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INNATE RECEPTORS FOR ADAPTIVE IMMUNITY

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Summary

Pattern recognition receptors (PRRs) are commonly known as sensor proteins crucial for the early detection of microbial or host-derived stress signals by innate immune cells. Interestingly, some PRRs are also expressed and functional in cells of the adaptive immune system. These receptors provide lymphocytes with innate sensing abilities; for example B cells express Toll-like receptors, which are important for the humoral response. Strikingly, certain other NOD-like receptors are not only highly expressed in adaptive immune cells, but also exert functions related specifically to adaptive immune system pathways, such as regulating antigen presentation. In this review, we will focus particularly on the current understanding of PRR functions intrinsic to B and T lymphocytes; a developing aspect of PRR biology.

Highlights

- PRRs are expressed by cells of the innate, but also of the adaptive immune system
- Certain PRRs endow B and T cells with innate sensing abilities
- Other PRRs evolved to fulfill functions related to the adaptive immune system

Keywords

T cell; B cell; TLR; NLR; RLR

Introduction

Pattern recognition receptors (PRRs) are defined as key sensors involved in detecting pathogens or danger signals and initiating inflammatory processes. The engagement of PRRs in innate immune cells, such as dendritic cells, is also crucial for indirect instruction of adaptive immune responses. While these aspects of PRR signaling are well understood, less is known about PRRs that are expressed by adaptive immune cells. Here, we will discuss evidence supporting a function of Toll-like, retinoic acid-inducible gene I (RIG-I)-like, or NOD-like receptors (TLRs, RLRs, and NLRs, respectively) intrinsic to B lymphocytes, conventional and regulatory T cells.

TOLL-LIKE RECEPTORS IN B AND T CELLS

The TLR family was the first identified among PRRs and is therefore the most characterized. TLRs are transmembrane glycoproteins that bind to a wide range of pathogen- and danger-associated molecular patterns (PAMPs and DAMPs). Thirteen mammalian TLRs have been identified; ten functional receptors in humans and twelve in mice [1]. While TLR10 and TLR11-13 are exclusively expressed in humans and mice, respectively, TLR1-9 are shared by both species [2]. These receptors are typically expressed in innate immune cells, but analyses at the mRNA level in human and mouse have demonstrated TLR expression in all peripheral blood leukocytes including B and T cells [3-7]. Such studies have provided a rationale for examining a cell-intrinsic function of TLRs in adaptive immune cells.

TLRs in B cells

The current understanding as to how TLRs modulate B lymphocyte activation, antigen presentation, proliferation, class switch recombination, and antibody production is comprehensively reviewed elsewhere [8,9]. Therefore, we will focus on a few selected studies investigating these aspects.

Several reports have described the expression of TLRs in different mouse and human B cell subsets and their regulation by cytokines as well as signaling from the B cell receptor [6-8,10,11]. TLR1, TLR2, TLR4, TLR6, TLR7 and TLR9 are expressed in most murine B cell subsets, including naïve B cells, but at varying levels [10], suggesting a subset-specific sensitivity to diverse TLR agonists. Similar data were obtained in human B cells, although constitutive TLR expression in humans is

most prominent among memory B cells, which has been suggested to play an important role in the maintenance of serological memory [7,12,13].

The first *in vivo* evidence for a B cell-autonomous role of TLRs in the regulation of humoral responses came from Pasare and Medzhitov [14]. Performing transfer experiments of B cells deficient for the TLR signaling adaptor *Myd88* or for *Tlr4*, they showed that TLR signaling in B cells is mandatory for the generation of optimal T cell-dependent antibody responses. Notably, the role of TLRs in B cells has been corroborated in B cell-specific *Myd88*-deficient mice, which showed impaired humoral response upon immunization with virus-like particles delivering TLR9 ligands [15]. However, as MyD88 is an adaptor shared also by the IL-1 receptor family, the use of conditional TLR-deficient animals would further strengthen these results.

The implications of these studies are highly relevant not only in the context of antiviral antibody-mediated responses, but also for vaccine development and understanding autoimmunity more broadly [8,16].

