REVIEW ARTICLE

MECHANISMS OF DISEASE

Robert S. Schwartz, M.D., *Editor*

Immunodeficiency and Genetic Defects of Pattern-Recognition Receptors

Mihai G. Netea, M.D., Ph.D., and Jos W.M. van der Meer, M.D., Ph.D.

From the Department of Medicine and Nijmegen Institute for Infection, Inflammation, and Immunity, Radboud University, Nijmegen Medical Center, Nijmegen, the Netherlands. Address reprint requests to Dr. Netea at the Department of Medicine (463), Radboud University, Nijmegen Medical Center, P.O. Box 9101, 6500 HB Nijmegen, the Netherlands or at m.netea@aig.umcn.nl.

N Engl J Med 2011;364:60-70.

The susceptibility of adopted children to infection correlates more with the susceptibility of their biologic parents than with that of their adoptive parents.[1] This suggests that genetic factors can increase the risk of infection. These factors are often genetic polymorphisms, but in a few cases monogenic defects underlie vulnerability to repeated infections. Genetic studies of susceptibility to infection have typically focused on defects of antibody production, or a lack of T cells, phagocytes, natural killer cells, or complement, each of which can cause a classic immunodeficiency syndrome. Recently, genetic defects have been identified that impair recognition of pathogens by the innate immune system, increasing susceptibility to specific classes of microorganisms. For example, defects in the interferon-γ pathway have been implicated in recalcitrant infections by intracellular pathogens such as mycobacteria and salmonella.[2,3] In this review, we focus on types of immunodeficiencies in which defects in pattern-recognition receptors and their downstream intracellular pathways predominate.

Pattern-Recognition Receptors and Innate Immunity

During an encounter with a pathogen, cells of the innate immune system recognize conserved structures of the microbe called pathogen-associated molecular patterns.[4] Complement factor 1q, C-reactive protein, and fibronectin also recognize microbial structures but are not usually considered pathogen-recognition receptors.[5] Cells of the innate immune system recognize pathogen-associated molecular patterns by means of germline-encoded pattern-recognition receptors, which allow for semispecific recognition of pathogens. An example of such a receptor is the macrophage mannose receptor, discovered in 1990.[6] In 1992, Charles Janeway, Jr., took the field of innate immunity in a new direction with his concept of selective recognition of conserved microbial structures by pattern-recognition receptors.[7]

There are four classes of pattern-recognition receptors: toll-like receptors (TLRs), C-type lectin receptors (CLRs), nucleotide-binding oligomerization domain (NOD) leucine-rich-repeat containing receptors (NLRs), and retinoic acid–inducible gene I protein (RIG-I) helicase receptors.[4] Table 1 summarizes the properties of these receptors and the corresponding pathogen-associated molecular patterns. These patterns are constituents of microbial cell-wall components, microbial nucleic acids, or metabolic products. We use the term pattern-recognition receptor to mean a cellular receptor that causes activation of innate immunity; we do not include molecules that microorganisms use for attachment to and invasion of host cells.

FAMILIES OF PATTERN-RECOGNITION RECEPTORS

Toll-like Receptors

The role of TLRs in antimicrobial defense was described in 1996 by Lemaitre and colleagues,[8] who observed that fruit flies lacking the insect homologue of a toll receptor rapidly die from aspergillosis. Since then, 13 mammalian TLRs have been discovered. All the extracellular domains of these receptors contain leucine-rich repeats that recognize microbial structures; the amino acid sequence of the cytoplasmic domain of the toll–interleukin-1 receptor is highly homologous with the sequences in the interleukin-1 receptor and the interleukin-18 receptor.[9] Ligand recognition by TLRs and intracellular signal transduction by adaptor molecules activate kinase cascades and translocate transcription factors to the nucleus, where they induce gene expression and production of cytokines (Fig. 1).[4,10,11] In addition to their role in innate immunity, TLRs and other pattern-recognition receptors activate antigen-presenting cells and bridge innate and adaptive immunity by coordinating responses of T cells and B cells.[12,13]

C-Type Lectin Receptors

The large family of CLRs includes dectin-1, macrophage mannose receptor, dendritic-cell–specific intercellular adhesion molecule 3–grabbing nonintegrin, dectin-2, and the circulating mannose-binding lectin. These receptors have carbohydrate-recognition domains[14] and recognize microbial polysaccharides. They appear to be essential for recognition of fungi and bacteria in the body.[15]

Cytoplasmic Pattern-Recognition Receptors

In addition to the mainly membrane-bound TLRs and CLRs, there are cytoplasmic pattern-recognition receptors — RIG-I helicase receptors and NLRs — that pathogens activate when they invade a cell. RIG-I helicase receptors are receptors mainly for the nucleic acids of viruses. NLRs recognize the peptidoglycans of bacterial cell walls and can activate inflammasomes, which are multiprotein complexes that convert inactive pro–interleukin-1β and pro–interleukin-18 into active cytokines (Fig. 1).[16-18] The NOD-containing receptors 1 and 2 (NOD1 and NOD2), members of the NLR family, recognize the muramyl peptide moieties of the peptidoglycans of gram-negative and gram-positive bacteria, respectively.[19,20] Interactions between the different pattern-recognition–receptor related pathways are essential for optimal antipathogen responses.[21-26] Synergy between TLRs and NOD2, for example, is crucial for activation of the defense against mycobacteria and staphylococci,[27] and cross-talk between TLRs and CLRs is needed for antifungal responses of the innate immune system.[21]

DEFECTS IN PATTERN-RECOGNITION RECEPTORS

Polymorphisms in genes encoding pattern-recognition receptors can affect susceptibility to infection. In addition, genetic defects in these receptors or the allied downstream pathways can cause immunodeficiency. We know of defects in three of the four classes of pattern-recognition receptors: TLRs, CLRs and NLRs (Table 2). To our knowledge, no deficiency of the RIG-I helicase receptors has been found.

