TOLL-LIKE RECEPTORS: LINKING INNATE AND ADAPTIVE IMMUNITY

Chandrashekhar Pasare and Ruslan Medzhitov*

1. ABSTRACT

Work in recent years has shown an essential role for Toll-like receptors (TLRs) in the activation of innate and adaptive immunity in vertebrate animals. These germ-line encoded receptors, expressed on a diverse variety of cells and tissues, recognize conserved molecular products derived from various classes of pathogens, including Gram-positive and -negative bacteria, DNA and RNA viruses, fungi and protozoa. Ligand recognition induces a conserved host defense program, which includes production of inflammatory cytokines, upregulation of costimulatory molecules, and induction of antimicrobial defenses. Importantly, activation of dendritic cells by TLR ligands is necessary for their maturation and consequent ability to initiate adaptive immune responses. How responses are tailored by individual TLRs to contain specific classes of pathogens is not yet clear.

2. INTRODUCTION

In all animals, the innate immune system provides essential protection against invading pathogens. A key component of this system is a collection of germ-line encoded receptors called pathogen recognition receptors (PRRs), which recognize a highly conserved set of molecular structures specific to microbes (Pathogen associated molecular patterns, or PAMPs) [1]. In addition to this system, vertebrates have a second line of defense called the adaptive immune system, which employs a diverse set of somatically rearranged receptors (T-cell receptors [TCRs] and B-cell receptors [BCRs]) with the ability to recognize a large spectrum of antigens.

*Howard Hughes Medical Institute, Section of Immunobiology, 300 Cedar Street, TAC S660, Yale University School of Medicine, New Haven, CT 06510.
The best understood and perhaps the most important subgroup of PRRs is the Toll-like receptor family. These receptors have the ability to recognize pathogens or pathogen derived products and initiate signaling events leading to activation of innate host defenses. Signaling by TLRs initiates acute inflammatory responses by induction of anti-microbial genes and inflammatory cytokines and chemokines [2,3]. In addition, TLRs have an important role in activation of adaptive immune responses [4,5]. Although T and B cells of the adaptive immune system express receptors of enormous diversity, activation of these cells depends on induction of co-stimulatory molecules and secretion of cytokines and chemokines by the cells of the innate immune system. A variety of cell surface receptors, secreted cytokines and chemokines participate in the induction of protective immunity. We will discuss here current paradigms of the importance of innate immune recognition by TLRs and the significance of that recognition for the outcome of adaptive immune responses. We will also discuss how inappropriate activation of TLRs under certain circumstances can lead to autoimmune diseases.

3. TLRs AND THEIR LIGANDS

The mammalian TLR family consists of 10 members with distinct ligand specificities and gene targets [2,3]. TLR4 recognizes lipopolysaccharide (LPS) [6,7] from gram-negative bacteria, TLR2 recognizes peptidoglycan from gram-positive bacteria [8], TLR3 recognizes double-stranded RNA from double stranded and negative strand viruses [9], TLR7 and 8 recognize RNA from single stranded viruses [10,11], and TLR9 recognizes unmethylated CpG DNA found abundantly in prokaryotic genomes and DNA viruses [12,13]. A comprehensive list of ligands and signaling events downstream of various TLRs is described elsewhere [3,14]. In addition, several reports have suggested that some TLRs can also recognize host-derived ligand. One example is the recognition of heat shock proteins by TLR2 and TLR4 [15-17]; however, it remains possible that the recombinant heat shock proteins used in these studies were contaminated with endotoxin (or other TLR ligands), consistent with more recent reports that more stringent purification of the hsp results in a loss of stimulatory activity [18-20]. Another example of recognition of a host ligand by a TLR (chromatin associated DNA by TLR9) is discussed in more detail below.

4. ADAPTIVE IMMUNE SYSTEM: MECHANISMS OF TOLERANCE AND IMPORTANCE OF INNATE IMMUNE RECOGNITION

Although most auto-reactive T and B lymphocytes undergo clonal deletion during their development in primary lymphoid organs (central tolerance), a few nevertheless escape into the periphery and must be held in check by mechanisms of peripheral tolerance [21].