The NLRP3 Inflammasome in Cerebrovascular Diseases

Subjects: Neurosciences

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The nucleotide-binding and oligomerization (NOD) domain-like receptor (NLR) family pyrin domain (PYD)-containing 3 (NLRP3) inflammasome is one of the most comprehensively investigated inflammasomes. An inflammasome is a multiple protein complex, which comprised of sensor proteins such as pattern recognition receptors (PRRs), an effector protein (i.e., caspase-1 in canonical inflammasome, and caspase-4,5,11 in non-canonical inflammasome), and an adaptor protein (i.e., apoptosis-associated speck-like protein, ASC—containing caspase activation and recruitment domain, CARD). In the presence of cardio-cerebrovascular disease risk factors such as aging, hypertension, type-2 diabetes mellitus (T2DM), and cerebral amyloid angiopathy (CAA) mediated by vascular deposition of β-amyloid, the common underlying pathophysiological mechanisms of CSVD are primarily linked to thrombo-inflammation and arteriolosclerosis of penetrating cerebral micro-vessels (50–400 μm in diameter).

cerebral small vessel disease NLRP3 inflammasome cerebral ischemia

1. The NLRP3 Inflammasome: Structure, Activation, and Role in Cardio-Cerebrovascular Diseases

An inflammasome is a multiple protein complex, which comprised of sensor proteins such as pattern recognition receptors (PRRs), an effector protein (i.e., caspase-1 in canonical inflammasome, and caspase-4,5,11 in non-canonical inflammasome), and an adaptor protein (i.e., apoptosis-associated speck-like protein, ASC—containing caspase activation and recruitment domain, CARD). An inflammasome modulates the innate immune signaling where PRRs respond to pathogen-associated molecular patterns (PAMPs) and/or damage-associated molecular patterns (DAMPs), which results in the activation and accumulation of caspase-1 that cleaves pro-interleukin (IL)-1β and 18 to their active forms. Activated pro-inflammatory cytokines (i.e., IL-1β) modulate inflammation in a series of disorders, including chronic inflammatory disease and neurodegenerative disease [1].

2. NLRP3 Inflammasome: Structure, Activation, and Role in Cardio-Cerebrovascular Diseases

As applied to PRRs, inflammasomes can be classified as interferon (IFN)-c inducible protein 16 (IFI16), absent in melanoma 2 (AIM2), and numerous NLR subsets [2]. Furthermore, PRRs can be sub-categorized into two main

groups based on their cellular localization: (1) some toll-like receptors (TLRs) that are located in the plasma membrane which help to recognize extracellular DAMPs and PAMPs, (2) AIM2-like receptors and NLRs that are found inside the cell and are responsible for detecting intracellular DAMPs and PAMPs, and (3) subcellular interferon gamma inducible protein 16 (IFI16) [3].

Structurally, the NLRs are made up of three main components. The first component is the middle nucleotide-binding and oligomerization domain (NACHT) that exists in all NLRs, which contain adenosine 5'-triphosphatase (ATPase) activity 110, which is crucial for NLRP3 oligomerization [4][5]. The second is C-terminal, which inhibits the function of the NLR protein when leucine-rich repeats (LRRs) are inactivated or in a resting state and adjusts the conformation following the recognition of stimuli to eliminate the inhibitory effect on the NLR protein [6]. The third component is the N-terminal effector domain made up of either pyrin, CARD, or the baculoviral inhibitor of apoptosis protein repeat (BIR) domain before the NACHT domain [7]. Moreover, the NLRs can be further sub-classified into two groups based on the N-terminal domain. Firstly, the NLR sub-family C (NLRC) that involves CARD, and secondly, the NLRP containing pyrin [3]. These N-terminal domains instigate a cascade of specific downstream signaling via certain homotypic protein interactions.

A well-established inflammasome complex that is encoded by the *nlrp3* gene is the NLRP3 inflammasome. This inflammasome is made up of three components: the innate immune receptor, i.e., a NLRP3 scaffold that contains three domains including the NACHT domain (which is made up of nucleotide-binding domain, NBD, helical domain, HD—1 and 2, and winged-helix domain, WHD), C-terminal LRRs domain, and N-terminal PYD effector domain [8]. The next component includes cysteine protease precursor pro-caspase (made up of caspase domain and CARD) [3][9]. Finally, the ASC is made up of PYCARD (i.e., N-terminal PYD and C-terminal CARD), which activates caspase-1 (**Figure 1**). Moreover, the NLRP3 inflammasome is primarily located in immune cells such as antigen-presenting cells macrophages, neutrophils, monocytes, and dendritic cells [3]. Furthermore, in the brain, the activated NLRP3 inflammasome is primarily derived from microglia cells whilst the activated ASC is derived from neuronal cells [10].

