

NOD-Like Receptors in Infection, Immunity, and Diseases

Young Keun Kim¹, Jeon-Soo Shin^{2,3,4}, and Moon H. Nahm^{5,6}

¹Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju;

²Department of Microbiology, ³Brain Korea 21 PLUS for Medical Science, ⁴Severance Biomedical Science Institute and Institute for Immunology and Immunological Diseases, Yonsei University College of Medicine, Seoul, Korea;

Departments of ⁵Pathology and ⁶Microbiology, University of Alabama at Birmingham, Birmingham, AL, USA.

Nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) are pattern-recognition receptors similar to toll-like receptors (TLRs). While TLRs are transmembrane receptors, NLRs are cytoplasmic receptors that play a crucial role in the innate immune response by recognizing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Based on their N-terminal domain, NLRs are divided into four subfamilies: NLRA, NLRB, NLRC, and NLRP. NLRs can also be divided into four broad functional categories: inflammasome assembly, signaling transduction, transcription activation, and autophagy. In addition to recognizing PAMPs and DAMPs, NLRs act as a key regulator of apoptosis and early development. Therefore, there are significant associations between NLRs and various diseases related to infection and immunity. NLR studies have recently begun to unveil the roles of NLRs in diseases such as gout, cryopyrin-associated periodic fever syndromes, and Crohn's disease. As these new associations between NLRs and diseases may improve our understanding of disease pathogenesis and lead to new approaches for the prevention and treatment of such diseases, NLRs are becoming increasingly relevant to clinicians. In this review, we provide a concise overview of NLRs and their role in infection, immunity, and disease, particularly from clinical perspectives.

Key Words: Innate immunity, pattern recognition receptors, NOD-like receptors, inflammasomes

INTRODUCTION

Essential to a host's immune responses to pathogens is discrimination of non-self molecules from self molecules. The innate immune system, which plays a pivotal role in the first line of host defense against infection, is equipped with pattern recognition receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs) not found in the host and then activate the host's immune response.^{1,2} Many PRRs have been

identified since toll-like receptors (TLRs) were first identified as PRRs about two decades ago.³ Based on distinct genetic and functional differences, PRRs are currently classified into five families:⁴ TLRs, nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs), retinoic acid inducible gene-I (RIG-I)-like receptors (RLRs), C-type lectins (CTLs), and absent-in-melanoma (AIM)-like receptors (ALRs). TLRs and CTLs are located in the plasma membrane, while the NLRs, RLRs, and ALRs are intracellular PRRs.

The recognition by NLRs of PAMPs and damage-associated molecular patterns (DAMPs) from microbial structures or self- or environment-derived molecules leads to the induction of the innate immune response.⁵ In humans, there are 22 known NLRs,⁶ all of which are associated with many human diseases.⁷ Readers who wish to know further basic aspects of NLRs should consult other excellent and recent reviews.^{4,7} In this review, we will provide a concise overview of the members of the NLR family and their role in infection, immunity, and disease, especially from clinical perspectives.

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Corresponding author: Dr. Moon H. Nahm, Departments of Pathology and Microbiology, University of Alabama at Birmingham, Bevell Building, Room 614 (BBRB 614), 845 19th Street South, Birmingham, AL 35294, USA.
Tel: 1-205-934-0163, Fax: 1-205-975-2149, E-mail: nahm@uab.edu

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CLASSIFICATION AND STRUCTURE OF THE NLR FAMILY

NLR proteins have a common domain organization with a central NOD (NACHT: NAIP, CIITA, HET-E, and TP-2), N-terminal effector domain, and C-terminal leucine-rich repeats (LRRs) (Fig. 1).⁶ The NACHT domain (consisting of seven distinct conserved motifs, including the ATP/GTPase-specific P-loop, the Mg²⁺-binding site, and five more-specific motifs) is involved in dNTPase activity and oligomerization.⁸ The C-terminal LRR domain is involved in ligand binding or activator sensing. The N-terminal domain performs effector functions by interacting with other proteins. There are four recognizable N-terminal domains, which are used to classify NLRs into four subfamilies: the acidic transactivation domain (NLRA), the baculoviral inhibitory repeat-like domain (NLRB), the caspase activation and recruitment domain (CARD; NLRC), and the pyrin domain (NLRP) (Fig. 1).⁶

