Cellular & Molecular Immunology (2011) 8, 135–145

www.nature.com/cmi

REVIEW

The inflammasomes in health and disease: from genetics to molecular mechanisms of autoinflammation and beyond

Cristina Conforti-Andreoni, Paola Ricciardi-Castagnoli and Alessandra Mortellaro

Nucleotide-binding oligomerization domain (NOD)-containing protein-like receptors (NLRs) are a recently discovered class of innate immune receptors that play a crucial role in initiating the inflammatory response following pathogen recognition. Some NLRs form the framework for cytosolic platforms called inflammasomes, which orchestrate the early inflammatory process *via* IL-1β activation. Mutations and polymorphisms in NLR-coding genes or in genetic loci encoding inflammasome-related proteins correlate with a variety of autoinflammatory diseases. Moreover, the activity of certain inflammasomes is associated with susceptibility to infections as well as autoimmunity and tumorigenesis. In this review, we will discuss how identifying the genetic characteristics of inflammasomes is assisting our understanding of both autoinflammatory diseases as well as other immune system-driven disorders.
Cellular & Molecular Immunology (2011) **8,** 135–145; doi:10.1038/cmi.2010.81; published online 24 January 2011

Keywords: autoinflammatory diseases; polymorphisms; NLRs; NLRP3

INTRODUCTION

The ability of innate immune cells to sense dangers to the host, such as microbial infections or a disruption in tissue homeostasis, depends upon a plethora of receptor families. The Toll-like receptor (TLR) family is the best-characterized of these,[1] but in the last decade new intracellular receptor families have been identified. They include nucleotide-binding oligomerization domain (NOD)-containing protein-like receptors (NLRs), retinoic acid-inducible gene-like receptors and C-type lectin receptors.[2–4] Some members of the NLR family have been deeply investigated for their central role in the formation of functional platforms, named inflammasomes, which mediate the initiation of the inflammatory process through IL-1β and IL-18 secretion.

All these receptors have generated a huge amount of interest recently due to their prominent role in a number of human autoinflammatory diseases. Linkage studies of inherited autoinflammatory conditions identified mutations or polymorphisms in a group of genes named hereditary periodic fever syndromes-associated genes encoding NLR proteins or their inflammasome-related partners. Since then, further genome-wide association studies have characterized specific genetic polymorphisms of NLR genes in relation to autoinflammatory diseases.

Alongside the involvement of NLR inflammasomes with spontaneous inflammatory disorders, other investigations have revealed inflammasome roles in protection against infective agents,[5] as well as in the pathogenesis of autoimmunity and tumors.[6–9] How genetic variations influence inflammasome structure and function leading to disease onset is the challenging target for future investigations.

THE NLR FAMILY

NLRs are fundamental components of the innate immune system that are evolutionarily conserved, having been detected in species as simple as sea urchins. NLR-like proteins functionally and structurally similar to mammalian ones have even been observed in plants.[10–12] This fascinating example of convergent evolution hints at NLR-like structures as an efficient and successful tool of innate immunity against a broad variety of pathogens.

NLRs are cytosolic receptors that are expressed predominately by macrophages and dendritic cells. To date, 23 NLRs have been described in humans and 33 identified in mice. In general, NLRs are composed of three domains: a C-terminal region leucine-rich repeat (LRR), the central nucleotide domain NACHT (also known as NOD) and the N-terminal containing either a caspase recruitment domain (CARD) or pyrin domain (PYD) (Figure 1). LRRs are domains of 20–30 residues forming alpha helix and beta strands, similar to plant disease-resistance genes.[13] Indeed, similarly to TLRs, LRR structures in NLRs are important for the recognition of pathogen-associated molecular patterns, although direct evidence of an interaction with known NLR-agonists has not yet been demonstrated. The central domain NACHT shares structural similarities with the central motif of apoptotic protease-activating factor 1, which promotes formation of oligomeric structures. Therefore, an analogous mechanism has been proposed for the formation of the NLR inflammasome platform.[14,15]

The N-terminal CARD and PYD are the key regions linking the NLR to its downstream functions *via* oligodimerization with an analogous domain harbored by specific adaptor proteins. NLRs with N-terminal

Singapore Immunology Network (SIgN), Agency for Science, Technology and Research (A*STAR), Immunos, Singapore
Correspondence: Dr A Mortellaro, Singapore Immunology Network (SIgN), Agency for Science, Technology and Research (A*STAR), 8A Biomedical Grove, #04-06 Immunos, Singapore 138648.
E-mail: alessandra_mortellaro@immunol.a-star.edu.sg
Received 19 November 2010; accepted 9 December 2010

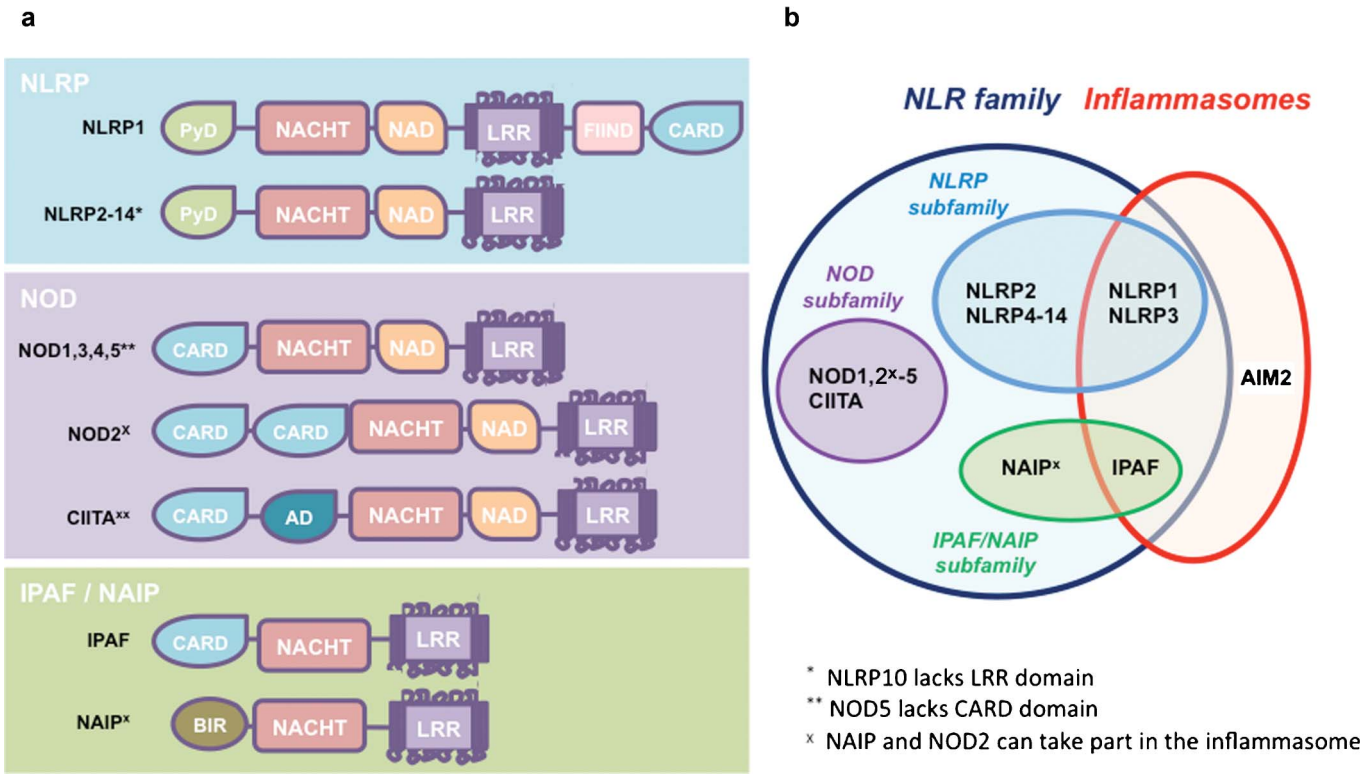

Figure 1 NLRs and inflammasomes. (**a**) Schematic representation of human NLR structures. NLR family comprises the three main subfamilies NLRP, NOD and IPAF/NAIP, characterized by the conserved central oligomerization NACHT domain and the C-terminal LRR domain. The N-terminal CARD or PYD are present in the NOD and NLRP subfamilies, respectively. (**b**) Among the NLRs, NLRP1, NLRP3 and IPAF participate in the formation of the inflammasome platform. AIM2, not belonging to the NLR family, has also been identified as forming part of a specific inflammasome. AIM2, absent in melanoma 2; CARD, caspase recruitment domain; IPAF, ICE-protease-activating factor; LRR, leucine-rich repeat; NAIP, neuronal apoptosis inhibitory protein; NLR, nucleotide-binding oligomerization domain-containing protein-like receptor; NOD, nucleotide-binding oligomerization domain; PYD, pyrin domain.

domains that contain CARD usually activate signaling cascades leading to transcription of proinflammatory genes (Figure 1). Alternatively an N-terminus PYD will recruit pro-inflammatory caspases.

Based on their molecular structure and function, NLRs can be divided into three subfamilies: NLRP, NOD and ICE-protease-activating factor (IPAF)/neuronal apoptosis inhibitory protein (NAIP) (Figure 1).[12] NLRP, also known as NALP (NACHT domain-, LRR- and PYD-containing protein), is the largest subfamily, having 14 members in human and 12 in mouse. The prototypical members are NLRP1 and NLRP3. NLRP3 contains N-terminal PYD, a central NATCH domain responsible for oligomerization and activation, and a NACHT-associated domain followed by the highly conserved LRR region of 171 nucleotides at its C-terminus (Figure 1).[16] NLRP1 has a similar structure to NLRP3 except that at the C-terminus of the LRR region, there is a FIIND (domain with function to find) followed by a C-terminal CARD for caspase recruitment. The two also differ in their expression patterns; the NLRP3 gene is strongly expressed in macrophages, dendritic cells, granulocytes and osteoblasts, whereas NLRP1 has a wider expression pattern, including brain, lung, placenta, small intestine, colon, kidney, liver, muscle, testes and epithelial cells. The functions and the tissue and cellular distribution of the other NLRP proteins have not yet been fully characterized.

