpA)	The gene expression of *NLRP2* as pathogenesis biomarker in peripheral blood of patients with SpA	Downregulation of *NLRP2* gene out of 20 genes involved in immunity.
(Peng et al. 2012)	Early Embryogenesis	The role of *NLRP2* gene in early embryonic development in oocytes of the mouse.	The reduction of *NLRP2* in the zygote resulted in the early fetal arrest, while the overexpression of *NLRP2* led to normal development.
(Huang et al. 2013)	Idiopathic repeated miscarriage	Association of gene polymorphisms in *NLRP2* led to idiopathic recurrent miscarriage [29].	Single tag SNP of *NLRP2* displays slight importance among patients and controls.
(Yang et al. 2015)	Rheumatoid arthritis (RA)	The relationship of polymorphisms in *NLRP2* with the susceptibility of rheumatoid arthritis in a Chinese Han people [36].	Three SNPs of *NLRP2* were examined in 624 RA patients and 1920 normal individuals.
(Sun et al. 2016)	Ischemic stroke	Examine the expression of *NLRP2* in the focal cerebra of the nervous system in both ischemic stroke mouse model and typical cases.	Significantly high in ischemic brains . Disability of the *NLRP2* gene reduces the apoptotic rate.
(Kuchmiy et al. 2016)	Age-associated maternal fertility.	The function of *NLRP2* in the stimulation of oocytes and reproductive average in vivo through advanced age of *NLRP2*-lacking mice.	Recognize the *NLRP2* as a regulator of oocyte excellence . Suggested reduced activity of NLRP2 protein might contribute to maternal age-associated fertility lack in humans.
(Al-Mubarak et al. 2017)	Autism Spectrum Disorder	Whole-exome sequencing on 19 trios from Saudi families with autism.	Out of 47 different genes that could play a vital role in the development of autism, the *NLRP2* gene was detected.
(Vizlin-Hodzic et al. 2017)	Bipolar Disorder (BD)	Suggest the defect in regulating gene expression of inflammatory *NLRP2* takes place through embryo brain development of BD patients.	Variation in *NLRP2* expression at both iPSC and NSC stages in BD patients mentions that inflammation already starts at early embryonic development.

References	Diseases	Type of study	Research Contribution
			The absence expression of *NLRP2* in adipocytes of BD patients suggests that the expression of *NLRP2* is varied between cell types.
(Matsuoka et al. 2019)	Inflammatory pain hypersensitivity	The role of NLRP2 inflammasome as a novel technique of the development of inflammatory pain in male rats [33].	Presence of NLRP2 inflammasome in dorsal root ganglion neurons that become increased via tissue inflammation.
(Yu et al. 2019)	Kidney ischemia	Investigate and examine the role of *NLRP2* in the kidney injury in mice model [37].	Expression of *NLRP2* was crucially increased in kidney injury model. Reduced apoptosis of cells through silencing *NLRP2* . It could be an essential marker for therapy severe kidney injury.
(Perryman et al. 2019)	Lung Inflammation	Identified the role of *NLRP2* as a regulator of proinflammatory signaling in the lung.	*NLRP2* is strongly exists in cell lines extracted from the lung mucosa . Increase IL-8 after silencing *NLRP2* in bronchial epithelial cells.
(Mu et al. 2019)	Female infertility	Effects of mutations in *NLRP2* in oocytes and embryos that cause female infertility [34].	There were mutations in *NLRP2* gene in five distinct individuals that cause a reduction in the protein expression in embryos and oocytes.
(Zhang et al. 2020)	Depression	The impact of Kynurenine (Kyn) on NLRP2 inflammasome in neural cells and its inclusion in the pathophysiology of depression in mice model [38].	Kynurenine stimulates the NF-κB signaling activity. Increase NLRP2 transcription in the astrocytes.
(Wang et al. 2020)	Head and neck carcinoma	Identified possibility applicant genes affecting tumor prognosis in patients with neck and head carcinoma by employing bioinformatics technology.	*NLRP2* gene was reported as a risk factor out of six genes in this study.

4. CONCLUSION AND FURTHER DIRECTIONS

Many studies examined the role of the NLRP family in several diseases. Few only focused on the *NLRP2* gene and define its primary functions. While various studies measured the *NLRP2* gene in human development and different diseases, the involvement of the *NLRP2* gene still controversial. Some studies indicated that the *NLRP2* gene is one of the genetic factors involved in various diseases and affects embryonic stages, which leads to miscarriage. Others have related *NLRP2* to auto-inflammatory diseases. Although studies of the *NLRP2* gene and its protein are reported in this literature, further investigation is required to investigate which pathways *NLRP2* gene is activated and further exploiting *NLRP2* in other diseases.

5. LIMITATION OF THIS STUDY

Despite that literature reviews are effective methods to evaluate *NLRP2* in human development and diseases, some limitations can result in uncertainty. Although all the selected articles are published in the databases, no unpublished data were used nor non-indexed papers. In addition, negative results are less likely to be obtained from electronic databases, leading to drawbacks. Some studies were lacking details on the molecular pathways. Considering these limitations, different molecular pathways of NLRP2 can offer sufficient information on the signal transduction of the gene and how to manipulate pathways to avoid diseases or mitigate symptoms of *NLRP-2*-related diseases.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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