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MINI-SYMPOSIUM: ROLE OF THE INFLAMMASOME IN BRAIN PATHOGENESIS: A POTENTIAL THERAPEUTIC TARGET?

What do we know about the inflammasome in humans?

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Abstract

The inflammasome complex is part of the innate immune system, which serves to protect the host against harm from pathogens and damaged cells. It is a term first proposed by Tschopp's group in 2002, with numerous original research articles and reviews published on the topic since. There have been many types of inflammasome identified, but all result in the common pathway of activation of caspases and interleukin 1β along with possible cell death called pyroptosis. Despite a growing body of research investigating the structure and function of the inflammasome in animal models, there is still limited evidence identifying inflammasome components in human physiology and disease. In this review, we explore the molecular structure and mechanism of activation of the inflammasome with a particular focus on inflammasome complexes expressed in humans. Inflammasome components have been identified in several human peripheral and brain tissues using both *in vivo* and *ex vivo* work, and the inflammasome complex has been shown to be associated with several genetic and acquired inflammatory and neoplastic disorders. We discuss the strengths and weaknesses of the information available on the inflammasome with an emphasis on the importance of prioritizing work on human tissue. There is a huge demand for more effective treatments for a number of inflammatory and neurodegenerative diseases. Modulation of the inflammasome has been proposed as a novel treatment for several of these diseases and there are currently clinical trials ongoing to test this theory.

INTRODUCTION

Inflammation is a protective immune response against pathogens and damaged host cells. The innate immune system must react rapidly and appropriately to harmful signals in order to eliminate threats whilst also preserving tissue function. The key step in this early inflammatory cascade is activation of the cytokine interleukin (IL)-1β. IL1β is an endogenous pyrogen, produced as a precursor protein (pro-IL1β) and proteolytically processed to its active form by cysteine proteases, such as caspase 1. In 2002, Tschopp's group proposed for the first time that caspase 1 activates pro-IL1β in a molecular complex termed the "inflammasome" (51).

THE INFLAMMASOME COMPLEX

The innate immune system senses pathogen-associated molecular patterns (PAMPs), derived from infecting pathogens, and damage-associated molecular patterns (DAMPs), derived from damaged host cells and extracellular matrix, via sensor receptors called pattern recognition receptors (PRRs) (68). After sensing danger from PAMPs/DAMPs, specific PRRs will oligomerize and associate with an adaptor protein and a specific caspase, triggering caspase activation (68). Activation of the caspase then initiates the processing and maturation of proinflammatory cytokines (IL1β and IL18) and/or inflammatory programmed cell death called pyroptosis. Therefore, the inflammasome is defined as an intracellular multimeric protein complex that contains (1) a sensor receptor (PRR), (2) an adaptor protein and (3) an effector enzyme (caspase), and catalyses a cellular reaction to protect against an immediate danger via cytokine secretion and cell death (68) (Figure 1). A variety of different harmful signals can activate a range of specific inflammasomes. Furthermore, specific inflammasomes can be divided into two groups based on the type of caspase involved: (1) the classical, canonical inflammasome that triggers activation of caspase 1 directly, and (2) and the non-canonical inflammasome, which uses other caspases to convey inflammation (Figure 1).

In this review, we will describe the concept embedded in the term "inflammasome." We will focus on evaluating current knowledge of this complex in humans, including molecular structure and associated genetics and disease processes.

MOLECULAR COMPONENTS OF THE INFLAMMASOME COMPLEXES

As stated above, the inflammasome encompasses a range of different molecular components. These will now be described in turn,

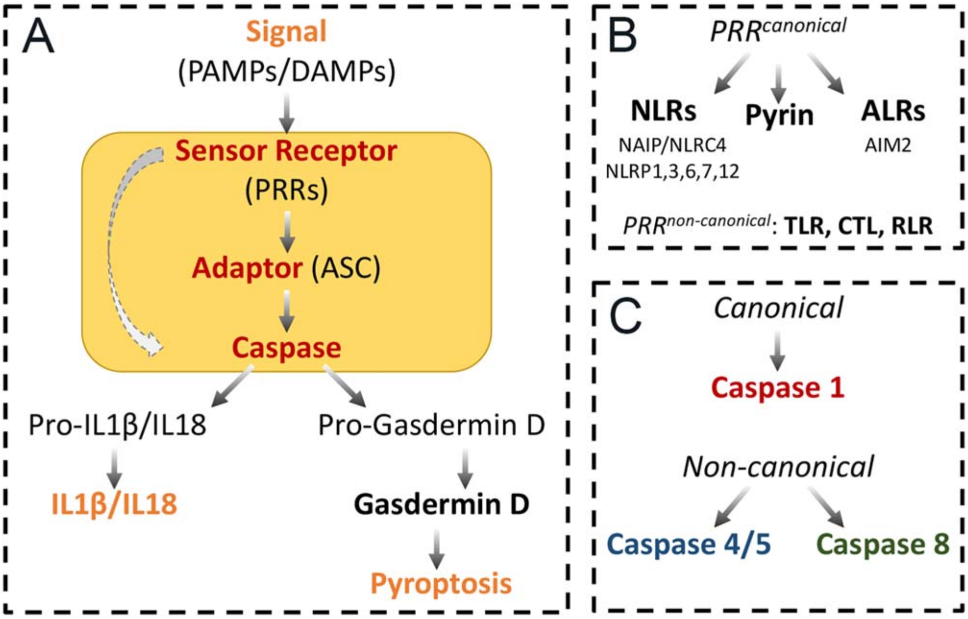

Figure 1. Schematic illustration of the inflammasome complex. (A) The different steps involved in inflammasome formation. Three main components of the inflammasome (sensor, adaptor and caspase) are shown in the yellow rectangle. Some PRRs, such as NLRP1, can bind caspase directly (large, curvy arrow), without need of the adaptor. (B) The members of PRR superfamily as part of the inflammasome complex: directly (canonical) or indirectly (non-canonical). (C) The inflammasome pathways: canonical directly initiates caspase 1 activation, and non-canonical uses other caspases to facilitate inflammation.

with a specific focus on those found in humans. As the regulatory elements and activity of many genes of the immune system vary between mice and humans (43), it should come as no surprise that there are differences in the structural and biochemical elements of inflammasome complexes between the two species (Table 1).

