Toll-like receptor signaling in hematopoietic homeostasis and the pathogenesis of hematologic diseases

Joseph Cannova1,2, Peter Breslin S.J. (✉)3,5,6,a, Jiwang Zhang (✉)1,3,4,b

1Biochemistry and Molecular Biology Program, Loyola University Chicago, Maywood, IL 60153, USA; 2Stritch School of Medicine, Loyola University Chicago, Maywood, IL 60153, USA; 3Oncology Institute, Loyola University Chicago, Maywood, IL 60153, USA; 4Department of Pathology, Loyola University Chicago, Maywood, IL 60153, USA; 5Department of Biology, Loyola University Chicago, Chicago, IL 60660, USA; 6Department of Molecular and Cellular Physiology, Loyola University Chicago, Maywood, IL 60153, USA

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Abstract Toll-like receptors (TLRs), which are found in innate immune cells, are essential mediators of rapid inflammatory responses and appropriate T-cell activation in response to infection and tissue damage. Accumulating evidence suggests that TLR signaling is involved in normal hematopoiesis and specific hematologic pathologies. Particular TLRs and their downstream signaling mediators are expressed not only in terminally differentiated innate immune cells but also in early hematopoietic progenitors. Sterile activation of TLR signaling is required to generate early embryonic hematopoietic progenitor cells. In adult animals, TLR signaling directly or indirectly promotes differentiation of myeloid cells at the expense of that of lymphoid cells and the self-renewal of hematopoietic stem cells during infection and tissue damage. Activating mutations of the MyD88 gene, which codes for a key adaptor involved in TLR signaling, are commonly detected in B-cell lymphomas and other B-cell hematopathologies. Dysregulated TLR signaling contributes to the pathogenesis of many hematopoietic disorders, including bone marrow failure, myelodysplastic syndrome, and acute myeloid leukemia. Complete elucidation of the molecular mechanisms by which TLR signaling mediates the regulation of both normal and pathogenic hematopoiesis will prove valuable to the development of targeted therapies and strategies for improved treatment of hematopoietic disorders.

Keywords TLR; MyD88; hematopoiesis; bone marrow failure; leukemia; myelodysplastic syndrome

Introduction

The innate immune system functions as the first line of immune defense in humans and other multicellular organisms. This system provides rapid protective response against numerous infections and injuries. Responses to infection or tissue damage are primarily mediated by tissue-resident immune cells (including macrophages, dendritic cells, mastocytes, and histiocytes) and circulating white blood cells (monocytes, neutrophils, and natural killer cells). Pattern recognition receptors (PRRs) expressed in immune or epithelial cells first detect the presence of invading bacteria or viruses in metazoans. PRRs are encoded in the genome and are highly conserved across a wide range of species. PRRs sense danger signals by recognizing conserved molecular patterns and then inducing appropriate responses, often involving inflammation, to eliminate danger factors or to limit factor-induced tissue damage [1]. During pathogenic infection, PRRs detect pathogen-associated molecular patterns (PAMPs), which are released from invading bacteria or viruses and are responsible for activating responses to limit infections and eliminate pathogens. The binding of PAMPs to specific PRRs activates downstream signaling, which stimulates innate anti-pathogen immunity by inducing a local accumulation of monocytes and neutrophils, and also facilitates pathogen-specific adaptive immune response by enhancing the activation of an antigen-specific memory T-cell response. In cases of tissue damage, PRRs recognize damage-associated molecular patterns (DAMPs), which are endogenous PRR ligands released from damaged or necrotic cells; moreover, healing and inflammatory responses are activated to clear cellular debris and repair the damaged tissue [1]. PRRs are divided into several
receptor classes, including toll-like receptors (TLRs) and C-type lectin receptors (CLRs), both of which are transmembrane receptors. PRRs include NOD-like receptors (NLRs) and retinoic acid inducible gene (RIG)-I-like receptors (RLRs) [1]. Of these classes, TLRs are commonly characterized with respect to their receptor structure, localization, known ligands, and downstream signaling patterns. Accumulating evidence suggests that TLR-mediated signaling not only serves an essential function in stimulating the innate immune response, which has been summarized in many excellent reviews [2,3], but also participates in the regulation of hematopoietic homeostasis and possibly hematopoietic pathologies.

