TABLE 372e-4 THE ROLE OF PATTERN RECOGNITION RECEPTORS (PRRs) IN MODULATION OF ADAPTIVE IMMUNE RESPONSES

PRR Family	PRRs	Ligand	DC or Macrophage Cytokine Response	Adaptive Immune Response
TLRs	TLR2 (heterodimer with TLR1 or 6)	Lipopeptides	Low IL-12p70	T_H1
		Pam-3-cys (TLR 2/1)	High IL-10	T_H2
		MALP (TLR 2/6)	IL-6	T regulatory
	TLR3	dsRNA	IL-12p70	T_H1
			IFN-α	
			IL-6	
	TLR4	*Escherichia coli* LPS	High IL-12p70	T_H1
			Intermediate IL-10	
			IL-6	
	TLR5	Flagellin	High IL-12p70	T_H1
			Low IL-12p70	T_H2
	TLR7/8	ssRNA	High IL-12p70	T_H1
		Imidazoquinolines	IFN-α	
			IL-6	
	TLR9	CpG DNA	High IL-12p70	T_H1
			Low IL-10	
			IL-6	
			IFN-α	
	TLR10	?	?	?
	TLR11	Profilin-like molecule Uropathogenic bacteria	?	?
C-type lectins	DC-SIGN	Env of HIV; core protein of HCV; components of *Mycobacterium tuberculosis*; *Helicobacter pylori*, Lewis Ag	*H. pylori*, Lewis Ag	T_H2
			Suppresses IL-12p70	T regulatory
			Suppresses TLR signaling in DCs	
NOD	NOD2	Muramyl dipeptide of peptidoglycan of bacteria	Induces IL-10 in DCs	Weak T cell response (tolerogenic?)
Mannose receptor	Mannose receptor	Mannosylated lipoarabinomannans from bacillus Calmette-Guérin and *M. tuberculosis*	Suppresses IL-12 and TLR signaling in DCs	Weak T cell response? (tolerogenic?)

Abbreviations: CpG, sequences in DNA recognized by TLR-9; DC, dendritic cell; DC-SIGN, DC-specific C-type lectin; dsRNA, double-strand RNA; HCV, hepatitis C; HIV, human immunodeficiency virus; LPS, lipopolysaccharide; MALP, macrophage-activating lipopeptide; NOD, NOTCH protein domain; ssRNA, single-strand RNA; T_H1, helper T cell; T_H2, helper T cell; TLR, Toll-like receptor.

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to T cells. Activated macrophages can also mediate antigen-nonspecific lytic activity and eliminate cell types such as tumor cells in the absence of antibody. This activity is largely mediated by cytokines (i.e., TNF-α and IL-1). Monocytes-macrophages express lineage-specific molecules (e.g., the cell-surface LPS receptor, CD14) as well as surface receptors for a number of molecules, including the Fc region of IgG, activated complement components, and various cytokines (Table 372e-7).

Dendritic Cells Human dendritic cells (DCs) contain several subsets, including myeloid DCs and plasmacytoid DCs. Myeloid DCs can differentiate into either macrophages-monocytes or tissue-specific DCs. In contrast to myeloid DCs, plasmacytoid DCs are inefficient APCs but are potent producers of type I interferon (IFN) (e.g., IFN-α) in response to viral infections. The maturation of DCs is regulated through cell-to-cell contact and soluble factors, and DCs attract immune effectors through secretion of chemokines. When DCs come in contact with bacterial products, viral proteins, or host proteins released as danger signals from distressed host cells (Figs. 372e-2 and 372e-3), infectious agent molecules bind to various TLRs and activate DCs to release cytokines and chemokines that drive cells of the innate immune system to become activated to respond to the invading organism, and recruit T and B cells of the adaptive immune system to respond. Plasmacytoid DCs produce antiviral IFN-α that activates NK cell killing of pathogen-infected cells; IFN-α also activates T cells to mature into antipathogen cytotoxic (killer) T cells. Following contact with pathogens, both plasmacytoid and myeloid DCs produce chemokines that attract helper and cytotoxic T cells, B cells, polymorphonuclear cells, and naïve and memory T cells as well as regulatory T cells to ultimately dampen the immune response once the pathogen is controlled. TLR engagement on DCs upregulates MHC class II, B7-1 (CD80), and B7-2 (CD86), which enhance DC-specific antigen presentation and induce cytokine production (Table 372e-7). Thus, DCs are important bridges between early (innate) and later (adaptive) immunity. DCs also modulate and determine the types of immune responses induced by pathogens via the TLRs expressed on DCs (TLR7–9 on plasmacytoid DCs, TLR4 on monocytoid DCs) and via the TLR adapter proteins that are induced to associate with TLRs (Fig. 372e-1, Table 372e-4). In addition, other PRRs, such as C-type lectins, NLRs, and mannose receptors, upon ligation by pathogen products, activate cells of the adaptive immune system and, like TLR stimulation, by a variety of factors, determine the type and quality of the adaptive immune response that is triggered (Table 372e-4).

Large Granular Lymphocytes/Natural Killer Cells Large granular lymphocytes (LGLs) or NK cells account for ~5–15% of peripheral blood lymphocytes. NK cells are nonadherent, nonphagocytic cells with large azurophilic cytoplasmic granules. NK cells express surface receptors for the Fc portion of IgG (FcR) (CD16) and for NCAM-I (CD56), and many NK cells express T lineage markers, particularly CD8, and proliferate in response to IL-2. NK cells arise in both bone marrow and thymic microenvironments.

Functionally, NK cells share features with both monocytes-macrophages and neutrophils in that they mediate both ADCC and NK cell activity. ADCC is the binding of an opsonized (antibody-coated) target cell to an Fc receptor-bearing effector cell via the Fc region of antibody, resulting in lysis of the target by the effector cell. NK cell cytotoxicity is the nonimmune (i.e., effector cell never having had previous contact with the target), MHC-unrestricted, non-antibody-mediated killing of target cells, which are usually malignant cell types, transplanted foreign cells, or virus-infected cells. Thus, NK cell cytotoxicity may play