PRR superfamily

Several families of PRRs exist and they can be divided into two groups, based on their cellular localization. Firstly, the transmembrane PRRs include toll-like receptors (TLRs) and C-type lectin (CTL) families. Secondly, the cytoplasmic PRRs include the nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs), retinoic acid inducible gene-I (RIG1)-like receptors (RLRs) and absent-in-melanoma (AIM)-like receptors (ALRs) (35). Recent studies have revealed that all PRRs may play a role in either the assembly or activation of inflammasome complexes (47).

NLR family

To date, 22 NLRs have been identified in humans (12, 35). The common structure of NLRs consists of a variable N-terminal effector domain (which exerts its function by interacting with other proteins), a central NACHT domain (which has dNTPase activity and mediates self-oligomerization) and a C-terminal LRR region (which plays a role in ligand binding or activator sensing). Four different N-terminal effector domains are used to classify NLRs into four respective subfamilies: (1) the **a**cidic activation domain (NLR**A** subfamily: MHC class II transcription activator—CIITA); (2) the **b**aculoviral inhibitory repeat(BIR)-like domain (NLR**B** subfamily: neuronal apoptosis inhibitory protein—NAIP); (3) the **c**aspase activation and recruitment (CARD) domain (NLR**C** subfamily: NLRC1 or NOD1, NLRC2 or NOD2, NLRC3-5, NLRX1) and (4) the **p**yrin domain (PYD) (NLR**P**: NLRP1-14).

NAIP (38, 81)/NLRC4 (48), NLRP1 (51), NLRP3 (29, 49, 53), NLRP6 (32), NLRP7 (33) and NLRP12 (75) have been identified as sensors involved in the formation of different inflammasomes (Figure 1). Most NLRs recognize various ligands including microbial pathogens (eg, PAMPs derived from bacteria, viruses, fungi and protozoa), self-derived DAMPs from host cells (eg, ATP, cholesterol crystals, monosodium urate/calcium pyrophosphate dehydrate crystals, and amyloid-β) and environmental sources (eg, alum, asbestos, silica) (35).

Pyrin

Pyrin is a product of the *MEFV* gene. Human pyrin features an N-terminal PYD, two B-boxes, CCD and a C-terminal B30.2 domain (Table 1). B30.2 is specific to humans and a target of many mutations, including one that causes Familial Mediterranean fever, which is discussed later. Assembly of the pyrin inflammasome can be triggered by bacteria (eg, *Burkholderia Cenocepacia*) or bacterial toxins (eg, *Clostridium difficile* toxin B and *Clostridium botulinum* C3 toxin) (5, 8). Pyrin can also act as a regulator of inflammasome signaling by targeting NLRP1, NLRP3 and caspase 1 for autophagic degradation (36).

ALR family

ALRs can also be referred to as pyrin and HIN domain-containing (PYHIN) receptors. The common structure of ALRs consists of an N-terminal effector domain pyrin (PYD), which initiates

Table 1. The molecular and biochemical characteristics of pattern-recognition receptors, adaptor protein ASC and caspases in mice and humans.

