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·Review·

Research progress on the NLRP3 inflammasome and its role in the central nervous system

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The NLRP3 inflammasome, which consists of the NLRP3 (nucleotide-binding oligomerization domain (Nod)–like receptor 3) scaffold, the ASC (apoptosis-associated speck-like protein containing a CARD) adaptor and pro-caspase-1, is assembled after the cytoplasmic LRRs (leucine-rich repeats) of NLRP3 sense pathogens or danger signals. The NLRP3 inflammasome controls the activation of the proteolytic enzyme caspase-1. Caspase-1 in turn regulates the maturation of the proinflammasome cytokines IL-1β and IL-18, which leads to an inflammatory response. The inflammasome plays an important role in the development of Alzheimer's disease and bacterial meningitis, and the NLRP3 inflammasome may become a new target for the prevention and treatment of central nervous system diseases.

Keywords: NLRP3; inflammasome; central nervous system

Introduction

There has been considerable interest in the recently-introduced inflammasome, a large molecular platform composed of the NLR (nucleotide-binding oligomerization domain (Nod)-like receptor) protein, the adaptor ASC (apoptosis-associated speck-like protein containing a CARD) and pro-caspase-1. The inflammasome is responsible for the proteolytic processing of immature forms of interleukin-1β (IL-1β) and IL-18, two powerful proinflammatory cytokines with pleiotropic activities. Since its proposal in 2002, the inflammasome has increasingly become a research hotspot with the number of publications increasing every year (Fig. 1A). Four types of inflammasome have been most intensely studied: the NLR pyrin domain containing 1 (NLRP1), NLRP3, NLR containing a caspase recruitment domain 4 (NLRC4), and AIM2 (absent in melanoma 2) inflammasomes. The NLRP3 inflammasome is the best-studied thus far with 274 publications, 67.8% of the currently available research articles on inflammasomes (Fig. 1B).

The NLRP3 inflammasome is linked to a number of diseases including inflammatory disease[1-5], metabolic disease[6] and carcinogenesis[7]. Currently, increasing attention is being paid to the function of the NLRP3 inflammasome in the central nervous system (CNS). Studies have reported that the NLRP3 inflammasome is associated with Alzheimer's disease (AD)[8-10], bacterial meningitis[11,12], and experimental autoimmune encephalomyelitis (EAE)[13]. During certain CNS diseases, the NLRP3 inflammasome is activated (Table 1). Therefore, the NLRP3 inflammasome may play a critical role in CNS physiopathology and function as a proinflammatory mediator. Here, we review the recent research advances on the NLRP3 inflammasome, particularly its role in the CNS.

NLRP3 Inflammasome Structure

NLRP3 is the main component of the NLRP3 inflammasome[24]. NLRP3, also known as cryopyrin, PYPAFI or Nalp3, has a tripartite structure containing a central Nod (or NACHT domain), a carboxy-terminal leucine-rich-repeat

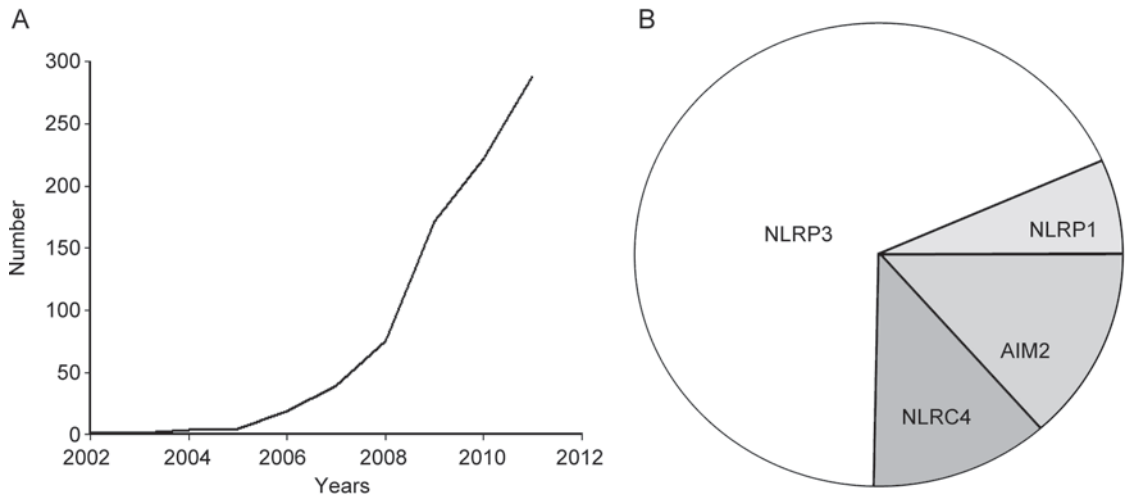

Fig. 1. Yearly publications and research trends on inflammasomes from 2002, when the inflammasome was proposed, to 2011. The search was performed in the Web of Science using the keywords "inflammasome", "NLRP1 inflammasome", "NLRP3 inflammasome", "NLRC4 inflammasome", and "AIM2 inflammasome". A: The research trend on inflammasomes from 2002 to 2011. B: Distribution of the four intensely-studied inflammasomes among published research articles.

