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Review article

Toll-like receptor 2: An important immunomodulatory molecule during *Helicobacter pylori* infection

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ABSTRACT

Toll like receptors (TLRs) are an essential subset of pathogen recognition receptors (PRRs) which identify the microbial components and contribute in the regulation of innate and adaptive immune responses against the infectious agents. The TLRs, especially TLR2, TLR4, TLR5 and TLR9, participate in the induction of immune response against *H. pylori*. TLR2 is expressed on a number of immune and non-immune cells and recognizes a vast broad of microbial components due to its potential to form heterodimers with other TLRs, including TLR1, TLR6 and TLR10. A number of *H. pylori*–related molecules may contribute to TLR2-dependent responses, including HP-LPS, HP-HSP60 and HP-NAP. TLR2 plays a pivotal role in regulation of immune response to *H. pylori* through activation of NF-κB and induction of cytokine expression in epithelial cells, monocytes/macrophages, dendritic cells, neutrophils and B cells. The TLR2-related immune response that is induced by *H. pylori*-derived components may play an important role regarding the outcome of the infection toward bacterial elimination, persistence or pathological reactions. The immunomodulatory and immunoregulatory roles of TLR2 during *H. pylori* infection were considered in this review. TLR2 could be considered as an interesting therapeutic target for treatment of *H. pylori*-related diseases.

Contents

Abbreviations: BCAP, B-cell adapter for PI3K; BMDCs, bone marrow-derived dendritic cells; CASP1, caspase-1; CagA, cytotoxin-associated gene A; CCL20, chemokine (C—C motif) ligand 20; CHO, Chinese hamster ovary; COX-2, cyclooxygenase 2; CXCL1, chemokine (C-X-C motif) ligand 1; DAMP, danger-associated molecular patterns; DCs, dendritic cells; Dok, downstream of kinase; ERK, extracellular signal regulated kinase; FOXP3, forkhead box P3; GROα, growth regulated protein α; HBcAg, hepatitis B core antigen; HCV, hepatitis C virus; HCVc, HCV core protein; HEK, Human embryonic kidney; HMGB1, High mobility group box protein 1; HP-LPS, *H. pylori*-LPS; HP-NAP, neutrophil-activating protein of *Helicobacter pylori*; *H. pylori*, *Helicobacter pylori*; HSP60, heat shock protein60; IFN-β, interferon beta; IFNs, interferons; IKKβ, IκB kinase B, and; IκBα, inhibitor of kappa Bα; IL, interleukin; iNOS, inducible nitric oxide synthase; IRAK1, interleukin-1 receptor-associated kinase 1; IRF, interferon regulatory transcription factor; JAK–STAT, Janus kinase/signal transducers and activators of transcription; LPS, lipopolysaccharide; MAL, MyD88 adapter-like; MALT, mucosa-associated lymphoid tissue; MAMP, microbe-associated molecular pattern; MAPKs, mitogen-activated protein kinases; MCP-1, monocyte chemoattractant protein-1; MHC, major histocompatibility complex; MIP-3α, macrophage inflammatory protein 3α; mTOR, mammalian target of rapamycin; MYD88, myeloid differentiation primary response gene; NAP, neutrophil-activating protein; Nef, negative regulatory factor; NF-κB, nuclear factor-kappa B; NLRP3, NACHT, LRR and PYD domains-containing protein 3; NOD2, nucleotide-binding oligomerization domain-containing protein 2; PAI, plasminogen activator inhibitor-1; PAMP, pathogen associated molecular patterns; PBMCs, peripheral blood mononuclear cells; PI3K/AKT, the phosphatidylinositol-3-kinase/Akt; PRRs, pathogen recognition receptors; RA, retinoic acid; SARM, sterile α and armadillomotifcontaining protein; sIL-4R, soluble interleukin-4 receptor; SNPs, single-nucleotide polymorphisms; SOCS, suppressor of cytokine signaling; STAT3, signal transducer and activator of transcription 3; TIR, Toll/interleukin-1 receptor; TIRAP, TIR domain-containing adaptor protein; TLR2, Toll-like receptor 2; TNFα, tumor necrosis factor-alpha; Tr1, T regulatory-1; TRAF, TNF receptor associated factor; TRAM, TRIF-related adaptor molecule; TRIB3, tribbles 3; TRIF, TIR-domain-containing adapter-inducing interferon-β; UreB, urease subunit beta; VacA, vacuolating cytotoxin A.

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1. Introduction

Several gastrointestinal diseases were powerfully related with *Helicobacter pylori* (*H. pylori*) colonization in the human stomach, including gastritis, peptic ulcers, gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma [1,2]. Some extra-gastrointestinal disorders including hematologic, cardiovascular, metabolic, neurologic and dermatologic diseases, were also associated with *H. pylori* infection [3–7]. The prevalence of *H. pylori* infection shows highly variations within and between countries, being 25–50% and >80% in the developed- and developing countries, respectively [2,8,9].

