TLR8 in Viral Infections

Subjects: Virology | Immunology

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Viruses are recognized by several Toll-like receptors (TLRs), including TLR8, which is known to bind ssRNA structures. However, the similarities between TLR8 and TLR7 have obscured the distinctive characteristics of TLR8 activation and its importance in the immune system.

TLRs TLR8 TLR7 virus viral infections TLR agonists

1. Activation and Regulation of TLR8

Human TLR8 is expressed in monocytes, macrophages, neutrophils, myeloid dendritic cells [1][2][3][4][5], and regulatory T (Treg) cells [6] (**Figure 1**a). TLR8 is a type I transmembrane receptor characterized by three structural components: an extracellular domain-containing leucine-rich repeats (LRRs), a transmembrane domain, and a cytoplasmic Toll-interleukin 1 receptor (TIR) domain [7]. Its extracellular domain is integrated by approximately 800 amino acids and 26 LRR modules and allows TLR8 to recognize ssRNA. In the absence of a ligand, TLR8 forms a dimer that suffers a conformational change upon activation by recognition of its target [8]. Different from other TLRs, TLR8 forms a ring-shaped structure [7], which requires proteolytic cleavage at the Z-loop region [9]. Between species, the ectodomain (LRRs) determines whether signaling is initiated in response to a ligand stimulation, and within the ectodomain the RQSYA motif has shown to be essential for the TLR8 activation [10]. Although the sequence-specific recognition of RNA by TLR8 has not been fully established, it is known that TLR8 senses ssRNA throughout its ability to form secondary structures [11] and by recognizing ssRNA AU- and GU-rich sequences [12]. That differentiates it from TLR7, which is activated by GU-rich sequences [13]. In both cases, TLR7 and TLR8 use the same ligand-binding site, but with different amino acid composition [7]. Apparently, TLR8 is able to distinguish the host RNA by nucleoside modifications and only activates the signaling response when a non-modified RNA enters the cell [14]. TLR8 is also suggested to be a vita-PAMP receptor that is able to recognize microbial structures from viable microbes [15], poly(A)/T sequences [16] or even small antiviral molecules [7]. Overall, there are several agonists identified to specifically activate TLR8 or TLR7, and those that can activate both receptors (**Table 1**).

Activation of TLR8 can be triggered by multiple known ligands such as viral ssRNA [17], miRNAs [11][18][19] and some agonists included in **Table 1**. That activation can promote co-stimulation and MHC class II expression to induce proliferation of naïve CD4 T cells [20] and Th1 differentiation [21]. In human regulatory T cells (Treg), TLR8 agonists can mediate the reversal of the suppressive function of Treg cells through the TLR8-MyD88-IRAK4 signaling pathway [6]. Additionally, TLR8 has proven to be an important driver of T follicular helper (Tfh) cell differentiation [15]. Interestingly, experimental evidence suggests that TLR8 may also have a regulatory effect on other endosomal TLRs. In fact, TLR8 is able to inhibit both TLR7 and TLR9 in in vitro cells [22]. This observation

was reproduced in *Tlr8*$^{-/-}$ mice, where the absence of TLR8 led to higher levels of expression of TLR7 and interferon-stimulated genes (ISGs), an effect that may account for an increased antiviral immunity in the infected mice [23].

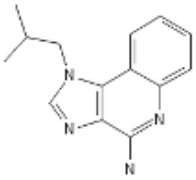
However, whether the inhibition of TLR7 and TLR9 by TLR8 is through direct or indirect physical contact is still unknown. Furthermore, the regulation of TLR8 by other TLRs has also been suggested. In THP1 cells, a human monocyte cell line, the addition of both TLR7 and TLR8 ligands has shown an apparent inhibition of TLR8-induced cytokine expression, suggesting that TLR7 could have a modulatory effect on TLR8 responsiveness [24]. The impact of other TLRs on TLR8 expression and activation is not yet well defined, as some contradictions exist. Studies in HEK cells suggest that TLR9 inhibits TLR7, but neither TLR7 nor TLR9 inhibit TLR8 [22][25]. However, studies in mice indicate that TLR7 may negatively regulate TLR8, where the absence of TLR7 led to an upregulation of TLR8 expression, suggesting a compensatory mechanism in the immune response [26]. Future research will define the contribution of other endosomal TLRs on TLR8 function.