DEFECTS OF TLRS

MyD88 and IRAK-4

Myeloid differentiation factor 88 (MyD88) is an adaptor molecule that transduces signals from TLR receptors (with the exception of TLR3) and from the receptors for interleukin-1 and interleukin-18.[28,29] The signaling involves a cascade of protein kinases, including the serine–threonine kinase IRAK-4.[10] Studies in the past decade have identified germline mutations in *IRAK-4*[30-37] and *MYD88*[38] in patients with increased susceptibility to pyogenic bacteria and pseudomonas species. These defects in the TLR–interleukin-1 receptor pathway were found in young patients with recurrent, severe pneumococcal infections. The lymphocytes of one of the first reported patients had a poor response, in vitro, to stimulation with endotoxin and interleukin-1.[39] The invasive infections associated with these mutations are usually meningitis and septicemia caused by *Streptococcus pneumoniae* and *Staphylococcus aureus* and less frequently by *Pseudomonas aeruginosa* and salmonella species. *S. aureus* is the main cause of localized infection, but *P. aeruginosa* and *S. pneumoniae* can also cause this complication.[40]

Invasive infections begin to appear in infancy, with a cumulative mortality of 30 to 40%.[36] Children with an MyD88 or IRAK-4 deficiency, by contrast, do not have major infections when they reach adulthood.[40] This difference suggests that the development of protective T-cell and B-cell

Table 1. Overview of Pattern-Recognition Receptors (PRRs) and Their Respective Pathogen-Associated Molecular Pattern (PAMP) Ligands, According to PRR Class.*

Recognized PAMP	Microorganism in Which PAMP Is Found	Signaling Molecule
TLRs		
TLR2-1		
Triacyl lipopeptides	Bacteria	MyD88–TIRAP
TLR2-2		MyD88–TIRAP
Peptidoglycan	Bacteria	
Lipoarabinomannan	Mycobacteria	
Phospholipomannan	Candida	
Glycosylphosphatidylinositol	Trypanosoma	
TLR2-6		MyD88–TIRAP
Diacyl lipopeptides	Mycoplasma	
Lipoteichoic acid	Streptococcus	
Zymosan	Saccharomyces	
TLR3		TRIF
ssRNA virus	West Nile virus	
dsRNA virus	Reovirus	
TLR4		MyD88–TIRAP, TRIF–TRAM
Lipopolysaccharide	Gram-negative bacteria	
Fungal mannans	Candida	
Envelope proteins	Respiratory syncytial virus	
TLR5		
Flagellin	Flagellated bacteria	MyD88
TLR7 and TLR8		
ssRNA viruses	Influenza virus, vesicular stomatitis virus	MyD88
TLR9		MyD88
dsDNA viruses	Herpes simplex virus	
CpG motifs	Bacterial and fungal DNA	
CLRs		
Mannose receptor		
Fungal mannans	Candida	Unknown
Dectin-1		
Beta-1,3-glucans	Fungi	SYK–CARD9, RAF1
Dectin-2–FcRγ		
Mannans	Candida hyphae	SYK–CARD9
MINCLE–FcRγ		SYK
Mannans	Candida	
Mycobacterial cord factor	Mycobacteria	
Mannose-binding lectin		Soluble receptor
Repetitive oligosaccharides	Bacteria and fungi	
NLRs		
NOD1		
Muramyl tripeptide peptidoglycans	Gram-negative bacteria	RIP2
NOD2		
Muramyl dipeptide peptidoglycans	Gram-positive bacteria	RIP2
NLRP1		
Anthrax toxin	Bacillus anthracis	ASC–caspase-1
NLRP3		
Peptidoglycans	Bacteria	
Bacterial toxins	Listeria, staphylococcus	
NLRC4		
Flagellin	Shigella, salmonella, legionella	ASC–NAIP5, caspase-1
AIM2		
dsDNA	Francisella tularensis	ASC–caspase-1

Table 1. (Continued.)

Recognized PAMP	Microorganism in Which PAMP Is Found	Signaling Molecule
RIG-I helicase receptors		
RIG-I		IPS1
Short dsRNA	Paramyxoviruses, orthomyxoviruses, rhabdoviruses, flaviviruses	
5′ Triphosphate ssRNA	Paramyxoviruses, orthomyxoviruses, rhabdoviruses, flaviviruses	
MDA5		
Long dsRNA	Picornaviruses, reoviruses, flaviviruses	IPS1

* AIM2 denotes absent in melanoma 2 protein, ASC apoptosis-associated speck-like protein containing a CARD, CARD9 caspase recruitment domain–containing protein 9, CLR C-type lectin receptor, CpG cytosine phosphate guanidine, ds double-stranded, FcRγ Fc receptor IgE high-affinity I gamma polypeptide, IPS1 interferon-β promoter stimulator protein 1, MDA5 melanoma differentiation-associated protein 5, MINCLE macrophage-inducible C-type lectin, MyD88 myeloid differentiation factor 88, NAIP5 NLR family apoptosis inhibitory protein 5, NLR nucleotide-binding oligomerization domain (NOD) leucine-rich-repeat–containing receptors, NLRC4 NLR family CARD-domain–containing protein 4 (also known as IPAF), NLRP NOD leucine-rich-repeat and pyrin domain–containing protein, RAF1 raf proto-oncogene serine–threonine protein kinase, RIG-I retinoic acid–inducible gene I protein, RIP2 receptor-interacting protein 2, ss single-stranded, SYK spleen tyrosine kinase, TIRAP toll-like–receptor adaptor protein, TLR toll-like receptor, TLR2-1 TLR2–TLR1 heterodimers, TLR2-2 TLR2–TLR2 heterodimers, TLR2-6 TLR2–TLR6 heterodimers, TRAM TRIF-related adaptor molecule, and TRIF toll-like receptor–adaptor molecule.

mediated immunity after infancy compensates for the defective TLR–interleukin-1 receptor pathway.[36]

TLR3–UNC93B Pathway

Two classes of intracellular pattern-recognition receptors, the RIG-I helicase receptors and TLRs, recognize viruses. The intracellular receptors TLR3, TLR7, TLR8, and TLR9 bind to microbial nucleic acids.[41] To our knowledge, no defects in the RIG-I helicase-receptor family are known. Patients with mutations in TLR3[42] or in UNC93B1, a protein in the TLR3 pathway,[43] are prone to recurrent encephalitis caused by herpesvirus. The disease occurs mainly in early childhood (from 3 months to 6 years of age) during an initial infection with herpes simplex virus type 1.[40,44]

TLR3 deficiency seems to be associated only with encephalitis caused by a herpes simplex virus; children with the deficiency have normal resistance to other pathogens. Recurrences have been documented in two patients, suggesting a role for TLR3 in herpesvirus latency.[40] A decreased capacity to release type I interferons was found in one patient's fibroblasts; blocking TLR3-dependent induction of interferons in vitro enhanced viral replication and caused cell death, effects that were reversed by recombinant interferon-β.[42] The role of inadequate levels of type I interferons in susceptibility to herpesvirus encephalitis was also shown in a child who was deficient in the signal transducer and activator of transcription 1 protein,[45,46] a signaling molecule in the type I interferon pathway.