The NOD family of NLRs includes NOD1–5 and the class II transactivator (Figure 1). An N-terminal CARD is characteristic of the NOD family. NOD1 and NOD2 are the two best-studied members. The natural ligands of NOD1 and NOD2 are moieties of peptidoglycan, a polymer of the glycan chains within bacterial cell walls; specifically, NOD1 detects mesodiaminopimelic acid, while NOD2 recognizes muramyl dipeptide (MDP).[17] Upon activation, NOD1 and NOD2 recruit the receptor-interacting protein-2 through homodimerization of CARDs, which leads to the activation of NF-κB.[18] NOD1 and NOD2 also engage CARD9, which mediates the activation of mitogen-activated protein kinase cascades responsible for nuclear translocation of Jun and ATF2 transcription factors.[19] NF-κB and mitogen-activated protein kinase-mediated pathways trigger a vigorous inflammatory response characterized by secretion of proinflammatory cytokines and chemokines.

The third NLR subfamily is evolutionarily separate from other NLRs and consists of IPAF and NAIP (Figure 1). IPAF contains a CARD, whereas NAIP includes three baculovirus inhibitor domains that are probably involved in inhibition of apoptosis.[20] Both IPAF and NAIP are involved in the formation of inflammasomes. Whole bacteria, such as *Salmonella typhimurium*, *Pseudomonas aeruginosa* or *Legionella pneumophila*, as well as bacterial components including flagellin, also promote IPAF oligomerization resulting in recruitment and activation of caspase-1.[21] IPAF seems to cooperate with NAIP to induce caspase-1-mediated secretion of IL-1β by macrophages. However, the exact mechanisms underlying IPAF/NAIP detection of bacterial compounds and activation of caspase-1 remain largely unclear.

THE INFLAMMASOMES

Inflammasomes are the multiprotein cytoplasmic complexes that facilitate activation of proinflammatory caspases.[22] To date, three inflammasomes have been described according to the NLR protein they engage: the NLRP1, NLRP3 and IPAF inflammasomes.

NLRP3 is one of the best-characterized inflammasomes. The framework of the NLRP3 inflammasome structure seems to form through homotypic reactions of NLRP3's PYD with the PYD of an adaptor protein called apoptotic-associated speck-like protein containing a caspase recruitment domain (ASC) (Figure 2). ASC then recruits procaspase-1 through CARD–CARD interactions. Similarly, NLRP1 can directly recruit both procaspase-1 and -5 *via* CARD homotypic interactions. The ability to form inflammasome platforms is not limited to NLRP subfamily members; IPAF can recruit caspase-1 directly *via* CARD–CARD interactions and therefore the IPAF platform is referred as a third inflammasome prototype.[23,24] There is some evidence that that NAIP can assemble with IPAF to form heterocomplex inflammasomes.[25,26] NLRP1 can also associate with NOD2 to mediate caspase-1-dependent IL-1β secretion in response to *Bacillus anthracis* and MDP.[27,28]

Recently a fourth type of inflammasome has been identified, involving the protein absent in melanoma 2 (AIM2) (Figure 1).[29] Despite the lack of NACHT domain, AIM2 can undergo oligodimerization and recruit ASC *via* PYD in response to double stranded cytosolic DNA through its C-terminal HIN domain. AIM2 is generating a strong interest as a sensor of DNA and therefore its putative involvement in viral surveillance, as well as onset of autoimmunity against self-DNA, as seen in systemic lupus erythematosus.[30–32] Since AIM2 does not belong to the NLR family, it will not be discussed further.

ACTIVATORS OF THE NLRP3 INFLAMMASOME

Similar to the TLR family, much work has focused on identifying the stimuli recognized by NLRs. Activation of the inflammasomes can be triggered by exposure to whole live bacterial, fungal or viral pathogens (*Salmonella typhimurium*, *Shigella flexneri*, *Legionella pneumonia*,

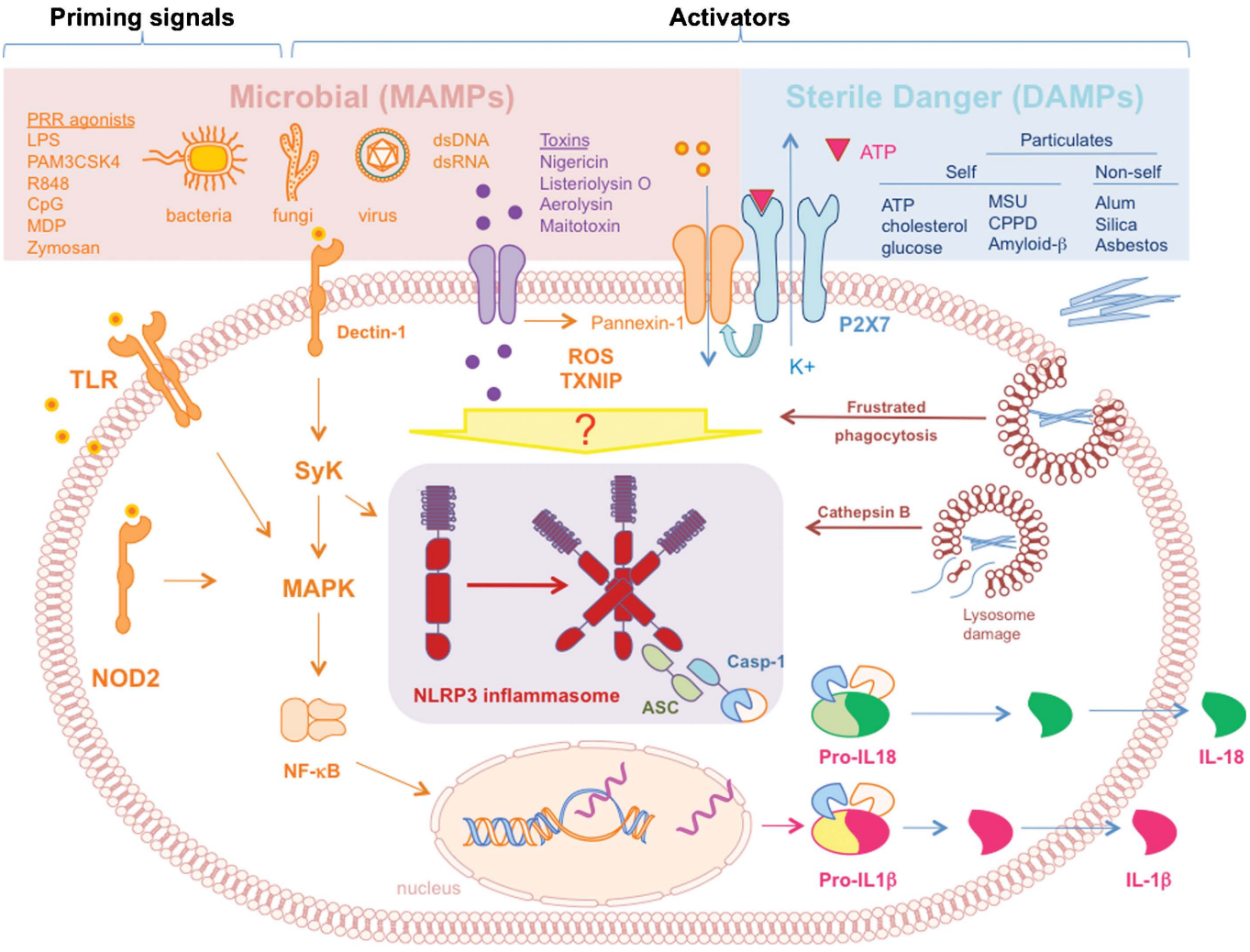

Figure 2 *NLRP3* inflammasome activation pathways. The assembly of the *NLRP3* inflammasome in innate cells is induced by several different stimuli, including MAMPs (pink box) or sterile DAMPs (light blue box). A first priming signal delivered predominantly by MAMPs, such as LPS, is required to promote IL-1β transcription *via* NF-κB translocation to the nucleus. Inflammasome oligomerization and activation can be induced by bacterial and fungal moieties, pore forming toxins, or viral dsDNA and RNA. Upon binding to the P2X7 receptor, ATP also triggers inflammasome formation through K^+ efflux and opening of the pannexin-1 channel. Particulates, such as MSU, fibrillar amyloid β, CPPD, silica, asbestos and alum, are phagocytosed and activate the inflammasome. MSU can also promote inflammasome formation *via* frustrated phagocytosis. ROS formation induced by certain inflammasome activators also mediates inflammasome assembly *via* recruitment of TXNIP. Inflammasome oligomerization results in ASC-mediated caspase-1 activation responsible for cleavage and release of IL-1β and IL-18 cytokines. ASC, apoptotic-associated speck like protein containing a caspase recruitment domain; CPPD, calcium pyrophosphate dihydrate; DAMP, danger-associated molecular pattern; LPS, lipopolysaccharide; MDP, muramyl dipeptide; MAMP, microbial-associated molecular pattern; MSU, monosodium urate; ROS, reactive oxygen species; TXNIP, thioredoxin-interacting protein; Casp-1, caspase-1.

Pseudomonas aeruginosa, *Candida albicans*, *Saccharomyces cerevisiae*, Sendai virus, adenovirus and influenza virus),[30,33–35] or their components (MDP flagellin),[36–38] but also by toxins required for pathogen entry into the host cell, such as membrane-disrupting and pore-forming compounds (maitotoxin, nigericin, aereolysis, anthrax lethal toxin and alpha-toxin of *Staphylococcus aureus*) (Figure 2).[39–43] Interestingly, NLRP3 also contributes to the ability of dendritic cells and macrophages to detect endogenous danger molecules released by dying cells. NLRP3 can signal the presence of adenosine triphosphate (ATP), crystals of monosodium urate (MSU) or calcium pyrophosphate crystals,[39,44] and other large particulates of non-microbial origin, such as alum, silica and asbestos (Figure 2).[45–47] The NLRP3 inflammasome has also been proposed as a sensor of adenoviral DNA, double-stranded RNA and viral RNA.[30,35]

PROPOSED MECHANISMS OF INFLAMMASOME ACTIVATION

The NLRP3 inflammasome is the best-characterized, but the precise mechanism of NLRP3 activation is still debated. At steady state, inflammasome components are present in the cytosol and their assembly is prevented by auto-inhibitory mechanisms mediated by chaperone proteins.[48] Inflammasome assembly is promoted by the application of specific stimuli. However there is no evidence that inflammasome-activating molecules would interact directly, as specific ligands, with the NLR proteins themselves. Moreover, it is still puzzling how many heterogeneous molecules, which differ broadly in biological properties and structures, could trigger NLRs, such as NLRP3. Multiple mechanisms of NLRP3 activation have been proposed, which may also cooperate in a unique and complex way (Figure 2).