Table 1. NLRP3 inflammasome activation in central nervous system diseases

	Pathology	NLRP3 activation	References
Alzheimer's disease	Overproduction of Aβ and phosphorylation of tau protein resulting in plaques and tangles	Oligomeric/fibrillar Aβ leads to NLRP3 inflammasome activation in microglia and processing of pro-IL-1β in a caspase-1-dependent manner	[9, 14, 15]
Meningitis	Inflammation of the leptomeninges resulting in tissue and vascular injury and increased intracranial pressure	Severity significantly reduced in NLRP3- and ASC-deficient animals	[11, 16–20]
Prion disease	Accumulation of an abnormal disease-associated prion protein	Prion protein fibrils activate NLRP3 inflammasome leading to release of IL-1β	[21–23]
Experimental autoimmune encephalomyelitis	Reactive glia trigger inflammatory processes and subsequent oligodendrocyte and axonal destruction	NLRP3 acts in the induction of EAE through effects on caspase-1-dependent cytokines which then influence Th1 and Th17	[13]

domain (LRR), and an N-terminal caspase-associated recruitment domain (CARD) or a heat protein domain (PYD). C-terminal LRRs provide a bracket for the interaction between pathogens and intracellular materials and identify pathogen-associated molecular patterns and other ligands. The central NACHT domain primarily mediates self-oligomerization during the activation process. The N-terminal PYD effector domain links NLRP3 to the downstream adapter protein ASC. Shenoy *et al.* found that guanylate-binding protein 5 (GBP5) directly interacts with NLRP3 and undergoes tetramerization in a GTPase-independent manner, and the GBP5 tetramer promotes oligomerization of the adaptor ASC *via* its interaction with NLRP3[25].

ASC was originally discovered as a detergent-insoluble

protein and was subsequently found to participate in apoptosis[26]. The ASC protein consists of 195 amino-acids and connects to NLRP3 *via* adjoining N-terminal PYD domains. The C-terminal portion contains a CARD effector domain that interacts with the CARD domain of pro-caspase-1. The oligmerization of two adjacent pro-caspase-1 molecules leads to enzymatic hydrolysis and the generation of biologically active caspase-1[27,28].

The NLRP3 inflammasome is composed of NLRP3, ASC and pro-caspase-1, which oligomerizes upon activation[29]. This activation results in the recruitment of ASC through homotypic PYD–PYD interactions. ASC, in turn, forms large speck-like structures and recruits pro-caspase-1 *via* CARD–CARD contact, leading to the autocatalytic activation of caspase-1[28]. Active caspase-1 converts the inactive pro-IL-1β and pro-IL-18 into their active and secreted forms, mediating the subsequent response.

Activation of the NLRP3 Inflammasome

Prior to activation, the NLRP3 inflammasome consists of an NLRP3 scaffold, known as ubiquitin ligase-associated protein SGT1 (suppressor of the G2, of skp1 allele) and HSP90 (heat shock protein 90 kD)[30], and the SGT1–HSP90 complexes work together to maintain the pre-activation status. However, upon activation by a corresponding irritant, the complex dissociates from NLRP3, and then NLRP3 becomes activated[31]. It has also been demonstrated that the tripartite-motif protein 30, a RING protein, negatively regulates the activation of NLRP3 through the generation of reactive oxygen species (ROS)[32].

The NLRP3 inflammasome can be activated by a wide range of signals of pathogenic, endogenous and environmental origins and also by endogenous danger signals. Several of the activating irritants are listed in Table 2.

Table 2. NLRP3 inflammasome-activating irritants

	Irritants	References
Pathogens	Influenza virus, adenovirus, sendai virus, *Staphylococcus aureus*, white yeast, *Candida albicans*, muramyl dipeptide, TNF-α, lipopolysaccharide, bacterial RNA, viral double-stranded DNA	[35–43]
Endogenous and environmental origin	Silica, asbestos, vaccine adjuvants, aluminum adjuvants	[33, 44–46]
Endogenous danger signals	Uric acid, uric acid monosodium, crystal, β-amyloid protein, adenosine triphosphate, hyaluronic acid	[1, 9, 47–50]

To date, three distinct mechanisms have been proposed to explain the assembly of the NLRP3 inflammasome: lysosomal rupture, the generation of mitochondrial DNA (mtDNA), and the generation of ROS (Fig. 2).

Lysosomal Rupture

NLRP3 is activated upon lysosome destabilization. The phagocytosis of specific crystalline and particulate structures leads to lysosome destabilization and the release of lysosomal contents, including cathepsin B. Cathepsin B binds to NLRP3 and induces the proteolytic activation of a positive regulator of NLRP3, resulting in inflammasome assembly[33,34].

