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Review

NLRP3 Inflammasome: A New Target in Psychiatric Disorders

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ABSTRACT

Inflammatory proteins by the innate immune system contribute to the body's responses to external and internal threats. One of these inflammatory proteins is the nucleotide-binding domain leucine-rich-repeat-containing receptor family pyrin domain containing 3 (NLRP3). The NLRP3 inflammasome can be activated by a wide range of stimuli. It helps the host's immunological responses to microbial infection and cellular damage but causes unresolved inflammatory reactions in case of persistence or excess of the inflammasome. Its most important feature is controlling the maturation of Interleukin 1 beta and Interleukin-18 cytokines. In many psychiatric disorders, high levels of IL-1 and IL-18 indicate the formation of the NLRP3 inflammasome. In this review, NLRP3 inflammasome, which is a valuable diagnostic marker in various mental disorders including depression, Alzheimer's disease, anxiety, memory and attention disorders, post-traumatic stress disorder, and autism spectrum disorders were described.

Keywords: IL-18, IL-1β, NLRP3 inflammasome pathway, NLRP3, psychiatric disorders

AAll animals and plants have immune systems that can detect and respond to tissue damage or attack by harmful microorganisms. The immune system is made up of two parts which are innate and adaptive immune systems.[1] Adaptive immunity is the hallmark of the immune system of advanced animals. In adaptive immunity, the response consists of antigen-specific reactions through T lymphocytes and B lymphocytes. Antigens are substances that, when introduced into the body, cause the formation of defense cells.[2]

Innate immune cells are based on classes of signal receptors encoded in the germ also knowns as conjunctional cell precursors that can directly detect foreign and dangerous types of molecules.[3] Since these receptors can recognize molecular patterns, they are also called pattern recognition receptors.[4] Innate immune signal receptors are expressed in cells such as macrophages, dendritic cells, or neutrophils. Their activations in these cells alter cellular functions by causing changes in cellular metabolism and signaling networks. Innate immune signal receptors contribute to inflammatory tissue responses to protect cells from infections. Therefore, it is generally advantageous to the host. However, chronic infections, repeated tissue damage, or an excess of innate immune triggers in tissues can lead to unresolved inflammatory reactions. An example of this is the ongoing inflammation[5] in various neurodegenerative disorders by the nucleotide-binding domain leucine-rich-repeat-containing receptor family pyrin domain containing 3 (NLRP3) inflammasome.[6]

The NLRP3 is the third of the protein family member that involves nucleotide-binding and oligomerization domain, leucine-rich repeat (LRR), and pyrin domain (PYD).[7] The inflammasome is a cytosolic protein complex formed to help the host's immune responses to microbial infection and cellular damage.[8] It is a crucial signaling node that controls the maturation of the two pro-inflammatory interleukin-1 (IL-1) families' cytokines, interleukin 1 beta (IL-1β) and interleukin-18 (IL-18).[9,10] It responds to several substances present in the tissues as a result of aging, physical inactivity, overnutrition, or environmental factors.[11]

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Microbial ligands and endogens are detected and monitored by the LRR region of NLRP3. The nucleotide-binding and oligomerization domain is vital for the oligomerization of the NLRP3 inflammasome and functions as an adenosine triphosphatase.[12] Activation of the NLRP3 inflammasome consists of two steps, priming, and activation.

During the priming stage, bacterial endotoxins activate toll-like receptor 4 (TLR4), and gene expression of inflammatory cytokine precursors such as NLRP3 and pro-IL-1β, pro-IL-18 are regulated along the nuclear factor kappa B (NF-kB) pathway.[13] The cleavage of ubiquitin-protein in the priming stage of NLRP3, also known as deubiquitination, which is dependent on the structure of NLRP3, promotes activation of the NLRP3 inflammasome.[14]

In the activation phase, upon recognition of danger signals by the LRR domain, amino-terminal PYD interacts with the PYD domain of the caspase activation and recruitment domains (CARD)-containing apoptosis-associated speck-like protein (ASC), followed by monomers of pro-caspase-1 through CARD-CARD interactions.[7] These proteins then oligomerize and cleave into active caspase-1 to convert pro-caspase-1, pro-IL-1β, and pro-IL-18 into active forms. Non inherited maternal antigen (NIMA)-related kinase 7 (NEK7), which acts downstream of the P2X7 protein and potassium (K) efflux, binds to the LRR domain of NLRP3 via its catalytic domain to form an NLRP3-NEK7 complex and regulates activation of the NLRP3 inflammasome.[15] The NLRP3 inflammasome can be activated by a variety of stimuli, none of which can interact directly with the inflammasome. It is mediated by K^+ influx, Cl^- influx, Ca^{2+} signaling, lysosome rupture, reactive oxygen species (ROS), and patterns of mitochondrial dysfunction.[16]