Using cell-free systems it was shown that the NLRP3 inflammasome can spontaneously assemble if potassium levels are lowered below the physiological intracellular concentration of 70 mM.[22,49,50] This observation suggested that inflammasome formation might also be triggered following disruption of cellular integrity that would similarly cause potassium levels to drop. Therefore, it was suggested that NLRP3 activators might act indirectly through pathways able to lower potassium concentration. This mechanism has been demonstrated for inflammasome activation driven by extracellular ATP, which induces inflammasome assembly and ASC-mediated IL-1β secretion.[33,51] ATP binds to the purinergic receptor P2X7, resulting in the opening of the protein channel pannexin-1.[52] This allows potassium efflux, inflammasome activation and ATP release.[53] However, it has been proposed that the pore formation following pannexin-1 recruitment could allow cytosolic access to microbial products, such as lipopolysaccharide (LPS), which can directly activate the inflammasome.[52] Although it is unclear whether the pore width would be sufficient to allow entrance of such microbial-derived molecules.

The inflammasome activators MSU, alum, asbestos and silica possess a crystal or particulate shape. Inhibition of cytoskeletal rearrangement with colchicine or cytochalasin D blocks IL-1β secretion.[44] These observations led to the second model of NLRP3 activation. The attempts to engulf large particulates by phagocytes *via* a mechanism known as frustrated phagocytosis can generate NADPH-dependent formation of reactive oxygen species (ROS).[45,46,54] Recently, the thioredoxin-interacting protein was identified as an NLRP3-binding protein linking ROS generation to assembly and activation of the NLRP3 inflammasome.[55] In support of this model, antioxidants and NAPDH inhibitors prevent inflammasome assembly.[34,46,47,49,54,56] Although ROS production is required for NLRP3 activation, several ROS-inducing agents do not promote inflammasome formation.[57,58]

A third mechanism of NLRP3 activation proposed by Hornung and colleagues was that, in the case of large particulates, inflammasome activation occurs as a result of lysosomal swelling and leakage.[57] In contrast to the hypothesis of frustrated phagocytosis, this model proposes that upon cellular uptake silica and aluminum salts cause lysosome acidification with consequent release of acidic contents into the cytosol. Indeed, inhibition of the lysosomal protease cathepsin B leads to a substantial decrease in activation of the NLRP3 inflammasome induced by silica.[57]

INFLAMMASOME-ACTIVATED CYTOKINES: IL-1β AND IL-18

The main outcome of NLRP3 inflammasome activation is the recruitment of caspase-1, inducing the cleavage and secretion of the proinflammatory cytokines IL-1β and IL-18. IL-1 family members are potent modulators of both innate and adaptive immunity and are important for host protection against infections. Notably, IL-1β is involved in the early pathogenesis and the sustained severity of a broad pattern of diseases, including many arthritic diseases and septic shock.[59] Blocking the IL-1R is a successful treatment for several immune-related disorders.[60,61]

IL-1β production is controlled by a two-step mechanism. TLR or NOD agonists transcribe the immature form, pro-IL-1β, *via* the NF-κB pathway followed by caspase-1-mediated cleavage of pro-IL-1β upon inflammasome activation.[59] The NF-κB pathway is also required for transcription of NLRP3.[62] To bypass this limitation, most *in vitro* studies have used inflammasome agonists in combination with other pathogen-associated molecular patterns, most often LPS, to 'license' inflammasome formation and activation.[33,44,57,63–65] It is important to consider, however, that LPS used as priming signal in several studies could contribute to NLR activation through additional mechanisms beyond pro-IL-1β and NLRP3 transcription.

NLRP3 activation also leads to IL-18 maturation, although this cytokine can also be activated by other caspase-1-independent mechanisms.[66,67] The immature form of IL-18 is constitutively expressed in some cells but only those with an active inflammasome, such as macrophages, dendritic cells and Kupffer cells, have the ability to release the mature form.[68]

In the last decade, a number of groups have focused on the study of inflammasomes as initiators of immune disorders mediated by IL-1β and IL-18. Thus, many genetic associations between members of NLR family and immune diseases have been discovered. Moreover, a correlation between NLR members and non-immune mediated disorders has also been proposed, suggesting that this protein family has as yet undefined functions crucial for the balanced physiology of the organism. For these reasons, involvement of genetic mutations of inflammasomes in several diseases will be discussed in detail with a particular focus on IL-1-mediated disorders.

GENETICS OF INFLAMMASOMES IN AUTOINFLAMMATORY DISEASES

NLRP3 mutations are associated with a group of rare hereditary autoinflammatory diseases called cryopyrin-associated periodic syndromes (CAPS), which includes familial cold auto-inflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and chronic infantile neurological, cutaneous, and articular (CINCA) syndrome, also known as neonatal onset multisystem inflammatory disorder.[69] These pathologies are listed in order of increasing disease severity and life-threatening potential, and are characterized by recurrent episodes of fever, rush, arthropathies and various degrees of neurological complications.[70–72] Genetic studies of CAPS identified more than 90 disease-associated genetic variants of the NLRP3 gene, the majority of

which are autosomal dominant missense point mutations located in exon 3, encoding the NATCH domain (Figure 3 and Table 1).[73,74] Despite the familial recurrence, some genetic variants inducing CAPS phenotypes result from *de novo* mutations. Interestingly, identical *de novo* mutations were independently found in different patients and often overlapped with hereditary mutations, suggesting the presence of hot-spot loci within the NLRP3 gene that exhibit high mutation susceptibility.[75]

It is presently unclear how NLRP3 point mutations affect the functional properties of the inflammasome at a molecular level, leading to the high expressivity and penetrance observed in several CAPS-related genetic variances. Exon 3 missense mutations result in continuous IL-1β secretion caused by constitutive inflammasome assembly and activation (Figure 3). NLRP3 hyperactivation bypasses the need for an NLR agonist. Indeed, blood monocytes from CINCA patients spontaneously release IL-1β upon stimulation by LPS alone without any inflammasome activator.[76–78] This hypothesis is also supported by knock-in mouse models carrying the point mutations *R258W* and *A350V* in the exon 3 of NLRP3 gene, which correspond respectively to the human NLRP3 *R260W* and *A352V* mutations associated with MWS (Figure 3 and Table 1).[75,77,79] *R258W* and *A350V* mutations result in spontaneous IL-1β release due to aberrant inflammasome structural conformation and hyperactivation in the absence of NLRP3 agonists. Intriguingly, mouse macrophages carrying the *L351P* mutation, analogous to the human *L353P* mutation in FCAS patients, showed increased IL-1β secretion when incubated at lower temperatures, mimicking the cold-sensitive phenotype observed in FCAS subjects.[79] The pathologies seen in knock-in mouse models of CAPS-associated mutations are similar to human disease syndromes, suggesting that IL-1β hyperactivation is sufficient to initiate and sustain several important inflammatory events. Indeed, therapies blocking the action of IL-1β using an IL-1R antagonist or humanized anti-IL-1β monoclonal antibody are successfully used to treat CAPS and other IL-1-mediated disorders.

Several CAPS-associated mutations and polymorphisms have been identified, but only a few have been analyzed for their effect on the molecular and cellular function. Using an *in silico* modeling prediction of the NACHT domain structure, Neven and coworkers investigated how the single residue substitutions in NLRP3 frequently associated with CAPS could affect secondary and tertiary protein configurations.[75] According to the putative tertiary structure, all the substitutions clustered close to the nucleotide binding cleft, suggesting that nucleotide binding site, located in proximity of the NACHT domain in a specific site outside the structure core, could be crucial for NLRP3 oligomerization. Hence, mutations affecting this region were also suggested to influence the quaternary structure determining aberrant inflammasome formation.[75]

Mutations in the C-terminal region of the NACHT domain correlate with the most severe CINCA syndrome phenotypes and are associated with significant neurological impairment (Figure 3 and Table 1). LPS-treated monocytes expressing the *Y570C* mutation showed an increased necrotic-like cell death associated with lysosomal leakage and other cellular metabolic alterations.[80,81] Moreover, monocytes transfected with *Y570C* exhibited higher NF-κB activity compared to healthy controls.[82,83]

A second important aspect is that some CINCA patients with milder symptoms apparently lack NLRP3 mutations but carry a latent low-level mosaicism. This implies that some missense mutations in the NLRP3 gene can exert a dominant phenotype leading to CAPS even when NLRP3 is expressed by less than 25% of the cells in mosaic patients.[81,84] This could be due to the positive feedback loop sustained by the IL-1/IL-1R axis.