Name	Mouse (genes)	Human (genes)	Human (protein)	Comments
NLRA	Ciita	CIITA	**CARD**-TA-NACHT-LRR	
NLRB	Naip:1-7	NAIP	BIR(3x)-NACHT-LRR	Serves as a receptor for NLRC4 inflammasome
NLRC	Nlrc1 (Nod1), Nlrc2 (NOD2), Nlrc3, Nlrc4, Nlrc5, Nlrx1	NLRC1 (NOD1), NLRC2 (NOD2), NLRC3, NLRC4, NLRC5, NLRX1	NRLC1, NRLC4: **CARD**-NACHT-LRR NRLC2: **CARD**(2x)-NACHT-LRR NLRC3, NLRC5: X-NACHT-LRR	NLRC4: uses NAIP as a receptor and can bind caspase directly (pyroptosis) or via ASC (cytokine release)
NLRP	Nlrp1 (a,b,c), Nlrp2, Nlrp3/Cias1, Nlrp4 (a,b,c,d,e,f,g), Nlrp5, Nlrp6, Nlrp9 (a,b,c), Nlrp10, Nlrp12, Nlrp14	NLRP1, NLRP2, NLRP3/CIAS1, NLRP4, NLRP5, NLRP6, NLRP7, NLRP8, NLRP9, NLRP10, NLRP11, NLRP12, NLRP13, NLRP14	NLRP1: **PYD**-NACHT-LRR-FIIND-**CARD** NRP2-9, 11-14: **PYD**-NACHT-LRR NLRP10: **PYD**-NACHT	*mNlrp1: lacks PYD* *mNlrp7,8,11,13: absent* NLRP1: can bind caspase directly via CARD
PYRIN	Mefv	MEFV	**PYD**-Bbox-CCD-B30.2	*mPyrin: lacks B30.2*
ALRs	Ifi202, Ifi203, Ifi203', Ifi204, Ifi205, Ifi206, Ifi207, Ifi208, Ifi209, Aim2/Ifi210, Ifi211, Mndal/Ifi212, Ifi213, Ifi214.	IFI16a, IFIXa1, MNDA, AIM2	IFI16a: **PYD**-HINA-HINB IFIXa1: **PYD**-HINA MNDA: **PYD**-HINA AIM2: **PYD**-HIN200	*mAim2/Ifi210: orthologue of hAIM2* *mIfi204: orthologue of hIFI16*
TLRs	Tlr1-9,11-13	TLR1-10	TLR1,2,4,6,10: LRR(3x)-TM-TIR TLR3,5,7,8,9: LRR-TM-TIR	
CTLs	Clec7A	CLEC7A	CTLD-TM-ITAM	
RLRs	Rig-i/Ddx58, Mda5/Ifih1, Lgp2/Dhx58	RIG-I/DDX58, MDA5/IFIH1, LGP2/DHX58	**CARD**(2x)-DEAD helicase-CTD	LGP2 lacks CARD
ASC	Pycard	PYCARD	**PYD-CARD**	
Caspases	Casp1, Casp2, Casp3, Casp6, Casp7, Casp8, Casp9, Casp11, Casp12, Casp14	CASP1, CASP2, CASP3, CASP4, CASP5, CASP6, CASP7, CASP8, CASP9, CASP10, CASP12, CASP14	C1,4,5,9,12,14: **CARD**-PD C2,8,10: DED-PD C3,6,7: PD	*mC11: orthologue of hC4 and hC5*hC12: mainly inactive Inflammatory: C1, C4, C5, mC11, C12 Apoptotic: C2i, C3a, C6a, C7a, C9i, C10i Both: C8i, Neither: C14

Notes: known inflammasome components are underlined; comments related to the mouse are in italic letters. Information has been collected from: (12) (NLRs), (5) (Pyrin), (10) (ALRs), (28) (TLRs), (4) (CTLs), (45) (RLRs), (52) (ASC), (47) (caspases). a: activator; h: human; I: initiator; m: mouse.

inflammasome formation, and a C-terminal HIN domain, which plays a role in double-stranded (ds)DNA binding (Table 1) (10). There are four known ALRs in humans: IFI16, IFIX, MNDA and AIM2. AIM2 is a cytoplasmic sensor that recognizes dsDNA of microbial (such as intracellular bacteria *Francisella tularensis* and *Listeria monocytogenes*) or host origin (self-DNA). AIM2 can assemble an inflammasome (6, 14, 22, 64) (Figure 1), and dsDNA was proposed to provide an oligomerization template (24). Regarding IFI16, one study has shown that it may activate an inflammasome by promoting caspase 1 activation (73).

TLR, CTL, RLR families

There is increasing evidence to suggest that other PRRs may also play a role in the activation (TLRs and CTLs) or assembly (RLRs) of inflammasomes, and that these may also promote caspase activation and an inflammatory response (46, 47) (Figure 1).

ASC

Apoptosis-associated speck-like protein containing a CARD (ASC), also known as a PYCARD, is an adaptor protein common to several inflammasomes. It is composed of two protein-protein interaction domains: N-terminal PYD and C-terminal CARD (Table 1). The PYD and CARD domains are members of the six-helix bundle death domain-fold superfamily that facilitates assembly of multimolecular complexes in inflammatory and apoptotic signaling pathways via the activation of caspases (52).

Caspase family

Caspases are members of a cysteine-aspartic acid protease family. There are 12 caspases identified in humans and traditionally these are divided into two groups: inflammatory and apoptotic (47). Several inflammatory caspases (caspase 1, caspase 4 and caspase 5) participate in assembly and/or activation of the inflammasome. The apoptotic caspases initiate (caspase 2, caspase 8, caspase 9 and caspase 10) and execute (caspase 3, caspase 6 and caspase 7) an immunologically silent form of programmed cell death known as apoptosis. The common structure of caspase consists of a C-terminal protease domain (PD). In addition, some caspases may possess a prodomain (CARD or DED; Table 1). Recent findings, neatly described in a review by Man and Kanneganti (47), have revealed a complex and synergistic role for caspases in maintaining homeostasis in the innate immune system. While caspase 1 is a key inflammatory caspase that has the ability to activate cytokines IL1β and IL18, or pyroptotic mediator gasdermin D, other caspases can also facilitate cytokine release and pyroptosis. For example, human caspase 4 and caspase 5, which are orthologues of mouse caspase 11, are activated following recognition of Gram-negative bacteria and may directly cleave gasdermin D to induce pyroptosis, and ultimately activate the NLRP3 inflammasome (2, 69). Caspase 8 can mediate both inflammation and apoptosis. Upon ligand recognition by TLRs, caspase 8 may initiate NF-κB signaling and the transcription of genes encoding pro-IL1β and pro-IL18 (9, 70). At the same time, caspase 8 can be recruited by the NAIP/NLRC4, NLRP3 and AIM2 inflammasomes and indirectly mediate maturation of IL1β, IL18 or gasdermin D (47). Finally, caspase 8 may be involved in the formation of a non-canonical caspase 8 inflammasome that directly mediates processing of pro-IL1β independently of caspase 1. Indeed, fungi (eg, *Candida* spp) and mycobacteria (eg, *Mycobacterium leprae*) can bind to the transmembrane receptor Dectin 1, a PRR from the CTL family, and initiate assembly of a caspase 8 inflammasome which is composed of CARD9, BCL10, MALT1, ASC and caspase 8 (17).

