Review

Toll-like receptor signalling and the clinical benefits that lie within

B. Verstak, P. Hertzog, A. Mansell

Centre for Functional Genomics and Human Disease, Monash Institute of Medical Research, Monash University, Clayton, Victoria, Australia, e-mail: Ashley.mansell@med.monash.edu.au

Received 4 June 2006; returned for revision 8 August 2006; accepted by K. Visvanathan 21 August 2006

Abstract. TLRs are of crucial importance to the innate immune system by recognising molecules that are broadly shared by pathogens but distinguishable from host molecules. The innate immune system works to defend the body from microbial infection by initiating inflammation, the extreme form of which is sepsis. The discovery that endogenous ligands, as well as microbial components, are recognised by TLRs, raise the possibility of these receptors and their associated adapter molecules, as potential targets for the development of agonists and antagonists for the treatment of various pathological diseases, and their manipulation as potential adjuvants in vaccine development. By elucidating the mechanisms of TLR signalling pathways involving adapter molecules like MyD88, Mal, TRIF and TRAM combined with the identification of single nucleotide polymorphisms (SNPs) within these receptors and the unique genes that are expressed upon recognition, will assist in the development of therapeutics to alleviate the consequences of microbial-mediated inflammation, which include inflammatory disorders and septic shock.

1. Introduction

Since the discovery of Toll-like receptors (TLRs), rapid progress has been made as to the understanding of the molecular and biochemical mechanisms of innate immunity. The innate immune system defends the body from microbial infection by initiating inflammation and orchestrating the acquired immune response. Uncontrolled innate response can lead to chronic inflammation, the extreme form of which is sepsis and autoimmune disease. The prototypic inducer of inflammation is Lipopolysaccharide (LPS), the major cell wall component of Gram-negative bacteria. The signalling receptor for LPS is Toll-like Receptor-4 (TLR4), which upon ligand-induced receptor dimerisation, initiates a signal transduction pathway involving one or more adapter molecules leading to activation of the prototypic inflammatory transcription factor, nuclear factor-κB (NF-κB) and interferon regulatory factors (IRF).

TLRs play a pivotal role in recognition of molecular patterns displayed by micro-organisms that subsequently lead to an immune response. Developments in the TLR field have focused on four main areas: identification of additional TLR ligands including putative endogenous ligands, further elucidation of components of individual TLR signalling pathways, and in vivo studies of the involvement of TLRs in the resistance to infections.

The purpose of this review is to discuss TLR4 signal transduction with an emphasis on the adaptor molecules and their role in mediating downstream events that induce an inflammatory response and the activation of transcription factors such as NF-κB, IRF-3 and activating protein-1 (AP-1). A greater understanding of the signalling pathways regulating the pro-inflammatory response to microbial infection is of crucial importance to developing new therapeutics to treat septic shock and chronic inflammation in human medicine.

2. Toll-like receptors

Toll-like receptors are a family of innate immune receptors whose critical role involves the recognition of invading pathogens. They are evolutionarily conserved, their homologs found in mammals, plants and insects. They were first described for their involvement in innate immunity in *Drosophila melanogaster*, where fruitflies with a mutant Toll receptor demonstrated high susceptibility to fungal infection [1]. This study led to the finding that Toll receptor is responsible for detecting fungal invasion and triggering a host defence [2]. Subsequently, mammalian orthologues of Toll receptors were identified and their role in innate immunity elucidated [3, 4].

TLRs are broadly distributed on the cells of the immune system such as macrophages, dendritic cells (DC), neutrophils, B cells, as well as mucosal epithelial and endothelial cells [5–9]. The family of mammalian TLRs are type I transmembrane receptors characterised by an ectodomain com-
posed of multiple copies of leucine-rich motifs and a Toll/interleukin-1 receptor (TIR) motif in the cytoplasmic domain. The TIR domain, found in other members of the interleukin (IL)-1 receptor family, mediates homophilic and heterophilic interactions between TLRs and TIR-containing adaptors.

2.1. Ligand specificity in Toll-like receptor signalling

In mammals, the TLR superfamily of receptors consists of 13 family members [10–15] (Fig. 1.1).

When bacteria enter hosts, they are recognised by pathogen recognition receptors, which elicit signal transduction events leading to both innate and adaptive immunity. The defence against invading micro-organisms is triggered by the ability of TLRs to recognise structurally conserved pathogen-associated molecular patterns (PAMP’s) of microbial origin [3]. Such specific microbial products include LPS, bacterial lipoproteins, peptidoglycan, bacterial DNA and viral nucleic acids. Activation of these conserved motifs initiates an inflammatory cascade that attempts to clear the offending pathogen and set in motion a specific immune response.

The recognition of a microbial molecule to its respective TLR, transmits a signal to the cell’s nucleus through a series of downstream events, ultimately leading to an immune response. All TLRs, except for TLR3, are thought to signal through a MyD88-IRAK-TRAF6 pathway to induce NF-κB and MAP kinases.

3. TIR domain-containing adapter molecules in TLR signalling

The ability of a TLR to tailor an inflammatory response, specific for individual ligands, has recently focused attention...