TLR5

TLR5 is a receptor for flagellin, a protein that forms the pathogen-associated molecular pattern of the flagellum in flagellated bacteria.[47] Hawn and colleagues[48] described a polymorphism of *TLR5* (consisting of a stop codon at position 392) that impairs recognition of flagellin and increases susceptibility to legionella pneumonia. The phenotype associated with this polymorphism is mild and affects the control of only certain flagellated pathogens. The frequency of this stop-codon allele in European populations is as high as 10%; carriers of the allele are susceptible to infection with *Legionella pneumophila*[48] and to recurrent cystitis,[49] but not to infection with the flagellated bacterium *Salmonella enterica serotype Typhi*, the agent of typhoid fever.[50] Protective effects of this *TLR5* polymorphism against systemic lupus erythematosus and Crohn's disease have been reported.[51,52] The high and variable population frequencies of the polymorphism suggest that it has a redundant role in host defense.[53]

DEFECTS OF CLRs

CLRs form a large family that specifically recognizes carbohydrate structures of microorganisms and endogenous ligands.[15] They have a role in the recognition of fungal pathogens and mycobacteria.

Dectin-1–CARD9 Pathway

Dectin-1 is the major pattern-recognition receptor for beta-1,3-glucan in the fungal cell wall[54,55]

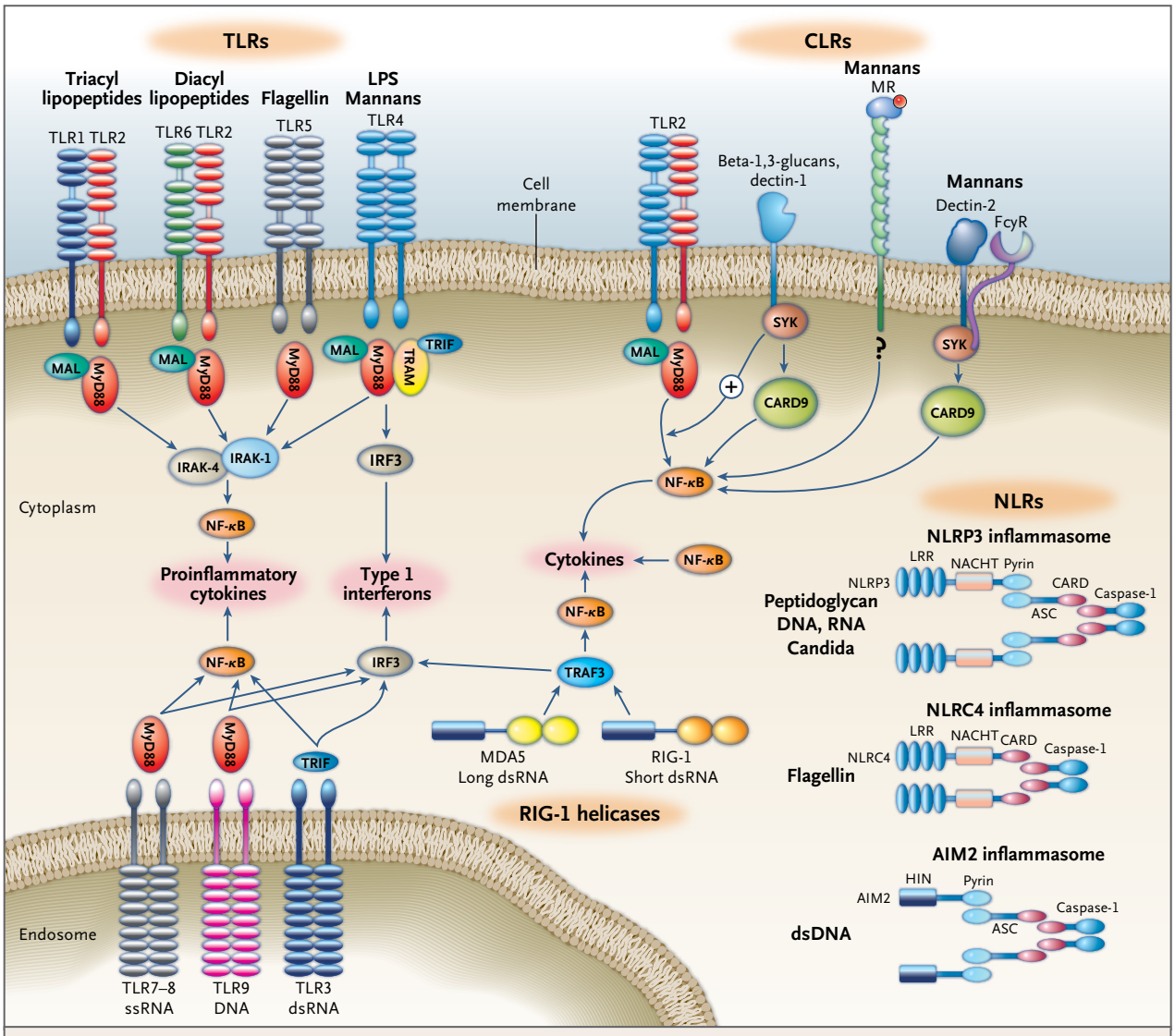

Figure 1. The Four Major Classes of Pattern-Recognition Receptors and Their Most Important Ligands.