ACTIVATION PATHWAYS OF THE INFLAMMASOME

Canonical inflammasome pathways

When NLRs, ALRs or pyrin detect PAMPs and DAMPs, they recruit ASC via a homotypic pyrin–pyrin domain interaction. Subsequently, pro-caspase 1 binds ASC through CARD–CARD domains, which completes the formation and activation of the canonical inflammasome, and drives IL1β/IL18 secretion and pyroptosis (Figure 2). In addition, caspase 8 may play a role in caspase 1-dependent processing of IL1β via direct binding to ASC in the NAIP/NLRC4, NLRP3 or AIM2 canonical inflammasome (47).

Non-canonical inflammasome pathways

To date, only two non-canonical inflammasomes have been described in the literature (47). Firstly, LPS from Gram-negative bacteria, directly or via TLR4, activates human caspase 4 and caspase 5, which in turn cleaves gasdermin D to mediate pyroptosis and activate the NLRP3 inflammasome resulting in caspase 1-dependent processing of IL1β (2, 69) (Figure 2). Secondly, non-canonical caspase 8 inflammasome can be promoted by certain microbes via CTL receptors, mediating maturation of IL1β in a caspase 1-independent manner (17) (Figure 2).

To summarize, all components involved in the different inflammasomes are present on the gene and/or protein levels in humans (Tables 1 and 2). However, there are structural and molecular differences in some inflammasome components between humans and mice (Table 1). The majority of inflammasome components play a role in humans, especially in the field of host defence and tumor progression, as revealed by looking at distinct genetic disorders (Table 3). A comprehensive understanding of how and where inflammasomes are formed in humans remains elusive. However, we may be able to gain clues by reviewing specific human disorders caused by dysregulation of inflammasome activation.

INFLAMMASOMOPATHIES

An inflammasomopathy is defined by the presence of autoinflammatory disease caused by disruption of inflammasome activity. The term “autoinflammatory” has become widely used in the last decade to describe a set of diseases that satisfy the definition above and are distinct from autoimmune conditions (30). Familial inflammasomopathies are rare genetic disorders of childhood onset that typically manifest with dysregulated IL1β release, leading to either enhanced or diminished inflammation (Table 3). Gain or loss-of-function mutations in several inflammasome-related genes have been linked with enhanced inflammation. For example, autosomal dominant, gain-of-function mutations in the *NLRP3/CIAS1* gene (21) encoding cryopyrin, have been shown to be responsible for three autoinflammatory disorders (30): familial cold-induced auto-

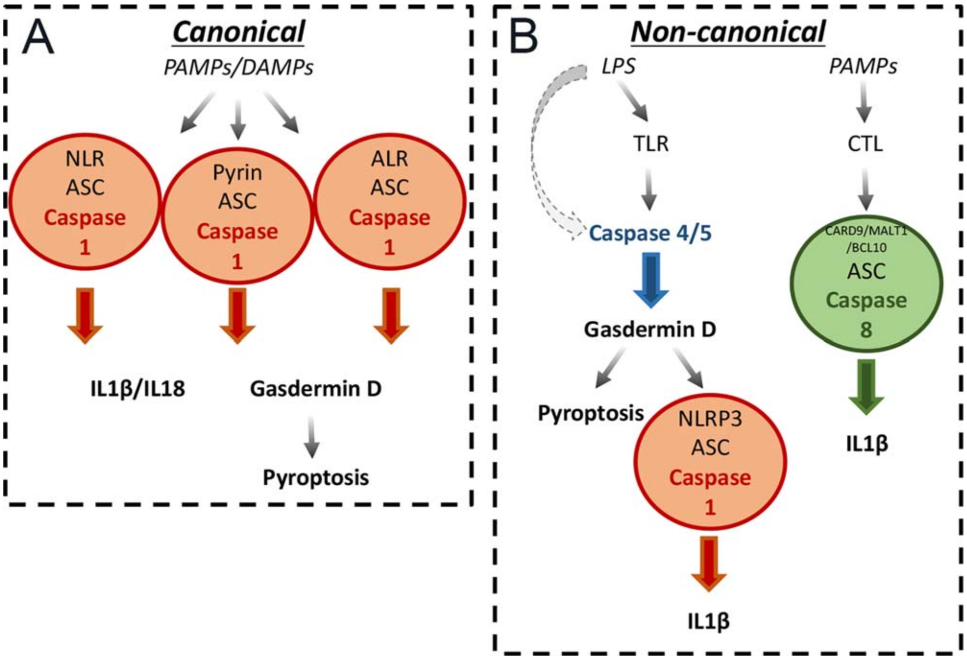

Figure 2. Schematic representation of the two pathways and components involved in inflammasome activation. (A) The canonical pathway. Upon inflammasome formation, caspase 1 (red) directly activates cytokines IL1β, IL18 and pyroptotic gasdermin D. (B) The non-canonical pathways. (i) LPS can activate caspase 4/5 (blue) directly (large, curvy arrow) or via the TLR4 receptor, leading to gasdermin D maturation and pyroptosis. Cleaved Gasdermin D may then activate the NLRP3 inflammasome. (ii) Various pathogen signals (PAMPs), via CTL receptor, may initiate formation of the caspase 8 inflammasome (green). The product of both non-canonical inflammasomes is IL1β.