Generation of mtDNA

The release of oxidative mtDNA upon mitochondrial damage can activate the NLRP3 inflammasome. There are two pathways for mitochondrial damage: intracellular K^+ efflux and Ca^{2+} mobilization.

K^+ efflux results in low K^+ concentrations in the intracellular environment, leading to mitochondrial dysfunction, apoptosis and the subsequent release of ROS and oxidative mtDNA, which can activate the NLRP3 inflammasome[48,51-53]. Several mechanisms underlying the outflow of K^+ have been proposed. Upon bacterial infection, the release of perforin can destroy cell membranes and allow for the outflow of K^+ down its concentration gradient[48]. ATP can activate the membrane selectivity of the K^+ channel P2X7, which leads to a rapid outflow of K^+. P2X7 activation gradually recruits the gap junction protein pannexin-1,

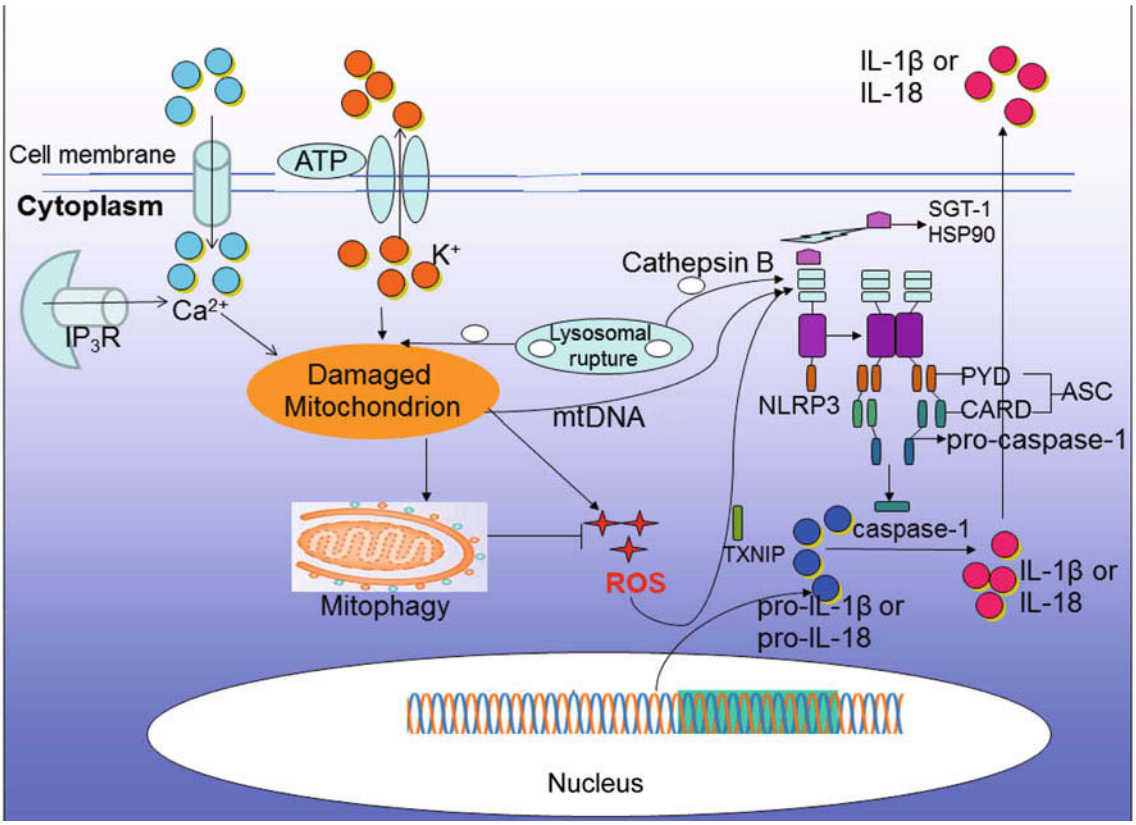

Fig. 2. Three primary mechanisms of NLRP3 assembly. The three primary mechanisms of inflammasome assembly are lysosomal rupture, the generation of mitochondrial DNA (mtDNA), and the generation of reactive oxygen species (ROS). Intracellular K^+ efflux and Ca^{2+} mobilization lead to mitochondrial dysfunction, apoptosis and the subsequent release of ROS and oxidative mtDNA, which activates the NLRP3 inflammasome. Lysosome destabilization releases the lysosomal contents, which include cathepsin B. Cathepsin B binds to NLRP3 and proteolytically activates a positive regulator of NLRP3, resulting in inflammasome assembly. With increased ROS, thioredoxin-interacting protein (TXNIP) dissociates from thioredoxin and binds to NLRP3, leading to the activation of NLRP3.

resulting in the formation of a larger-aperture channel[54,55]. In addition, studies have shown that, after the formation of gap junctions by pannexin-1, NLRP3 inflammasome activators such as muramyl dipeptide can pass through the plasma membrane and directly trigger the activation of caspase-1[56].