The four classes are toll-like receptors (TLRs), C-type lectin receptors (CLRs), nucleotide-binding oligomerization domain (NOD) leucine-rich-repeat (LRR)–containing receptors (NLRs), and retinoic acid–inducible gene I protein (RIG-I) helicase receptors. NLRs, the central components of the inflammasomes, are complex protein platforms that lead to the activation of caspase 1 and interleukin-1β processing. The most extensively studied inflammasomes are as follows: the NOD leucine-rich-repeat and pyrin domain–containing protein 3 (NLRP3) inflammasome, activated by bacterial and fungal pathogen-associated molecular patterns; the NLR family caspase recruitment domain–containing protein (CARD) 4 (NLRC4) inflammasome, activated during intracellular bacterial infections by flagellin; and the absent in melanoma 2 (AIM2) inflammasome, activated by double-stranded (ds) DNA. ASC denotes apoptosis-associated speck-like protein containing a CARD, HIN hematopoietic interferon-inducible nuclear protein, IRF3 interferon regulatory factor 3, LPS lipopolysaccharide, MAL myelin and lymphocyte protein, MDA5 melanoma differentiation-associated protein 5, MR mineralocorticoid receptor, MyD88 myeloid differentiation factor 88, NF-κB nuclear factor-κB, NLRC4 NLR family CARD-domain–containing protein 4 (also known as IPAF), ss single-stranded, SYK spleen tyrosine kinase, TRAM TRIF-related adaptor molecule, and TRIF toll-like–receptor adaptor molecule.

and in unknown components of *Mycobacterium tuberculosis*.[56] Genetic analyses of members of a family with recurrent vulvovaginal candidiasis and onychomycosis identified an early stop codon in *CLEC7A* (the gene encoding dectin-1), causing a loss of 10 amino acids from the extracellular carbohydrate-recognition domain of the protein.[57] In consequence, the cell cannot display dectin-1 on its membrane, thereby negating the ability of monocytes to bind beta-glucans. This defect impairs the production of interleukin-6, tumor necrosis factor, and especially interleukin-17. In

contrast, neutrophils from affected persons can ingest and kill *Candida albicans* normally, indicating redundancy of dectin-1 in the phagocytosis and killing of yeast. Defective cytokine release most likely explains the phenotype. Defective dectin-1 signaling in epithelial cells and intraepithelial gamma–delta T cells may also contribute to the clinical picture, especially since these cells express dectin-1 and produce cytokines and antimicrobial peptides on activation.[58,59]

We should be cautious in concluding that genetic variants of the gene encoding dectin-1 have a role in disease. About 6 to 8% of Europeans are heterozygous for a disabling variant of the gene, which implies that approximately 1 in 400 Europeans has a deficiency of the protein; they do not, however, have an apparent immunodeficiency. In some African populations, such as the San people of southern Africa, the allele frequency reaches almost 40%.[57] The phenotype of patients with dectin-1 deficiency is relatively mild and less severe than that of patients with classic chronic mucocutaneous candidiasis.[60,61] Heterozygous carriers of the dectin-1 polymorphism are more likely to be colonized with *C. albicans* when undergoing stem-cell transplantation, and need antifungal therapy more often, than noncarriers.[62] For all these reasons, dectin-1 deficiency resembles a genetic polymorphism, which in some people or under some circumstances is associated with susceptibility to fungi but not with severe immunodeficiency.

CARD9

Several members of a family with increased susceptibility to infection with fungi,[63] mucocutaneous fungal infections in particular, have been shown to have mutations in caspase recruitment domain–containing protein 9 (CARD9), the adaptor molecule that mediates signaling induced by dectin-1. These clinical findings support the role of the beta-glucan recognition pathway in antifungal defense. A severe defect of interleukin-17 production has been reported in patients with *CARD9* mutations.[63] The more severe phenotype of CARD9 deficiency is most likely due to mechanisms that are independent of dectin-1.[64-66]

MANNOSE-BINDING LECTIN

Some components of the complement system that have the capacity to interact with microbial polysaccharides can function as recognition re-

Table 2. Characteristics of Immunodeficiency Due to Defective Recognition by Pattern-Recognition Receptors (PRRs).*

PRR Defect	Presumed Pathogenesis	Infections or Conditions for Which Susceptibility Is Conferred	Inheritance	Frequency
TLR defect				
MyD88 deficiency or IRAK-4 deficiency	TLR-pathway defect (exception: TLR3 pathway)	Pyogenic bacteria (staphylococci, streptococci), pneumococcus, pseudomonas	Autosomal dominant	Very rare
UNC93B deficiency	dsRNA-recognition defect	Herpes simplex virus (encephalitis)	Autosomal recessive	Very rare
TLR3 deficiency	dsRNA-recognition defect	Herpes simplex virus (encephalitis)	Autosomal dominant	Very rare
TLR5 deficiency	Flagellin-recognition defect	Legionella	Autosomal recessive	Common
CLR defect				
Dectin-1 deficiency	Beta-glucan–recognition defect	Candida, trichophyton	Autosomal recessive	Common
CARD9 deficiency	Beta-glucan–recognition defect	Candida	Autosomal recessive	Very rare
Mannose-binding lectin deficiency	Complement-activation defect	Bacteria and fungi	Autosomal recessive	Common
NLR defect				
NOD2 deficiency	Peptidoglycan-recognition defect	Local defense defect in Crohn's disease	Autosomal recessive	Rare
NLRP3 deficiency	Dysregulation of interleukin-1β	Autoinflammatory syndromes	Autosomal dominant	Very rare

* CARD9 denotes caspase recruitment domain-containing protein 9, CLR C-type lectin receptor, ds double-stranded, IRAK-4 a serine–threonine kinase, MyD88 myeloid differentiation factor 88, NLR nucleotide-binding oligomerization domain (NOD) leucine-rich-repeat–containing receptors, NLRP NOD leucine-rich-repeat pyrin domain–containing protein, NOD2 NOD-containing receptor 2, TLR toll-like receptor, and UNC93B a protein in the TLR3 pathway.