Table 2. Inflammasome genes, proteins and brain locations in humans (from http://www.proteinatlas.org).

	Gene	Protein—tissue	Brain location	Cell location
NAIP	Many organs	Many organs	Neocortex	Neurons
NLRC4	Many organs	Many organs	Neocortex	Endothelial cells, neurons
NLRP1	Many organs	Many organs	Neocortex	Endothelial cells, neurons, neuropil
			Hippocampus	Neurons
NLRP3	Many organs	Many organs	Hippocampus	Neurons
NLRP6	Gastrointestinal (GI)	Brain and GI	Cortex and hippocampus	Neurons
NLRP7	Testis	No detection	No detection	No detection
NLRP12	Immune system	Many organs	Cortex and hippocampus	Neurons
Pyrin	Immune system	No detection	No detection	No detection
AIM2	Bone marrow	Many organs	Cortex	Endothelial cells, neurons, neuropil, glia
			Hippocampus	Neurons, glia
ASC	Many organs	Many organs	Hippocampus	Glia
Caspase 1	Many organs	Many organs	Cortex	Endothelial cells, glia, neurons
			Hippocampus	Neurons, glia
Caspase 4	Many organs	Many organs	Cortex	Endothelial cells, neurons, neuropil
			Hippocampus	Neurons
Caspase 5	A few organs	Many organs	Cortex	Neurons, glia
			Hippocampus	Neurons
Caspase 8	Many organs	Many organs	Cortex	Endothelial cells, neurons
			Hippocampus	Neurons
Pro-IL1β	Many organs	No detection	No detection	No detection
Pro-IL18	Many organs	Many organs	No detection	No detection
Gasdermin D	Many organs	Many organs	Cortex	Neuropil

Table 3. Familial disorders linked to inflammasome components.

Gene	Protein	Function	Phenotype	Mutation/inheritance	Clinical relevance
NAIP	NAIP	Inhibits apoptosis; initiates inflammation	Spinal muscular atrophy (SMA)	Gene deletion	Pathogenic
NLRC4	NLRC4	Initiates inflammation	Autoinflammation with infantile enterocolitis (AIFEC)	Val341Ala, Thr337Ser **AD–GoF–EI**	Pathogenic
			Familial cold autoinflammatory syndrome (FCAS) 4	His443Pro **AD–GoF–EI**	Pathogenic
NLRP1	NLRP1	Initiates inflammation	Vitiligo-associated multiple auto-immune disease susceptibility 1	Leu155His	Risk factor
			Corneal intraepithelial dyskeratosis and ectodermal dysplasia	Met77Thr **AD**	Pathogenic
NLRP3/CIAS1	CRYOPYRIN	Initiates inflammation	FCAS 1	Ala439Val, Val198Met, Glu627Gly, Leu353Pro **AD–GoF–EI**	Pathogenic
			Muckle-Wells syndrome (MWS)	Ala352Val, Gly569Arg **AD–GoF–EI**	Pathogenic
			MWS with FCAS	Arg260Trp **AD–GoF–EI**	Pathogenic
			Chronic infantile neurological cutaneous articular (CINCA) syndrome	Phe573Ser, Phe309Ser **AD–GoF–EI**	Pathogenic
			CINCA syndromewith MWS	Asp303Asn **AD–GoF–EI**	Pathogenic
NLR6	NLRP6	Initiates inflammation		None	
NLRP7	NLRP7	Silencing of maternal genes; Cell proliferation; Negative regulator of IL1β	Hydatidiform mole, recurrent, 1	Ivs3ds, G-A, +1, Ivs7ds, G-A, +1, Arg693Trp, Arg693Pro, Asn913Ser, Arg432Ter, 1-Bp Ins, 337g, Arg693Gln, Leu398Arg, Pro651Ser, 14-Bp Dup, Nt939, 1-Bp Del, 2030t **AR–LoF–DI**	Pathogenic
NLRP12	MONARCH 1	Initiates inflammation	FCAS 2	Arg284ter, Ivs3ds, 1-Bp Ins, +3t **AD–GoF–EI**	Pathogenic
MEFV	PYRIN or marenostirin	Initiates inflammation	Familial Mediterranean fever	Mutations within the B30.2/SPRY domain **AR or AD-GoF-EI**	Pathogenic
			Autoinflammation with neutrophilic dermatosis	S242R **AD-GoF-EI**	Pathogenic
AIM2, IFI16 (ALRs)	AIM2, IFI16	Initiates inflammation		None	
RIGI/DDX58 (RLRs)	RIG I	Initiates inflammation	Singleton-Merten syndrome (SMS) 2	Glu373Ala, Cys268Phe **AD–GoF–EI**	Pathogenic
TLR4 (TLRs)	TLR4	Initiates inflammation		None	
DECTIN 1/CLEC7A (CTLs)	DECTIN 1	Initiates inflammation	Candidiasis, familial, 4 (CANDF4)	Tyr238Ter **AR–LoF–DI**	Pathogenic
PYCARD	PYCARD (ASC)	Mediates apoptosis and inflammation		None	