TLRs in T cells

Murine and human T cells express several functional TLRs, which are regulated depending on T cell activation status [6,11]. The first evidence of a functional effect of TLR ligands on T cell physiology was on clonal expansion. Bendigs and collaborators demonstrated that CpG-DNA treatment enhanced antigen-mediated proliferation of murine T cells, whereas no effect was observed on naive cells [17]. Furthermore, in murine $CD4^+$ T cells, TLR9 engagement was shown to be important for cell survival through the activation of mitogen-activated protein kinases (MAPKs) and NF-κB [18,19].

Several studies demonstrated a costimulatory effect of TLR2 ligands on antigen-mediated proliferation of $CD4^+$ and $CD8^+$ T cells of human and murine origin [20-23]. TLR2 is well expressed on mouse cytotoxic $CD8^+$ T cells and human memory $CD4^+$ T cells [20,22]. Cooperation of TLR2 and TLR5 engagement was also described to enhance activated $CD8^+$ T cell expansion [24]. Furthermore, homeostatic proliferation of memory $CD4^+$ T cells was increased by ligands of TLR2, TLR5 or TLR7/8, suggesting a role for TLR engagement in long-term maintenance of memory T cells [20,25].

Concerning effector functions and cytokine production, TLR2 signaling was shown to be essential for promoting the production of interleukin (IL)-17 and interferon (IFN)-γ by effector $CD4^+$ T cells [26,27], but also chemokine (C-C motif) ligand 3 (CCL3), and CCL4 [28]. TLR2 or TLR3 engagement on T cell receptor (TCR)-activated $CD8^+$ T cells also enhanced IFN-γ secretion [21,22,29].

Finally, a dual effect of TLR ligands was described on the regulatory T cell (Treg) compartment. TLR8 ligands were shown to reverse the suppressive function of human T regulatory cells [30], while it was reported that LPS might induce proliferation and enhance suppressive activity of murine regulatory cells [31].

Given the high expression of many TLRs among APCs, and the sensitivity of T cells to APC-derived activating signals, it is important to remember that a small number of contaminating APCs could confound the analysis. Nonetheless, an effect of TLRs on T cell physiology at the intrinsic level is nowadays supported by several independently conducted and well-controlled experiments, clearly demonstrating that TLR agonists affect expansion, differentiation, or activity of effector/memory T cells as well as the regulatory T cell population. However, the impact of TLR ligands on other T-cell subsets, as for instance Th17 or Th22, still awaits further investigation *in vitro* and particularly *in vivo*. Such studies may open up potential therapeutic applications in vaccination or autoimmune diseases [32].

RIG-I-LIKE RECEPTORS IN T LYMPHOCYTES

The RLR family members RIG-I and melanoma differentiation-associated gene 5 (MDA5) act as cytoplasmic RNA sensors inducing type I IFN responses. The third family member, laboratory of genetics and physiology 2 (LGP2), is instead a positive regulator of their signaling (see Table 1) [33]. RLR signaling is mediated by the downstream adaptor mitochondrial antiviral-signaling protein (MAVS), which is required for IFN induction.

Both, RIG-I and MDA5, are highly expressed in T lymphocytes [6]. Interestingly, stimulation of Tregs with Encephalomyocarditis virus has been shown to decrease Treg inhibitory function in an MDA5-dependent manner, as demonstrated by the use of knockout cells [34]. However, no additional insights were provided on the mechanism underlying this phenomenon.

A recent paper showed the involvement of LGP2 in cytotoxic T cell survival upon West Nile virus infection, an outcome that was surprisingly independent of MAVS. [35]. This was achieved by down-modulating sensitivity to Fas-mediated apoptosis. Given that RLRs specifically detect RNAs, it is however still unclear whether LGP2 mediates T cell survival only upon infection by RNA viruses [35].

Despite the expression of RLRs in T cells, there is little evidence that these lymphocytes efficiently produce type I IFN in response to RNA. Accordingly, emerging data show that RLRs in T cells can fulfill functions unrelated to classical MAVS-mediated signaling; a novel aspect that deserves further investigation.

NLRs IN ADAPTIVE IMMUNE CELLS

NLRs are intracellular proteins involved in diverse immune processes [36-40]. In this review, we will focus on family members that are expressed by adaptive immune cells (Table 2).