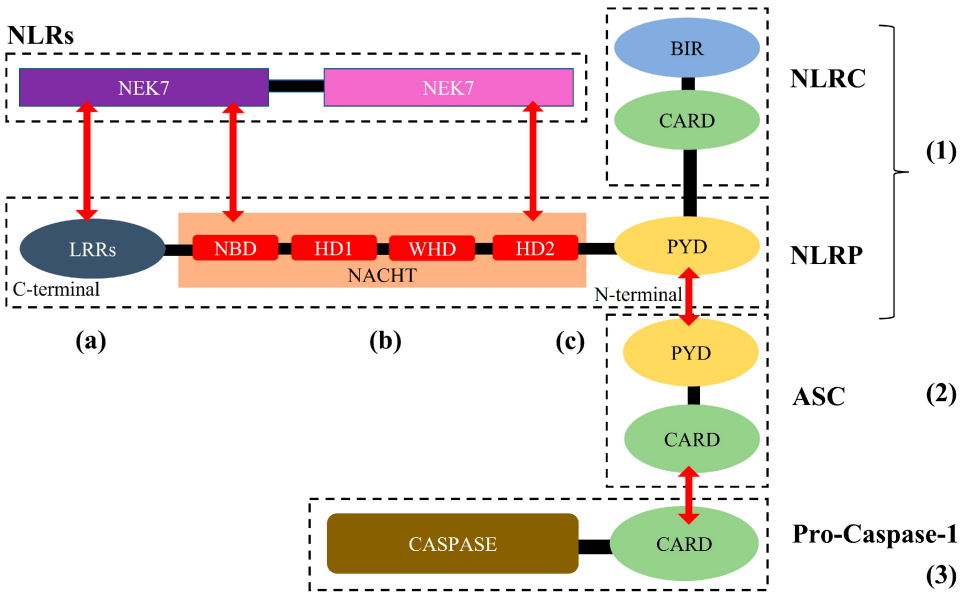

Figure 1. Structure of nucleotide-binding and oligomerization (NOD) domain-like receptor (NLR) family pyrin domain (PYD)-containing 3 (NLRP3) inflammasome. NLRs comprised of (**a**) C-terminal leucine-rich repeats (LRRs); (**b**) the central nucleotide-binding and oligomerization domain (NACHT)—made up of nucleotide-binding domain, NBD, helical domain, HD–1 and 2, and winged-helix domain, WHD; and (**c**) N-terminal pyrin domain (PYD). When the N-terminal part with PYD and caspase activation and recruitment domain (CARD)—the structure is called NLRP, but when the N-terminal consists of PYD and baculoviral inhibitor of apoptosis protein repeat (BIR)—the structure is called NLRC. The NLRP3 inflammasome is made-up of three components (or domains), which are the (1) LRRs-NACHT-PYD, (2) PYCARD (or PYD-CARD) or known as apoptosis-associated speck-like protein (ASC), and (3) Pro-caspase-1 (CARD + Caspase). The three-component merged through interaction of PYD-PYD and CARD-CARD, hence forming NLRP3 inflammasome complex. Moreover, NIMA-related kinase 7 (NEK7) is another part of NLRP3 inflammasome that is related to ROS-induced priming.

3. Activation of the NLRP3 Inflammasome

Distinct from other PRRs (i.e., TLR, C-type lectin receptors [CLR], and RIG-I-like receptors [RLR]), the primary amount of the NLRP3 inflammasome in immune cells is limited [11]. The pyrin domain of ASC is the site where NLRP3 can adhere to in order to recruit pro-caspase-1 by CARD–CARD interactions. The recruitment of pro-caspase-1 leads to the liberation of active catalytic p10 and p20 caspase-1 fragments, enabling the cleaving of inflammatory cytokine, i.e., pro-IL-1β and pro-IL-18 to their active states [6].

The activation of the NLRP3 inflammasome consists of a two-step process: priming and inflammasome activation. Priming refers to the signaling of inflammasome activation that is prompted by TLRs/nuclear factor kappa-light-chain enhancer of the activated B cells (NF-κB) pathway [12]. The NF-κB pathway can be activated by either TLRs that sense DAMPs and PAMPs, or cytokines (i.e., tumor necrosis factor α, TNF-α), or physiological stress that can result in an overexpression of NLRP3, pro-IL-18, and pro-IL-1β [13]. Besides that, the NLRP3 activation threshold is modulated by both post-transcriptional and translational activation of the *nlrp3* gene [4]. The activation of the NLRP3 inflammasome (particularly in macrophages) is dependent on *nlrp3* gene expression [14]. However, the NLRP3 remains inactive following the priming, although it is more reactive to any danger signals [15] (**Figure 2**).