Recently disease-correlated missense mutations in exons other than exon 3 have been identified. Exon 6 encodes the LRR domain and the *Y859C* mutation has been associated with a different CAPS phenotype lacking the typical urticarial rush, while other symptoms were overlapping with late on-set phenotypes of MWS and CINCA (Figure 3).[83] Similar to mutations in the NACHT domain, *Y859C* mutations lead

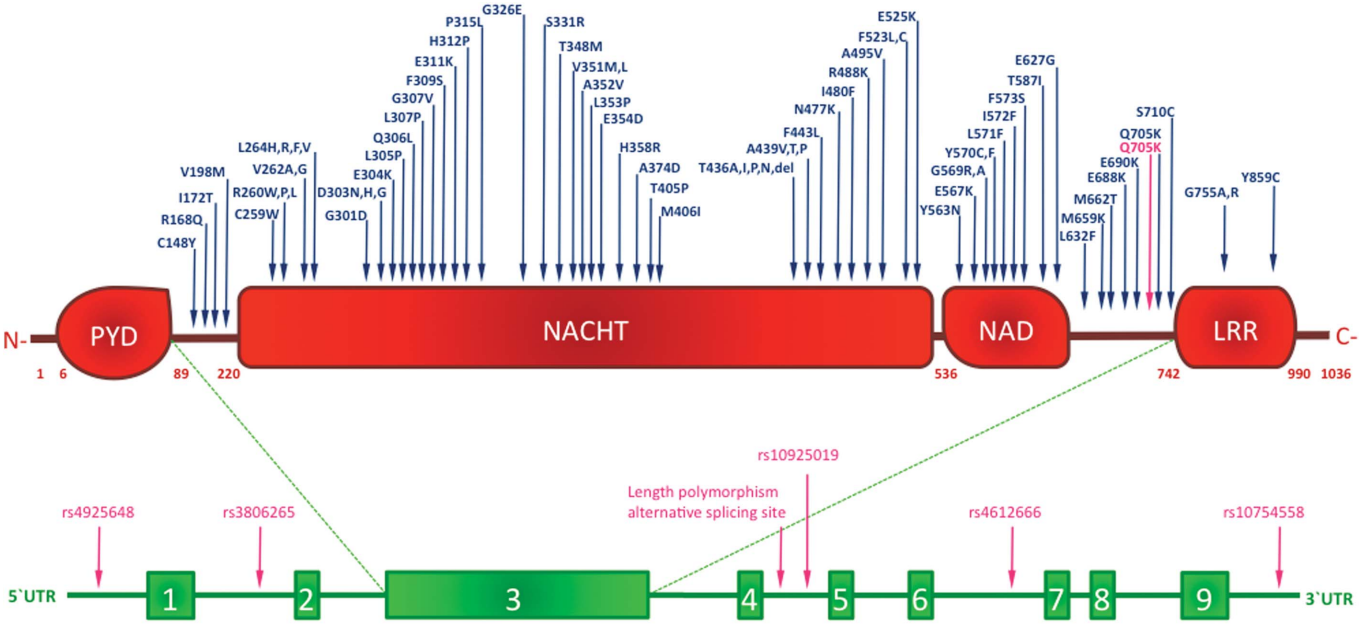

Figure 3 Mutations and polymorphisms in the *NLRP3* gene are associated with diseases. Schematic representation of residue substitutions in *NLRP3* protein (upper panel), or polymorphysms in *NLRP3* gene intronic regions (lower panel). Single residue-allelic variants associated with cryopyrin-associated periodic syndromes or with other *NLRP3*-related diseases are highlighted in blue and pink, respectively. LRR, leucine-rich repeat; NAD, NACHT-associated domain; PYD, pyrin domain.

Table 1 Inflammasome-related genes correlating with human diseases

Disease	Gene	Allele	Mechanism	Ref.
MWS	NLRP3	*V198M, R260L, R260W, V262G, L264V, D303N, E311K, H312P, T348M, A352V, A439T, I480F, A495V, F523C(t>g), E567K, G569R, S710C*	Spontaneous inflammasome assembly, IL-1β hyperproduction	69, 71, 72, 74, 75
FCAS	NLRP3	*V198M, C259W, G301D, L353P, T436A, A439V, R488K, E525K, Y563N, E627G, M659K*	Spontaneous inflammasome assembly, IL-1β hyperproduction	71, 72, 74, 75
CINCA syndrome	NLRP3	*C148Y, R168Q, I172T, V198M, R260P, R260W, V262A, V262G, L264H,R,F, D303N, D303H, D303G, E304K, Q306L, G307V, F309S, P315L, G326E, S331R, V351M,L, E354D, H358R, A374D, T405P, M406I, T436I,P,N, T436del, A439P, F443L, N477K, I480F, F523L(c>a), F523L(c>g), G569A, Y570C,F, L571F, I572F, F573S, T587I, L632F, M662T, E688K, E690K, G755A, G755R, Y859C*	Spontaneous inflammasome assembly, IL-1β hyperproduction, necrosis-like cell death?	69, 74, 75, 76, 81, 83
FCAS-like diseases	NLRP12	*R284X*	Non-canonical NF-κB activation	90, 91
Familial Mediterranean fever-like syndrome	PYPAF1	*R554X*	Non-canonical NF-κB activation	97
HIV infection	NLRP3	*SNP 3′ UTR rs10754558 G*	Unknown	99
C. albicans infection (vulvar vestibulitis)	NLRP3	*Intron 4*, alternative splicing site	Reduced inflammasome activity? Impaired IL-1β production?	103
Mycoplasm infection (infertility)	NLRP3	*Intron 4*, alternative splicing site	Reduced inflammasome activity? Impaired IL-1β production?	104
C. trachomatis infection (tubal pathology)	NLRP3	*rs12065526 G>A*	Unknown	105
Crohn's disease	NLRP3	*Q705K* (+ *C10X CARD8* gene) *SNP 5′ UTR rs4925648 C/T* *SNP rs10925019 C/T*	IL-1-mediated?	85, 86, 87, 88
Psoriatic juvenile idiopathic arthritis	NLRP3	*SNP rs3806265*	IL-1-mediated?	117
Rheumatoid arthritis	NLRP3	*Q705K* (+ *C10X CARD8* gene)	IL-1-mediated?	120
Food-induced anaphylaxis	NLRP3	*SNP rs4612666* *SNP rs10754558*	IL-1-mediated?	123
Aspirin-induced asthma	NLRP3	*SNP rs4612666*	IL-1-mediated?	123
Urticaria	NLRP3	?	IL-1β hyperproduction in the skin?	125
Vitiligo	NLRP1	*5′ UTR ?* *3′ UTR rs6502867*	IL-1-mediated autoimmunity? Aberrant apoptosome formation?	126, 127
Autoimmune Addison's disease	NLRP1	*rs12150220*	IL-1-mediated autoimmunity?	128
Type 1 diabetes	NLRP1	*rs12150220*	IL-1-mediated autoimmunity?	128
Type 2 diabetes	NLRP3	?	Activation of NLRP3 by glucose?	133
Hypertension	NLRP3	Intronic mutation	Activation of NLRP3 by cholesterol?	131
Alzheimer's disease	IL-1β	?	Activation of NLRP3 by amyloid β?	136, 138
Cancer	NLRP3	?	IL-1β-mediated inflammation?	8

Abbreviations: CINCA, chronic infantile neurological, cutaneous and articular; FCAS, familial cold autoinflammatory syndrome; MWS, Muckle–Wells syndrome.

to spontaneous inflammasome formation, ASC recruitment and IL-1β secretion. Remarkably, treatment of patients carrying the *Y859C* mutation with an IL-1R antagonist was effective, suggesting that a complete screening of the whole NLRP3 gene should be recommended, especially for patients showing non-classical autoinflammatory symptoms.[83]

Two additional NLRP3 variants, *G755R* and *G755A* of exon 4, also result in a CAPS phenotype probably through enhancement of NF-κB activation (Figure 3 and Table 1). However, the role of NLRP3 in regulating the NF-κB pathway is still widely debated. A hint comes from studying the homology among NLRs. Indeed, the missense mutation *R334W* in the NOD2 gene associated with Crohn's disease exhibits a strong positional and structural analogy to *R260W* in the NLRP3 gene, which results in aberrant NF-κB activation. Interestingly, an association between Crohn's disease and NLRP3 polymorphisms leading to impaired IL-1β secretion has been proposed.[85–87] However, recent studies in a larger patient group failed to replicate this observation.[88] Further work is needed to clarify the possible association of inflammasome genetics to multifactorial diseases.

Although several missense mutations in NLRP3 inflammasomes strongly correlate with CAPS, a significant number of patients with CAPS-like phenotype do not present any mutation in NLRP3 gene.[75,89] Some autoinflammatory syndromes resembling CAPS have been correlated with mutations in inflammasome or IL-1 pathway regulators. NLRP12 mutations are associated with hereditary periodic fever syndromes, and while NLRP12 shares strong homology with NLRP3, it is not involved in inflammasome formation but regulates the NF-κB cascade.[90,91] A nonsense mutation causing defective splicing and introducing a premature stop codon in NLRP12 causes a dominant phenotype due to the lack of regulation of the inflammatory pathway.

Despite its typical inflammasome-promoting structure, another member of NLRP family, NLRP7, acts as a negative regulator of caspase-1 activation.[92,93] Mutations in NLRP7 have mainly been

associated with aberrant development of the reproductive tract, such as endometrial cancer tissues and familial recurrent hydatidiform moles.[94]

Mutations in genes encoding pyrin and proline-serine-threonine phosphatase-interacting protein 1 are associated with two autoinflammatory diseases with hereditary periodic fever syndrome-like symptoms: familial mediterranean fever and pyogenic arthritis pyoderma gangrenosum and acne syndrome, respectively. Pyrin and proline–serine–threonine phosphatase-interacting protein 1 interacts with and modulates pyrin function, which affects inflammasome activity. However, it is still unknown whether pyrin acts as an ASC activator, inducing inflammasome-independent IL-1β release or as negative inflammasome regulator able to dampen NLRP3 function by competing for ASC.[95,96] In both hypotheses pyrin and proline–serine–threonine phosphatase-interacting protein 1 mutations are thought to induce dysregulation of IL-1β secretion.[97]

A similar hypothesis was formulated for caspase-12, which is expressed in several mammals but commonly present as a null allele in humans, where a mutation leads to a truncated non-functional form of the protein. Caspase-12 is a negative regulator of the NF-κB pathway and for this reason it can increase susceptibility to sepsis following infection. It is likely that in humans the null allele of caspase-12 has been selected for under evolutionary pressure in areas subject to persistent infections. However, in some populations of Africa, South Asia and South America, a caspase-12 mutation causing expression of a full-length protein is responsible for a dominant negative autoinflammatory phenotype.

GENETICS OF INFLAMMASOME-RELATED NON-AUTOINFLAMMATORY DISORDERS

Besides auto-inflammation, IL-1β is involved in the pathogenesis of other immune-related disorders ranging from autoimmunity to pathogen clearance and tumorigenesis. Therefore, it follows that mutations in NLR-proteins and inflammasome-related components may also be implicated in this broad spectrum of conditions.