The NLRA subfamily includes only one member, the MHC-II transactivator (CIITA). Similarly, the human NLRB subfamily has only one member, NAIP. The NLRC subfamily consists of six members: NLRC1 (NOD1), NLRC2 (NOD2), NLRC3, NLRC4, NLRC5, and NLRX1. NLRC3, NLRC5, and NLRX1 are classified as belonging to the NLRC subfamily due to their homology and phylogenetic relationship, although their N-terminal domains have not been named.^{4,6,9} The NLRP subfamily consists of 14 members, NLRP1-14. No LRR domain is observed in NLRP10, which may indicate a role for this protein as a signaling adaptor rather than as an NLR sensor.⁷

FUNCTION OF NLRs

The NLRs recognize various ligands from microbial pathogens (peptidoglycan, flagellin, viral RNA, fungal hyphae, etc.), host cells (ATPs, cholesterol crystals, uric acid, etc.), and environmental sources (alum, asbestos, silica, alloy particles, UV radiation, skin irritants, etc.). Most NLRs act as PRRs, recognizing the above ligands and activate inflammatory responses. However, some NLRs may not act as PRRs but instead respond to cytokines such as interferons. The activated NLRs show various functions that can be divided into four broad categories: inflammasome formation, signaling transduction, transcription activation, and autophagy (Fig. 2).⁴ Below, we describe each function.

Inflammasome formation

Inflammasome is a multimeric protein complex that activates caspase-1.¹⁰ Activation of caspase-1 results in the processing and maturation of proinflammatory cytokine interleukin (IL)-1 β and IL-18 as well as an inflammatory cell death termed pyroptosis (Fig. 2).¹⁰ As IL-1 β is a potent mediator of inflammatory responses, its overproduction is associated with many autoinflammatory syndromes, such as gout and periodic fever syndromes, which include Familial Mediterranean fever (FMF) and cryopyrin-associated periodic fever syndromes (CAPS).^{11,12} Pyroptosis is an inflammatory cell death that results in the release of DAMPs and reinforcement of the immune response. Inflammasomes are activated by eight members of NLRs (NLRP1, NLRP2, NLRP3, NLRP6, NLRP7, NLRP12, NLRC4, and NAIP) and AIM2, which is not discussed in this review (Table 1).^{7,10}

Inflammasome formation is triggered by either pathogen-associated or sterile activators. Pathogen-associated activators of inflammasomes include various PAMPs derived from bacteria