Recently, it has been reported that Ca^{2+} mobilization-mediated mitochondrial damage can also activate the NLRP3 inflammasome, and Ca^{2+}-sensing receptors regulate the inflammasome through Ca^{2+} and cAMP[57-59]. In response to ATP and perhaps other stimuli, Ca^{2+} release from endoplasmic reticulum stores or the extracellular space can trigger mitochondrial damage.

Generation of ROS

ROS are induced by activators of the NLRP3 inflammasome and are mainly produced by the mitochondria[60,61]. The complex of thioredoxin and thioredoxin-interacting protein (TXNIP) dissociates with increased ROS levels. The subsequent binding of TXNIP to NLRP3 leads to the activation of NLRP3, the recruitment of ASC and pro-caspase-1, and the formation of the active inflammasome complex[62]. Studies have found that reducing the damage to mitochondria by regulating mitochondrial autophagy inhibits ROS-induced NLRP3 inflammasome activation; in the absence of autophagy, activation of the NLRP3 inflammasome increases dramatically[52,61,63].

Regulation of NLRP3 Inflammasome Activity

The host needs to tightly regulate NLRP3 inflammasome

activity to avoid excess production of cytokines and cell death, and in fact, distinct mechanisms have evolved to regulate its activation and prevent serious consequences. This regulation occurs at both the transcriptional and post-transcriptional levels.

First, alternative splicing of the NLRP3 inflammasome components generates protein variants with different activities. Splice variants of ASC have been identified with distinct adaptor capabilities, with one variant ASC-c displaying inhibitory activity[64]. The host expresses proteins that regulate NLRP3 inflammasome activity primarily by sequestering inflammasome components through homotypic interactions with CARDs or PYDs or through the direct inhibition of caspase-1 function[65,66].

Furthermore, inflammasome activity is also regulated through crosstalk between cellular stress-associated processes, such as autophagy. The induction of autophagy leads to the degradation of cellular substrates, such as protein aggregates and organelles, in autolysosomes for the recycling of metabolites. Strikingly, cells deficient in autophagy have a decreased threshold for NLRP3 inflammasome activation[67]. This may result from the impaired clearance of defective mitochondria, resulting in elevated levels of ROS, suggesting the involvement of NLRP3 as a sensor[52,53,68].

Another aspect of inflammasome activity is its downregulation either through secreted factors or cell–cell interactions. The signaling interactions between $CD4^+$ T cells and macrophages or dendritic cells lead to the transcriptional and post-transcriptional downregulation of inflammasome activity, respectively[69,70].

Roles of the NLRP3 Inflammasome in the CNS

The NLRP3 inflammasome is expressed at high levels in microglia when activated by irritants[71]. An unresolved question, however, is whether astrocytes and neurons possess NLRP3 inflammasomes. Recent studies have reported that the NLRP3 inflammasome is associated with several CNS diseases, such as AD and EAE.

NLRP3 Inflammasome and AD

During the development of AD, β-amyloid deposits are phagocytosed by microglia in the brain[72] and enter lysosomes, leading to lysosomal swelling and instability. Cathepsin B released from lysosomes activates the formation of the NLRP3 inflammasome and caspase-1, resulting in the secretion of mature IL-1β[9]. IL-1β plays an important role in neuronal injury, and leads to NO and TNF-α production, causing neurotoxicity[15]. NO and TNF-α promote the transformation of diffuse amyloid plaques into inflammatory plaques, resulting in the decay of cortical neurons and brain atrophy[14].

NLRP3 Inflammasome and Meningitis

ASC or NLRP3 knockout mice, upon infection with pneumococcal meningitis, exhibit decreased scores of clinical and histological disease severity and brain inflammation[11,16,17]. Besides, during pneumococcal meningitis, the NLRP3 inflammasome is activated by ATP-dependent lysosomal cathepsin B release[18-20].

NLRP3 Inflammasome and Prion Disease

Prion diseases are neuroinflammatory and neurodegenerative disorders characterized by the accumulation of the abnormal disease-associated prion protein, PrP^{Sc}[21,22]. The accumulation of PrP^{Sc} leads to the activation of microglia which in turn produce chemotactic factors, pro-inflammatory cytokines and neurotoxic factors[73-75]. Activation of the NLRP3 inflammasome by PrP fibrils leads to the release of IL-1β, which signals through IL-1R. Upon activation, IL-1R recruits the intracellular adaptor MyD88[23]. It has also been reported that activation of the NLRP3 inflammasome is indispensable for PrP106–126-induced IL-1β release, and K^+ efflux and ROS production are implicated in PrP106–126-induced NLRP3 activation[76].

NLRP3 Inflammasome and EAE

In the mice spinal cord, the NLRP3 expression was elevated upon infection with pneumococcal meningitis during EAE, and it is proposed that NLRP3 participates in the induction of EAE through effects on capase-1-dependent cytokines which then influence Th1 and Th17[13]. More recently, Inoue *et al.* found that the NLRP3 inflammasome induces chemotactic immune cell migration to the CNS during EAE, and the NLRP3 inflammasome enhances the migration of Th17 and Th1 cells to the CNS[77].