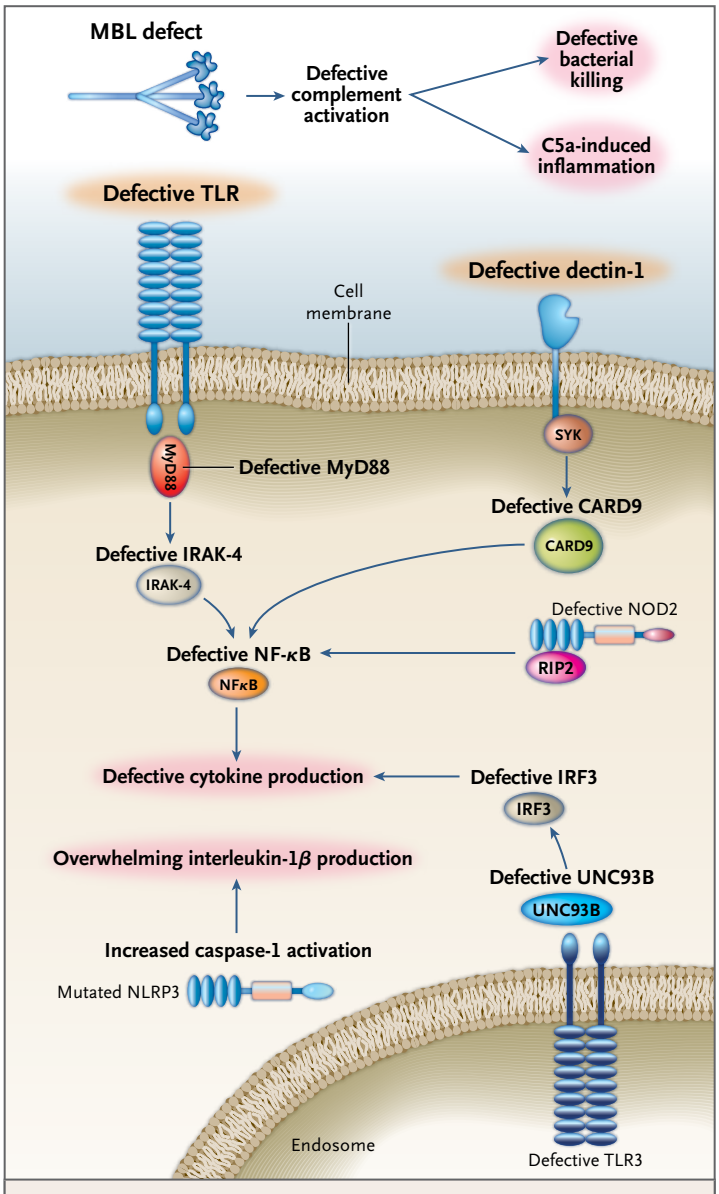

Figure 2. Clinical Features of Defects in Pattern-Recognition Receptors.

The major pathophysiological disturbance in syndromes characterized by defective pattern-recognition receptors is dysregulated cytokine-production capacity. This could come about by means of defective cytokine production (e.g., in cases of myeloid differentiation factor 88 [MyD88] or serine–threonine kinase IRAK-4 deficiency, dectin-1 or caspase recruitment domain–containing protein 9 [CARD9] deficiency, or toll-like receptor 3 [TLR3] or UNC93B [a protein in the TLR3 pathway] deficiency) or increased cytokine production (e.g., high interleukin-1β production in the case of the nucleotide-binding oligomerization domain [NOD] leucine-rich-repeat–containing receptor [NLR] family pyrin-domain–containing protein 3 [NLRP3] deficiency). One exception is deficiency of mannose-binding lectin (MBL), which leads to defective complement activation. IRF3 denotes interferon regulatory factor 3, NF-κB nuclear factor-κB, NOD2 NOD-containing receptor 2, RIP2 receptor-interacting protein 2, and SYK spleen tyrosine kinase.

ceptors. The complement molecule that most closely resembles a pattern-recognition receptor is mannose-binding lectin, which binds carbohydrate structures of microorganisms and activates the complement system.[67] Deficiency in mannose-binding lectin was initially reported in an infant with recurrent bacterial infections and has been associated with bacterial infections (especially with *Neisseria meningitidis*), in addition to fungal and viral infections.[68-70] Subsequent studies showed, however, that polymorphisms in the mannose-binding lectin gene result in low levels of mannose-binding lectin in approximately 40% of whites, with very low levels in about 8%. Most people in the general population with low or high levels of mannose-binding lectin do not have obvious clinical consequences. Thus, deficiency of mannose-binding lectin should be considered a risk factor for infection rather than an outright immunodeficiency.[71]

Other leukocyte molecules that recognize microbial polysaccharides are the β_2-integrins, such as complement receptor 3 (CD11b–CD18), which is known to function as a neutrophil beta-glucan receptor[72] as well as playing a part in leukocyte adhesion. The immunologic defects in patients with β_2-integrin deficiency (leukocyte adhesion deficiency I) are mainly due to defective leukocyte adhesion.[73] Neither complement factors nor β_2-integrins are considered classic pattern-recognition receptors.[5,74]

NLRs

Members of the large family of intracellular NLRs have two major functions: NOD1 and NOD2 recognize bacterial peptidoglycans,[19,20] and NOD leucine-rich-repeat and pyrin domain–containing proteins (NLRPs) participate in the formation of inflammasomes and the processing of interleukin-1β–interleukin-18 (Fig. 1).[16,17]

NOD2

Genetic defects in the pattern-recognition receptor NOD2 constitute a major mechanism in Crohn's disease. Mutations that affect the leucine-rich-repeat domain of NOD2 occur in familial cases of Crohn's disease.[75,76] In another granulomatous disease, Blau's syndrome — a rare autosomal dominant disorder characterized by the early onset of granulomatous inflammation and camptodactyly — there is a mutation in the nu-

cleotide-binding domain of NOD2.[77] Missense mutations in the NACHT domain of NOD2 in several families with Blau's syndrome caused a gain-of-function phenotype with increased basal activation of the transcription factor nuclear factor-κB and uncontrolled inflammation.[77]

Does the NOD2 defect cause the inflammation in patients with Crohn's disease?[78,79] Most of the data indicate a loss-of-function mutation in *NOD2*, resulting in decreased production of defensins in the gut mucosa[80] and an unregulated cytokine response.[81,82] These abnormalities could impair the elimination of invading microorganisms in the mucosa and thereby cause reactive granulomatous inflammation. Studies of autophagy genes (*ATG16L1* and *IRGM*), which encode proteins that regulate the breakdown by the cell of its own constituents, add weight to the hypothesis that genetic defects affecting innate immunity lead to Crohn's disease.[83,84] Neutrophil dysfunction and unregulated cytokine responses are also found in patients with Crohn's disease,[85,86] leading some researchers to suggest that the disease is a primary immunodeficiency syndrome of gut mucosal immunity.[87,88]

NLRP3

The inflammasome is a protein platform that participates in activating caspase-1 and the proinflammatory cytokines interleukin-1β and interleukin-18. Members of the NLR family are components of inflammasomes. The most extensively studied member of the NLR family is NLRP3. The *NLRP3* gene encodes cryopyrin, which, when activated, assembles with other proteins into an inflammasome. Mutations in *NLRP3* occur in the cryopyrin-associated periodic syndromes, such as the familial cold autoinflammatory syndrome, the Muckle–Wells syndrome, and neonatal-onset multisystem inflammatory disorder (NOMID, also known as the chronic infantile neurologic, cutaneous, and articular syndrome).[89] Features of the familial cold autoinflammatory syndrome are cold-induced fever, urticaria, and constitutional symptoms; characteristics of the Muckle–Wells syndrome are fever, hives, sensorineural hearing loss, and arthritis unrelated to cold exposure; and NOMID is characterized by fever, urticaria, epiphyseal overgrowth of the long bones, and chronic aseptic meningitis.[90] In these syndromes, the high level of interleukin-1β, due to increased production, causes most of the symptoms.[91] However, a secondary role of interleukin-18 and interleukin-33 cannot be ruled out because the inflammasome also processes these cytokines. Immunodeficiency is not a feature of this group of diseases, which are autoinflammatory syndromes. Deficiency of NLRP12, a protein that inhibits inflammation mediated by activated monocytes, has recently been found in a form of autoinflammatory syndrome.[92]