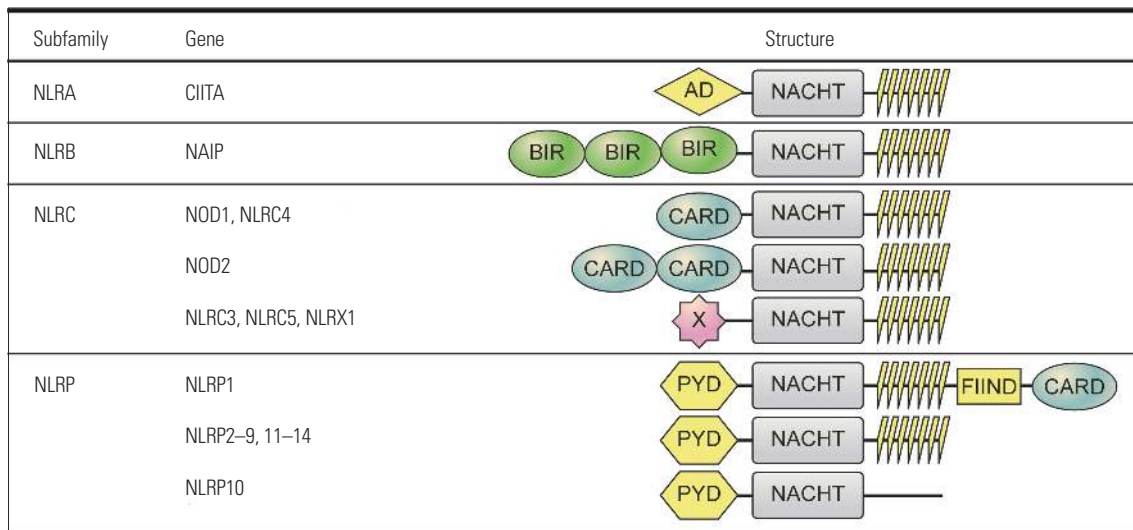


Fig. 1. Classification and protein structure of human NOD-like receptor family (based on Ref. 6). AD, acidic transactivation domain; NACHT, for NAIP, CIITA, HET-T, and TP-1; BIR, baculovirus inhibitor of apoptosis repeat; CARD, caspase activation and recruitment domain; X, unidentified; PYD, pyrin domain, FIIND, function to find domain; leucine-rich repeat; NOD, nucleotide-binding and oligomerization domain.

[pore-forming toxins, lethal toxins, flagellin/rod proteins, muramyl dipeptide (MDP), RNA, and DNA], viruses (RNA and M2 protein), fungus (β -glucans, hyphae, mannan, and zymosan), and protozoa (hemozoin).¹⁰ Sterile activators include self-derived DAMPs (ATP, cholesterol crystals, monosodium urate/calcium pyrophosphate dihydrate crystals, glucose, amyloid β , and hyaluronan) and environment-derived stimulants (alum, asbestos, silica, alloy particles, UV radiation, and skin irritants).¹⁰ When the eight NLRs detect these PAMPs and DAMPs (Fig. 2), NLRs recruit apoptosis-associated speck-like protein containing a CARD (ASC) via a pyrin-pyrin domain interaction.¹³ Subsequently, pro-caspase-1 binds to ASC through CARD-CARD domains, which completes the formation of inflammasome.¹³ NLRP1 contains the CARD domain that can interact directly with procaspase-1 and can thus form inflammasomes without ASC.¹⁴ NLRC4, which has no pyrin domain, can form two types of inflammasomes. The recruitment of ASC to the NLRC4 inflammasome results in IL- 1β and IL-18 production, while NLRC4 inflammasome formed without the recruitment of ASC results in pyroptosis.¹⁵

NAIP and NLRC4 form NAIP-NLRC4 inflammasomes upon recognition of bacterial flagellin and the bacterial type III secretion system.¹⁶⁻¹⁸ Therefore, NAIP and NLRC4 are linked to sus-

ceptibility to bacterial infections.^{7,19} NLRP1 inflammasomes are activated by MDP,¹⁴ a common peptidoglycan motif in both Gram-positive and Gram-negative bacteria, and by anthrax lethal toxin.²⁰ NLRP3-inflammasome activation is triggered by various PAMPs and DAMPs including alum, silica, ATP, and uric acid.⁴ NLRP7 can recognize bacterial lipopeptide.²¹

Signaling transduction

NOD1 recognizes γ -D-glutamyl-meso-diaminopimelic acid (iE-DAP), which is a peptidoglycan component found only in Gram-negative bacteria.²² NOD2 recognizes MDP from both Gram-positive and Gram-negative bacteria.²³ Both NOD1 and NOD2 activate the nuclear factor kappa B (NF- κ B) signaling pathway, which plays an important role in regulating the host immune response (Fig. 2). Specifically, recognition of cytosolic peptidoglycan ligands allows NOD1/NOD2 to interact with a common downstream adaptor molecule, receptor interacting protein 2 (RIP2), which is a serine/threonine kinase that can activate NF- κ B.²⁴ Activated NF- κ B can move to the nucleus and enhance transcription of proinflammatory cytokines.^{22,25} In contrast to NOD1/NOD2, NLRC3, and NLRP2/4 act as negative regulators of the NF- κ B pathway by modifying tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6) (Fig. 2).²⁶⁻²⁹