Conclusion

The inflammasome is a multiprotein complex that promotes the maturation of inflammatory cytokines, such as IL-1β and IL-18. These cytokines are extremely powerful molecules with myriad functions that are widely and rapidly induced

in the CNS upon infection, trauma or stress. Therefore, inflammasomes are likely to control many aspects of neuroinflammation. However, research on the role of the NLRP3 inflammasome in the CNS is still in the preliminary stage, and a number of questions remain unresolved. The distribution of NLRP3 inflammasomes in the cell and the CNS needs further investigation. In addition, whether the NLRP3 inflammasome is involved in other CNS diseases, such as stroke, Parkinson's disease, epilepsy, or pain remains unclear. Furthermore, the exact molecular mechanisms by which the NLRP3 inflammasome is activated should also be further examined. Whether this protein complex is biochemically and genetically regulated may be a focus in years to come. Clinical trials have confirmed that IL-1β and its receptor antagonist can be used to treat a variety of diseases[78-80], and the widely-used drug glyburide plays a role in the treatment of diabetes through inhibition of the NLRP3 inflammasome[81]. Thus, investigations into the NLRP3 inflammasome will shed light on the pathogenesis of CNS diseases and provide critical clues for seeking new targets for clinical drug development.

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REFERENCES

[1] Martinon F, Petrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 2006, 440: 237–241.

[2] Schoultz I, Verma D, Halfvarsson J, Torkvist L, Fredrikson M, Sjoqvist U*, et al.* Combined polymorphisms in genes encoding the inflammasome components NALP3 and CARD8 confer susceptibility to Crohn's disease in Swedish men. Am J Gastroenterol 2009, 104: 1180–1188.

[3] Roberts RL, Topless RK, Phipps-Green AJ, Gearry RB, Barclay ML, Merriman TR. Evidence of interaction of CARD8 rs2043211 with NALP3 rs35829419 in Crohn's disease. Genes Immun 2010, 11: 351–356.

[4] Villani AC, Lemire M, Fortin G, Louis E, Silverberg MS, Collette C*, et al.* Common variants in the NLRP3 region contribute to Crohn's disease susceptibility. Nat Genet 2009, 41: 71–76.

[5] Cummings JR, Cooney RM, Clarke G, Beckly J, Geremia A, Pathan S*, et al.* The genetics of NOD-like receptors in Crohn's disease. Tissue Antigens 2010, 76: 48–56.

[6] Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG*, et al.* NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature 2010, 464: 1357–1361.

[7] Kastbom A, Verma D, Eriksson P, Skogh T, Wingren G, Soderkvist P. Genetic variation in proteins of the cryopyrin inflammasome influences susceptibility and severity of rheumatoid arthritis (the Swedish TIRA project). Rheumatology (Oxford) 2008, 47: 415–417.

[8] Richard KL, Filali M, Prefontaine P, Rivest S. Toll-like receptor 2 acts as a natural innate immune receptor to clear amyloid beta 1-42 and delay the cognitive decline in a mouse model of Alzheimer's disease. J Neurosci 2008, 28: 5784–5793.

[9] Halle A, Hornung V, Petzold GC, Stewart CR, Monks BG, Reinheckel T*, et al.* The NALP3 inflammasome is involved in the innate immune response to amyloid-beta. Nat Immunol 2008, 9: 857–865.

[10] Holley MM, Kielian T. Th1 and Th17 cells regulate innate immune responses and bacterial clearance during central nervous system infection. J Immunol 2012, 188: 1360–1370.

[11] Hoegen T, Tremel N, Klein M, Angele B, Wagner H, Kirschning C*, et al.* The NLRP3 inflammasome contributes to brain injury in pneumococcal meningitis and is activated through ATP-dependent lysosomal cathepsin B release. J Immunol 2011, 187: 5440–5451.

[12] Koedel U, Rupprecht T, Angele B, Heesemann J, Wagner H, Pfister HW*, et al.* MyD88 is required for mounting a robust host immune response to Streptococcus pneumoniae in the CNS. Brain 2004, 127: 1437–1445.

[13] Jha S, Srivastava SY, Brickey WJ, Iocca H, Toews A, Morrison JP*, et al.* The inflammasome sensor, NLRP3, regulates CNS inflammation and demyelination via caspase-1 and interleukin-18. J Neurosci 2010, 30: 15811–15820.

[14] Griffin WS, Stanley LC, Ling C, White L, MacLeod V, Perrot LJ*, et al.* Brain interleukin 1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer disease. Proc Natl Acad Sci U S A 1989, 86: 7611–7615.

[15] Lee CY, Landreth GE. The role of microglia in amyloid clearance from the AD brain. J Neural Transm 2010, 117: 949–960.

[16] Mustafa MM, Lebel MH, Ramilo O, Olsen KD, Reisch JS, Beutler B*, et al.* Correlation of interleukin-1 beta and cachectin concentrations in cerebrospinal fluid and outcome from

bacterial meningitis. J Pediatr 1989, 115: 208–213.

