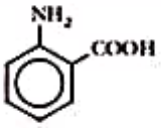
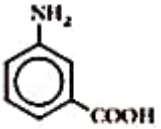
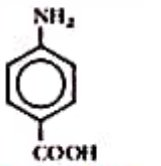
Pattern-Recognition Receptors

The receptors of adaptive and innate immunity differ. Antibodies and T-cell receptors, the receptors of adaptive immunity, recognize details of molecular structure and can discriminate with exquisite specificity between antigens featuring only slight structural differences. The receptors of innate immunity recognize broad structural motifs that are highly conserved within microbial species but are generally absent from the host. Because they recognize particular overall molecular patterns, such receptors are called **pattern-recognition receptors (PRRs).** Patterns recognized by this type of receptor include combinations of sugars, certain proteins, particular lipid-bearing molecules, and some nucleic acid motifs. Typically, the ability of pattern-recognition receptors to distinguish between self and nonself is perfect because the molecular pattern targeted by the receptor is produced only by the pathogen and never by the host. This contrasts sharply with the occasional recognition of self

TABLE 3-6 Reactivity of antisera with various haptens

	REACTIVITY WITH			
				
Antiserum against	**Aminobenzene (aniline)**	**o-Aminobenzoic acid**	**m-Aminobenzoic acid**	**p-Aminobenzoic acid**
Aminobenzene	+	0	0	0
o-Aminobenzoic acid	0	+	0	0
m-Aminobenzoic acid	0	0	+	0
p-Aminobenzoic acid	0	0	0	+

KEY: 0 = no reactivity; + = strong reactivity

SOURCE: Based on K. Landsteiner, 1962, *The Specificity of Serologic Reactions*, Dover Press. Modified by J. Klein, 1982, *Immunology: The Science of Self-Nonself Discrimination*, John Wiley.

antigens by receptors of adaptive immunity, which can lead to autoimmune disorders. Like antibodies and T-cell receptors, pattern-recognition receptors are proteins. However, the genes that encode PRRs are present in the germline of the organism. In contrast, the genes that encode the enormous diversity of antibodies and TCRs are not present in the germline. They are generated by an extraordinary process of genetic recombination that is discussed in Chapter 5.

Many different pattern-recognition receptors have been identified and several examples appear in Table 3-7. Some are present in the bloodstream and tissue fluids as soluble circulating proteins and others are on the membrane of cells such as macrophages, neutrophils, and dendritic cells. Mannose-binding lectin (MBL) and C-reactive protein (CRP) are soluble pattern receptors that bind to microbial surfaces and promote their opsonization. Both of these receptors also have the ability to activate the complement system when they are bound to the surface of microbes, thereby making the invader a likely target of complement-mediated lysis. Yet another soluble receptor of the innate immune system, lipopolysaccharide-binding protein, is an important part of the system that recognizes and signals a response to lipopolysaccharide, a component of the outer cell wall of gram-negative bacteria.

Pattern-recognition receptors found on the cell membrane include scavenger receptors and the toll-like receptors. Scavenger receptors (SRs) are present on macrophages and many types of dendritic cells, and are involved in the binding and internalization of gram-positive and gram-negative bacteria, as well as the phagocytosis of apoptotic host cells. The exact roles and mechanisms of action of the many types of scavenger receptors known to date are under active investigation. The toll-like receptors (TLRs) are important in recognizing many microbial patterns. This family of proteins is ancient—toll-like receptors mediate the recognition and generation of defensive responses to pathogens in organisms as widely separated in evolutionary history as humans and flies. Typically, signals transduced through the TLRs cause transcriptional activation and the synthesis and secretion of cytokines, which promote inflammatory responses that bring macrophages and neutrophils to sites of inflammation.