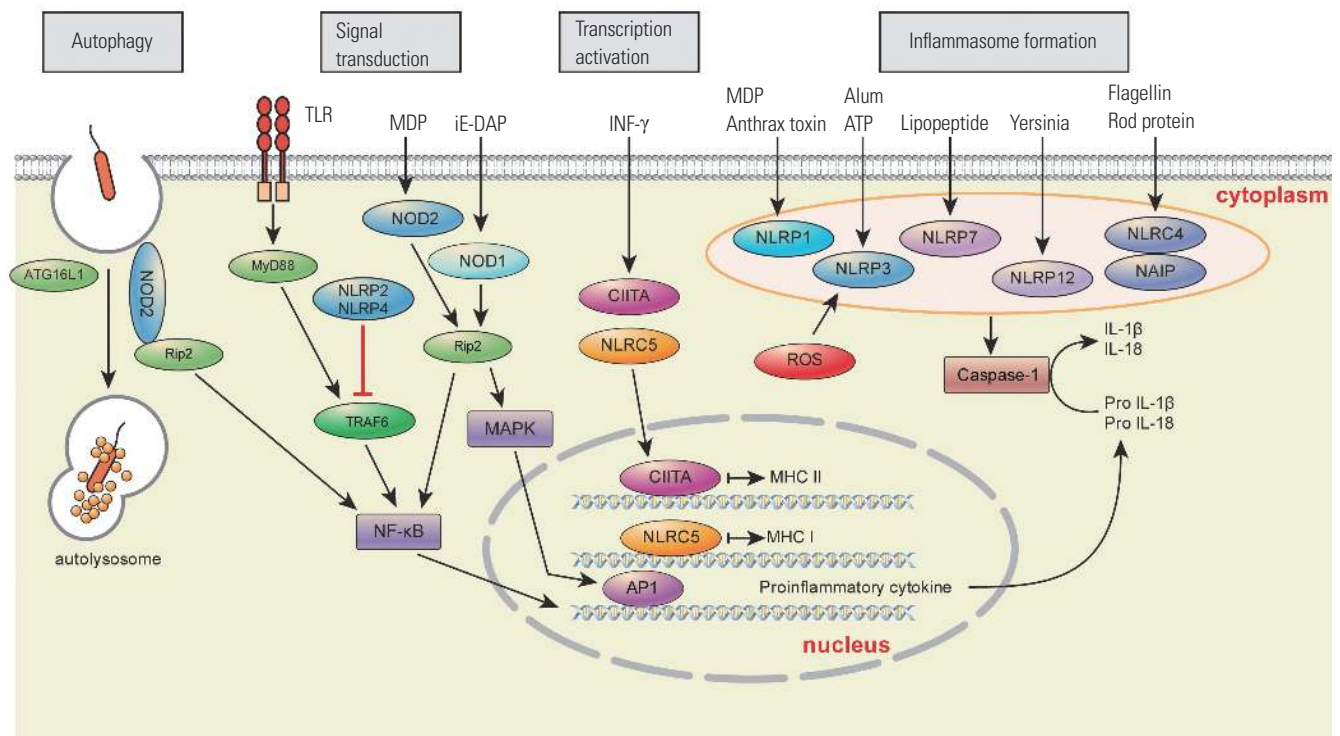


Fig. 2 Functions of NOD-like receptors. The NLRs activities can be divided into four broad categories; autophagy, signal transduction, transcription activation, and inflammasome formation. NOD2 induces autophagy to remove pathogens by recruiting ATG16L1 to the plasma membrane at the site of bacterial entry. NOD1 and NOD2 recognize γ -D-glutamyl-meso-diaminopimelic acid (iE-DAP) and muramyl dipeptide (MDP) respectively; thereafter they activate the NF- κ B and MAPK signaling pathways. NLRP2 and NLRP4 act as negative regulators of NF- κ B pathway by modifying TRAF6. CIITA and NLRC5 are transactivators of major histocompatibility complexes (MHC). Inflammasome-forming NLRs (orange circle) convert procytokines to active IL- 1β and IL-18 by activating caspase-1. NOD, nucleotide-binding and oligomerization domain; NLRs, NOD-like receptors; NF- κ B, nuclear factor kappa B; MAPK, mitogen-activated protein kinase; TRAF, tumor necrosis factor (TNF) receptor-associated factor; IL, interleukin; INF- γ , interferon- γ .