[17] Fassbender K, Mielke O, Bertsch T, Muehlhauser F, Hennerici M, Kurimoto M*, et al.* Interferon-gamma-inducing factor (IL-18) and interferon-gamma in inflammatory CNS diseases. Neurology 1999, 53: 1104–1106.

[18] Quagliarello VJ, Wispelwey B, Long WJ Jr, Scheld WM. Recombinant human interleukin-1 induces meningitis and blood-brain barrier injury in the rat. Characterization and comparison with tumor necrosis factor. J Clin Invest 1991, 87: 1360–1366.

[19] Zwijnenburg PJ, van der Poll T, Florquin S, Roord JJ, Van Furth AM. IL-1 receptor type 1 gene-deficient mice demonstrate an impaired host defense against pneumococcal meningitis. J Immunol 2003, 170: 4724–4730.

[20] Koedel U, Winkler F, Angele B, Fontana A, Flavell RA, Pfister HW. Role of Caspase-1 in experimental pneumococcal meningitis: Evidence from pharmacologic Caspase inhibition and Caspase-1-deficient mice. Ann Neurol 2002, 51: 319–329.

[21] Scott JR. Scrapie pathogenesis. Br Med Bull 1993, 49: 778–791.

[22] Prusiner SB. Molecular biology of prion diseases. Science 1991, 252: 1515–1522.

[23] Hafner-Bratkovic I, Bencina M, Fitzgerald KA, Golenbock D, Jerala R. NLRP3 inflammasome activation in macrophage cell lines by prion protein fibrils as the source of IL-1beta and neuronal toxicity. Cell Mol Life Sci 2012, 69: 4215–4228.

[24] Mathews RJ, Sprakes MB, McDermott MF. NOD-like receptors and inflammation. Arthritis Res Ther 2008, 10: 228.

[25] Shenoy AR, Wellington DA, Kumar P, Kassa H, Booth CJ, Cresswell P*, et al.* GBP5 promotes NLRP3 inflammasome assembly and immunity in mammals. Science 2012, 336: 481–485.

[26] Masumoto J, Taniguchi S, Ayukawa K, Sarvotham H, Kishino T, Niikawa N*, et al.* ASC, a novel 22-kDa protein, aggregates during apoptosis of human promyelocytic leukemia HL-60 cells. J Biol Chem 1999, 274: 33835–33838.

[27] Stutz A, Golenbock DT, Latz E. Inflammasomes: too big to miss. J Clin Invest 2009, 119: 3502–3511.

[28] Stehlik C, Lee SH, Dorfleutner A, Stassinopoulos A, Sagara J, Reed JC. Apoptosis-associated speck-like protein containing a caspase recruitment domain is a regulator of procaspase-1 activation. J Immunol 2003, 171: 6154–6163.

[29] Martinon F, Tschopp J. Inflammatory caspases and inflammasomes: master switches of inflammation. Cell Death Differ 2007, 14: 10–22.

[30] Martinon F. Detection of immune danger signals by NALP3. J Leukoc Biol 2008, 83: 507–511.

[31] Mayor A, Martinon F, De Smedt T, Petrilli V, Tschopp J. A crucial function of SGT1 and HSP90 in inflammasome activity links mammalian and plant innate immune responses. Nat Immunol 2007, 8: 497–503.

[32] Hu Y, Mao K, Zeng Y, Chen S, Tao Z, Yang C*, et al.* Tripartite-motif protein 30 negatively regulates NLRP3 inflammasome activation by modulating reactive oxygen species production. J Immunol 2010, 185: 7699–7705.

[33] Hornung V, Bauernfeind F, Halle A, Samstad EO, Kono H, Rock KL*, et al.* Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. Nat Immunol 2008, 9: 847–856.

[34] Bruchard M, Mignot G, Derangere V, Chalmin F, Chevriaux A, Vegran F*, et al.* Chemotherapy-triggered cathepsin B release in myeloid-derived suppressor cells activates the Nlrp3 inflammasome and promotes tumor growth. Nat Med 2013, 19: 57–64.

[35] Allen IC, Scull MA, Moore CB, Holl EK, McElvania-TeKippe E, Taxman DJ*, et al.* The NLRP3 inflammasome mediates in vivo innate immunity to influenza A virus through recognition of viral RNA. Immunity 2009, 30: 556–565.

[36] Owen DM, Gale M Jr. Fighting the flu with inflammasome signaling. Immunity 2009, 30: 476–478.

[37] Gross O, Poeck H, Bscheider M, Dostert C, Hannesschlager N, Endres S*, et al.* Syk kinase signalling couples to the Nlrp3 inflammasome for anti-fungal host defence. Nature 2009, 459: 433–436.

[38] Barlan AU, Griffin TM, McGuire KA, Wiethoff CM. Adenovirus membrane penetration activates the NLRP3 inflammasome. J Virol 2011, 85: 146–155.