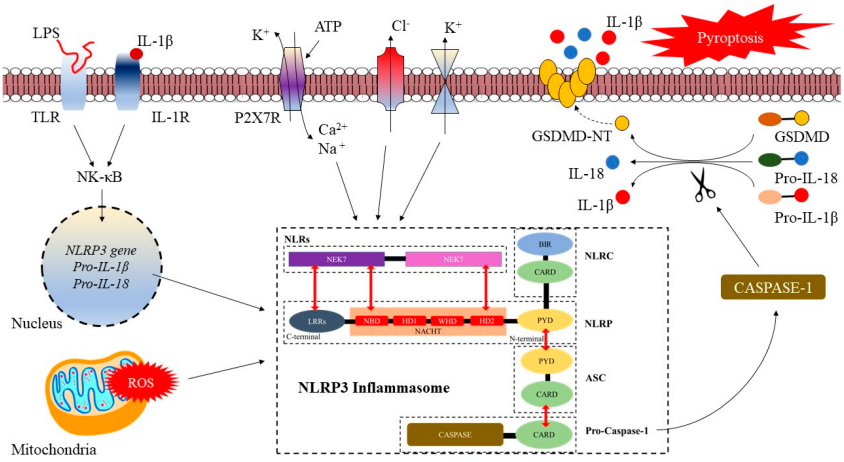

Figure 2. Mechanism of nucleotide-binding and oligomerization (NOD) domain-like receptor (NLR) family pyrin domain (PYD)-containing 3 (NLRP3) inflammasome activation. Upon certain cellular stress and/or elevated thrombo-inflammation, the increase in oxidative stress induced the over-activation of adenosine triphosphate (ATP), activates the purinergic ligand-gated ion channel 7 receptor (P2X7R), hence elevating calcium ion (Ca^{2+}) and sodium ions (Na^{+}) influx, and potassium ions (K^{+}) efflux. Following that is the increased production of reactive oxygen species (ROS). The elevated production of ROS is also due to mitochondria dysfunction mediated by oxidative stress. Besides, following physiological stress, an increased stimulation of toll-like receptors (TLRs) by lipopolysaccharide (LPS) and interleukin (IL)–1 receptor (IL-1R) by extracellular IL-1β induced the activation of nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) that subsequently elevated the gene expression of NLRP3, pro-IL-18, and pro-IL-1β. The activated NLRP3 inflammasome mediates the pro-caspase self-cleavage into caspase 1. Caspase-1 lyses pro-IL-1β, pro-IL-18, and gasdermin-D-mediated cell death (GSDMD) into their active form, leading to pyroptosis or cell-death.

The second step is the activation or trigger, whereby under certain signals or conditions (i.e., oxidative stress, thrombo-inflammation, or infection), the NLR will be activated and associated with ASC and pro-caspase-1 in a cascade response to form a complex structure. Synonymously, this complex mediates the pro-caspase-1 self-cleavage into caspase-1. Caspase-1 will then cleave pro-IL-1β, pro-IL-18, and the pore-forming molecule gasdermin-D (GSDMD) into their active forms [16][17]. Moreover, several conditions trigger or activate the NLRP3 inflammasome, and such conditions include the most crucial one, i.e., potassium (K^{+}) efflux, an increase of reactive oxygen species (ROS) induced by PAMPs and DAMPs, and the release of cathepsin B by lysosomes [18]. Additionally, mitochondrial dysfunction, calcium (Ca^{2+}) influx, chloride (Cl^{-}) efflux, and sodium (Na^{+}) influx also play an important role in the second signals for the activation of NLRP3 inflammasome [5][6] (**Figure 2**).

Previous reports have revealed that the activation of purinergic ligand-gated ion channel 7 receptor (P2X7R) plays a key role in neurodegenerative disease. Increased activation of P2X7R signaling influences the pro-inflammatory cytokines (i.e., IL-18, IL-1b, and TNF-α) and ROS (i.e., hydrogen peroxide) [19], which induced NF-kB signaling, and hence activates the NLRP3 inflammasome and subsequent cellular death [19]. The dying cells may increase the production and release of ATP and degenerative cycle. Moreover, P2X7R can mediate the over-production of intracellular ATP, hence increasing the upregulation of purinergic signaling and inflammation [20]. Following that is the elevation of Ca^{2+}, Na^{+} influx, and K^{+} efflux, which increases the production of ROS. The elevated production of ROS is also due to mitochondria dysfunction mediated by oxidative stress [21].