Inflammasome-forming NLRs

Upon detection of stress signals, certain NLRs assemble into complexes called "inflammasomes" [37]. Inflammasomes trigger the cleavage of caspase-1, which proteolytically activates interleukin (IL)-1β and mediates an inflammatory cell death called "pyroptosis" [37].

Although inflammasomes have mainly been described in myeloid cells, caspase-1 and the adaptor protein ASC (apoptosis speck protein with CARD) are also expressed in lymphocytes [6,11]. This supports the possibility that these multiprotein platforms can also be formed in adaptive immune cells. Indeed, a very interesting study suggested formation of an inflammasome in T cells upon abortive HIV infection, with viral DNA being the trigger [41], though the sensor inducing inflammasome assembly has not been identified.

Indeed, certain inflammasome-forming NLRs are expressed in lymphoid cells. For instance, NLR family, pyrin domain containing 1a (NLRP1a) is expressed in common myeloid and lymphoid progenitors [6,36,37,42-45]. This NLR has recently been shown to induce pyroptosis upon stresses such as chemotherapy or infection, prolonging cytopenia in both myeloid and lymphoid compartments, therefore supporting the possibility that an inflammasome is formed in lymphoid precursor

cells [42]. In addition, human NLRP1 is highly expressed in T and B cells, though its function in lymphocytes remains unexplored [6,43,46-48].

The prototypical inflammasome-forming NLR, NLRP3, is however barely detectable in T cells at the steady-state [6,43,44,49,50], although it could be upregulated upon activation, which is the case in B cells, particularly following C-type lectin stimulation [51]. In B cells, Nlrp3 is involved in activation and immunoglobulin production downstream of C-type lectin stimulation. Though the molecular details of this phenomenon remain elusive, it was found to be independent of MyD88, suggesting that it was not mediated by IL-1 receptor signaling [51].

NOD1 and NOD2

NOD1 and NOD2 activate NF-κB and MAPK pathways upon sensing peptidoglycans [36,38]. Whilst the function of NOD1 and NOD2 has largely been explored in innate immune and mucosal epithelial cells, NOD1 and, to a lesser extent, NOD2 are expressed by cells of the adaptive immune system [6,43,44,47,50,52]. Stimulation of B and $CD8^+$ T cells with a NOD1 agonist improved antigen receptor-driven proliferation, and the use of *Nod1*$^{-/-}$ T cells nicely demonstrated the specificity of this effect [44,47].

Similar to the LGP2 effect in T cells, NOD2 stimulation increased survival of Tregs by decreasing sensitivity to Fas-mediated apoptosis [50]. Furthermore, *Nod2*$^{-/-}$ conventional T cells produced less IL-2, effector cytokines, and showed reduced nuclear accumulation of the NF-κB family member c-Rel in the context of *Toxoplasma gondii* infection [53]. However, these data were not substantiated in a later study [52], reminiscent of the debated T cell-autonomous role of receptor-interacting serine/threonine-protein kinase 2, the kinase acting downstream of NOD1 and NOD2 [44,54]. Therefore, future work is required to clarify these discrepancies.

Signaling and transcription regulatory NLRs

NLR family, CARD domain containing 3 (NLRC3) is a poorly studied NLR, predominantly expressed in T and NK lymphocytes [6,55]. An early study suggested a negative role in T cell activation because NLCR3 transcript abundance decreased upon TCR triggering and NLRC3 overexpression impaired TCR-induced NF-κB signaling [55]. However, a recent report demonstrated experimental artifacts can be generated using NLRC3 overexpression assays, suggesting caution should be taken

when interpreting such overexpression studies [56]. Nonetheless, an increase in TLR-driven NF-κB activation was shown in macrophages derived from *Nlrc3*-deficient mice, though T lymphocytes were not investigated in this study [57].