Infections

The involvement of the inflammasome in controlling bacterial infections has mainly been linked to its central role in IL-1β production, which is required for effective pathogen clearance. In this regard, the control of *Mycobacterium tuberculosis* (MTB) infection by innate cells through inflammasome-derived IL-1β can be taken as an example. IL-1R-deficient mice are more susceptible to MTB infection due to defective bacterial clearance. Moreover, IL-1β is thought to kill MTB bacilli by promoting phagosome maturation. The MTB gene *Zmp1*, which encodes a Zn^{2+} metalloprotease, may suppress inflammasome activity in the host macrophage, supporting the idea of a key role for the inflammasome in this system.[98] However, while there are no data yet to link inflammasome genetics in the host to MTB susceptibility, there is an association between NLRP3 genetics and immune protection against viruses. Recent studies have suggested a role of inflammasomes in the recognition of viral DNA and RNA during infection.[30,35] For example, NLRP3-deficient mice exhibited limited protection to influenza A infection. Furthermore, an association between NLRP3 polymorphisms and HIV-1 infection has been described; a lower frequency of the *3' UTR SNP rs10754558 G* allele was found within HIV-seropositive patients compared to controls.[99] Interestingly, such association was seen in infected adults as well as in vertically infected children, suggesting that mutations in NLRP3-mediated immune response could impair protection against HIV-1, independent of the route of transmission. However, the precise mechanism of NLRP3-mediated control of HIV-1 has not yet been revealed. Although several independent studies have uncovered a protective function of the inflammasome during viral infections[35,100,101], others observed that inflammasome activation by certain viruses was mainly crucial for innate and healing response but not for virus control and adaptive immune activation.[102] Thus, the exact mechanism of virus recognition and the possible influence of genetics of inflammasomes on protection from viruses remain unclear.

NLRP3 has also been associated with the control of fungal infections.[34] An intronic polymorphism in NLRP3 that causes production of a shorter form of the protein is linked to candidiasis-mediated vulvar vestibulitis.[103] In addition, the same splicing variant of NLRP3 correlated with susceptibility to mycoplasma infection causing infertility.[104] The NLRP3 polymorphism *rs12065526 G>A* was identified as a risk factor for the development of tubal pathology symptoms induced by *Chlamydia trachomatis* infection (Figure 3).[105]

All these association studies suggest a crucial role for NLRP3 in immune surveillance against a broad spectrum of different infective agents invading the host through the mucosal barriers.

Adaptive immunity-mediated diseases

The boundaries between autoimmunity and autoinflammation are not clearly defined for many immune disorders and the adaptive components in autoinflammation, as well as the innate component in autoimmunity, may have been underestimated.[106] A growing body of evidence suggests that inflammasome activation could also drive adaptive immunity and the correlation between inflammasome dysfunction and autoimmunity has become the subject of intense investigation.

In a transgenic mouse model of CAPS, excessive IL-1β secretion resulted in NLRP3-dependent pathogenic activation of a specific IL-17-secreting T-cell subset, namely, Th17 cells.[77] Nonetheless, another study excluded an involvement of adaptive immunity in a very similar model of CAPS.[79] IL-1β plays an important role in activating and sustaining the Th17-mediated response, especially in humans.[107–110] Considering the central role of Th17 cells in autoimmune diseases including rheumatoid arthritis (RA) and psoriasis, mutations in inflammasome-encoding genes may result in a broad spectrum of Th17 cell-mediated autoimmune disorders, through deregulation of IL-1β secretion.[107,111–116] Genetic variants in several inflammatory genes, including NLRP3, are associated with two forms of autoimmune arthritis: juvenile idiopathic arthritis and RA, characterized by Th17 cells.[117,118] Indeed, increased expression of NLRP3 was observed in the synovium of RA patients compared to subjects suffering from non-autoimmune osteoarthritis.[119] Moreover, in a Swedish cohort, RA susceptibility and severity are significantly influenced by the combination of the *Q705K* variant of NLRP3, already known for its low-penetrance in FCAS, and the *C10X* variant of caspase recruitment domain family, member 8.[120] Notably, these two polymorphisms are highly recurrent: *Q705K* polymorphism in NLRP3 was found in 6.5% of the Caucasian population and CARD-8 gene polymorphism *C10X* is present in 40%.[121,122] However, their penetrance in the pathogenesis of immune-immune mediated disorders is very low, and leads to susceptibility to autoimmunity only when in combination.

Polymorphisms in the NLRP3 gene also correlate with different forms of allergies, including susceptibility to food-induced anaphylaxis, aspirin-induced asthma and urticaria.[123,124] Urticarial reactions are recurrent clinical manifestations in the continuum of CAPS, and skin disorders are a phenotypic feature of knock-in mice carrying NLRP3 hypermutations.[77] Moreover, mast cells from CAPS patients

express NLRP3 and constitutively secrete IL-1β.[124,125] Therefore, we can speculate that genetics of inflammasome components could be involved in the onset of other types of dermatitis and skin-related allergies, as well as asthma.[124]

NLRP1 is expressed not only by innate cells but also by T cells, and therefore has a role in adaptive immunity as well as innate. A strong correlation links some intronic variants of NLRP1 with vitiligo and vitiligo-associated autoimmune disorders (Table 1).[126,127] In addition, new associations of NLRP1 SNPs with other autoimmune disorders such as Addison's disease, type 1 diabetes, multiple sclerosis and RA have been identified, even though a genome-wide study does not support all of these associations.[128–130]. However, as well as its role in inflammasomes, NLRP1 also contributes to the formation of the apoptosome *via* caspase-2 and -9 recruitment. For this reason, the genetics of NLRP1 could be associated with susceptibility to autoimmune disorders where apoptosis plays a crucial role.

Chronic tissue damage disorders

NLRP3 is now considered as an intracellular sensor of tissue damage. Environmental threats (silica and asbestos) and endogenous signals (ATP and urate crystals) together with genetic predisposition can significantly contribute to inflammasome-related disorders. Indeed, silica and asbestos leads to chronic pulmonary inflammation, and urate crystals are responsible for gout. A clear correlation between gout and NLRP3 polymorphism has not yet been described. However, hypertension, which affects 57% of gouty patients, has been correlated to a specific intron 4 polymorphism of the NLRP3 gene causing a dominant expression of the transcript.[131]

IL-1β can promote pathogenesis of disorders associated with tissue damage, in which hyperinflammatory responses worsen the disease rather than promote its resolution. For example, inflammasome-mediated IL-1β overproduction is involved in the pathogenesis of type 2 diabetes, liver damage and muscular dystrophy.[132–134] Inflammasome-mediated processes were also observed in cancer, but the association between the inflammasome/IL-1β axis and cancer development is ambiguous. In some studies the inflammasome seems to promote inflammation-mediated tumor development, also confirmed in lung mesotheliomas caused by silica and asbestos.[8,47] However, *in vivo* animal models of cancer showed that ATP from dying cells promoted production of IL-1β and interferon-γ-secreting $CD8^+$ T cells able to eliminate the tumor.[9] Remarkably, supporting this finding, breast cancer patients with defects in the ATP receptor P2X7 have a higher probability of developing metastases.[135] To date, no mutation in NLRP3 has been correlated to tumor susceptibility.

Finally, IL-1β polymorphisms are associated with Alzheimer's disease, a neurological disorder characterized by fibrillar peptide amyloid β accumulation in the brain.[136,137] Notably, amyloid β has been identified as a NLRP3 activator.[138] Considering the pleiotropic functions of IL-1β in the nervous system, these observations underline the importance of studying inflammasome genetics in the context of disorders that apparently do not involve the immune system.

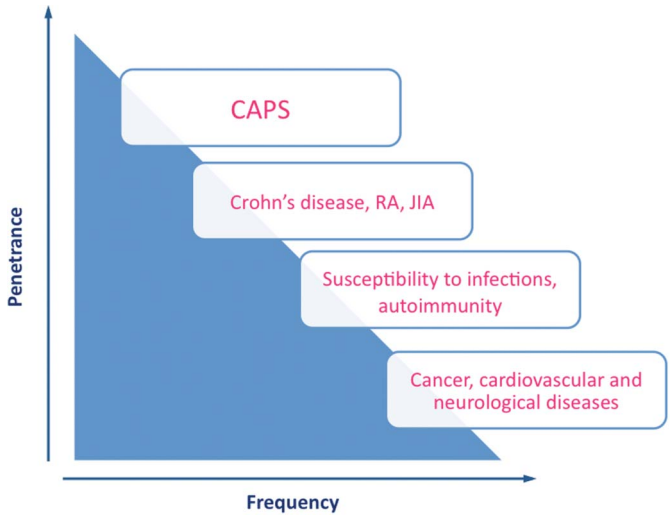

Figure 4 Proposed ranking of human diseases based on penetrance and frequency of inflammasome polymorphisms. Missense point mutations in genes encoding inflammasome components exhibit high penetrance and contribute to the pathogenic autoinflammation, leading to severe but rare autoinflammatory syndromes, such as CAPS. Allelic variants of inflammasome encoding genes in combination with other genetic polymorphisms affecting immune cells lead to more common autoinflammatory-like syndromes, including Crohn's diseases, RA and JIA. Multifactorial disorders highly diffused in the human population, such as infections, autoimmunity, cancer, cardiovascular and neurological diseases, might be associated with polymorphisms in inflammasome-encoding genes of low and variable penetrance. CAPS, cryopyrin-associated periodic syndrome; JIA, juvenile idiopathic arthritis; RA, rheumatoid arthritis.

CONCLUDING REMARKS

The genetics of inflammasomes have been deeply investigated in relation to autoinflammation, where missense point mutations in NLR-coding genes determine with high penetrance the pathogenesis of autoinflammatory processes (Figure 4). This discovery allowed better characterization of the genotype of patients exhibiting autoinflammatory symptoms, in order to design a specific anti-IL-1β therapy. Moreover, transgenic animal models bearing these pathological mutations helped in defining the molecular mechanisms mediating aberrant inflammasome activation. However, several genome-wide screenings have recently uncovered the association between genetic variants of NLRs and other diseases beyond autoinflammation. These findings suggest that specific polymorphisms in NLR genes could contribute, albeit with lower penetrance, to the susceptibility to more common multifactorial diseases such as autoimmune disorders and cancer (Figure 4). The study of inflammasome genetics is also important to help in the diagnostic process and in the design of effective therapeutic strategies. Further investigations aimed to define the genetics of inflammasomes in human diseases are urgently needed to reveal the potent mechanisms mediating the pathology of rare autoinflammatory disorders, but also to depict the complexity of widespread multifactorial diseases, where NLR polymorphisms may play an important hidden role.

ACKNOWLEDGEMENTS

We thank Lucy Robinson for critically reviewing the manuscript. This work was supported by Agency for Science, Technology and Research (A*STAR) of Singapore.