Table 3. *Continued.*

Gene	Protein	Function	Phenotype	Mutation/inheritance	Clinical relevance
CASP 1, 4, 5	CASPASE 1,4,5	Mediate apoptosis and inflammation		None	
CASP8	CASPASE 8	Mediates apoptosis and inflammation	Caspase-8 deficiency state (CEDS)	Arg248Trp **AR–LoF–DI**	Pathogenic
			Hepatocellular carcinoma	2-Bp Del, 1225tg	Pathogenic
			Breast cancer	Asp302His	Protective
			Lung Cancer	6-Bp Del, Nt-652	Protective
IL1B, IL18 and GASDERMIN D	IL1β, IL18, GASDERMIN D	Mediate inflammation and pyroptosis		None	

AD, autosomal dominant; AR, autosomal recessive; GoF, gain-of-function; LoF, loss-of-function; EI, enhanced inflammation; DI, diminished inflammation (immunodeficiency). Information has been gathered from OMIM (http://www.omim.org).

inflammatory syndrome 1 (FCAS 1), Muckle–Wells syndrome (MWS) and neonatal onset multisystem inflammatory disorder (NOMID). These three disorders are commonly known as cryopyrinopathies or cryopyrin-associated periodic syndromes (CAPS) and often cause periodic fever, rashes, arthralgia and cold sensitivity (12). The most severe phenotype of the three disorders is NOMID, also known in Europe as chronic infantile neurological, cutaneous and articular syndrome (CINCA), which typically presents with near-continuous fever and chronic aseptic meningitis that can result in hearing loss and mental retardation (30). In addition, autosomal dominant, gain-of-function mutations in the *NLRC4* gene, encoding NLRC4, have been associated with two diseases: autoinflammation with infantile enterocolitis [AIFEC (7, 65)] and familial cold-induced autoinflammatory syndrome 4 [FCAS 4 (37)]. Likewise, autosomal recessive gain-of function mutations in *MEFV*, the gene coding for pyrin (formerly known as marenostrin), can result in conditions called Familial Mediterranean fever [FMF (8, 55, 67)] and autoinflammation with neutrophilic dermatosis (54). Additionally, mutations in the *NRLP1* gene, encoding NLRP1, have been linked to susceptibility to develop a condition called vitiligo-associated multiple autoimmune disease 1 (25). Lastly, autosomal dominant gain-of-function mutations in *NLRP12*, encoding NLRP12, have been associated with familial cold-induced autoinflammatory syndrome 2 [FCAS 2 (23)].

Conversely, some mutations in genes coding for other inflammasome proteins may have the potential to cause immunodeficiency disorders. For instance, an autosomal recessive loss-of-function mutation in the *CASP8* gene leaves the caspase 8 protein enzymatically inactive and causes a disease termed Caspase 8 deficiency state (CEDS), which is also known as autoimmune lymphoproliferative syndrome IIB [ALPS IIB (9, 70)]. Also, a loss-of-function mutation in the *CLEC7A* gene, encoding the Dectin 1 receptor, is responsible for chronic mucocutaneous candidiasis [candidiasis familial 4, CANDF4 (15)]. Finally, recurrent hydatidiform mole has been linked to numerous autosomal recessive loss-of-function mutations in the *NRLP7* gene, encoding NLRP7, which plays role in imprinting of embryonic maternal genes as well as in negative regulation of IL1β signaling (57).

Therapeutic interventions have targeted blockade of IL1β in the treatment of familial inflammasomopathies. Specifically, antibody mediated inhibition of IL1β has been trialed in CAPS with two drugs now approved by the US Food and Drug Administration, following successful randomized controlled trials of Rilonacept (20) and Canakinumab (40). Other molecules currently in development are reportedly targeting several other inflammasome components, including NRLP3, IL18, caspase 1 and ASC (59).

HUMAN DISEASES ASSOCIATED WITH EXPRESSION OF THE INFLAMMASOME

The few years of research into the inflammasome have seemingly focused on establishing the presence and role of the complex in animal models of human disease. More recently, there has been a shift toward the application of these findings to human tissue and disease processes. Inflammasome proteins have now been identified on multiple peripheral and central cell types in humans and across a number of diseases (Table 2). However, the extent of literature available regarding the inflammasome based on human work is still

Table 4. Summary of research identifying inflammasome components in peripheral human cells or tissue. Includes information on techniques used for identification and a brief summary of research findings from each article.