Table 1. Functions and Associated Diseases of Human NOD-Like Receptors

Sub-family	NLR	Signaling pathway	Function	Associated diseases	Ref.
NLRB	NLRA	MHC-II transcriptional regulator	Regulation of MHC-II expression	Bare lymphocyte syndrome, Hodgkin disease, and primary mediastinal B-cell lymphoma	35, 85
	NLRB	TAK1-dependent JNK1 activation, inflammasome assembly	Flagellin sensing, pyroptosis, inhibition of apoptosis	Increased susceptibility to legionella, spinal muscular dystrophy	18, 19, 77, 86
NLR	NOD1	RIP2-dependent NF-κB and MAPK activation	PRR for DAP	Asthma, inflammatory bowel diseases	22, 83, 84
	NOD2	RIP2-dependent NF-κB and MAPK activation	PRR for MDP and viral ssRNA, autophagy	Crohn's disease, Blau syndrome, atopic eczema, atopic dermatitis, susceptibility to leprosy and tuberculosis	23, 25, 34, 39, 75, 79-82
	NLRC3	Interaction with STING to reduce STING-TBK1 association	Negative regulation of T cell activation and TLR response		27, 29, 87
	NLRC4	Inflammasome formation	PRR for flagellin and rod protein, pyroptosis, phagosome maturation	Increased susceptibility to bacterial infection	7, 16, 17, 88
	NLRC5	MHC-I regulation, type I interferon response	MHC-I upregulation, regulates innate immune response		36, 89
	NLRX1	Mitochondria	ROS generation, viral-induced autophagy	Increased susceptibility to chronic hepatitis B	40, 90, 91
NLRP	NLRP1	Inflammasome formation	PRR for MDP, anthrax lethal toxin	Vitiligo, celiac disease, Addison's disease, type 1 diabetes, autoimmune thyroid disorders, systemic lupus erythematosus, systemic sclerosis, giant cell arteritis, congenital toxoplasmosis, rheumatoid arthritis, Alzheimer's disease, corneal intraepithelial dyskeratosis	14, 20, 57-69, 92
	NLRP2	Inflammasome formation	Negative regulation of NF-κB, embryonic development	Beckwith-Wiedemann syndrome	26, 70, 93, 94
	NLRP3	Inflammasome formation	PRR for DAMPs	Cryopyrin-associated periodic fever syndrome, gout, type 1 diabetes, celiac disease, psoriasis, increased susceptibility to HIV-1 infections, inflammatory bowel diseases, type 2 diabetes	4, 44, 46-48, 51-55, 95
	NLRP4	DTX4-dependent TBK1 degradation, beclin-1 dependent autophagy	Negative regulation of type I interferon, autophagy		28
	NLRP5	Unknown	Embryogenesis		96
	NLRP6	Inflammasome formation	Negative regulation of NF-κB	Colitis and colon cancer	30, 71

Table 1. Functions and Associated Diseases of Human NOD-Like Receptors (Continued)

Sub-family	NLR	Signaling pathway	Function	Associated diseases	Ref.
NLRP	NLRP7	Inflammasome formation	PRR for lipopeptide	Hydatidiform mole, testicular seminoma, endometrial cancer	21, 72-74
	NLRP8	Unknown	Unknown		
	NLRP9	Unknown	Unknown		
	NLRP10	Unknown	Dendritic cell migration	Increased susceptibility to bacterial infection, atopic dermatitis	7, 97, 98
	NLRP11	Unknown	Unknown		
	NLRP12	Inflammasome formation	Negative regulation of NF- κ B	Atopic dermatitis, periodic fever syndrome	31, 75, 76, 99
	NLRP13	Unknown	Unknown		
	NLRP14	Unknown	Spermatogenesis	Spermatogenic failure	100

PRR, pattern recognition receptor; DAP, diaminopimelic acid; MDP, muramyl dipeptide; TLR, toll-like receptor; ROS, reactive oxygen species; DAMPs, damage-associated molecular patterns; NOD, nucleotide-binding and oligomerization domain; NLR, NOD-like receptor; MHC, major histocompatibility complex; RIP2, receptor interacting protein 2; NF- κ B, nuclear factor kappa B; MAPK, mitogen-activated protein kinase; STING, stimulator of interferon genes; HIV, human immunodeficiency virus.