FLOW MODEL OF POTASSIUM

In normal cells, the K^+ concentration is in equilibrium between the inside and outside of the cells. The NLRP3 inflammasome is not activated unless this balance is disrupted. A low K^+ level in the cytoplasm directly activates the NLRP3 inflammasome, while a high K^+ level prevents activation of the NLRP3 inflammasome.[17] The increased level of extracellular adenin triphosphate (ATP) can open the P2X7 receptor channel in the cell membrane and create a pore consisting of a pannexin-1 hemichannel. As a result, K^+ in the cytoplasm flows out of these pores.[18,19] In addition, bacterial pore-forming toxins[20] and the antibiotic nigericin may form nuclear pores and allow K^+ to be drained.[21]

LYSOSOMAL RUPTURE MODEL

Crystalline substances, proteinaceous uric acid, or cholesterol crystals cannot directly activate the NLRP3 inflammasome,[20] but they induce lysosomal imbalance through crystal absorption. Nuclear cathepsins, such as cathepsin B and cathepsin K, are then released into the cytoplasm[22] and by an unknown action, cause activation of the NLRP3 inflammasome.[23]

REACTIVE OXYGEN SPECIES AND MITOCHONDRIAL DYSFUNCTION MODEL

Reactive oxygen species are short-lived signaling messengers and are important for maintaining normal cell conditions. Cytosolic ROS are mainly produced by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and are regulated to maintain normal levels. Phagocytized material can cause chronic activation of NADPH oxidase and continued ROS production. The majority of NLRP3 activators, such as ATP and particulate matter, induce ROS production, but reactive oxygen stimuli such as tumor necrosis factor (TNF) have no effect on the NLRP3 inflammasome pathway.[24] Therefore, additional regulatory factors are required between ROS and activation of the NLRP3 inflammasome. Under normal conditions, thioredoxin interacting protein (TXNIP) oxidoreductase binds to thioredoxin (TRX). When intracellular ROS are abundant or persistent, TXNIP dissociates from TRX and interacts with LRRs of NLRP3, leading to its activation.[25] Both mitochondrial ROS (mtROS) and oxidized mitochondrial DNA released into the cytosol can induce activation of the NLRP3 inflammasome.[26] In addition, the mitochondrial lipid cardiolipin can bind to the LRR of the NLRP3 protein.[27]

CALCIUM SIGNALLING MODEL

Phospholipase C and diacylglycerol, a regulator of the inositol 1,4,5-trisphosphate receptor, block the action of phosphoinositide-specific phospholipase C inhibitors while promoting Ca^{2+} release of the active NLRP3 inflammasome from the endoplasmic reticulum (ER). In addition, the store-operated Ca^{2+}entry (SOCE) channel is known to have a role in activating the NLRP3 inflammasome.[28] The imbalance of Ca^{2+} and cyclic adenosine

monophosphate (cAMP) signals can lead to activation of the NLRP3 inflammasome. Furthermore, Ca^{2+} is released from the ER influx into mitochondria via the mitochondrial calcium uniporter, which causes excessive release of mitochondrial Ca^{2+} and mtROS and leads to activation of the NLRP3 inflammasome.[29] However, the role of Ca^{2+} in the activation of the NLRP3 inflammasome is controversial.[30]

FLOW MODEL OF CHLORIDE

Verhoef et al.[31] argued that the influx of intracellular Cl can induce P2X7 receptor-dependent caspase-1 activation and IL-1β secretion. Interestingly, chloride intracellular channels (CLIC1, CLIC4, and CLIC5) transferred to the plasma membrane facilitate Cl influx to promote NEK7-NLRP3 interaction and induce ASC oligomerization.[32] Daniels et al.[33] have recently shown that nonsteroidal anti-inflammatory drugs(NSAID) inhibit the volume-regulated anion channel to regulate NLRP3 activation. Further work is needed to interpret how intracellular chloride efflux inhibits NLRP3 activation.