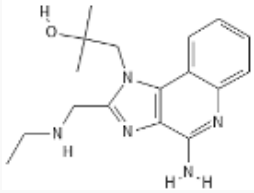
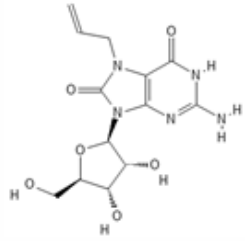
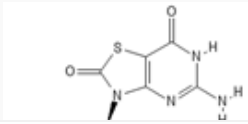
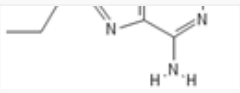
2. TLR8 and Viral Infections

The strategic localization of TLR8 in the endosomes allows for the recognition of several viruses, mainly because it recognizes ssRNAs. Viral ssRNA entering the cell would colocalize into early endosomes around 15 to 20 min after infection, where the RNA could bind to TLR8 [27].

Nevertheless, in the case of human immunodeficiency virus (HIV), the protein SNAPIN inhibits the colocalization of TLR8 with HIV[28]. Interestingly, studies with vaccinia virus (VV) infection in murine plasmacytoid dendritic cells (pDCs) indicate that poly(A)/T-rich DNA could also be recognized by TLR8, upregulating the expression of IFN-α and IFN-β [16]. Another example of TLR8 activation by viruses is provided by Coxsackie B virus (CBV), which induced an inflammatory response mediated mostly through TLR8 and, to a lesser extent, through TLR7 [17], similar effect is observed in Influenza A Virus (H3N2) [29]. In West Nile virus (WNV)-infected bone-marrow-derived dendritic cells from *tlr8*$^{-/-}$ mice, the lack of TLR8 resulted in an improved antiviral response due to an increase of TLR7 expression, likely as a result of a compensatory effect [23].

Table 1. TLR8 and TLR7 agonists.

TLR	Name	Structure	Class	Ref.
TLR7	*Imiquimod*		Imidazoquinoline amine analog to guanosine	[30][31]

TLR	Name	Structure	Class	Ref.
	Gardiquimod		Imidazoquinoline compound	[8][32][33]
	Loxoribine		Guanosine analogue	[34][35][36][37]
	Isatoribine		Nucleoside analogue	[38]
				[44]

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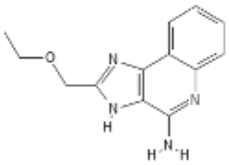
BECN1-

[27] [45] [47]

DNA Virus		
Virus	**Effect on TLR8 Activation**	**Cells**
DNA Viruses		
Vaccinia virus	Induces the expression of IFN-α, IFN-β	pDCs, HEK cells [16]
Hepatitis B virus	HBV infection inhibits innate immunity by decreasing TLR8 levels	PBMC [48]
RNA Viruses		
Influenza A virus (H3N2)	Induces the expression of IL-8	HEK cells, neutrophils [29]
Coxsackie B virus	Induces the expression of IFN-β, IL-6	Human cardiac cells [17]
HIV-1	Induces the expression of IL-6 and IL-1β	Human primary CD4+ T cells [46]
	Colocalization of HIV and TLR8 is decreased	Dendritic cells [28]
West Nile virus	TLR8 favors the infection in infected mice	Bone-marrow-derived dendritic cells (BMDCs) [23]
Zika virus	TLR8 and MyD88 expression decreases	Peripheral blood [49]

ences with TLR7

TLR7 and TLR8 recognize ssRNA, they activate different signaling pathways to promote the expression of inflammatory cytokines and interferons used in the defense against viruses (**Figure 1**b). Both TLR7 and TLR8 signaling pathways are mediated by the adaptor molecule MyD88, which is expressed ubiquitously in the cell cytoplasm. After a viral infection, there is a rapid redistribution of MyD88 to the endosomal compartment, where

TLR	Name	Structure [17][7]	Class	Ref.
	CL097		Imidazoquinoline compound derivative	[17][21] [44]

