

## **Summary**

**Kasper Hoebe and Bruce Beutler**

### **TLRs as bacterial sensors**

Humans, like all higher organisms, are daily challenged by an indefinite number of microbial pathogens. In order to survive, the immune system has evolved to efficiently detect and remove infectious microbes from the body. The discovery of Toll-like receptors (TLRs) has provided a leap in our understanding of how we recognize pathogens. Although limited in number, the TLRs have been shown to collectively recognize a broad variety of microbes and to induce unique signaling cascades that are often pathogen specific. In this chapter we will discuss the mechanisms by which TLRs recognize gram-positive and/or gram-negative bacteria and how some specificity of the innate immune response is acquired via adaptor molecules and/or involvement of co-receptors.

## **Summary**

**Sandra M. Sacre, Stefan K. Drexler and Brian M. Foxwell**

### **Toll-like receptors and rheumatoid arthritis: is there a connection?**

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases, affecting ~0.5-1% of the adult population. RA is associated with a persistent inflammatory state affecting the joints. Although environmental factors and a genetic component make a contribution to the aetiology of RA, the triggering cause still remains elusive. Infectious pathogens have been suggested as an initiating factor. Toll-like receptors (TLR) that have an important role in innate immunity are able to identify microbial products and endogenous molecules released on cell damage or cell necrosis. They have been suggested to be involved in the inflammatory response seen in RA. TLRs have been shown to be expressed in RA tissue, promoting more interest in these receptors in RA. They make good candidates to be involved in the early inflammatory mechanisms of this disease. Even though there is an ever increasing amount of supporting evidence, a functional link between the RA and this family of receptors has not yet been shown.

**Key words:** inflammation, rheumatoid arthritis, Toll-like receptor

## **Summary**

**Simon Rothenfusser and Eicke Latz**

### **Toll-like receptor 9 and systemic autoimmune diseases**

Toll like receptors (TLRs) are involved in the innate recognition of foreign material and their activation leads to a multitude of effects directed against invading pathogens. TLR9 recognizes unmethylated CpG motifs that are more prevalent in microbial DNA than in mammalian DNA. TLR9 is intracellularly expressed in specialized immune cells and the DNA activates TLR9 in endo-lysosomal compartments. By detecting foreign DNA signatures TLR9 can sense the presence of certain viruses or bacteria and can mount the appropriate immune response of the host organism. However under certain conditions, TLR9 can also recognize self-DNA and promote immune pathologies with uncontrolled chronic inflammation. In the auto-immune disease systemic lupus erythematosus (SLE) endogenous DNA-containing autoantibody complexes present in the serum of patients can activate the innate immune system via TLR9.

**Key words:** SLE, systemic lupus erythematosus; IL, interleukin; IFN, interferon, IRF, interferon regulatory factor; LPS, lipopolysaccharide; TLR, Toll-like receptor; TNF, tumour necrosis factor; CpG, cytosine-phosphate-guanosine; PRR, pattern recognition receptor; PAMP, pathogen associated molecular pattern

#### **Summary**

**John W. Hollingsworth, Donald N. Cook and David A. Schwartz**

**Toll-like receptors and airway disease**

(No summary and key words available)

#### **Summary**

**Kathrin S. Michelsen, Terence M. Doherty and Moshe Arditi**

**Toll-like receptors and vascular disease**

Toll-like receptors constitute the proximal sensory apparatus that allows immune defenses to detect foreign pathogens and trigger a defensive response characterized by inflammation and recruitment of further highly specific defenses mechanisms. But TLRs also play a prominent role in non-infectious diseases characterized by inflammation, notably atherosclerosis and related vascular diseases. Studies reviewed here will summarize the current status of what we know about the involvement of TLR signaling in vascular disease, with a particular emphasis on atherosclerosis-based disease processes that lead to myocardial infarction, stroke, and sudden death. Without question, future studies will reveal in far more detail how TLR signaling and innate immune defenses participate in atherogenesis and lead to clinical events, and will be a top priority for future investigation. We will attempt to highlight directions that should yield insights with significant potential for development of novel therapeutic approaches. We anticipate that TLRs will be shown to play a central and perhaps decisive role governing the course of atherosclerosis and its clinical sequelae.

**Key words:** immunity; innate immune system; atherosclerosis; inflammation; dendritic cells; Toll-like receptors; MyD88; vascular biology

#### **Summary**

**Masayuki Fukata and Maria T. Abreu**

**Toll-like receptors and inflammatory bowel disease**

The human intestine has evolved in the presence of diverse enteric microflora. In order to maintain intestinal homeostasis, the mucosal immune response to the microflora must be actively suppressed. The enteric microflora are also required to activate a variety of genetic programs necessary for the intestinal epithelium to function properly.