NLRP6 and NLRP12 are also suggested as negative regulators.^{30,31}

In addition to activating the NF- κ B pathway, NOD1/NOD2 activate the mitogen-activated protein kinase (MAPK)-signaling pathway, which results in proinflammatory cytokine secretion (Fig. 2).^{32,33} NOD2 can also sense viral ssRNA, after which it activates interferon production and antiviral defense.³⁴

Transcription activation

Antigen presentation by major histocompatibility complex (MHC) class I and II molecules is central to the function of the adaptive immune system. Therefore, the regulation of these MHC genes and their accessory molecules is crucial for the adaptive immune response. In 1993, NLRA (CIITA) was found to function as a transactivator of MHC class II gene expression. Complementary experiments showed that the NLRA fully corrected the MHC class II regulatory defect of cells from patients with bare lymphocyte syndrome. This rare genetic disorder is characterized by severe combined immunodeficiency and a complete lack of the expression of MHC class II molecules in all tissues.³⁵ Recent studies have shown that NLRC5 plays a crucial role in the expression of the MHC class I gene. NLRC5 induced by interferon- γ acts as a transactivator of the MHC class I gene by assembling regulatory factor X (RFX), cAMP-responsive-element-binding protein 1 (CREB1), activating transcription factor 1 (ATF1), and nuclear transcription factor Y (NFY) on the SXY module in the MHC class I promoter.^{36,37} Although MHC-I and -II expression depends on several transcription factors such as NF- κ B, the IFN regulatory factor family, RFX, CREB1, ATF1, and NFY, MHC expression requires the presence of the NLRA and NLRC5.^{4,37}

Autophagy

Autophagy is a fundamental cellular homeostatic mechanism in which cells autodigest parts of their cytoplasm for removal or turnover. Based on the target of degradation, autophagy has been described as mitophagy, reticulophagy, and pexophagy for autodigestion of the mitochondria, endoplasmic reticulum, and peroxisomes, respectively. In contrast to autophagy, xenophagy refers to an autophagic pathway that targets intracellular bacteria and viruses.³⁸ Autophagy is mediated by unique organelles called autophagosomes, which fuse with lysosomes and allow lysosomal enzymes to degrade the sequestered cytoplasmic materials in autolysosomes.³⁸ Autophagosome formation involves many autophagy-related (ATG) proteins.³⁸

NOD1 and NOD2 can induce autophagy to remove pathogens by recruiting ATG16L1 to the plasma membrane at the site of bacterial entry (Fig. 2).³⁹ NLRX1, located in mitochondria, regulates virus-induced autophagy by interacting with the Tu translation elongation factor of mitochondria (TUFM) that then interacts with ATG5-ATG12 and ATG16L1.⁴⁰ NLRP4 is known as a negative regulator of autophagic processes through an association with beclin1, one of the key initiators of the autophagic process.⁴¹

CLINICAL RELEVANCE OF NLR

In addition to NLRs playing a crucial role in defending against pathogens as a pattern recognition receptor, they also have other functions unrelated to pathogen detection, such as apoptosis and playing a role in early development. Therefore, their abnormalities are linked to various diseases associated with infections, inflammation, and cancer. Understanding their roles in the pathogenesis of certain diseases may help us develop new drugs or new approaches to prevent and treat these diseases. Genome-wide association studies have shown a significant association of polymorphisms of NLR genes with various diseases.^{7,10} NLR-associated diseases are summarized in Table 1. Described below are several examples of NLR studies that have shed new insights into disease mechanisms.

