Toll-Like Receptor Signaling in the Liver

ROBERT F. SCHWABE, EKIHIRO SEKI, and DAVID A. BRENNER
Department of Medicine, Columbia University, College of Physicians and Surgeons, New York, New York

Toll-like receptors (TLRs) recognize pathogen-associated molecular patterns and are crucially involved in the regulation of innate immune responses. Despite chronic exposure to a high load of bacterial products, the normal liver shows no activation of TLR-signaling pathways. However, under pathologic conditions, Toll-like receptors promote proinflammatory signaling such as the nuclear factor-κB, c-Jun-N-terminal kinase (JNK), p38, and interferon pathways in the liver and regulate antiviral and antibacterial responses, hepatic injury, and wound healing. This review will summarize recent findings on TLR signaling; describe the functional expression of TLRs in resident and nonresident cell populations of the liver; and analyze the role of TLR-mediated signals in hepatic diseases such as hepatitis B and C virus infection, systemic endotoxemia, hepatic ischemia-reperfusion injury, liver regeneration, alcoholic liver injury, nonalcoholic steatohepatitis, primary biliary cirrhosis, and hepatic fibrosis.

Toll-like receptors (TLRs) are a group of highly conserved molecules that allow the immune system to sense molecules that are present in most classes of pathogens, but not the host, and to coordinate defense mechanisms against these pathogens. The recognition of pathogen-associated molecular patterns (PAMPs) by Toll-like receptors is a cornerstone of innate immunity and provides a quick and highly efficient response to pathogens in both vertebrate and invertebrate species.[1–4] In addition, there is accumulating evidence that TLRs contribute significantly to activation of adaptive immune responses such as dendritic cell maturation and T- and B-cell responses.[5]

Because of its anatomic links to the gut, the liver is constantly exposed to gut-derived bacterial products and functions as a major filter organ and a first line of defense. Eighty percent of intravenously injected endotoxin is detected in the liver within 20–30 minutes.[6,7] Kupffer cells, the resident macrophages of the liver, are able to take up efficiently endotoxin and phagocytose bacteria carried through portal vein blood and are considered to play a major role in the clearance of systemic bacterial infection.[8–11] Despite the constant exposure to low levels of gut-derived bacteria and bacterial products, there are no signs of ongoing inflammation in the normal liver. This lacking response is to some extent explained by very specific immunologic properties of the liver,[12] which contribute to a high degree of tolerance as seen by graft survival across major histocompatibility antigen disparities, induction of systemic tolerance to food antigens, and persistence of some viral infections for decades.[13] In addition, the healthy liver contains low messenger RNA (mRNA) levels of TLRs such as TLR1, TLR2, TLR4, TLR6, TLR7, TLR8, TLR9, and TLR10 and signaling molecules such as MD-2 and MyD88 in comparison with other organs.[14–16] However, under pathologic conditions, TLRs activate inflammatory-signaling pathways in the liver and are actively involved in the pathophysiology in a large number of hepatic diseases. In this article, we will present an overview of recent advances in TLR signaling and review the role of TLRs in the pathophysiology of infectious, toxic, metabolic, and autoimmune liver disease.

I. TLR Signaling

TLRs and Coreceptors

The human TLR family consists of currently 10 members, which are structurally characterized by the presence of a leucine-rich repeat (LRR) domain in their extracellular domain and a Toll/interleukin (IL)-1 receptor (TIR) domain in their intracellular domain. The existence of a large number of TLRs enables the innate immune system to discriminate between PAMPs that are characteristic of different microbial classes and launch specific defense mechanisms. A comparison of the amino acid sequences of the human TLRs reveals that members of the TLR family can be structurally divided into 5 subfamilies: the TLR3, TLR4, TLR5, TLR2, and TLR9 subfamilies. Whereas the TLR3, TLR4, and TLR5 subfamilies consist of only 1 member, the TLR2 subfamily is composed of TLR1, TLR2, TLR6, and TLR10 and the

Abbreviations used in this paper: ER, endoplasmic reticulum; LPS, lipopolysaccharide; LRR, leucine-rich repeat; PAMPs, pathogen-associated molecular patterns; PH, partial hepatectomy; SOCS1, suppressing of cytokine signaling 1; TIR, Toll/interleukin-1 receptor; TIRAP, TIR domain containing adapter protein; TLRs, Toll-like receptors.