CONCLUSIONS

The clinical features of defects in pattern-recognition receptors are usually due to disturbed cytokine homeostasis (Fig. 2) — either decreased cytokine production and increased susceptibility to infections (in the case of TLR3 or MyD88 deficiency) or overwhelming release of cytokines (in the case of NLRP3 defects). The clinical presentation ranges from severe (in cases of MyD88 and IRAK-4 deficiencies) to mild (in cases of mannose-binding lectin and TLR5 deficiencies). The clinical severity is greatest in infancy but decreases thereafter, perhaps because adaptive immune responses that develop after infancy compensate for the ineffective innate immunity. By contrast, the level of severity of classic primary immunodeficiencies usually persists throughout life.

In 2007, Casanova and Abel predicted that the field of primary immunodeficiency would shift from research on rare familial defects in the adaptive immune response to studies of sporadic and selective disorders of innate immunity that are more common than the classic immunodeficiencies.[93] The defects in pattern-recognition receptors are an instructive example of this shift. The uncovering of these defects has given clinical relevance to immunologic pathways, which until now have been studied exclusively in the laboratory or in experimental models of infection.

Supported by a Vici grant from the Netherlands Organization of Scientific Research (to Dr. Netea).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Dr. Marcel van Deuren and Dr. Frank van de Veerdonk for discussions and suggestions regarding the manuscript.

REFERENCES

1. Sørensen TI, Nielsen GG, Andersen PK, Teasdale TW. Genetic and environmental influences on premature death in adult adoptees. N Engl J Med 1988;318:727-32.
2. Al-Muhsen S, Casanova JL. The genetic heterogeneity of mendelian susceptibility to mycobacterial diseases. J Allergy Clin Immunol 2008;122:1043-51.
3. van de Vosse E, van Dissel JT, Ottenhoff TH. Genetic deficiencies of innate immune signalling in human infectious disease. Lancet Infect Dis 2009;9:688-98.
4. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell 2006;124:783-801.
5. Botto M, Kirschfink M, Macor P, Pickering MC, Würzner R, Tedesco F. Complement in human diseases: lessons from complement deficiencies. Mol Immunol 2009;46:2774-83.
6. Ezekowitz RA, Sastry K, Bailly P, Warner A. Molecular characterization of the human macrophage mannose receptor: demonstration of multiple carbohydrate recognition-like domains and phagocytosis of yeasts in Cos-1 cells. J Exp Med 1990;172:1785-94.
7. Janeway CA Jr. The immune system evolved to discriminate infectious nonself from noninfectious self. Immunol Today 1992;13:11-6.
8. Lemaitre B, Nicolas E, Michaut L, Reichhart J-M, Hoffmann JA. The dorsoventral regulatory gene cassette Spaetzle/Toll/Cactus controls the potent antifungal response in Drosophila adults. Cell 1996;86:973-83.
9. Rock FL, Hardiman G, Timans JC, Kastelein JA, Bazan JF. A family of human receptors structurally related to Drosophila Toll. Proc Natl Acad Sci U S A 1998;95:588-93.
10. Akira S, Takeda K. Toll-like receptor signalling. Nat Rev Immunol 2004;4:499-511.
11. Beutler B. Inferences, questions and possibilities in Toll-like receptor signalling. Nature 2004;430:257-63.
12. Iwasaki A, Medzhitov R. Regulation of adaptive immunity by the innate immune system. Science 2010;327:291-5.
13. Netea MG, Van der Graaf C, Van der Meer JWM, Kullberg BJ. The role of Toll-like receptors in host defense: bringing specificity to the innate immune response. J Leukoc Biol 2004;75:749-55.
14. Zelensky AN, Gready JE. The C-type lectin-like domain superfamily. FEBS J 2005;272:6179-217.
15. Willment JA, Brown GD. C-type lectin receptors in antifungal immunity. Trends Microbiol 2008;16:27-32.
16. Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. Mol Cell 2002;10:417-26.
17. Lamkanfi M, Dixit VM. The inflammasomes. PLoS Pathog 2009;5(12):e1000510.
18. Martinon F, Tschopp J. Inflammatory caspases: linking an intracellular innate immune system to autoinflammatory diseases. Cell 2004;117:561-74.
19. Girardin SE, Boneca IG, Carneiro LAM, et al. Nod1 detects a unique muropeptide from Gram-negative bacterial peptidoglycan. Science 2003;300:1584-7.
20. Girardin SE, Boneca IG, Viala J, et al. Nod2 is a general sensor of peptidoglycan through muramyl dipeptide (MDP) detection. J Biol Chem 2003;278:8869-72.
21. Netea MG, Brown GD, Kullberg BJ, Gow NA. An integrated model of the recognition of Candida albicans by the innate immune system. Nat Rev Microbiol 2008;6:67-78.
22. Gantner BN, Simmons RM, Canavera SJ, Akira S, Underhill DM. Collaborative induction of inflammatory responses by dectin-1 and Toll-like receptor 2. J Exp Med 2003;197:1107-17.
23. Brown GD, Herre J, Williams DL, Willment JA, Marshall AS, Gordon S. Dectin-1 mediates the biological effects of beta-glucans. J Exp Med 2003;197:1119-24.
24. Dennehy KM, Ferwerda G, Faro-Trindade I, et al. Syk kinase is required for collaborative cytokine production induced through Dectin-1 and Toll-like receptors. Eur J Immunol 2008;38:500-6.
25. Jouault T, El Abed-El Behi M, Martínez-Esparza M, et al. Specific recognition of Candida albicans by macrophages requires galectin-3 to discriminate Saccharomyces cerevisiae and needs association with TLR2 for signaling. J Immunol 2006;177:4679-87.
26. Agrawal S, Agrawal A, Doughty B, et al. Different Toll-like receptor agonists instruct dendritic cells to induce distinct Th responses via differential modulation of extracellular signal-regulated kinase-mitogen-activated protein kinase and c-Fos. J Immunol 2003;171:4984-9.
27. Ferwerda G, Girardin SE, Kullberg BJ, et al. NOD2 and Toll-like receptors are two non-redundant recognition systems of Mycobacterium tuberculosis. PLoS Pathog 2005;1:279-85.
28. Adachi O, Kawai T, Takeda K, et al. Targeted disruption of the MyD88 gene results in loss of IL-1 and IL-18-mediated function. Immunity 1998;9:143-50.
29. Takeuchi O, Hoshino K, Akira S. TLR2-deficient and MyD88-deficient mice are highly susceptible to Staphylococcus infection. J Immunol 2000;165:5392-6.
30. Picard C, Puel A, Bonnet M, et al. Pyogenic bacterial infections in humans with IRAK-4 deficiency. Science 2003;299:2076-9.
31. Medvedev AE, Lentschat A, Kuhns DB, et al. Distinct mutations in IRAK-4 confer hyporesponsiveness to lipopolysaccharide and interleukin-1 in a patient with recurrent bacterial infections. J Exp Med 2003;198:521-31.
32. Davidson DJ, Currie AJ, Bowdish DM, et al. IRAK-4 mutation (Q293X): rapid detection and characterization of defective post-transcriptional TLR/IL-1R responses in human myeloid and non-myeloid cells. J Immunol 2006;177:8202-11.
33. Cardenes M, von Bernuth H, Garcia-Saavedra A, et al. Autosomal recessive interleukin-1 receptor-associated kinase 4 deficiency in fourth-degree relatives. J Pediatr 2006;148:549-51.
34. Chapel H, Puel A, von Bernuth H, Picard C, Casanova JL. Shigella sonnei meningitis due to interleukin-1 receptor-associated kinase-4 deficiency: first association with a primary immune deficiency. Clin Infect Dis 2005;40:1227-31.
35. Comeau JL, Lin TJ, Macken MB, et al. Staphylococcal pericarditis, and liver and paratracheal abscesses as presentations in two new cases of interleukin-1 receptor associated kinase 4 deficiency. Pediatr Infect Dis J 2008;27:170-4.
36. Ku CL, von Bernuth H, Picard C, et al. Selective predisposition to bacterial infections in IRAK-4-deficient children: IRAK-4-dependent TLRs are otherwise redundant in protective immunity. J Exp Med 2007;204:2407-22.
37. Szabó J, Dobay O, Erdos M, Borbély A, Rozgonyi F, Maródi L. Recurrent infection with genetically identical pneumococcal isolates in a patient with interleukin-1 receptor-associated kinase-4 deficiency. J Med Microbiol 2007;56:863-5.
38. von Bernuth H, Picard C, Jin Z, et al. Pyogenic bacterial infections in humans with MyD88 deficiency. Science 2008;321:691-6.
39. Kuhns DB, Long Priel DA, Gallin JI. Endotoxin and IL-1 hyporesponsiveness in a patient with recurrent bacterial infections. J Immunol 1997;158:3959-64.
40. Bousfiha A, Picard C, Boisson-Dupuis S, et al. Primary immunodeficiencies of protective immunity to primary infections. Clin Immunol 2010;135:204-9.
41. Akira S, Hemmi H. Recognition of pathogen-associated molecular patterns