1 Takeuchi O, Akira S. Pattern recognition receptors and inflammation. *Cell* 2010; **140**: 805–820.
2 Franchi L, Warner N, Viani K, Nunez G. Function of Nod-like receptors in microbial recognition and host defense. *Immunol Rev* 2009; **227**: 106–128.
3 Wilkins C, Gale M Jr. Recognition of viruses by cytoplasmic sensors. *Curr Opin Immunol* 2010; **22**: 41–47.
4 Garcia-Vallejo JJ, van Kooyk Y. Endogenous ligands for C-type lectin receptors: the true regulators of immune homeostasis. *Immunol Rev* 2009; **230**: 22–37.
5 Kanneganti TD. Central roles of NLRs and inflammasomes in viral infection. *Nat Rev Immunol* 2010; **10**: 688–698.

6 Allen IC, TeKippe EM, Woodford RMT, Uronis JM, Holl EK, Rogers AB *et al*. The NLRP3 inflammasome functions as a negative regulator of tumorigenesis during colitis-associated cancer. *J Exp Med* 2010; **207**: 1045–1056.
7 Zaki MH, Vogel P, Body-Malapel M, Lamkanfi M, Kanneganti TD. IL-18 production downstream of the NLRP3 inflammasome confers protection against colorectal tumor formation. *J Immunol* 2010; **185**: 4912–4920.
8 Okamoto M, Liu W, Luo Y, Tanaka A, Cai X, Norris DA *et al*. Constitutively active inflammasome in human melanoma cells mediating autoinflammation *via* caspase-1 processing and secretion of interleukin-1beta. *J Biol Chem* 2010; **285**: 6477-6488.
9 Ghiringhelli F, Apetoh L, Tesniere A, Aymeric L, Ma Y, Ortiz C *et al*. Activation of the NLRP3 inflammasome in dendritic cells induces IL-1beta-dependent adaptive immunity against tumors. *Nat Med* 2009; **15**: 1170–1178.
10 Lespinet O, Wolf YI, Koonin EV, Aravind L. The role of lineage-specific gene family expansion in the evolution of eukaryotes. *Genome Res* 2002; **12**: 1048–1059.
11 Hibino T, Loza-Coll M, Messier C, Majeske AJ, Cohen AH, Terwilliger DP *et al*. The immune gene repertoire encoded in the purple sea urchin genome. *Dev Biol* 2006; **300**: 349–365.
12 Proell M, Riedl SJ, Fritz JH, Rojas AM, Schwarzenbacher R. The Nod-like receptor (NLR) family: a tale of similarities and differences. *PLoS One* 2008; **3**: e2119.
13 Bella J, Hindle KL, McEwan PA, Lovell SC. The leucine-rich repeat structure. *Cell Mol Life Sci* 2008; **65**: 2307–2333.
14 Martinon F, Tschopp J. Inflammatory caspases: linking an intracellular innate immune system to autoinflammatory diseases. *Cell* 2004; **117**: 561–574.
15 Faustin B, Lartigue L, Bruey JM, Luciano F, Sergienko E, Bailly-Maitre B *et al*. Reconstituted *NALP1* inflammasome reveals two-step mechanism of caspase-1 activation. *Mol Cell* 2007; **25**: 713–724.
16 Martinon F, Gaide O, Petrilli V, Mayor A, Tschopp J. NALP inflammasomes: a central role in innate immunity. *Semin Immunopathol* 2007; **29**: 213–229.
17 McDonald C, Inohara N, Nunez G. Peptidoglycan signaling in innate immunity and inflammatory disease. *J Biol Chem* 2005; **280**: 20177–20180.
18 Tattoli I, Travassos LH, Carneiro LA, Magalhaes JG, Girardin SE. The Nodosome: Nod1 and Nod2 control bacterial infections and inflammation. *Semin Immunopathol* 2007; **29**: 289–301.
19 Hsu YM, Zhang Y, You Y, Wang D, Li H, Duramad O *et al*. The adaptor protein CARD9 is required for innate immune responses to intracellular pathogens. *Nat Immunol* 2007; **8**: 198–205.
20 Liston P, Roy N, Tamai K, Lefebvre C, Baird S, Cherton-Horvat G *et al*. Suppression of apoptosis in mammalian cells by NAIP and a related family of IAP genes. *Nature* 1996; **379**: 349–353.
21 Case CL, Shin S, Roy CR. Asc and Ipaf Inflammasomes direct distinct pathways for caspase-1 activation in response to *Legionella pneumophila*. *Infect Immun* 2009; **77**: 1981–1991.
22 Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. *Mol Cell* 2002; **10**: 417–426.
23 Miao EA, Andersen-Nissen E, Warren SE, Aderem A. TLR5 and Ipaf: dual sensors of bacterial flagellin in the innate immune system. *Semin Immunopathol* 2007; **29**: 275–288.
24 Shaw PJ, Lamkanfi M, Kanneganti TD. NOD-like receptor (NLR) signaling beyond the inflammasome. *Eur J Immunol* 2010; **40**: 624–627.
25 Ren T, Zamboni DS, Roy CR, Dietrich WF, Vance RE. Flagellin-deficient *Legionella* mutants evade caspase-1- and Naip5-mediated macrophage immunity. *PLoS Pathog* 2006; **2**: e18.
26 Zamboni DS, Kobayashi KS, Kohlsdorf T, Ogura Y, Long EM, Vance RE *et al*. The Birc1e cytosolic pattern-recognition receptor contributes to the detection and control of *Legionella pneumophila* infection. *Nat Immunol* 2006; **7**: 318–325.
27 Hsu LC, Kobayashi KS, Kohlsdorf T, Ogura Y, Long EM, Vance RE *et al*. A NOD2–NALP1 complex mediates caspase-1-dependent IL-1beta secretion in response to *Bacillus anthracis* infection and muramyl dipeptide. *Proc Natl Acad Sci USA* 2008; **105**: 7803–7808.
28 Ferwerda G, Ali SR, McGillivray S, Tseng PH, Mariathasan S, Humke EW *et al*. Engagement of NOD2 has a dual effect on proIL-1beta mRNA transcription and secretion of bioactive IL-1beta. *Eur J Immunol* 2008; **38**: 184–191.
29 Poyet JL, Srinivasula SM, Tnani M, Razmara M, Fernandes-Alnemri T, Alnemri ES *et al*. Identification of Ipaf, a human caspase-1-activating protein related to Apaf-1. *J Biol Chem* 2001; **276**: 28309–28313.
30 Muruve DA, Petrilli V, Zaiss AK, White LR, Clark SA, Ross J *et al*. The inflammasome recognizes cytosolic microbial and host DNA and triggers an innate immune response. *Nature* 2008; **452**: 103–107.
31 Hornung V, Ablasser A, Charrel-Dennis M, Bauernfeind F, Horvath G, Caffrey DR *et al*. AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC. *Nature* 2009; **458**: 514–518.
32 Schroder K, Muruve DA, Tschopp J. Innate immunity: cytoplasmic DNA sensing by the AIM2 inflammasome. *Curr Biol* 2009; **19**: R262–R265.
33 Mariathasan S, Newton K, Monack DM, Vucic D, French DM, Lee WP *et al*. Differential activation of the inflammasome by caspase-1 adaptors ASC and Ipaf. *Nature* 2004; **430**: 213–218.
34 Gross O, Poeck H, Bscheider M, Dostert C, Hannesschläger N, Endres S *et al*. Syk kinase signalling couples to the NLRP3 inflammasome for anti-fungal host defence. *Nature* 2009; **459**: 433–436.
35 Kanneganti TD, Body-Malapel M, Amer A, Park JH, Whitfield J, Franchi L *et al*. Critical role for *Cryopyrin/Nalp3* in activation of caspase-1 in response to viral infection and double-stranded RNA. *J Biol Chem* 2006; **281**: 36560–36568.
36 Pan Q, Mathison J, Fearns C, Kravchenko VV, Da Silva Correia J, Hoffman HM *et al*. MDP-induced interleukin-1beta processing requires NOD2 and *CIAS1/NALP3*. *J Leukoc Biol* 2007; **82**: 177–183.
37 Martinon F, Agostini L, Meylan E, Tschopp J. Identification of bacterial muramyl dipeptide as activator of the *NALP3/cryopyrin* inflammasome. *Curr Biol* 2004; **14**: 1929–1934.
38 Lightfield KL, Persson J, Brubaker SW, Witte CE, von Moltke J, Dunipace EA *et al*. Critical function for Naip5 in inflammasome activation by a conserved carboxy-terminal domain of flagellin. *Nat Immunol* 2008; **9**: 1171–1178.
39 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.
40 Craven RR, Gao X, Allen IC, Gris D, Bubeck Wardenburg J, McElvania-Tekippe E *et al*. *Staphylococcus aureus* alpha-hemolysin activates the NLRP3-inflammasome in human and mouse monocytic cells. *PLoS One* 2009; **4**: e7446.
41 Gurcel L, Abrami L, Girardin S, Tschopp J, van der Goot FG. Caspase-1 activation of lipid metabolic pathways in response to bacterial pore-forming toxins promotes cell survival. *Cell* 2006; **126**: 1135–1145.
42 Ozoren N, Masumoto J, Franchi L, Kanneganti TD, Body-Malapel M, Erturk I *et al*. Distinct roles of TLR2 and the adaptor ASC in IL-1beta/IL-18 secretion in response to *Listeria* monocytogenes. *J Immunol* 2006; **176**: 4337–4342.
43 Boyden ED, Dietrich WF. *Nalp1b* controls mouse macrophage susceptibility to anthrax lethal toxin. *Nat Genet* 2006; **38**: 240–244.
44 Martinon F, Petrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the *NALP3* inflammasome. *Nature* 2006; **440**: 237–241.
45 Eisenbarth SC, Colegio OR, O'Connor W, Sutterwala FS, Flavell RA. Crucial role for the *Nalp3* inflammasome in the immunostimulatory properties of aluminium adjuvants. *Nature* 2008; **453**: 1122–1126.
46 Dostert C, PÃŠtrilli V, van Bruggen R, Steele C, Mossman BT, Tschopp J. Innate immune activation through *Nalp3* inflammasome sensing of asbestos and silica. *Science* 2008; **320**: 674–677.
47 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 USA* 2008; **105**: 9035–9040.
48 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.
49 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.
50 Kahlenberg JM, Dubyak GR. Mechanisms of caspase-1 activation by P2X7 receptor-mediated K^+ release. *Am J Physiol Cell Physiol* 2004; **286**: C1100–C1108.
51 Laliberte RE, Eggler J, Gabel CA. ATP treatment of human monocytes promotes caspase-1 maturation and externalization. *J Biol Chem* 1999; **274**: 36944–36951.
52 Kanneganti TD, Lamkanfi M, Kim YG, Chen G, Park JH, Franchi L *et al*. Pannexin-1-mediated recognition of bacterial molecules activates the cryopyrin inflammasome independent of Toll-like receptor signaling. *Immunity* 2007; **26**: 433–443.
53 Locovei S, Bao L, Dahl G. Pannexin 1 in erythrocytes: function without a gap. *Proc Natl Acad Sci USA* 2006; **103**: 7655–7659.
54 Cruz CM, Rinna A, Forman HJ, Ventura AL, Persechini PM, Ojcius OM *et al*. ATP activates a reactive oxygen species-dependent oxidative stress response and secretion of proinflammatory cytokines in macrophages. *J Biol Chem* 2007; **282**: 2871–2879.
55 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.
56 Shio MT, Eisenbarth SC, Savaria M, Vinet AF, Bellemare MJ, Harder KW *et al*. Malarial hemozoin activates the NLRP3 inflammasome through Lyn and Syk kinases. *PLoS Pathog* 2009; **5**: e1000559.
57 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.
58 Rutault K, Alderman C, Chain BM, Katz DR. Reactive oxygen species activate human peripheral blood dendritic cells. *Free Radic Biol Med* 1999; **26**: 232–238.
59 Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol* 2009; **27**: 519–550.
60 Hawkins PN, Lachmann HJ, McDermott MF. Interleukin-1-receptor antagonist in the Muckle–Wells syndrome. *N Engl J Med* 2003; **348**: 2583–2584.
61 Chen CJ, Shi Y, Hearn A, Fitzgerald K, Golenbock D, Reed G *et al*. MyD88-dependent IL-1 receptor signaling is essential for gouty inflammation stimulated by monosodium urate crystals. *J Clin Invest* 2006; **116**: 2262–2271.
62 Bauernfeind FG, Horvath G, Stutz A, Alnemri ES, MacDonald K, Speert D *et al*. Cutting edge: NF-kappaB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. *J Immunol* 2009; **183**: 787–791.
63 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.
64 Kool M, Petrilli V, de Smedt T, Rolaz A, Hammad H, van Nimwegen M *et al*. Cutting edge: alum adjuvant stimulates inflammatory dendritic cells through activation of the *NALP3* inflammasome. *J Immunol* 2008; **181**: 3755–3759.
65 Sutterwala FS, Ogura Y, Szczepanik M, Lara-Tejero M, Lichten-Berger GS, Grant EP *et al*. Critical role for *NALP3/CIAS1/Cryopyrin* in innate and adaptive immunity through its regulation of caspase-1. *Immunity* 2006; **24**: 317–327.