Approximately, 15–20%, 0.1%–3% and <0.01% of *H. pylori*-infected subjects exhibit peptic ulcer, gastric cancer and gastric MALT lymphoma, respectively [2]. The clinical outcome of *H. pylori* infection is determined by a reciprocal communication between bacteria virulence factors as well as by host genetic factors, such as immune response genes, in addition to environmental factors [8,10,11]. The cytotoxin-associated gene A (CagA) and VacA (vacuolating cytotoxin A) molecules are the most powerful bacterium virulence factors associated with the severity of *H. pylori*-related gastrointestinal diseases [1,12]. The $CagA^+$ strains of *H. pylori* induce more serious gastric mucosal injuries and stronger inflammatory responses [13–15].

Different types of inflammatory cells such as dendritic cells (DCs), macrophages, neutrophils, mast cells, and T and B cells, are accumulated into the stomach of the *H. pylori*-infected subjects [16]. In contrast to the great types of bacteria, which cause disease and then are cleared by the pathogen-specific immune response, *H. pylori* establishes a permanent infection and can persist for long time, in spite of the induction of a powerful innate and adaptive immune responses [17]. Therefore, *H. pylori* has acquired several adaptive mechanisms that allow the bacterium to escape the host immune responses. The specific immune response that is induced during *H. pylori* infection may be an important determining parameter that influences the outcome of the infection toward bacterium elimination, protection, evasion, or pathologic process [18].

Toll-like receptors (TLRs) contribute in the regulation of innate and adaptive immune responses against the infectious agents that may influence the infection outcome toward pathogen elimination, persistence and occurrence of clinical consequence [19]. A number of TLRs, especially TLR2, TLR4, TLR5 and TLR9, participate in the induction of immune response against *H. pylori* [20]. TLR2 recognizes a vast broad of microbial components due to its potential to form heterodimers with other TLRs including TLR1, TLR6 and TLR10 [21]. The powerful immunomodulatory effects have been attributed to TLR2. It has been clearly demonstrated that TLR2 influences the outcome of some infections such as *Mycobacterium tuberculosis*, hepatitis C virus and *Candida albicans* [22–24]. The immunomodulatory and immunoregulatory roles of TLR2 during *H. pylori* infection were considered in this review. We aimed also to describe the potential application of this TLR for the development of future anti-*H. pylori* therapies.

2. Structure and properties of toll-like receptors

TLRs are integral membrane glycoproteins that are composed of three parts: an N-terminal extracellular domain with leucine-rich repeats (LRRs) that binds to ligand, a single transmembrane motif and a signaling C-terminal cytoplasmic domain, which is also known as Toll/interleukin-1 receptor (TIR) domain due to its homology with interleukin-1 receptors (IL-1R) [19].

TLRs are an important subset of membrane-related pathogen recognition receptors (PRRs) that play fundamental roles in identification of exogenous pathogen-associated molecular patterns (PAMPs) and endogenous components that specified as damage-associated molecular patterns (DAMPs) [25]. PAMPs are conserved components that originate from microorganisms such as peptidoglycan, lipopolysaccharide (LPS), flagellin, and microbial nucleic acids, whereas most endogenous DAMPs derive from dying host cells following cellular stress (such as oxidative stress) or tissue injury, for example heat shock proteins [26]. The binding of TLRs to PAMPs or DAMPs induces a variety of intracellular signaling pathways that result in the expression of pro-inflammatory cytokines and chemokines, and regulate the type, extent or duration of the inflammatory response [25]. Ten operative TLRs were identified in humans, of which TLR1, 2, 4, 5, 6, and 10 are placed on the cell surface and recognize microbial membrane components, including lipoproteins, lipids and proteins, while TLR 3, 7, 8, and 9 are located in intracellular compartments, such as the endosome and the endoplasmic reticulum, and bind to microbial nucleic acids [25].

3. Expression and functions of TLR2

TLR2 was identified in 1998 and acts as a receptor for a number of PAMPs which are originated from bacterial, fungal, viral and parasitic agents [27]. TLR2 is expressed by antigen presenting cells (APCs) including macrophages, monocytes and DCs, including plasmacytoid DCs in mice and Langerhans DCs but not plasmacytoid DCs in humans. Although human naive T, B and NK cells do not express TLR2, activated B cells in germinal centers of tonsils, lymph nodes and appendices express this molecule [28].

TLR2 recognizes a largest number of ligands, such as bacterial cell wall-associated molecules [including lipoproteins, peptidoglycan, lipoteichoic acid, di- and tri-acylated lipopeptides, lipoproteins, lipopolysaccharides (LPS) from some bacterial species (e.g., *Porphyromonas gingivalis*), porins from *Neisseria*, lipoarabinomannan from