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Toll-like receptor function and signaling

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Mammals sense pathogen invasion through pattern-recognition receptors. A group of transmembrane proteins, Toll-like receptors (TLRs), play critical roles as pattern-recognition receptors. They are mainly expressed on antigen-presenting cells, such as macrophages or dendritic cells, and their signaling activates antigen-presenting cells to provoke innate immunity and to establish adaptive immunity. Each TLR has common effects, such as inflammatory cytokine induction or upregulation of costimulatory molecule expression, but also has its specific function, exemplified by type I IFN-inducing ability. These immunoadjuvant effects are not only critical in antimicrobial immunity but are also involved in manifestations of autoimmunity. Furthermore, some TLR agonists are now promising therapeutic tools for various immune disorders, including allergy. Therefore understanding molecular mechanisms on TLRs should be quite useful in the development of therapeutic maneuvers against allergy and autoimmune diseases. (J Allergy Clin Immunol 2006;117:979-87.)

Key words: *Pattern-recognition receptor, Toll-like receptor, dendritic cell, type I IFN, MyD88, allergy, adjuvant, plasmacytoid dendritic cell, CpG DNA*

Abbreviations used

APC:	Antigen-presenting cell
CARD:	Caspase activation and recruitment domain
DC:	Dendritic cell
ds:	Double stranded
IKK:	IκB kinase
IPS-1:	IFN-βstimulator 1
IRAK:	IL-1 receptor–associated kinase
IRF:	IFN regulatory factor
MAMP:	Microorganism-associated molecular pattern
MAPK:	Mitogen-activated protein kinase
NF:	Nuclear factor
NOD:	Nucleotide-binding oligomerization domain
PDC:	Plasmacytoid dendritic cell
PRR:	Pattern-recognition receptor
RF:	Rheumatoid factor
RIG-I:	Retinoic acid–inducible gene I
RIP:	Receptor interacting protein
SARM:	Sterile α and armadillo motifs
SLE:	Systemic lupus erythematosus
TAK:	TGF-β–activated kinase
TBK1:	TANK-binding kinase 1
TIR:	Toll/IL-1 receptor homologous
TIRAP:	TIR domain–containing adapter protein
TLR:	Toll-like receptor
TRIF:	TIR domain–containing adapter protein inducing IFN-β

Host defense in mammals copes with pathogens through 2 types of immunity: innate and adaptive immunity. Innate immunity functions as a pathogen sensor and contributes to the eradication of pathogens and the establishment of adaptive immunity. These functions heavily depend on pattern-recognition receptors (PRRs).[1] Among PRRs, a group of transmembrane proteins, Toll-like receptors (TLRs), are featured by their potent immunoadjuvant ability to activate antigen-presenting cells (APCs).[2,3] TLRs include 10 (TLRs 1-10) and 12 (TLRs 1-9 and 11-13) family members in human subjects and mice, respectively (Fig 1). Most TLR ligands have been identified as a variety of molecular components derived from microorganisms. They can be categorized into lipid, protein, and nucleic acids, according to their ingredients. Importantly, all of these TLR ligands function as immune adjuvants. Principally, TLR signaling activates APCs to support T_H1 cell differentiation. Blocking or augmenting TLR function can modify T_H1/T_H2 balance and

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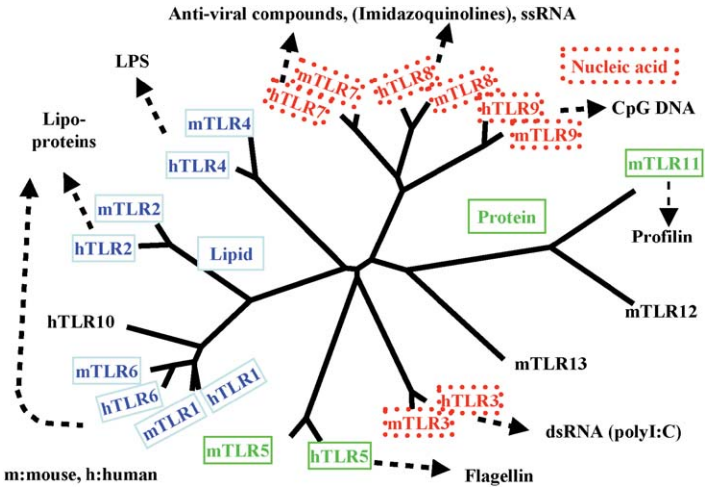