66 Meylan E, Tschopp J, Karin M. Intracellular pattern recognition receptors in the host response. *Nature* 2006; **442**: 39–44.
67 Sugawara S, Uehara A, Nochi T, Yamaguchi T, Ueda H, Sugiyama A *et al*. Neutrophil proteinase 3-mediated induction of bioactive IL-18 secretion by human oral epithelial cells. *J Immunol* 2001; **167**: 6568–6575.
68 Puren AJ, Fantuzzi G, Dinarello CA. Gene expression, synthesis, and secretion of interleukin 18 and interleukin 1beta are differentially regulated in human blood mononuclear cells and mouse spleen cells. *Proc Natl Acad Sci USA* 1999; **96**: 2256–2261.
69 Gattorno M, Tassi S, Carta S, Delfino L, Ferlito F, Pelagatti MA *et al*. Pattern of interleukin-1beta secretion in response to lipopolysaccharide and ATP before and after interleukin-1 blockade in patients with *CIAS1* mutations. *Arthritis Rheum* 2007; **56**: 3138–3148.
70 Shinkai K, McCalmont TH, Leslie KS. Cryopyrin-associated periodic syndromes and autoinflammation. *Clin Exp Dermatol* 2008; **33**: 1–9.
71 Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle–Wells syndrome. *Nat Genet* 2001; **29**: 301–305.
72 Aganna E, Martinon F, Hawkins PN, Ross JB, Swan DC, Booth DR *et al*. Association of mutations in the *NALP3*/*CIAS1*/*PYPAF1* gene with a broad phenotype including recurrent fever, cold sensitivity, sensorineural deafness, and AA amyloidosis. *Arthritis Rheum* 2002; **46**: 2445–2452.
73 Touitou I, Lesage S, McDermott M, Cuisset L, Hoffman H, Dode C *et al*. Infevers: an evolving mutation database for auto-inflammatory syndromes. *Hum Mutat* 2004; **24**: 194–198.
74 Masters SL, Simon A, Aksentijevich I, Kastner DL. Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease (*). *Annu Rev Immunol* 2009; **27**: 621–668.
75 Neven B, Callebaut I, Prieur AM, Feldmann J, Bodemer C, Lepore L *et al*. Molecular basis of the spectral expression of *CIAS1* mutations associated with phagocytic cell-mediated autoinflammatory disorders CINCA/NOMID, MWS, and FCU. *Blood* 2004; **103**: 2809–2815.
76 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.
77 Meng G, Zhang F, Fuss I, Kitani A, Strober W. A mutation in the NLRP3 gene causing inflammasome hyperactivation potentiates Th17 cell-dominant immune responses. *Immunity* 2009; **30**: 860–874.
78 Aksentijevich I, Remmers EF, Goldbach-Mansky R, Reiff A, Kastner DL. Mutational analysis in neonatal-onset multisystem inflammatory disease: comment on the articles by Frenkel *et al* and Saito *et al*. *Arthritis Rheum* 2006; **54**: 2703–2704; author reply 2704–2705.
79 Brydges SD, Mueller JL, McGeough MD, Pena CA, Misaghi A, Gandhi C *et al*. Inflammasome-mediated disease animal models reveal roles for innate but not adaptive immunity. *Immunity* 2009; **30**: 875–887.
80 Fujisawa A, Kambe N, Saito M, Nishikomori R, Tanizaki H, Kanazawa N *et al*. Disease-associated mutations in *CIAS1* induce cathepsin B-dependent rapid cell death of human THP-1 monocytic cells. *Blood* 2007; **109**: 2903–2911.
81 Saito M, Nishikomori R, Kambe N, Fujisawa A, Tanizaki H, Takeichi K *et al*. Disease-associated *CIAS1* mutations induce monocyte death, revealing low-level mosaicism in mutation-negative cryopyrin-associated periodic syndrome patients. *Blood* 2008; **111**: 2132–2141.
82 Kambe N, Satoh T, Tanizaki H, Fujisawa A, Saito MK, Nishikomori R. Enhanced NF-kappaB activation with an inflammasome activator correlates with activity of autoinflammatory disease associated with NLRP3 mutations outside of exon 3: comment on the article by Jeru *et al*. *Arthritis Rheum* 2010; **62**: 3123–3124; author reply 3124–3125.
83 Jeru I, Marlin S, Le Borgne G, Cochet E, Normand S, Duquesnoy P *et al*. Functional consequences of a germline mutation in the leucine-rich repeat domain of NLRP3 identified in an atypical autoinflammatory disorder. *Arthritis Rheum* 2010; **62**: 1176–1185.
84 Arostegui JI, Lopez Saldaña MD, Pascal M, Clemente D, Aymerich M, Balaguer F *et al*. A somatic NLRP3 mutation as a cause of a sporadic case of chronic infantile neurologic, cutaneous, articular syndrome/neonatal-onset multisystem inflammatory disease: novel evidence of the role of low-level mosaicism as the pathophysiologic mechanism underlying mendelian inherited diseases. *Arthritis Rheum* 2010; **62**: 1158–1166.
85 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.
86 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.
87 Schoultz I, Verma D, Halfvarsson J, Torkvist L, Fredrikson M, Sjöqvist 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.
88 Lewis GJ, Massey DC, Zhang H, Bredin F, Tremelling M, Lee JC, *et al*. Genetic association between NLRP3 variants and Crohn's disease does not replicate in a large UK panel. Inflamm Bowel Dis 2010 Oct 25. [Epub ahead of print] DOI: 10.1002/ibd.21499.
89 Aksentijevich I, Nowak M, Mallah M, Chae JJ, Watford WT, Hofmann SR *et al*. *De novo CIAS1* mutations, cytokine activation, and evidence for genetic heterogeneity in patients with neonatal-onset multisystem inflammatory disease (NOMID): a new member of the expanding family of pyrin-associated autoinflammatory diseases. *Arthritis Rheum* 2002; **46**: 3340–3348.
90 Jeru I, Duquesnoy P, Fernandes-Alnemri T, Cochet E, Yu JW, Lackmy-Port-Lis M *et al*. Mutations in *NALP12* cause hereditary periodic fever syndromes. *Proc Natl Acad Sci USA* 2008; **105**: 1614–1619.
91 Lich JD, Williams KL, Moore CB, Arthur JC, Davis BK, Taxman DJ *et al*. Monarch-1 suppresses non-canonical NF-kappaB activation and p52-dependent chemokine expression in monocytes. *J Immunol* 2007; **178**: 1256–1260.
92 Pinheiro AS, Proell M, Eibl C, Page R, Schwarzenbacher R, Peti W *et al*. Three-dimensional structure of the NLRP7 pyrin domain: insight into pyrin–pyrin-mediated effector domain signaling in innate immunity. *J Biol Chem* 2010; **285**: 27402–27410.
93 Kinoshita T, Wang Y, Hasegawa M, Imamura R, Suda T. *PYPAF3*, a PYRIN-containing APAF-1-like protein, is a feedback regulator of caspase-1-dependent interleukin-1beta secretion. *J Biol Chem* 2005; **280**: 21720–21725.
94 Deveault C, Qian JH, Chebaro W, Ao A, Gilbert L, Mehio A. NLRP7 mutations in women with diploid androgenetic and triploid moles: a proposed mechanism for mole formation. *Hum Mol Genet* 2009; **18**: 888–897.
95 Yu JW, Fernandes-Alnemri T, Datta P, Wu J, Juliana C, Solorzano L *et al*. Pyrin activates the ASC pyroptosome in response to engagement by autoinflammatory *PSTPIP1* mutants. *Mol Cell* 2007; **28**: 214–227.
96 Chae JJ, Komarow HD, Cheng J, Wood G, Raben N, Liu PP *et al*. Targeted disruption of pyrin, the FMF protein, causes heightened sensitivity to endotoxin and a defect in macrophage apoptosis. *Mol Cell* 2003; **11**: 591–604.
97 Jeru I, Hayrapetyan H, Duquesnoy P, Sarkisian T, Amselem S. *PYPAF1* nonsense mutation in a patient with an unusual autoinflammatory syndrome: role of *PYPAF1* in inflammation. *Arthritis Rheum* 2006; **54**: 508–514.
98 Master SS, Rampini SK, Davis AS, Keller C, Ehlers S, Springer B *et al*. *Mycobacterium tuberculosis* prevents inflammasome activation. *Cell Host Microbe* 2008; **3**: 224–232.
99 Pontillo A, Brandao LA, Guimaraes RL, Segat L, Athanasakis E, Crovella S. A 3'UTR SNP in NLRP3 gene is associated with susceptibility to HIV-1 infection. *J Acquir Immune Defic Syndr* 2010; **54**: 236–240.
100 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.
101 Ichinohe T, Lee HK, Ogura Y, Flavell R, Iwasaki A. Inflammasome recognition of influenza virus is essential for adaptive immune responses. *J Exp Med* 2009; **206**: 79–87.
102 Thomas PG, Dash P, Aldridge JR, Jr, Ellebedy AH, Reynolds C, Funk AJ *et al*. The intracellular sensor NLRP3 mediates key innate and healing responses to influenza A virus *via* the regulation of caspase-1. *Immunity* 2009; **30**: 566–575.
103 Lev-Sagie A, Prus D, Linhares IM, Lavy Y, Ledger WJ, Witkin SS. Polymorphism in a gene coding for the inflammasome component *NALP3* and recurrent vulvovaginal candidiasis in women with vulvar vestibulitis syndrome. *Am J Obstet Gynecol* 2009; **200**: 303–306.
104 Witkin SS, Bierhals K, Linhares I, Normand N, Dieterle S, Neuer A. Genetic polymorphism in an inflammasome component, cervical mycoplasma detection and female infertility in women undergoing *in vitro* fertilization. *J Reprod Immunol* 2010; **84**: 171–175.
105 Wang W, Stassen FR, Surcel HM, Öhman H, Tiitinen A, Paavonen J *et al*. Analyses of polymorphisms in the inflammasome-associated NLRP3 and *miRNA-146A* genes in the susceptibility to and tubal pathology of Chlamydia trachomatis infection. *Drugs Today (Barc)* 2009; **45**Suppl B: 95–103.
106 McGonagle D, McDermott MF. A proposed classification of the immunological diseases. *PLoS Med* 2006; **3**: e297.
107 Sutton C, Brereton C, Keogh B, Mills KH, Lavelle EC. A crucial role for interleukin (IL)-1 in the induction of IL-17-producing T cells that mediate autoimmune encephalomyelitis. *J Exp Med* 2006; **203**: 1685–1691.
108 Chung Y, Chang SH, Martinez GJ, Yang XO, Nurieva R, Kang HS *et al*. Critical regulation of early Th17 cell differentiation by interleukin-1 signaling. *Immunity* 2009; **30**: 576–587.
109 Acosta-Rodriguez EV, Napolitani G, Lanzavecchia A, Sallusto F. Interleukins 1beta and 6 but not transforming growth factor-beta are essential for the differentiation of interleukin 17-producing human T helper cells. *Nat Immunol* 2007; **8**: 942–949.
110 van Beelen AJ, Zelinkova Z, Taanman-Kueter EW, Muller FJ, Hommes DW, Zaat SA *et al*. Stimulation of the intracellular bacterial sensor NOD2 programs dendritic cells to promote interleukin-17 production in human memory T cells. *Immunity* 2007; **27**: 660–669.
111 Nistala K, Moncrieffe H, Newton KR, Varsani H, Hunter P, Wedderburn LR. Interleukin-17-producing T cells are enriched in the joints of children with arthritis, but have a reciprocal relationship to regulatory T cell numbers. *Arthritis Rheum* 2008; **58**: 875–887.
112 Tzartos JS, Friese MA, Craner MJ, Palace J, Newcombe J, Esiri MM *et al*. Interleukin-17 production in central nervous system-infiltrating T cells and glial cells is associated with active disease in multiple sclerosis. *Am J Pathol* 2008; **172**: 146–155.
113 Pernis AB. Th17 cells in rheumatoid arthritis and systemic lupus erythematosus. *J Intern Med* 2009; **265**: 644–652.
114 Lubberts E. Th17 cytokines and arthritis. *Semin Immunopathol* 2010; **32**: 43–53.
115 van den Berg WB, Miossec P. IL-17 as a future therapeutic target for rheumatoid arthritis. *Nat Rev Rheumatol* 2009; **5**: 549–553.