NON-CANONICAL AND ALTERNATIVE INFLAMMASOME PATHWAY OF NLRP3

In addition to the canonical activation of NLRP3 inflammation described above, there are non-canonical ways to activate this inflammation. Lipopolysaccharide (LPS)[34] directly binds to the CARD region of caspase-11 and causes oligomerization and activation of caspase-11 in mouse macrophages.[35] The amino-terminal part of gasdermin D, which is cleaved by caspase-11, can damage cell membranes. Furthermore, this part can also regulate IL-1β production to promote caspase-1 self-cleavage and pyroptosis. Pyroptosis is a process independently from NLRP3 by which the inflammatory programmed cell death pathway is activated with the help of various caspases.[36] Caspase-4 and caspase-5 have a similar function in human macrophages.[37] Potassium is also required in these activation paths.[35] Activation of the TLR4-toll/interleukin-1 receptor/resistance protein-domain-containing adapter-inducing interferon-β (TRIF)-caspase-8 pathway by LPS[38] in human monocytes leads to activation of the NLRP3 inflammasome pathway and maturation of IL-1β, known as the alternative NLRP3 inflammasome pathway.[39] This signaling pathway is specific to species that occur in human and pig monocytes.[40]

NLRP3 AND PSYCHIATRIC DISORDERS

Given the diversity of activators and complexity of signaling pathways of NLRP3 inflammatory, it is clear that NLRP3 inflammasome has a role in inflammatory diseases.[16] The occurrence of inflammation in and around neurons can be beneficial in terms of brain plasticity, tissue repair, and neuroprotection in normal processes. This is the situation in which the brain defends itself against endogenous and exogenous factors, but chronic neuroinflammation leads to the death of neurons after a while.[41]

Neuroinflammation plays a role in the pathogenesis[42,43] of neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease, Huntington's disease, and Multiple sclerosis, as well as dementia that leads to memory loss and cognitive impairment during neuronal aging[44] while causing a decrease in cognitive ability and memory.[45-47] It also has a role in psychiatric disorders such as depression.[48,49] There is an association between age-related depression and levels of proinflammatory cytokines such as IL-1β, known as the alternative NLRP3 inflammasome pathway in the brain.[50] These proinflammatory cytokines migrate from the systemic circulation to the brain. An opposite mechanism occurs in older ages.[51] The neurovegetative syndrome, characterized by symptoms of fatigue, psychomotor slowing, anorexia, and altered sleep patterns, develops rapidly in nearly every individual exposed to cytokines and persists throughout cytokine exposure. In contrast, mood and cognitive syndrome, characterized by symptoms of depressive mood, anxiety, memory, and attention disorders, usually occur in patients in later stages of cytokine therapy.[52] In a different study, it was shown that the NLRP3 inflammasome was activated in the brain by increasing the IL-1β protein concentration in the brain of mice treated with LPS and the expression level of IL-1β messenger ribonucleic acid (mRNA) in the brain of LPS group mice. All three components of the NLRP3 inflammasome, including NLRP3, ASC, and caspase-1, appeared to have mRNA expression levels as measured by real-time reverse transcription-polymerase chain reaction in the brain of LPS group mice compared to control mice. Thus, it was understood that the NLRP3 inflammasome has essential roles in the depressive behavior of LPS-induced mice.[53] Similar findings were seen in a study of human participants when activated NLRP3 inflammasome was detected in blood mononuclear cells from depressed patients.[54] In fact, elevated levels of IL-1β and IL-18 in body fluids

are a hallmark of NLRP3 inflammatory activation and have been reported as a useful diagnostic marker in various mental disorders.[55] Moreover, the resistance of caspase-1-deficient mice to LPS-induced depressive-like behaviors further supports the role of inflammations in depression.[56] ROS released from mitochondria in response to certain stressors activate the NLRP3 inflammasome in microglia cells. Oxidative stress and ROS have a role in the pathogenesis of anxiety disorders, depression, schizophrenia, and bipolar disorder.[52,57,58]

Abnormal activation of NLRP3 inflammasome and caspase-1 has been implicated in the pathogenesis of AD.[59,60] The accumulation of amyloid-beta (Aβ), one of the pathologies of AD,[61] acts as an NLRP3 inflammatory, causing a harmful chronic inflammation that leads to exacerbation of synaptic dysfunction and cognitive impairment. NLRP3, ASC, and other related proteins such as caspase-1, IL-1β, and IL-18 are upregulated in AD patients at both protein[60] and mRNA[62] levels.[60] In addition, NLRP3 inflammasome activation affects Aβ clearance of proteolytic enzymes that increase Aβ phagocytosis and Aβ plaque deposition in microglia. The NLRP3 deficiency is also skewed towards a phenotype characterized by an increase in Aβ clearance and protecting mice from loss of cognitive function, suggesting that AD progression of the NLRP3 inflammasome plays an important role in memory loss.[16]