[39] Pontillo A, Silva LT, Oshiro TM, Finazzo C, Crovella S, Duarte AJ. HIV-1 induces NALP3-inflammasome expression and interleukin-1beta secretion in dendritic cells from healthy individuals but not from HIV-positive patients. AIDS 2012, 26: 11–18.

[40] Munoz-Planillo R, Franchi L, Miller LS, Nunez G. A critical role for hemolysins and bacterial lipoproteins in Staphylococcus aureus-induced activation of the Nlrp3 inflammasome. J Immunol 2009, 183: 3942–3948.

[41] Joly S, Ma N, Sadler JJ, Soll DR, Cassel SL, Sutterwala FS. Cutting edge: Candida albicans hyphae formation triggers activation of the Nlrp3 inflammasome. J Immunol 2009, 183: 3578–3581.

[42] Yu M, Levine SJ. Toll-like receptor, RIG-I-like receptors and the NLRP3 inflammasome: key modulators of innate immune responses to double-stranded RNA viruses. Cytokine Growth Factor Rev 2011, 22: 63–72.

[43] Franchi L, Eigenbrod T, Nunez G. Cutting edge: TNF-alpha mediates sensitization to ATP and silica via the NLRP3 inflammasome in the absence of microbial stimulation. J Immunol 2009, 183: 792–796.

[44] Aimanianda V, Haensler J, Lacroix-Desmazes S, Kaveri SV, Bayry J. Novel cellular and molecular mechanisms of induc-

tion of immune responses by aluminum adjuvants. Trends Pharmacol Sci 2009, 30: 287–295.

[45] Dostert C, Petrilli V. Asbestos triggers inflammation by activating the Nalp3 inflammasome. Med Sci (Paris) 2008, 24: 916–918.

[46] Harris J, Sharp FA, Lavelle EC. The role of inflammasomes in the immunostimulatory effects of particulate vaccine adjuvants. Eur J Immunol 2010, 40: 634–638.

[47] Li H, Ambade A, Re F. Cutting edge: Necrosis activates the NLRP3 inflammasome. J Immunol 2009, 183: 1528–1532.

[48] Mariathasan S, Weiss DS, Newton K, McBride J, O'Rourke K, Roose-Girma M*, et al.* Cryopyrin activates the inflammasome in response to toxins and ATP. Nature 2006, 440: 228–232.

[49] Liu-Bryan R. Intracellular innate immunity in gouty arthritis: role of NALP3 inflammasome. Immunol Cell Biol 2010, 88: 20–23.

[50] Yamasaki K, Muto J, Taylor KR, Cogen AL, Audish D, Bertin J*, et al.* NLRP3/cryopyrin is necessary for interleukin-1beta (IL-1beta) release in response to hyaluronan, an endogenous trigger of inflammation in response to injury. J Biol Chem 2009, 284: 12762–12771.

[51] Petrilli V, Papin S, Dostert C, Mayor A, Martinon F, Tschopp J. Activation of the NALP3 inflammasome is triggered by low intracellular potassium concentration. Cell Death Differ 2007, 14: 1583–1589.

[52] Zhou R, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in NLRP3 inflammasome activation. Nature 2011, 469: 221–225.

[53] Shimada K, Crother TR, Karlin J, Dagvadorj J, Chiba N, Chen S*, et al.* Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. Immunity 2012, 36: 401–414.

[54] Pelegrin P, Surprenant A. Pannexin-1 couples to maitotoxin- and nigericin-induced interleukin-1beta release through a dye uptake-independent pathway. J Biol Chem 2007, 282: 2386–2394.

[55] de Rivero Vaccari JP, Bastien D, Yurcisin G, Pineau I, Dietrich WD, De Koninck Y*, et al.* P2X4 receptors influence inflammasome activation after spinal cord injury. J Neurosci 2012, 32: 3058–3066.

[56] Marina-Garcia N, Franchi L, Kim YG, Miller D, McDonald C, Boons GJ*, et al.* Pannexin-1-mediated intracellular delivery of muramyl dipeptide induces caspase-1 activation via cryopyrin/NLRP3 independently of Nod2. J Immunol 2008, 180: 4050–4057.

[57] Lemasters JJ, Theruvath TP, Zhong Z, Nieminen AL. Mitochondrial calcium and the permeability transition in cell death. Biochim Biophys Acta 2009, 1787: 1395–1401.

[58] Murakami T, Ockinger J, Yu J, Byles V, McColl A, Hofer AM*, et al.* Critical role for calcium mobilization in activation of the NLRP3 inflammasome. Proc Natl Acad Sci U S A 2012, 109: 11282–11287.

[59] Lee GS, Subramanian N, Kim AI, Aksentijevich I, Goldbach-Mansky R, Sacks DB*, et al.* The calcium-sensing receptor regulates the NLRP3 inflammasome through Ca2+ and cAMP. Nature 2012, 492: 123–127.