Crohn's disease and ulcerative colitis are the most common forms of idiopathic inflammatory bowel disease (IBD), which is characterized by chronic intestinal inflammation in the absence of pathogen. There is no known medical cure for either ulcerative colitis or Crohn's disease. Frequently surgery is required and occasionally the disease or its treatment may be fatal. Subsets of these patients carry polymorphisms in some genes which are required for appropriate recognition of pathogen-associated molecular pattern (PAMP)s. Although the exact etiology of IBD is still unknown, patients with IBD demonstrate aberrant adaptive immune responses to the normal flora. In addition, animal models are recently beginning to reveal how the innate immune response might also be aberrant in IBD.

In this chapter, we will review the role of the innate immune response, specifically toll-like receptor (TLR) signaling, in maintaining gut homeostasis in the presence of the intestinal microflora. In particular, TLR signaling is involved in anti-microbial peptide expression, barrier fortification, clearance of bacteria, and proliferation of epithelial cells. We will also highlight how TLR signaling may play a role in human IBD and animal models of IBD.

**Key words:** Toll-like receptors, TLR, IBD, innate immune system, PAMP, polymorphisms

### **Summary**

**Ekihiro Seki, David A. Brenner and Robert F. Schwabe**

#### **Toll-like receptor signaling in the liver**

The liver is the main target of gut-derived bacterial products in the body and constantly exposed to low levels of lipopolysaccharides (LPS). The low expression of toll like receptors (TLRs) in the liver may account for the high degree of tolerance towards LPS under normal circumstances. However, in several disease states including alcoholism, massive loss of functional hepatic mass and microbial infection of the liver, LPS rises above threshold levels and induces proinflammatory and regenerative response in the liver. This chapter, describes the role of TLRs in the resident and non-resident cell populations of the liver and highlights the importance of TLRs in the pathophysiology of alcoholic liver disease, hepatic regeneration, hepatic ischemia reperfusion injury, hepatic fibrosis, HCV infection, systemic endotoxemia and microbial infection of the liver.

### **Summary**

**Sinéad E. Keating and Andrew G. Bowie**

#### **Toll-like receptors as key sensors of viral infection**

It has long been recognised that virus infection leads to the activation of host transcription factors, such as NF $\kappa$ B and IRF-3, which in turn induce the expression of a wide panel of proteins involved in triggering the ensuing type I interferon response. Research in the Toll-like receptor (TLR) field has now firmly placed these innate immune receptors as a critical link between virus infection and this cellular activation of the anti-viral response. A role for TLRs in sensing bacterial and fungal infections is well established and it is now clear that these PRRs play an equivalent role in host immunity to virus infection. In this role, the TLRs may be divided into two sub-groups containing (1) TLR2 and TLR4 which have both been shown to detect specific viral proteins at the cell surface and (2) TLR3, TLR7, TLR8 and TLR9 which are located within subcellular endosomal compartments and sense the presence of viral nucleic acids during infection. The relative importance of TLRs in triggering an effective immune response to virus infection is unclear. Nevertheless, the fact that viruses have been found not only to harness TLR-mediated cellular activation to their own advantage but also, to specifically block TLR-induced signal transduction in an effort to dampen down host innate immunity, certainly suggests a central role for TLRs in controlling virus infections.

**Key words:** Toll-like receptor, NF $\kappa$ B, IRF, IFN, virus, immune evasion

## **Summary**

**Andrei E. Medvedev, Douglas B. Kuhns, John I. Gallin and Stefanie N. Vogel**

### **IRAK-4: A key kinase involved in toll-like receptor signaling and resistance to bacterial infection**

IRAK-4 mediates TLR and IL-1R signaling due to its ability to trigger IRAK-1 phosphorylation, which results in release of IRAK-1 from the receptor, its interaction with the TRAF-6 complex, and induction of inflammatory gene expression. We and others have identified IRAK-4 mutations in patients with histories of recurrent bacterial infection and hyporesponsiveness to TLR agonists and IL-1. In one patient, two different mutations were found on distinct alleles of IRAK-4: a C877T point mutation and a 620-621 AC deletion (in IRAK-4 mRNA). When overexpressed, both mutations encode IRAK-4 proteins with truncated kinase domains that show impaired IL-1- or LPS-inducible interactions with the IL-1RI, TLR4, and IRAK-1, and block IRAK-1 activation by inhibiting recruitment of MyD88 and IRAK-1 to the receptors. These findings suggest that it may be feasible to develop inhibitors that mimic the interaction between kinase domain-deficient IRAK-4 and MyD88 as a novel therapeutic approach to block hyperinflammatory states.