Autoinflammatory diseases and NLRs

Autoinflammatory diseases are self-directed inflammatory diseases involving innate immune cells without autoantibodies or autoreactive T cells, whereas autoimmune diseases involve dysfunctional adaptive immune systems producing autoreactive B or T cells.⁴² Reflecting the important roles of NLRs in inflammation, abnormalities of NLRs have been associated with several (but not all) autoinflammatory diseases. Based on the genes involved, autoinflammatory diseases can be classified into monogenic and polygenic diseases.^{11,42} Monogenic autoinflammatory diseases are caused by abnormalities of a single gene and include FMF (*MEFV*), CAPS (*NLRP3*), deficiency of interleukin-1 receptor antagonist (*IL1RN*), TNF receptor-associated periodic syndrome (*TNFRSF1A*), hyperimmunoglobulinemia D with periodic fever syndrome (*MVK*), and Blau syndrome (*NOD2*).^{11,42} Polygenic autoinflammatory diseases include gout and Crohn's disease.^{11,42} Most autoinflammatory diseases can be explained by the overproduction of IL-1, which occurs as a consequence of inflammasome activation.¹¹ For example, FMF is the most prevalent hereditary autoinflammatory disease in the world and is characterized by recurrent one- to three-day attacks of fever, serositis presenting as abdominal or pleuritic chest pain, and arthritis.^{11,12} FMF is caused by mutations of the *MEFV* gene, which encodes pyrin.¹² Although the association between FMF and pyrin mutations is well established, how pyrin mutation develops into FMF has not been explained. The *MEFV* gene does not belong to the NLRs family; however, the mutation of the *MEFV* gene leads to dysregulation of caspase-1, which is similar to the result of NLRP3 (NLR family, "pyrin" domain containing 3) activation.¹¹ Nevertheless, the involvement of NLR genes with some autoinflammatory diseases reflects their important roles in inflammation.

Diseases associated with inflammasome-forming NLRs

Although several NLRs can form inflammasome,^{7,10} the NLRP3 inflammasome has been the most studied. Studies found that NLRP3 can recognize a wide range of endogenous and exoge-

nous DAMPs such as uric acid, alum, silica, and asbestos.¹⁰ Below are descriptions of how NLRP3 is associated with gout, sili-
ciosis, asbestosis, and CAPS and how it is related to the role of alum as a vaccine adjuvant.

Gout is a common metabolic disease described from 2600 BC as podagra, although today it is understood as uric acid arthropathy.⁴³ It is characterized by recurrent, sudden, and severe attacks of pain, redness, and tenderness in joints due to deposition of monosodium urate, a crystallized form of uric acid. However, it was unclear how uric acid could cause inflammatory events until uric acid was found to activate the NLRP3 inflammasome.⁴⁴ The NLRP3 inflammasome becomes activated in response to uric acid, and its activation induces the formation of IL-1, which leads to the development of gouty arthropathy. Several randomized controlled trials have shown that IL-1-blocking therapy results in significant relief of pain and a reduction in the occurrence of acute flare-ups in gouty patients.¹¹

Silicosis, an occupational disease related to mining and construction work, is characterized by pulmonary fibrosis after inhalation exposure to silica. Asbestosis is a similar pulmonary fibrotic disorder following inhalation of asbestos. A recent study showed that silica and asbestos can cause alveolar macrophages to activate NLRP3 inflammasome and produce IL-1 β , which leads to the development of pulmonary fibrosis.⁴⁵

CAPS are rare autoinflammatory diseases, which include familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease.⁴⁶ Patients with CAPS usually present to physicians with overlapping symptoms such as fever, urticarial skin rash, varying degrees of arthralgia/arthritis, and neutrophil-mediated inflammation.⁴⁶ CAPS are associated with gain-of-function mutations in the *NLRP3* gene,⁴⁶⁻⁴⁸ with these mutations inducing an overproduction of IL-1 β , which causes CAPS.⁴⁶⁻⁴⁸ When IL-1-blocking therapy was given to CAPS patients, significant clinical responses were reported.⁴⁹

Aluminum hydroxide (alum) has been used as a vaccine adjuvant since the 1920s; however, its mechanism of action was unknown. However, recently, a link has been reported between alum and the NLRP3 inflammasome.⁵⁰ Alum promotes local necrosis in vaccinated muscle tissue, which leads to the release of DAMPs such as uric acid. DAMPs as well as the alum itself activate NLRP3 inflammasome, which enhances the immune response to vaccine.⁵⁰ Gaining a better understanding of the role that alum adjuvant plays in the immune response may lead to the development of new vaccine adjuvants.