[60] Cassel SL, Eisenbarth SC, Iyer SS, Sadler JJ, Colegio OR, Tephly LA*, et al.* The Nalp3 inflammasome is essential for the development of silicosis. Proc Natl Acad Sci U S A 2008, 105: 9035–9040.

[61] Tschopp J, Schroder K. NLRP3 inflammasome activation: The convergence of multiple signalling pathways on ROS production? Nat Rev Immunol 2010, 10: 210–215.

[62] Zhou R, Tardivel A, Thorens B, Choi I, Tschopp J. Thioredoxin-interacting protein links oxidative stress to inflammasome activation. Nat Immunol 2010, 11: 136–140.

[63] Schroder K, Zhou R, Tschopp J. The NLRP3 inflammasome: a sensor for metabolic danger? Science 2010, 327: 296–300.

[64] Bryan NB, Dorfleutner A, Kramer SJ, Yun C, Rojanasakul Y, Stehlik C. Differential splicing of the apoptosis-associated speck like protein containing a caspase recruitment domain (ASC) regulates inflammasomes. J Inflamm (Lond) 2010, 7: 23.

[65] Stehlik C, Dorfleutner A. COPs and POPs: modulators of inflammasome activity. J Immunol 2007, 179: 7993–7998.

[66] Young JL, Sukhova GK, Foster D, Kisiel W, Libby P, Schonbeck U. The serpin proteinase inhibitor 9 is an endogenous inhibitor of interleukin 1beta-converting enzyme (caspase-1) activity in human vascular smooth muscle cells. J Exp Med 2000, 191: 1535–1544.

[67] Saitoh T, Fujita N, Jang MH, Uematsu S, Yang BG, Satoh T*, et al.* Loss of the autophagy protein Atg16L1 enhances endotoxin-induced IL-1beta production. Nature 2008, 456: 264–268.

[68] Nakahira K, Haspel JA, Rathinam VA, Lee SJ, Dolinay T, Lam HC*, et al.* Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. Nat Immunol 2011, 12: 222–230.

[69] Guarda G, Braun M, Staehli F, Tardivel A, Mattmann C, Forster I*, et al.* Type I interferon inhibits interleukin-1 production and inflammasome activation. Immunity 2011, 34: 213–223.

[70] Guarda G, Dostert C, Staehli F, Cabalzar K, Castillo R, Tardivel A*, et al.* T cells dampen innate immune responses through inhibition of NLRP1 and NLRP3 inflammasomes. Nature 2009, 460: 269–273.

[71] Hanamsagar R, Torres V, Kielian T. Inflammasome activation and IL-1beta/IL-18 processing are influenced by distinct pathways in microglia. J Neurochem 2011, 119: 736–748.

[72] Lin LF, Liao MJ, Xue XY, Zhang W, Yan L, Cai L*, et al.* Com-

bination of Abeta clearance and neurotrophic factors as a potential treatment for Alzheimer's disease. Neurosci Bull 2013, 29: 111–120.

[73] Marella M, Chabry J. Neurons and astrocytes respond to prion infection by inducing microglia recruitment. J Neurosci 2004, 24: 620–627.

[74] Rock RB, Gekker G, Hu S, Sheng WS, Cheeran M, Lokensgard JR*, et al.* Role of microglia in central nervous system infections. Clin Microbiol Rev 2004, 17: 942-964.

[75] Tribouillard-Tanvier D, Striebel JF, Peterson KE, Chesebro B. Analysis of protein levels of 24 cytokines in scrapie agent-infected brain and glial cell cultures from mice differing in prion protein expression levels. J Virol 2009, 83: 11244–11253.

[76] Shi F, Yang L, Kouadir M, Yang Y, Wang J, Zhou X*, et al.* The NALP3 inflammasome is involved in neurotoxic prion peptide-induced microglial activation. J Neuroinflamm 2012, 9: 73.

[77] Inoue M, Williams KL, Gunn MD, Shinohara ML. NLRP3 inflammasome induces chemotactic immune cell migration to the CNS in experimental autoimmune encephalomyelitis. Proc Natl Acad Sci U S A 2012, 109: 10480–10485.

[78] Goldbach-Mansky R, Dailey NJ, Canna SW, Gelabert A, Jones J, Rubin BI*, et al.* Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition. N Engl J Med 2006, 355: 581–592.

[79] Hoffman HM, Throne ML, Amar NJ, Sebai M, Kivitz AJ, Kavanaugh A*, et al.* Efficacy and safety of rilonacept (interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies. Arthritis Rheum 2008, 58: 2443–2452.

[80] Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, Leslie KS, Hachulla E, Quartier P*, et al.* Use of canakinumab in the cryopyrin-associated periodic syndrome. N Engl J Med 2009, 360: 2416–2425.

[81] Lamkanfi M, Mueller JL, Vitari AC, Misaghi S, Fedorova A, Deshayes K*, et al.* Glyburide inhibits the Cryopyrin/Nalp3 inflammasome. J Cell Biol 2009, 187: 61–70.