4. The Role of NLRP3 Inflammasome in Cerebrovascular Diseases

An increased expression of pro-inflammatory cytokines such as IL-1β has been widely studied and linked to cerebral infarction with the NLRP3 inflammasome and its inflammatory pathways (including caspase-1 and IL-1β) [22][23][24]. Moreover, IL-1β is mainly activated by the IL-1β converting enzyme called caspase-1 [25], which causes the elevation of cerebral infarct size by instigating the infiltration of neutrophil, and adherence at the infarct locus [22]. However, the infarct size and volume, as well as the neurological deficits caused by middle cerebral artery

occlusion, were reported to be ameliorated after caspase-1 and IL-1β were knocked out or inhibited [26][27]. Furthermore, previous studies have linked the increased IL-1β expression to early brain aneurysm in pre-clinical mice models, and that IL-1β gene knockout diminishes the occurrence of cerebral vascular ballooning [28].

Previous reports also indicated that the activation of the NLRP3 inflammasome and its pathway elevate the blood–brain barrier (BBB) permeability, microglial aggregation, and neuronal cell death [29]. This may indicate that the NLRP3 inflammasome could interrupt the integrity of the neuro-glio-vascular unit system dynamics [30], thereby influencing cerebral interstitial fluidopathy (i.e., aberrant glymphatic clearance) [31][32] and age-related low-grade inflammation (i.e., inflammaging) [33]. Interestingly, recent studies have highlighted the inhibition of the NLRP3 inflammasome and its pathway mitigates the cerebral and cerebellar infarction in terms of size and volume, secondary brain injury and/or inflammation following cerebral hemorrhage, preserving the integrity and permeability of the BBB, and helping against neurological function loss and deficits [34][35][36].

The interrelation of the NLRP3 inflammasome and other cerebrovascular and/or neurodegenerative diseases such as Alzheimer's disease (AD) has also been investigated. Neuroinflammation has been reported to cause the progression of AD, and elevated activation of pro-inflammatory cytokines such as IL-1β was detected in serum, cerebrospinal fluid (CSF), and brain parenchyma of patients with AD, whereby IL-1β caused a neurotoxic reaction against the neuro-glio-vascular unit [37][38][39]. Furthermore, IL-1β has also been found in patients with Parkinson's disease (PD) [40][41]. The accumulation of α-synuclein (or Lewy bodies) that impedes the release of neurotransmitters has been identified as a general indicator of PD. Lewy bodies may activate the NLRP3 inflammasome via both mitochondrial dysfunction and TLRs [42]. The inhibition of IL-1β and the NLRP3 inflammasome has emerged as a new target of interest for the prevention and treatment of AD and PD.

Hence, there are sufficient plausible leads to posit that the NLRP3 inflammasome plays an important role in the pathophysiology of cerebrovascular disease, and the modulation (i.e., activation or blocking) of the NLRP3 inflammasome or caspase-1 may influence IL-1β synthesis and offer therapeutic avenues for cerebrovascular diseases, notably CSVD.

5. The Mutation of nlrp3 Gene against NLRP3 Inflammasome Pathway

As described previously, the activation of the NLRP3 inflammasome is dependent on *nlrp3* gene expression [14]. Where the priming step of NLRP3 inflammasome activation is proportionate to the increment of *nlrp3* gene expression [43]. Furthermore, an increased pathogenic stimulus may influence the activation of the NLRP3 inflammasome following *nlrp3* gene expression upregulation. A recent study has shown that *nlrp3* gene expression was upregulated through the NF-κB pathways following the interaction of TLR with its various agonists, such as Poly (I:C) and Pam3CysK4 [14].

Pre-clinical studies have shown that the ablation (i.e., genetic deletion) or mutation of the *nlrp3* gene potentially mitigates various age-related degenerative changes (i.e., bone loss, cardiac aging, ovarian aging, and insulin

sensitivity with glycemic control) by interfering in the NLRP3 inflammasome activation pathways [44][45][46][47]. Moreover, Osario and colleagues, in their animal study, have shown that genetic modification and/or deletion of NF-κB signaling may help in the prevention of age-associated disorders [48]. Besides that, the deletion of the *nlrp3* gene has been shown to inhibit IGF-1 signaling and PI3K/AKT/mTOR (i.e., the intracellular energy sensor—associated with increase cellular autophagy), and other stressors (i.e., hypercaloric diet), hence improved various organism lifespan and aging [45][49][50].

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