by TLR family. Immunol Lett 2003;85:85-95.
42. Zhang SY, Jouanguy E, Ugolini S, et al. TLR3 deficiency in patients with herpes simplex encephalitis. Science 2007;317:1522-7.
43. Casrouge A, Zhang SY, Eidenschenk C, et al. Herpes simplex virus encephalitis in human UNC-93B deficiency. Science 2006;314:308-12.
44. De Tiège X, Rozenberg F, Héron B. The spectrum of herpes simplex encephalitis in children. Eur J Paediatr Neurol 2008;12:72-81.
45. Chapgier A, Kong XF, Boisson-Dupuis S, et al. A partial form of recessive STAT1 deficiency in humans. J Clin Invest 2009;119:1502-14.
46. Dupuis S, Jouanguy E, Al-Hajjar S, et al. Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. Nat Genet 2003;33:388-91.
47. Hayashi F, Smith KD, Ozinsky A, et al. The innate immune response to bacterial flagellin is mediated by Toll-like receptor 5. Nature 2001;410:1099-103.
48. Hawn TR, Verbon A, Lettinga KD, et al. A common dominant TLR5 stop codon polymorphism abolishes flagellin signaling and is associated with susceptibility to Legionnaires' disease. J Exp Med 2003;198:1563-72.
49. Hawn TR, Scholes D, Li SS, et al. Toll-like receptor polymorphisms and susceptibility to urinary tract infections in adult women. PLoS ONE 2009;4(6):e5990.
50. Dunstan SJ, Hawn TR, Hue NT, et al. Host susceptibility and clinical outcomes in toll-like receptor 5-deficient patients with typhoid fever in Vietnam. J Infect Dis 2005;191:1068-71.
51. Hawn TR, Wu H, Grossman JM, Hahn BH, Tsao BP, Aderem A. A stop codon polymorphism of Toll-like receptor 5 is associated with resistance to systemic lupus erythematosus. Proc Natl Acad Sci U S A 2005;102:10593-7.
52. Gewirtz AT, Vijay-Kumar M, Brant SR, Duerr RH, Nicolae DL, Cho JH. Dominant-negative TLR5 polymorphism reduces adaptive immune response to flagellin and negatively associates with Crohn's disease. Am J Physiol Gastrointest Liver Physiol 2006;290:G1157-G1163.
53. Wlasiuk G, Khan S, Switzer WM, Nachman MW. A history of recurrent positive selection at the Toll-like receptor 5 in primates. Mol Biol Evol 2009;26:937-49.
54. Brown GD, Gordon S. Immune recognition: a new receptor for beta-glucans. Nature 2001;413:36-7.
55. Brown GD. Dectin-1: a signalling non-TLR pattern-recognition receptor. Nat Rev Immunol 2006;6:33-43.
56. Yadav M, Schorey JS. The beta-glucan receptor dectin-1 functions together with TLR2 to mediate macrophage activation by mycobacteria. Blood 2006;108:3168-75.
57. Ferwerda B, Ferwerda G, Plantinga TS, et al. Human dectin-1 deficiency and mucocutaneous fungal infections. N Engl J Med 2009;361:1760-7.
58. Saegusa S, Totsuka M, Kaminogawa S, Hosoi T. Candida albicans and Saccharomyces cerevisiae induce interleukin-8 production from intestinal epithelial-like Caco-2 cells in the presence of butyric acid. FEMS Immunol Med Microbiol 2004;41:227-35.
59. Martin B, Hirota K, Cua DJ, Stockinger B, Veldhoen M. Interleukin-17-producing gammadelta T cells selectively expand in response to pathogen products and environmental signals. Immunity 2009;31:321-30.
60. Puel A, Döffinger R, Natividad A, et al. Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. J Exp Med 2010;207:291-7.
61. Lilic D, Gravenor I, Robson N, et al. Deregulated production of protective cytokines in response to Candida albicans infection in patients with chronic mucocutaneous candidiasis. Infect Immun 2003;71:5690-9.
62. Plantinga TS, van der Velden WJ, Ferwerda B, et al. Early stop polymorphism in human DECTIN-1 is associated with increased candida colonization in hematopoietic stem cell transplant recipients. Clin Infect Dis 2009;49:724-32.
63. Glocker EO, Hennigs A, Nabavi M, et al. A homozygous *CARD9* mutation in a family with susceptibility to fungal infections. N Engl J Med 2009;361:1727-35.
64. Sato K, Yang XL, Yudate T, et al. Dectin-2 is a pattern recognition receptor for fungi that couples with the Fc receptor gamma chain to induce innate immune responses. J Biol Chem 2006;281:38854-66.
65. Bugarcic A, Hitchens K, Beckhouse AG, Wells CA, Ashman RB, Blanchard H. Human and mouse macrophage-inducible C-type lectin (Mincle) bind Candida albicans. Glycobiology 2008;18:679-85.
66. Yamasaki S, Ishikawa E, Sakuma M, Hara H, Ogata K, Saito T. Mincle is an ITAM-coupled activating receptor that senses damaged cells. Nat Immunol 2008;9:1179-88.
67. Jack DL, Turner MW. Anti-microbial activities of mannose-binding lectin. Biochem Soc Trans 2003;31:753-7.
68. Worthley DL, Bardy PG, Mullighan CG. Mannose-binding lectin: biology and clinical implications. Intern Med J 2005;35:548-55.
69. Eisen DP, Minchinton RM. Impact of mannose-binding lectin on susceptibility to infectious diseases. Clin Infect Dis 2003;37:1496-505.
70. Kilpatrick DC. Mannan-binding lectin: clinical significance and applications. Biochim Biophys Acta 2002;1572:401-13.
71. Sprong T, van Deuren M. Mannose-binding lectin: ancient molecule, interesting future. Clin Infect Dis 2008;47:517-8.
72. van Bruggen R, Drewniak A, Jansen M, et al. Complement receptor 3, not Dectin-1, is the major receptor on human neutrophils for beta-glucan-bearing particles. Mol Immunol 2009;47:575-81.
73. Notarangelo LD, Badolato R. Leukocyte trafficking in primary immunodeficiencies. J Leukoc Biol 2009;85:335-43.
74. Etzioni A. Genetic etiologies of leukocyte adhesion defects. Curr Opin Immunol 2009;21:481-6.
75. Hugot J-P, Chamaillard M, Zouali H, et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature 2001;411:599-603.
76. Ogura Y, Bonen DK, Inohara N, et al. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature 2001;411:603-6.
77. Miceli-Richard C, Lesage S, Rybojad M, et al. CARD15 mutations in Blau syndrome. Nat Genet 2001;29:19-20.
78. Eckmann L, Karin M. NOD2 and Crohn's disease: loss or gain of function? Immunity 2005;22:661-7.
79. Ting JP, Duncan JA, Lei Y. How the noninflammasome NLRs function in the innate immune system. Science 2010;327:286-90.
80. Kobayashi KS, Chamaillard M, Ogura Y, et al. NOD2-dependent regulation of innate and adaptive immunity in the intestinal tract. Science 2005;307:731-4.
81. Kullberg BJ, Ferwerda G, de Jong DJ, et al. Crohn's disease patients homozygous for the 3020insC NOD2 mutation have a defective NOD2/TLR4 cross-tolerance to intestinal stimuli. Immunology 2008;123:600-5.
82. Watanabe T, Kitani A, Murray PJ, Strober W. NOD2 is a negative regulator of Toll-like receptor 2-mediated T helper type 1 responses. Nat Immunol 2004;5:800-8.
83. Hampe J, Franke A, Rosenstiel P, et al. A genome-wide association scan of nonsynonymous SNPs identifies a susceptibility variant for Crohn disease in ATG16L1. Nat Genet 2007;39:207-11.
84. Rioux JD, Xavier RJ, Taylor KD, et al. Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. Nat Genet 2007;39:596-604.
85. Smith AM, Rahman FZ, Hayee B, et al. Disordered macrophage cytokine secre-

