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]

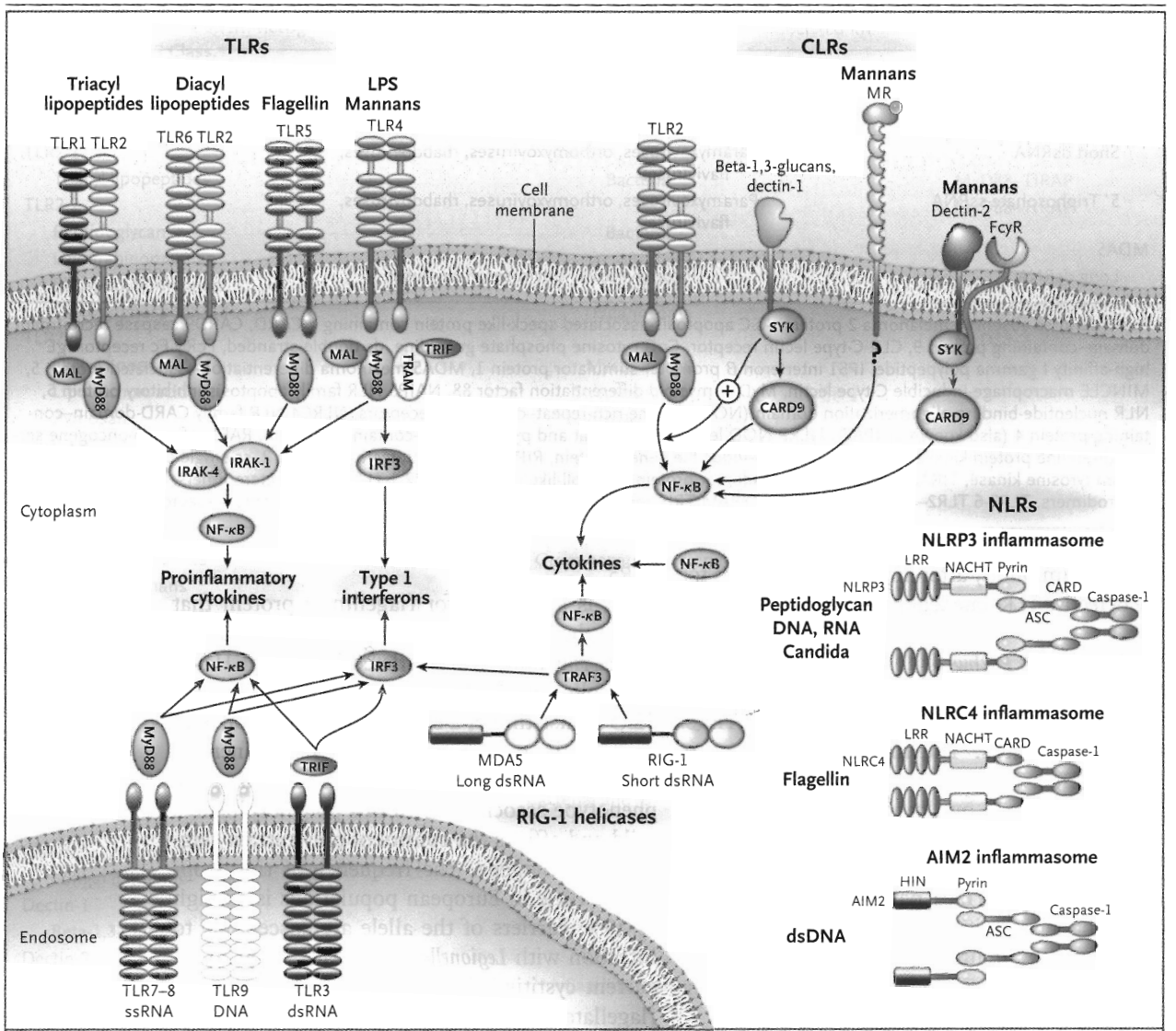

Figure 1. The Four Major Classes of Pattern-Recognition Receptors and Their Most Important Ligands.

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