One of the most exciting areas of PRR function in adaptive immunity is in transcriptional regulation. Whilst they belong to NLRs, CIITA and NLRC5 act as transcriptional regulators of major-histocompatibility complex class II (MHCII) and class I (MHCI), respectively [39,40,58]. In humans and in mouse, CIITA deficiency causes a lack of MHCII, leading to severe immunodeficiency [39]. CIITA expression is virtually restricted to antigen-presenting cells (APCs) and in humans also to recently activated $CD4^+$ T cells [6,39]. MHCII expression is crucial for the homeostasis and the activity of helper T cells, and its expression specifically by B lymphocytes is essential for the maturation of the humoral response.

Under homeostatic conditions, NLRC5 is highly expressed in lymphocytes, predominantly in T cells [6,40,58]. Accordingly, *Nlrc5* deficiency caused a dramatic defect in MHCI expression in T cells and an intermediate phenotype in B cells, and a milder defect was observed in innate APCs. Notably, reduced MHCI levels on *Nlrc5*$^{-/-}$ lymphocytes facilitated evasion from cytotoxic T cell-mediated surveillance, while *Nlrc5*$^{-/-}$ B cells were defective in priming $CD8^+$ T cell responses [40,58].

A prerequisite for the activation of several NLRs, as well as for RLRs, is the internalization of their specific stimuli. It is currently unclear how this is achieved by T lymphocytes, which are considered non-phagocytic cells. However, NLRs such as CIITA and NLRC5 acquired regulatory functions that are independent from a DAMP or PAMP type of ligand, delineating a novel and fascinating evolution of their activity (as schematically illustrated in Figure 1).

Concluding Remarks

Although detailed studies into the role of PRRs in adaptive immunity are relatively few, there is growing evidence to suggest an important function for innate receptors in adaptive immunity. On the one hand, B and T lymphocytes can be clearly endowed with innate immune-sensing properties, often integrating antigen-receptor signaling. This is illustrated by the example of B cells, where TLR engagement is important for the development of antibody responses, or by emerging data supporting formation of an inflammasome platform in lymphoid cells.

On the other hand, the dependency on a ligand and the signaling pathways activated downstream of PRRs in lymphoid cells can differ from what we have learned from innate immune cells (Figure 1). Some PRRs even fulfill their functions constitutively, as in the case of CIITA and NLRC5. In this evolution from PAMP/DAMP-inducible to constitutive function, several questions remain to be answered. Is a ligand required for the function of these NLRs or for LGP2 in T cells? The former of these are active even in the absence of infectious or inflammatory signals, so what could be the nature of the ligand or 'activator'? Indeed, the inaptitude of T cells to phagocytose suggests that an agonist, if existing, would be of endogenous origin. Could there be a 'modern surrogate' that has evolved in place of the innate pathogen- or danger-associated pattern? To some extent, this is reminiscent of the intensively investigated mechanism leading to the activation of NLRP3 [45]. Though NLRP3 activity depends on DAMPs or PAMPs, the wide spectrum of activating stimuli suggests that NLRP3 itself is unlikely to interact directly with them, leading to the hypothesis that a secondary 'event' or 'messenger' is mediating inflammasome assembly.

With regard to this idea, the study of PRRs in B and T cells might unveil aspects of their activity, which could inform studies on PRRs in the innate immune system, and *vice versa*. Further understanding of classical and novel roles of PRRs in lymphocytes could ultimately open new avenues for therapeutic targeting of the adaptive immune system.

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Tables and Figure Legends

Table 1. RLRs in adaptive immune cells

The current knowledge on RLR expression in adaptive immune cells, their accepted function, and their specific role in T or B cells are summarized.

symbol	expression in B/T cells	refs	role	refs
RIG-I Ddx58	well expressed	6;11; 34;35; 48	detects viral RNA inducing type I IFN	33
MDA5 Ifih1	expressed	6;11; 34;35; 48	detects viral RNA inducing type I IFN; stimulation in Tregs reverts their suppressive effect	33;34
LGP2 Dhx58	expressed	6;35; 48	enhances RIG-I/MDA5 signaling; MAVS-independent, $CD8^+$ T cell-intrinsic role in promoting survival upon viral challenge	33;35

Table 2. NLRs in adaptive immune cells

This table focuses on NLRs, which have been reported to be expressed in T or B cells. Their established function and their adaptive cell-intrinsic roles are summarized.