tion underlies impaired acute inflammation and bacterial clearance in Crohn's disease. J Exp Med 2009;206:1883-97. [Erratum, J Exp Med 2009;206:2301.]
86. Marks DJ, Harbord MW, MacAllister R, et al. Defective acute inflammation in Crohn's disease: a clinical investigation. Lancet 2006;367:668-78. [Erratum, Lancet 2007;370:318.]
87. Sewell GW, Marks DJ, Segal AW. The immunopathogenesis of Crohn's disease: a three-stage model. Curr Opin Immunol 2009;21:506-13.
88. Marks DJ, Rahman FZ, Sewell GW, Segal AW. Crohn's disease: an immune deficiency state. Clin Rev Allergy Immunol 2010;38:20-31.
89. Simon A, van der Meer JW. Pathogenesis of familial periodic fever syndromes or hereditary autoinflammatory syndromes. Am J Physiol Regul Integr Comp Physiol 2007;292:R86-R98.
90. Masters SL, Simon A, Aksentijevich I, Kastner DL. Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease. Annu Rev Immunol 2009;27:621-68.
91. Aksentijevich I, Nowak M, Mallah M, 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;46:3340-8.
92. Jéru I, Duquesnoy P, Fernandes-Alnemri T, et al. Mutations in NALP12 cause hereditary periodic fever syndromes. Proc Natl Acad Sci U S A 2008;105:1614-9.
93. Casanova JL, Abel L. Primary immunodeficiencies: a field in its infancy. Science 2007;317:617-9.