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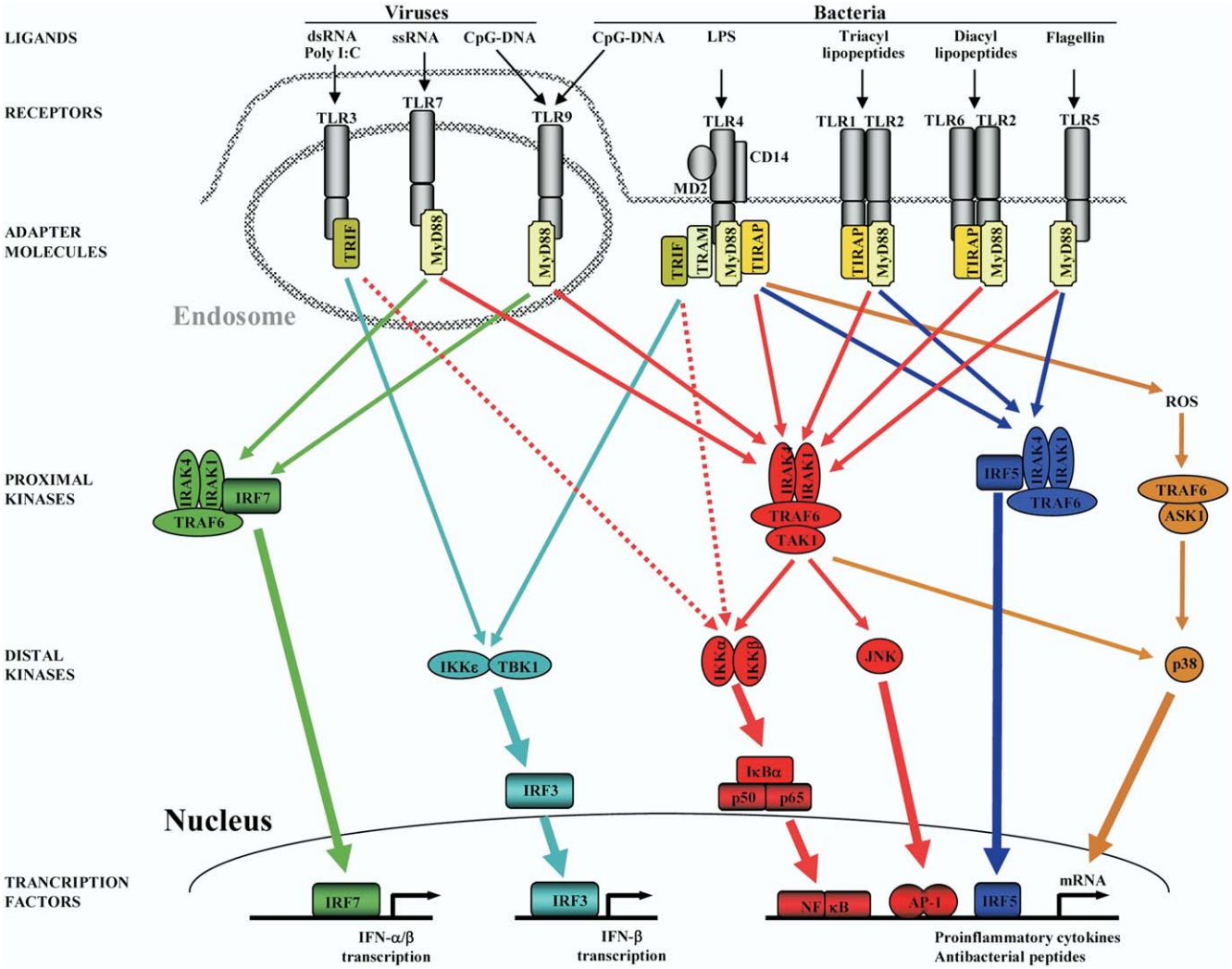

Figure 1. Schematic overview of TLR signaling pathways. Viral PAMPS activate TLR3, TLR7, and TLR9, whereas bacterial PAMPs activate TLR1, TLR2, TLR4, TRL6, and TLR9. Each receptor interacts with 1 or several adapter molecules (MyD88, TRIF, TRAM, and TIRAP) to then induce activation of 1 or several downstream kinases and transcription factors, which up-regulate proinflammatory, antiviral, and antibacterial mediators. The main signaling pathways induced are the IRF7-IFN pathway (*green*), IRF3-IFN pathway (*light blue*), NF-κB pathway (*red*), AP-1 pathway (*red*), IRF5 pathway (*dark blue*), and p38 pathway (*orange*).

TLR9 subfamily of TLR7, TLR8, and TLR9. TLRs are able to detect a variety of PAMPs including lipopolysaccharide (LPS; TLR4), lipoproteins (TLR2/TLR1 and TLR2/TLR6 heterodimers), double-stranded RNA (TLR 3) and single-stranded RNA (TLR 7 and TLR8), flagellin (TLR5), and unmethylated CpG-containing DNA (TLR9) (Figure 1). TLR10 is an orphan receptor with currently unknown ligands. TLR1 and TLR2 form heterodimers with TLR6 and TLR10 as well as with each other, which may even broaden the ligand repertoire of these receptors. TLRs that mainly serve to detect bacterial lipopolysaccharides and lipoproteins are located on the cell surface. TLRs such as TLR3, TLR7, TLR8, and TLR9 that mainly recognize viral RNA and bacterial DNA are located in late endosome-lysosomes in which these materials are processed and host DNA is not present, thus avoiding aberrant self-recognition. Although each TLR detects specific PAMPs, many of the signaling molecules that mediate intracellular response are shared by the TLRs and form a complex signaling network that activates several pathways that initiate the transcription of a specific set of genes to induce proinflammatory, antiviral, and antibacterial responses. In addition, TLR ligands also repress the transcription of a large number of genes.[17,18] The TLR-signaling pathway shows remarkable similarity to the IL-1 receptor signaling pathway with which it shares many components including highly conserved cytoplasmic TIR domains and several intracellular adapter molecules.

Two cell surface molecules, CD14 and MD-2, are involved in addition to TLR4 to transmit signals in response to LPS. Mice that are deficient in CD14 are