**Key words:** TLR, signaling, LPS, IRAK, mutations, innate immunity

## **Summary**

**Elizabeth Brint**

### **Endogenous regulation of toll-like receptor signalling**

Toll-like Receptor (TLR)-mediated recognition of pathogens represents one of the most important mechanisms of the innate immune response and disease resistance. This is, however, a potentially damaging response if not adequately controlled potentially resulting in a multitude of disease states. The tight regulation of TLR mediated pathways is therefore essential to maintain a strict immunological balance between the protective effects of TLRs and the harmful effects which would result if TLR signalling were allowed to proceed in an uncontrolled manner. This chapter reviews all known negative regulatory mechanisms of TLR functions. Any impairment of these regulatory processes will contribute to an augmentation of TLR-mediated inflammation and disease.

## **Summary**

**Cecilia Garlanda, Michela Mosca, Alessia Cotena, Virginia Maina, Federica Moalli, Federica Riva and Alberto Mantovani**

### **Tuning of inflammatory cytokines and toll-like receptors by TIR8/SIGIRR, a member of the IL-1 receptor family with unique structure and regulation**

The activation of the signaling cascade leading to the production of proteins involved in inflammation and immunity by Interleukin-1 receptors (IL-1Rs) and Toll like receptors (TLRs) is tightly regulated. The control is exerted at different levels; both extracellularly and intracellularly. One of the molecules involved in the control of the pathways activated by IL-1, IL-18 and some TLR ligands is TIR8 (also known as SIGIRR), a member of the IL-1R family. TIR8 has a unique pattern of expression, with high mRNA levels in organs with an epithelial component. TIR8 gene transfer experiments have revealed that it reduces NF- $\kappa$ B activation by the IL-1R complex, as well as by members of the TLR family such as TLR4 by sequestering key signalling elements such as TRAF6 and IRAK. TIR8 deficiency in mice is associated with increased susceptibility to LPS toxicity or with a selective increase in

susceptibility to mucosal inflammation. Thus, available information *in vitro* and *in vivo* is consistent with the hypothesis that TIR8 negatively regulates IL-1R/TLR signaling by acting as a decoy for key components of the signaling cascade.

**Key words:** TIR8/SIGIRR, IL-1R/TLR family, inflammation, inflammatory bowel disease, dendritic cells, cytokine production, NF- $\kappa$ B, mucosal inflammation, decoy receptor, signaling, DSS-induced colitis

## **Summary**

**Bruno Conti, Christopher N. Davis, M. Margarita Behrens, Julius Rebek and Tamas Bartfai**

### **Toll-like receptors as pharmacological targets**

The toll-like receptors (TLRs) are the first responders in the major pathway by which the immune system detects infection or damaged tissue. Through the recognition of microbial products and endogenous molecules released from injured tissue, TLRs provide a critical link between the innate and the adaptive immunity [1]. Since the first human TLR was identified in 1997 [2], ten additional TLRs have been described in mammals [3, 4]. Furthermore, more than thirty molecules from *Xenopus*, *Drosophila* and plants were added to what is now collectively known as the interleukin 1 receptor (IL-1R)/TLR superfamily [5]. Considerable information has been collected on the structure, function and signaling of the TLRs. The biological function of these receptors as sensors of infection and tissue damage makes them attractive drug targets for designing vaccine adjuvants and for the treatment of immune related disorders including inflammation, infections, autoimmunity, allergies and cancer.

In the present chapter we address the rationale for the exploitation of TLRs as drug targets based on the existence of naturally occurring agonists and antagonists. In addition, existing synthetic molecules described to interact with the receptors leading to enhanced or blocked signaling are reviewed. Finally we describe the design of a novel, low molecular weight, systemically active inhibitor of IL-1R signaling. The pharmacological effects of this molecule are described as an example of a rational drug design to block the intracellular signaling of a specific member of the IL1R/TLR family. The structural and biochemical aspects of TLRs will be summarized as necessary only to improve clarity of the concepts exposed. Detailed and comprehensive reviews of such aspects are covered by other contributors to this volume and within the published literature over the past eight years.

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