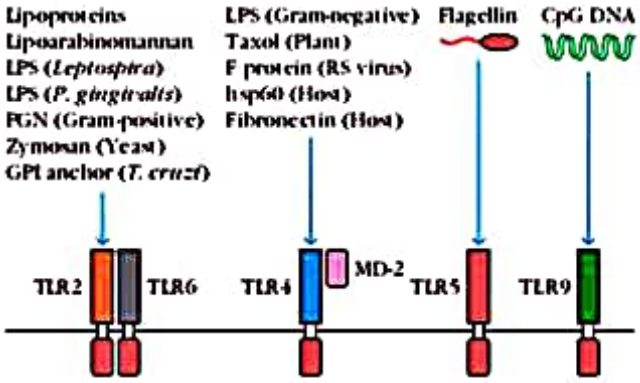


FIGURE 3-11 Location and targets of some pattern-recognition receptors. Many pattern-recognition receptors are extracellular and target microbes or microbial components in the bloodstream and tissue fluids, causing their lysis or marking them for removal by phagocytes. Other pattern-recognition receptors are present on the cell membrane and bind to a broad variety of microbes or microbial products. Engagement of these receptors triggers signaling pathways that promote inflammation or, in the case of the scavenger receptors, phagocytosis or endocytosis. dsRNA = double stranded RNA; LPS = lipopolysaccharide. [S. Akira et al., 2001, Nature Immunology 2:675.]

TABLE 3-7 Receptors of innate and adaptive immunity

Characteristic	Innate immunity	Adaptive immunity
Specificity	Specific for conserved molecular patterns or types	Specific for details of antigen structure
Self/nonself discrimination	Perfect: evolutionarily selected to distinguish phylogenetic differences. Never recognizes self.	Excellent: but imperfect. Occasional reaction with self antigens
RECEPTORS OF THE ADAPTIVE IMMUNE SYSTEM		
Receptor (location)	**Target (source)**	**Effect of recognition**
Antibody (B-cell membrane, blood, tissue fluids)	Specific components of pathogen	Labeling of pathogen for destruction and removal
T-cell receptor (T-cell membrane)	Proteins or certain lipids of pathogen	Induction of pathogen-specific humoral and cell-mediated immunity
RECEPTORS OF THE INNATE IMMUNE SYSTEM		
Complement (bloodstream, tissue fluids)	Microbial cell-wall components	Complement activation, opsonization
Mannose-binding lectin (MBL) (bloodstream, tissue fluids)	Mannose-containing microbial carbohydrates (cell walls)	Complement activation, opsonization
C-reactive protein (CRP) (bloodstream, tissue fluids)	Phosphatidylcholine (microbial membranes)	Complement activation, opsonization
LPS-binding protein (LBP) (bloodstream, tissue fluids)	Bacterial lipopolysaccharide (LPS)	Delivery to cell-membrane LPS receptor (TLR-CD14-MD-2 complex*)
TLR2 (cell membrane)	Cell-wall components of gram-positive bacteria, LPS*. Yeast cell-wall component (zymosan)	Attracts phagocytes, activates macrophages, dendritic cells. Induces secretion of several cytokines
TLR3 (cell membrane)	Double-stranded RNA (dsRNA) (replication of many RNA viruses)	Induces production of interferon, an antiviral cytokine
TLR4 (cell membrane)	LPS*	Attracts phagocytes, activates macrophages, dendritic cells. Induces secretion of several cytokines
TLR5 (cell membrane)	Flagellin (flagella of gram-positive and gram-negative bacteria)	Attracts phagocytes, activates macrophages, dendritic cells. Induces secretion of several cytokines
TLR9 (cell membrane)	CpG	Attracts phagocytes, macrophages, dendritic cells. Induces secretion of several cytokines
Scavenger receptors (many) (cell membrane)	Many targets; gram-positive and gram-negative bacteria, apoptotic host cells	Induces phagocytosis or endocytosis

*LPS is bound at the cell membrane by a complex of proteins that includes CD14, MD-2, and a TLR (usually TLR4).