Inflammasome components	Method	Location or cell type	Disease	Summary	Reference
NLRP3, IL1β	WB ELISA	Human macrophage cell line	*(In-vitro)*	Saturated fatty acids activate the NLRP3 inflammasome and stimulate secretion of IL1β.	50
NLRP3, AIM2	WB ELISA RT-PCR	Liver Kupffer primary cell culture	*(In-vitro)*	NLRP3 and AIM2 inflammasome present in primary cultured Kupffer cells but not hepatocytes.	79
NLRP3, caspase 1, IL1β	WB ELISA RT-PCR	Lung epithelial cell line	*(In-vitro)*	Silica induces NLRP3 inflammasome activation with increased caspase 1 and IL1β.	62
NLRP1, NLRP3, ASC, caspase 1, caspase 5, pro-IL1β, IL18	WB ELISA RT-PCR	Keratinocytes	*(In-vitro)*	NLRP1, NRLP3, ASC, caspase 1 and caspase 5 detected in primary keratinocytes.	77
NLRP1, NLRP3, caspase 1, caspase 5, caspase 8, IL1β, IL18	WB RT-PCR	Monocyte culture from peripheral blood mononuclear cells	*(In-vitro)*	Increase in NLRP1, NRLP3, caspase 1, caspase 5, caspase 8, IL1β and IL18 in monocytes cultured from peripheral blood mononuclear cells taken from patients with Alzheimer's disease, compared with healthy controls.	66
NLRP3, IL1β	WB ELISA RT-PCR	Fibroblast-like synoviocyte cell culture	Gout	Urate crystals increase IL1β via the NLRP3 inflammasome.	82
NLRP3, IL1β, ASC	RT-PCR	Adipose tissue	Type 2 Diabetes mellitus (DM)/Obesity	Exercise-mediated weight loss is associated with reduced NLRP3/IL1β but not with ASC.	74
NLRP3, ASC, caspase 1, IL1β, IL18	WB RT-PCR	Monocyte-derived macrophages	Type 2 Diabetes mellitus (DM)	Increased expression of NLRP3, ASC, caspase 1, IL1β and IL18 in monocyte-derived macrophages from patients with newly diagnosed Type 2 DM.	41
NLRP3, ASC, caspase 1, IL1β, IL18	RT-PCR IHC	Carotid artery vessel plaques	Atherosclerosis	ASC, caspase 1, IL1β, IL18 mRNA increased in atherosclerotic plaques compared with non-atherosclerotic vessels.	60
NLRP3. ASC, caspase 1, IL1β, IL18	IHC	Oropharyngeal squamous cells	Oropharyngeal squamous cell carcinoma	NLRP3, ASC, IL1β, IL18, caspase 1 strongly expressed in oropharyngeal squamous cell carcinoma but not in control tonsil tissue.	71
NLRP1, ASC, caspase 1	WB	Cerebrospinal fluid	Subarachnoid hemorrhage (SAH)	NLRP1, ASC, caspase 1 levels associated with more severe SAH and poorer clinical outcome.	78
NLRP3, caspase 1, IL1β, IL18	RT-PCR	Blood peripheral blood mononuclear cells	Multiple sclerosis (MS)	NLRP3, caspase 1, IL1β increased in MS compared with controls, but IL18 is not.	61
NLRP1, ASC, caspase 1	WB	Cerebrospinal fluid	Traumatic brain injury (TBI)	NLRP1, ASC and caspase 1 levels in CSF correlated with unfavorable outcome after TBI, including death and severity of disability.	1
Caspase 1, IL18	WB ELISA	Psoriatic skin lesions	Psoriasis	Psoriatic lesion biopsies show increased caspase 1 compared with controls; with cultured keratinocytes showing increased IL18 expression.	27
NLRP1, NLRP3	WB IHC	Tissue specimens from various locations	N/A	NLRP1 and NRLP3 abundantly expressed on myeloid cells and lymphocytes.	39
	WB	Aortic vessel wall			13

Table 4. *Continued.*

Inflammasome components	Method	Location or cell type	Disease	Summary	Reference
Caspase 1, ASC, AIM2, IL1β	RT-PCR		Abdominal aortic aneurysm	AIM2, ASC, pro-caspase 1 and pro- IL1β increased in aortic aneurysm vessel wall compared with healthy controls.	
NLRP3, caspase1, IL1β, IL18	IHC WB RT-PCR ELISA	Nasal epithelial cells	Chronic rhinosinusitis with nasal polyps	Increased NLRP3, caspase1, IL1β and IL18 in chronic rhinosinusitis compared with control tissue.	42

WB Western Blot, IHC Immunohistochemistry, RT-PCR real time Polymerase Chain Reaction, ELISA Enzyme-Linked Immunosorbent Assay.

very limited compared with the widening pool of published animal work. Inflammasome proteins identified to date in human cells or tissue, along with the associated disease when applicable, are summarized in Tables 4 and 5, along with the techniques used to identify the inflammasome component and a brief summary of the study findings.

In the periphery, inflammasome components have been shown to be expressed by a number of cell types, including innate immune cells (eg, macrophage, Kupffer cells), adaptive immune cells (eg, lymphocytes) and various tissues that function as the first line of defence against environmental pathogens (eg, lung epithelial cells, skin, nasal epithelial cells). This emphasizes the role the inflammasome may play in the innate immune response to environmental pathogens. In addition, several diseases associated with inflammation have been shown to be related to the expression of inflammasome components. Of note, several of these conditions, such as gout, diabetes mellitus and atherosclerosis, have been shown to be associated with the expression of NLRP3. This may be because the NLRP3 inflammasome has been the most studied type in humans, following the broad research base into this specific complex in experimental models. Also, the NRLP3 inflammasome has been shown to be particularly sensitive to activation by a variety of stimuli, including microbial and endogenous stimuli, and particulate matter such as urate crystals and beta-amyloid (16). These points may explain the broad expression of the NLRP3 inflammasome in conditions associated with inflammation.

Inflammasome proteins have been identified on a variety of cell types of the central nervous system, including microglia, astrocytes and neurons. However, much of this work appears to have been performed using *in vitro* cell models, which has limited direct applicability to human physiological and pathological conditions. In particular, the use of primary cell cultures and immortalized cell lines can result in the study of cellular models that markedly differ from those found within normal physiological and diseased human tissue (3). The extent of the literature identifying NLRP3 in the human central nervous system (CNS) appears to be much more limited compared with research in the human periphery.