116 Evans HG, Gullick NJ, Kelly S, Pitzalis C, Lord GM, Kirkham BW *et al*. *In vivo* activated monocytes from the site of inflammation in humans specifically promote Th17 responses. *Proc Natl Acad Sci USA* 2009; **106**: 6232–6237.
117 Day TG, Ramanan AV, Hinks A, Lamb R, Packham J, Wise C *et al*. Autoinflammatory genes and susceptibility to psoriatic juvenile idiopathic arthritis. *Arthritis Rheum* 2008; **58**: 2142–2146.
118 Agarwal S, Misra R, Aggarwal A. Interleukin 17 levels are increased in juvenile idiopathic arthritis synovial fluid and induce synovial fibroblasts to produce proinflammatory cytokines and matrix metalloproteinases. *J Rheumatol* 2008; **35**: 515–519.
119 Rosengren S, Hoffman HM, Bugbee W, Boyle DL. Expression and regulation of cryopyrin and related proteins in rheumatoid arthritis synovium. *Ann Rheum Dis* 2005; **64**: 708–714.
120 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.
121 Hoffman HM, Gregory SG, Mueller JL, Tresierras M, Broide DH, Kolodner RD. Fine structure mapping of *CIAS1*: identification of an ancestral haplotype and a common FCAS mutation, *L353P*. *Hum Genet* 2003; **112**: 209–216.
122 McGovern DP, Butler H, Ahmad T, Paolucci M, van Heel DA, Negoro K *et al*. *TUCAN* (*CARD8*) genetic variants and inflammatory bowel disease. *Gastroenterology* 2006; **131**: 1190–1196.
123 Hitomi Y, Ebisawa M, Tomikawa M, Imai T, Komata T, Hirota T *et al*. Associations of functional NLRP3 polymorphisms with susceptibility to food-induced anaphylaxis and aspirin-induced asthma. *J Allergy Clin Immunol* 2009; **124**: 779–785.
124 Kambe N, Nakamura Y, Saito M, Nishikomori R. The inflammasome, an innate immunity guardian, participates in skin urticarial reactions and contact hypersensitivity. *Allergol Int* 2010; **59**: 105–113.
125 Nakamura Y, Kambe N, Saito M, Nishikomori R, Kim YG, Murakami M *et al*. Mast cells mediate neutrophil recruitment and vascular leakage through the NLRP3 inflammasome in histamine-independent urticaria. *J Exp Med* 2009; **206**: 1037–1046.
126 Jin Y, Mailloux CM, Gowan K, Riccardi SL, LaBerge G, Bennett DC *et al*. *NALP1* in vitiligo-associated multiple autoimmune disease. *N Engl J Med* 2007; **356**: 1216–1225.
127 Jin Y, Birlea SA, Fain PR, Spritz RA. Genetic variations in *NALP1* are associated with generalized vitiligo in a Romanian population. *J Invest Dermatol* 2007; **127**: 2558–2562.
128 Magitta NF, Boe Wolff AS, Johansson S, Skinningsrud B, Lie BA, Myhr KM *et al*. A coding polymorphism in *NALP1* confers risk for autoimmune Addison's disease and type 1 diabetes. *Genes Immun* 2009; **10**: 120–124.
129 Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 2007; **447**: 661–678.
130 Todd JA, Walker NM, Cooper JD, Smyth DJ, Downes K, Plagnol V *et al*. Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. *Nat Genet* 2007; **39**: 857–864.
131 Omi T, Kumada M, Kamesaki T, Okuda H, Munkhtulga L, Yanagisawa Y *et al*. An intronic variable number of tandem repeat polymorphisms of the cold-induced autoinflammatory syndrome 1 (*CIAS1*) gene modifies gene expression and is associated with essential hypertension. *Eur J Hum Genet* 2006; **14**: 1295–1305.
132 Rawat R, Cohen TV, Ampong B, Francia D, Henriques-Pons A, Hoffman EP *et al*. Inflammasome up-regulation and activation in dysferlin-deficient skeletal muscle. *Am J Pathol* 2010; **176**: 2891–2900.
133 Masters SL, Dunne A, Subramanian SL, Hull RL, Tannahill GM, Sharp FA *et al*. Activation of the NLRP3 inflammasome by islet amyloid polypeptide provides a mechanism for enhanced IL-1beta in type 2 diabetes. *Nat Immunol* 2010; **11**: 897–904.
134 Tsutsui H, Imamura M, Fujimoto J, Nakanishi K. The TLR4/TRIF-mediated activation of NLRP3 inflammasome underlies endotoxin-induced liver injury in mice. *Gastroenterol Res Pract* 2010; **2010**: 641865.
135 Gu LQ, Li FY, Zhao L, Liu Y, Chu Q, Zang XX *et al*. Association of XIAP and P2X7 receptor expression with lymph node metastasis in papillary thyroid carcinoma. *Endocrine* 2010; **38**: 276–282.
136 Ravaglia G, Paola F, Maioli F, Martelli M, Montesi F, Bastagli L *et al*. *Interleukin-1beta* and *interleukin-6* gene polymorphisms as risk factors for AD: a prospective study. *Exp Gerontol* 2006; **41**: 85–92.
137 Forlenza OV, Diniz BS, Nunes PV, Memória CM, Yassuda MS, Gattaz WF *et al*. Increased serum IL-1beta level in Alzheimer's disease and mild cognitive impairment. *Dement Geriatr Cogn Disord* 2009; **28**: 507–512.
138 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.