Fear memory plays a role in the development of trauma and stress-related disorders such as post-traumatic stress disorder (PTSD).[63] Chronic neuroinflammation occurs in PTSD, anxiety, and major depressive disorders.[64-66] Such disorders are associated with high concentrations of proinflammatory cytokines such as tumour necrosis factor-alpha , IL-1β, interleukin-6 (IL-6), and interferon.[66-68] Exposure to stress increases IL-1β concentrations in multiple brain regions.[69] Both insufficient and excessive levels of IL-1β impair memory formation,[70] suggesting that IL-1β is important for normal learning and memory formation. Mutant mice lacking the IL-1β receptor show enhanced fear memory and reduced anxiety behavior.[71] Central administration of IL-1β can trigger anxiety-like behaviors and strengthen fear memory after encountering stress.[71,72] In an experiment, it was observed that the levels of cleaved caspase-1 in the hippocampus increased and the NLRP3 inflammasome was formed 3 hours after the electric foot shocks were applied to the mice to induce fear. Subsequently, there was a decrease in upregulation of Retinoic Acid-Inducible Gene 1 signaling by TLR and retinoic acid, and a decrease in the postsynaptic density (PSD)-related proteins in the hippocampus 72 hours after electric foot shocks. Similarly, ASC occurred 3 hours after the electric foot shocks.[73]

Autism spectrum disorder is a genetically heterogeneous developmental disorder. Individuals with ASD are characterized by repetitive limited behavioral activities and often multiple emotionalities, social reciprocity, and consequent communication abnormalities.[74] There are many genetic, environmental, and immunological factors in the etiopathogenesis of ASD.[75] It is known that there is an aberrant expression of many inflammatory cytokines in serum, brain, and gastrointestinal tract in ASD. These cytokine imbalances can affect neural activity and cause abnormal behavior.[76] In children with ASD, an increase in the NLRP3 inflammasome and another inflammasome complex, absent in melanoma 2, and accordingly the production of IL-1β and IL-18 inflammatory cytokines were observed.[77] Central and peripheral IL-1β reduces neurogenesis and increases anxiety, stress, and abnormal social interaction.[78] The application of IL-1 receptor antagonist (IL-1RA) in experimental animals reduced abnormal social interaction caused by IL-1β.[79] In addition, polymorphisms were reported in IL-1β genes and receptors in cognitive disorders.[80] In addition, polymorphisms in genotype variants, IL-1β-511 and IL-1RA have positive correlations with autism severity and behavioral abnormalities.[81] In addition, hippocampal ROS levels and abundance of NLRP3 cells in mice exposed to diesel exhaust particles are known to increase compared to those in control mice.[82]

In conclusion, the NLRP3 inflammatory, which defends the immune system against external and internal threats, interacts with the monomers of procaspase-1, which is recognized by the LRR field of NLRP3 for hazard signals, and then undergoes oligomerization.Pro-caspase-1 cleaves into active caspase-1 to convert pro-IL-1β and pro-IL-18 into active forms. There are many stimuli to activate the NLRP3 inflammasome, such as low K^+ level in the cytoplasm, lysosomal imbalance through crystal resorption, induction of ROS production, SOCE channel, imbalance of Ca^{2+} and cyclic adenosine monophosphate signals, intracellular chloride flux, and direct effect of LPS. The occurrence of activated NLRP3 inflammasome in and around neurons is important for the protection of the brain, but chronic neuroinflammation causes many psychiatric disorders after a while. In the light of experimental

studies, it can be said that there is a linear relationship between IL-1β and IL-18 and NLRP3, in addition to ASC formation and abnormal activation of caspase-1 in psychiatric disorders. Neuroinflammation, which is permanent throughout an individual's life, can then lead to psychological disorders. Targeting the NLRP3 inflammatory complex, genetic knockout or pharmaceutical inhibition of the NLRP3 inflammatory may limit neuroinflammatory conditions in psychiatric disorders such as major depressive disorders.

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