When reviewing the specific inflammasome proteins identified in humans (Tables 4 and 5), it is possible to draw some notable conclusions. Firstly, *in vitro* studies have identified numerous inflammasome proteins across a number of different cell types. However, when considering only *in vivo* work, it appears that the components most frequently detected across a number of different cell types in the CNS and periphery are: NLRP3, caspase 1 and ASC. Thus, the NLRP3 inflammasome seems to be the most frequently studied complex in humans, as it is in animal models. Secondly, there does not appear to be an association between specific inflammasome proteins identified in human tissue and the location of their identification. For example, the inflammasome component ASC has been identified in Kupffer cells of the liver, vascular atherosclerotic plaques, skin cells and in the cerebrospinal fluid. No obvious pattern can be ascertained where certain inflammasome components are only identified in certain locations in the human body. Interestingly, this latter point suggests that many inflammasome proteins may be ubiquitous across central and peripheral areas of the human body. Lastly, there appears to be variability in the validation of findings in these studies. Many publications have shown the presence of all the components needed to form an inflammasome and used several techniques to confirm this, for

Table 5. Summary of research identifying inflammasome components in the human central nervous system. Includes information on techniques used for identification and a brief summary of research findings from each article.

Inflammasome components	Method	Location or cell type	Disease	Summary	Reference
NLRP1, AIM2	RT-PCR	Primary cultures of neurons, astrocytes, microglia	*(In vitro)*	Neurons, astrocytes and microglia express NLRP1 and AIM2, but not NLRP3.	31
NLRC4, NLRC5, NLRP1, NLRP3, NLRP5, NLRP9, NLRP10, NLRP12, NLRA, and NLRX, AIM2, ASC, caspase 1, IL1β, IL18	RT-PCR WB ELISA	Cerebral endothelial cell line	*(In vitro)*	Multiple inflammasome proteins expressed on a cerebral endothelial cell line.	58
NLRP2, Caspase 1, ASC	WB ICC	Astrocyte cell line	*(In vitro)*	NLRP2, caspase 1, ASC expressed on a stimulated human astrocyte cell line.	56
NLRP3, IL1	IHC RT-PCR WB	Glioblastoma cell line	*(In vitro)*	NLRP3 and IL1 expressed on a glioblastoma cell line.	72
Caspase 1	IHC WB	Brain	Alzheimer's disease	Increased caspase 1 expression in brain tissue lysates of Alzheimer's disease patients.	19
NRLP3, ASC	RT-PCR WB	Brain	Alzheimer's disease	Increased ASC expression, but not NRLP3, in Alzheimer's disease patients compared with controls.	44
NLRP1, NLRP3, ASC, caspase 1, IL1β, IL18	RT-PCR IHC	Brain	HIV	Increased caspase 1, IL1β and IL18 in HIV-positive patients compared with controls, largely in microglia. In addition, an *in vitro* microglial cell line showed expression of NLRP1, NLRP3, NLRC4, AIM2 and ASC at higher levels than on astrocytes and neurons.	76
NLRP3, caspase 1, IL1β	RT-PCR ELISA	Monocyte-derived dendritic cells	HIV	HIV patients showed increased NLRP3 expression at baseline. HIV-1 induces higher NLRP3, caspase 1, IL1β in controls but not in HIV patients.	63
NLRP3, ASC, caspase 1, IL1β	IHC	Cerebral blood vessel wall	Cerebral aneurysms	Increased NLRP3, ASC and caspase 1 expression in ruptured cerebral aneurysms compared with unruptured aneurysms, all colocalized with T cells and macrophages.	80
NLRP3, caspase 1, ASC, IL1β	WB ELISA Luminex	Brain	Bipolar affective disorder and schizophrenia	Mitochondrial NLRP3 and ASC higher in bipolar affective disorder compared with schizophrenia and controls. IL1β and caspase 1 increased in both bipolar affective disorder and schizophrenia.	34
IL18, ASC, NLRP3	RT-PCR WB	Spinal cord tissue	Sporadic amyotrophic lateral sclerosis (ALS)	Significant increase of IL18 and ASC in ALS. Non-significant increase of NLRP3.	26

WB, Western Blot; IHC, Immunohistochemistry; RT-PCR, real time Polymerase Chain Reaction; ELISA, Enzyme-Linked Immunosorbent Assay.

example using real-time polymerase chain reaction to confirm gene expression and Western blotting to confirm the presence of associated proteins. Some studies have also utilized immunohistochemical double staining to confirm the co-location of inflammasome proteins expressed in certain cell types (60, 80).

Overall, despite confirmation of the presence of inflammasome components in a variety of human cell types and tissues, there is still a lack of clear understanding regarding the significance of the different types of inflammasome in physiology and human disease. Direct imaging of an inflammasome complex may provide pointers to the exact location of the complex and its interactions with normal physiological processes. Electron microscopy has already allowed visualization of the NLRC4 inflammasome following reconstitution of the complex from an embryonic human cell line (18), but this has not yet been possible *in vivo*, perhaps due to the relative difficulty in applying this methodology to human tissue.

CONCLUSION

Research in the field of the inflammasome is expanding at a fast rate. Whilst much work has been performed in animal models, to date there is limited evidence of the role and function of the inflammasome in human tissue. Despite a proliferation of review articles compared with research articles in recent years, there is a need to focus efforts on examining the role of the inflammasome in human conditions. Animal work is important to develop our understanding of what the inflammasome is, but human work will allow us to grasp the importance of the role of these proteins in normal physiology and disease.

Intriguingly, non-steroidal anti-inflammatory drugs have been shown to inhibit the NLRP3 inflammasome in rodent models (11). Recent review articles have suggested that the inflammasome may be a therapeutic target for inflammatory diseases and Alzheimer's disease (as reviewed by White and colleagues in this mini-symposium). This is an exciting era to be involved in inflammasome research, with the potential development of drugs to target the inflammasome as a treatment for a multitude of severe and disabling diseases.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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