FIG 1. Phylogenetic tree of human and murine TLRs. Human and murine TLRs are connected with *solid lines* on the basis of the phylogenetic analysis of their amino acid structures. Branch length is proportional to evolutionary distances. *Dotted arrows* indicate representative ligands. Human TLR8 can function as a sensor, whereas there are no reports on the function of murine TLR8. *h,* Human; *m,* murine.

manipulate a variety of immune disorders, such as cancer, allergy, and autoimmunity. In this review we will summarize current knowledge of TLR function and signaling by relating them to some immune disorders.

TLRs AS TRANSMEMBRANE SIGNALING PRRs

PRRs can be functionally classified into 2 classes: nonsignaling and signaling PRRs. Nonsignaling PRRs include soluble factors or transmembrane proteins. Acute-phase proteins, such as C-reactive protein or lectins, are important soluble molecules that can bind to the invading microorganisms. Those microorganisms bound by these molecules are vulnerable to phagocytosis or recognized by the complement system followed by activation of protease cascades. Transmembrane proteins, such as scavenger receptors, also bind to the microorganisms. Then the organisms are internalized and transported to lysosomal compartments. These recognition systems do not principally activate the signaling cascades in innate immune cells.

Innate immune cells carry the molecules that can not only recognize the microorganisms but can also trigger the signaling pathways, leading to production of inflammatory cytokines or type I IFNs. These signaling PRRs include transmembrane and cytosolic proteins. TLRs are representative as transmembrane-signaling PRRs. Their extracellular domain includes a repetitive structure rich in leucine residues, called leucine-rich repeat, that is involved in the ligand recognition. The intracellular region contains a common structure in TLR and IL-1 receptor family members, called Toll/IL-1 receptor homologous (TIR) domain, which is essential for signal transduction.

The nucleotide-binding oligomerization domain (NOD) molecules Nod1 and Nod2 are cytosolic signaling PRRs.[4] Both Nod1 and Nod2 have leucine-rich repeat regions at their carboxy terminus, thereby recognizing bacterial peptidoglycans. They also carry a Nod domain and a caspase activation and recruitment domain (CARD), which can stimulate signaling pathways that lead to the activation of nuclear factor (NF) κB or mitogen-activated protein kinases (MAPKs). Retinoic acid–inducible gene I (RIG-I) and Mda-5 are also cytosolic signaling PRRs that can recognize double-stranded RNA (dsRNA; see below).[5]

TLR LIGANDS

TLRs can recognize common molecular structures detected in certain groups of microorganisms (Fig 1). These were originally called pathogen-associated molecular patterns, but here we call them microorganism-associated molecular patterns (MAMPs) because they are found not only in pathogenic but also in nonpathogenic commensal microorganisms. Principally, toxins, which are involved in pathogenicity, are not recognized by TLRs. Furthermore, MAMPs are not expressed in the host and behave as nonself, although nucleic acids can act as nonself to some extent (see below).

MAMPs are generated through metabolic pathways specific for a group of microorganisms. MAMPs are required for the survival of microorganisms and therefore are highly conserved over the course of evolution. They are not as heterogeneous as viral proteins, the structure of which can be rapidly changed to escape immune surveillance. Therefore the structural stability of MAMPs enables germline-encoded PRRs to recognize MAMPs with a limited repertoire.

Representative MAMPs are bacterial cell-wall components. The cell walls of gram-negative bacteria contain LPS, an immune adjuvant identified first as a TLR ligand.[6] LPS is recognized by TLR4 and a TLR4-associated soluble factor, MD-2, derived from the host.[7] Gram-positive