symbol	expression in B/T cells	refs	role	refs
NLRP1 Nlrp1a-c	NLRP1: well expressed Nlrp1a: reported in lymphoid progenitors	6;42; 43;44; 46;47	inflammasome activation and pyroptosis	37;38; 42
NLRP3 Nlrp3	inducible in B cells, barely detectable in T cells	43;44; 47;49; 50;51	inflammasome formation upon different stimuli; supports B cell activation upon C-type lectin stimulation	37;38; 51
NOD1 Nod1	expressed	6;11; 43;44; 47;48	activates NF-kB and MAPK upon peptidoglycan detection; integrates antigen receptor-driven T and B cell activation	36;38; 44;47
NOD2 Nod2	weakly expressed	44;47; 48;50; 52	activates NF-kB and MAPK upon peptidoglycan detection; integrates antigen receptor-driven T cell activation and increases Treg survival	36;38; 50;53
CIITA Ciita	highly expressed in B cells CIITA: expressed in TCR-triggered $CD4^+$ T cells	6;11; 39	master trancriptional regulator of MHCII in myeloid and lymphoid APCs	39
NLRC3 Nlrc3	highly expressed in T, intermediately in B cells	6;11; 55	negative regulator of NF-κB activation in myeloid and T cells	55;57
NLRC5 Nlrc5	highly expressed	6;11; 40;58	transcriptional regulator of MHCI, mainly in lymphocytes	40;58

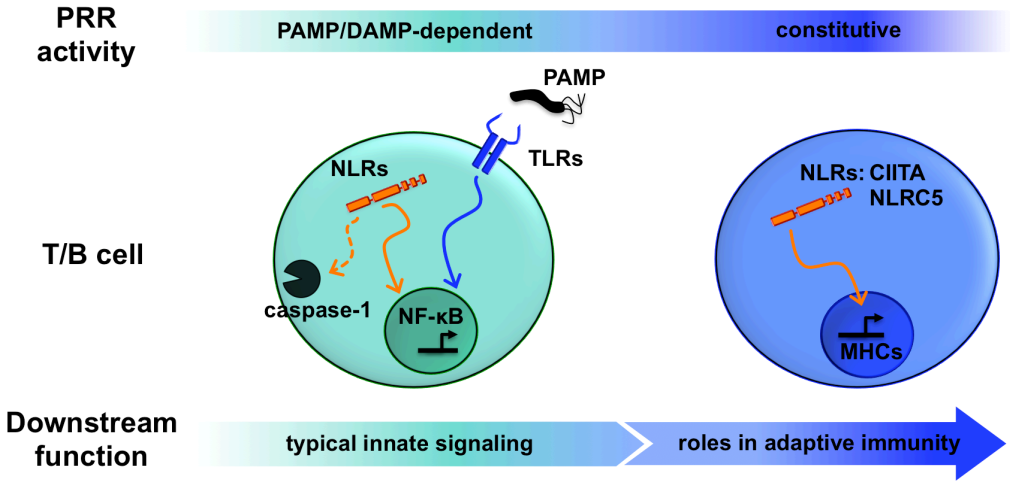

Figure 1. PRRs in adaptive immune cells: from microbial sensing to constitutive functions

This figure covers the spectrum of possible activities played by PRRs in B and T lymphocytes, referring to their mode of activation and downstream signaling cascade. As depicted on the left-hand side, PRRs can act in their canonical way in cells of the adaptive immune system; that is, their activity is induced by PAMPs or DAMPs, and triggers innate signaling pathways such as NF-κB. This is well exemplified by TLRs in B cells.

Conversely, the NLRs CIITA and NLRC5 fulfill an 'atypical' function, acting as transcriptional regulators of MHCs, the key molecules for adaptive immune responses. Moreover, these NLRs transactivate MHC expression also constitutively, indicating that they evolved activities, which are independent of pathogen-derived or danger signals. Moving from innate to adaptive, from inducible to constitutive, the function of PRRs reveals exciting evolutionary paths.

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¨ By using a knockout mouse, this work demonstrates that NLRC5 drives MHCI transcription in particular in lymphocytes.