Although particular tissue-resident innate immune cells can self-renew, proliferate, and expand to an extent, tissue-innate immune cells are largely dependent on replenishment by circulating monocytes derived from hematopoietic stem/progenitor cells (HSPCs) in the bone marrow (BM) niche [4,5]. Most innate immune effector cells are short-lived and rapidly consumed during inflammation [5]. Therefore, during infection or injury, augmented hematopoiesis is required to fulfill the high demand for innate immune cells. However, the chronic, abnormal activation of TLR signaling may disrupt the homeostatic state of normal hematopoiesis and even induce hematopoietic disorders. In this paper, we review the studies that have explored TLR signaling in the regulation of both normal and pathogenic hematopoiesis. We believe that research on hematopoietic TLR signaling will enhance our ability to promote normal hematopoiesis and target pathologic processes through precise molecular modulation of this important signaling pathway.

**TLRs and their ligands**

TLRs are type 1 transmembrane proteins with an N-terminal extracellular domain characterized by leucine-rich repeats (LRRs), a singular transmembrane helix, and a C-terminal cytoplasmic Toll/IL-1 receptor (TIR) domain. To date, 10 unique TLRs have been characterized in humans, whereas 12 functional murine TLRs have been described [2]. TLRs are divided into subtypes based on which specific PAMPs they recognize. TLR1–TLR9 are functionally conserved and expressed in both mice and humans. TLR10 is functional in humans but not expressed in mice. TLR11, TLR12, and TLR13 are found only in mice [6]. TLR1, TLR2, TLR4, TLR5, TLR6, and TLR11 are found on cell surfaces and are associated with the detection of extracellular molecular patterns, mostly bacterial PAMPs and endogenous DAMPs. TLR3, TLR7, TLR8, and TLR9, are localized in intracellular vesicles and endosomes and can recognize molecular patterns associated with intracellular infections, such as bacterial or viral nucleic acids (Fig. 1) [6]. Notably, TLR4 may be found on either the plasma membrane or endosomes. Analyses of the crystal structures of TLR extracellular domains reveal that LRRs form horseshoe-like concave structures in which distinct LRR patterns confer receptor specificity for several distinct PAMPs [7]. TLR3, TLR4, TLR5, and TLR9 homodimers recognize double-stranded RNA (dsRNA), lipopolysaccharide (LPS), bacterial flagellin, and unmethylated CpG DNA motifs, respectively [6,8–11]. TLR1/TLR2 and TLR2/TLR6 heterodimers recognize triacylated and diacylated lipoproteins, respectively [12–14]. Both TLR7 and TLR8 homodimers recognize single-stranded RNA [15]. Recently, TLR8 has been shown to detect uridine and RNA oligonucleotide sequences at two distinct sites in its extracellular domain, both of which are essential for receptor activation [16].

Depending on the TLR subtype, TLRs may exist as monomers that dimerize in the presence of their ligands or as dimers that undergo a conformational change upon exposure to a ligand. Ligand-induced dimerization has been demonstrated for TLR1/TLR2, TLR2/TLR6, TLR3, TLR4, and TLR5 [8,17–21]. In contrast, TLR7, TLR8, and TLR9 exist as dimers in the absence of their ligands. Crystal structural studies have demonstrated that the ligand stimulation of TLR7, TLR8, or TLR9 induces conformational changes [9,10]. Dimerization and conformational changes induced by TLR-ligand binding are believed to bring their cytoplasmic TIR domains into close proximity with each other, thereby enabling the recruitment of downstream adaptor proteins via homotypic TIR domain interactions [7,10]. Further crystallization studies, particularly those on cytoplasmic TIR domains upon ligand stimulation, are needed to confirm these mechanisms. To fully activate ligand-stimulated TLR signaling, other coreceptors or facilitators may also be required in certain cases. For instance, efficient LPS-induced TLR4 activation depends on two co-receptors of TLR4, namely, CD14 and MD-2 [22–24]. Intracellular TLR3, TLR7, and TLR9 have been shown to interact with the ER protein UNC93B1, which assists in the translocation from the ER to endosomes, a necessary step for functional TLR7 and TLR9 signaling [25].

Additionally, several TLRs are believed to recognize DAMPs produced as endogenous ligands. The ligation of DAMPs may signal through separate complementary pathways unlike those of PAMPs and function in an undetermined physiologic purpose. The accumulation of DAMPs has been associated with many aging-related diseases, including atherosclerosis, gout, Parkinson’s disease, Alzheimer’s disease, and age-related macular degeneration [26]. Known DAMPs include extracellular matrix proteins biglycan, versican, hyaluronic acid, and heparin sulfate, as well as particular cellular components, such as high-mobility group box 1 (HMGB1) protein, hsp70, hsp72, and S100A/B [27]. Modified forms of