Single nucleotide polymorphisms (SNPs) in the *NLRP3* gene are associated with many disorders such as type 1 diabetes,⁵¹ celiac disease,⁵¹ psoriasis,⁵² increased susceptibility to human immunodeficiency virus (HIV)-1 infections,⁵³ and inflammatory bowel diseases.⁵⁴ NLRP3 is also associated with type 2 diabetes in obese individuals.⁵⁵ NLRP3 inflammasome in adipose tissue macrophages senses ceramides generated from free fatty

acids in obese patients, which can cause obesity-induced inflammation and insulin resistance.⁵⁵ The development of an effective inhibitor of the NLRP3 inflammasome could, thus, provide a potential therapeutic agent for these NLRP3-associated diseases.⁵⁶

In addition to the NLRP3 inflammasome, the other NLR inflammasomes are also associated with many diseases. *NLRP1* polymorphisms are significantly associated with vitiligo,^{57,58} celiac disease,⁵⁹ Addison's disease,^{60,61} type 1 diabetes,⁶⁰ autoimmune thyroid disorders,⁶² systemic lupus erythematosus,⁶³ systemic sclerosis,⁶⁴ giant cell arteritis,⁶⁵ congenital toxoplasmosis,⁶⁶ rheumatoid arthritis,⁶⁷ Alzheimer's disease,⁶⁸ and corneal intraepithelial dyskeratosis.⁶⁹ *NLRP2* gene mutations are associated with Beckwith-Wiedemann syndrome, which is a congenital overgrowth syndrome associated with developmental abnormalities and a predisposition to embryonic tumors.⁷⁰ *NLRP6* expression is predominantly localized in intestinal tissue and is associated with increased susceptibility to colitis and colon cancer in a mouse model.⁷¹ Mutations in the maternal gene *NLRP7* are associated with recurrent hydatid moles,⁷² and increased *NLRP7* gene expression is observed in testicular seminoma⁷³ and endometrial cancer.⁷⁴ *NLRP12* mutations are associated with atopic dermatitis⁷⁵ and hereditary periodic fever syndrome.⁷⁶ *NAIP* gene mutations are associated with spinal muscular atrophies that are characterized by autosomal recessive disorder and spinal cord motor neuron depletion.⁷⁷

Diseases associated with non-inflammasome-forming NLRs

Crohn's disease is a chronic inflammatory disease in the gastrointestinal tract. Mutations of the *NOD2* gene are associated with Crohn's disease, although many patients with Crohn's disease do not have *NOD2* mutations.^{25,78} Most *NOD2* mutations (93%) in Crohn's disease patients are located in the leucine-rich-repeat region,^{4,78} which is responsible for ligand binding. Loss-of-function mutation of *NOD2* prevents responses to bacterial MDP in the gut, which might lead to proliferation of commensal or pathogenic gut microbiota in the crypts and disruption of mucosal integrity.⁴

Mutations and SNPs of the *NOD2* gene are also associated with Blau syndrome, which is characterized by familial granulomatous arthritis, uveitis, and skin granulomas.⁷⁹ Atopic eczema,⁸⁰ atopic dermatitis,⁷⁵ and susceptibility to leprosy⁸¹ and tuberculosis⁸² are associated with *NOD2* gene mutations. Polymorphisms of the *NOD1* gene are linked to asthma⁸³ and inflammatory bowel diseases.⁸⁴

Bare lymphocyte syndrome type II, also called hereditary MHC class II deficiency, is a severe combined immunodeficiency that results from a lack of expression of MHC class II molecules in all tissues.³⁵ Patients with this disease suffer from multiple infections and frequently die at an early age.³⁵ Loss-of-function due to *NLRA* mutations leads to reduced expression of MHC class II genes that affect CD4+ T cell function, which in

turn causes immune deficiency. Therefore, bare lymphocyte syndrome is an attractive candidate for gene therapy.

Breaks in the *NLRA* gene were found to occur in B-cell lymphomas, such as primary mediastinal B-cell lymphoma and classical Hodgkin's lymphoma. In addition, *NLRA* gene alterations have been associated with decreased survival in primary mediastinal B-cell lymphoma.⁸⁵

CONCLUSION

NLRs are important in the recognition of PAMPs and DAMPs; they also play a crucial role in immune response and pathogen detection. However, NLRs are also important in basic biologic processes, such as apoptosis and embryonic development. Many human NLRs remain poorly characterized and understood. Thus, as we learn more about the function of human NLRs, we will find their pathogenic roles in more diseases and develop novel strategies for treating and/or preventing these diseases.

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