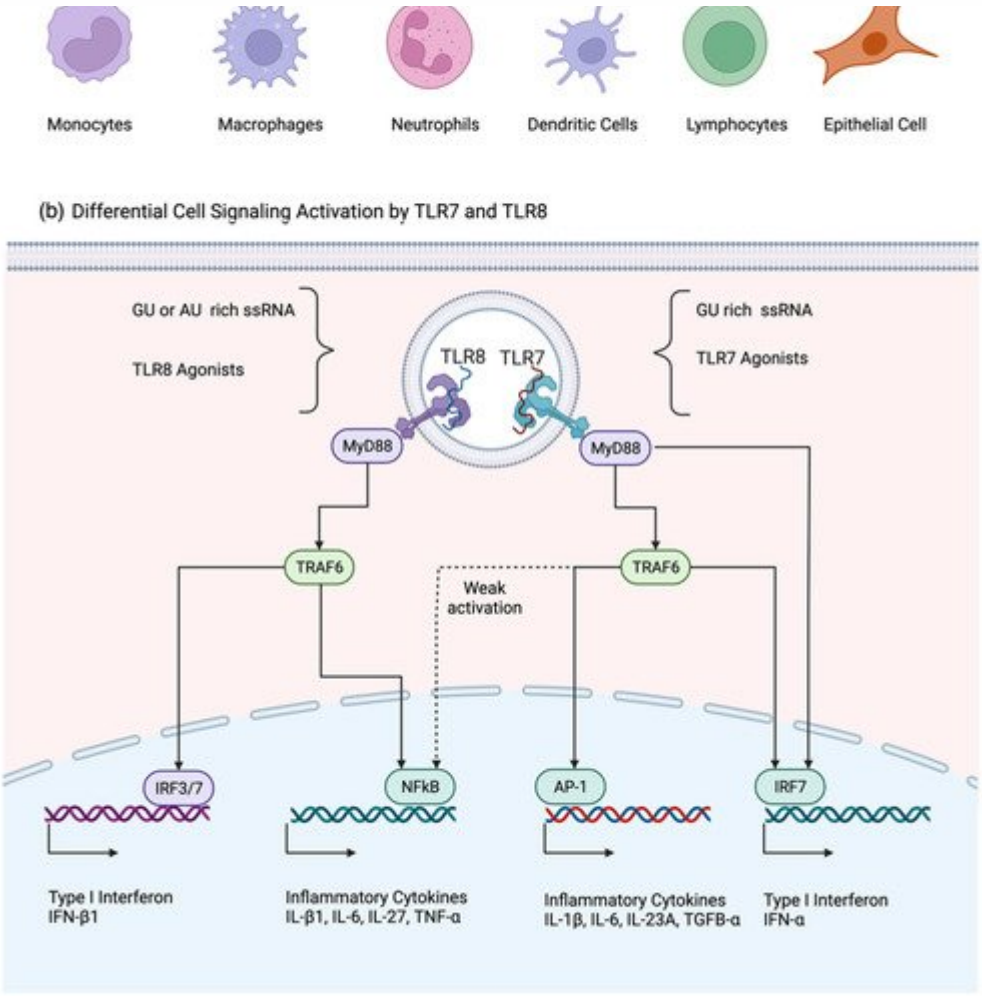


Figure 1. (**a**) Cells that are reported to express TLR8 under basal conditions; (**b**) TLR7 and TLR8 signaling pathways have the common adaptor protein MyD88. IFN-α expression after TLR7 can be achieved by forming the complex MyD88-IRF7 or by the activation of IRF7 via TRAF6. TRAF6 also activates AP-1 and weakly NF-kB, promoting inflammatory cytokine expression. TLR8 induces a more potent inflammatory cytokine response than TLR7 via the activation of TRAF6-NF-kB pathway, while the induction of IFN-b by TLR8 is achieved through the activation of the IRF3/7 pathway. Created with BioRender.com. (Accessed on 17 December 2021.)

Although MyD88 has been seen as a common adaptor molecule to TLR7 and TLR8, the activation of this protein in monocytes and macrophages modulates different immune responses with different signature profiles of pro-inflammatory cytokines and type I interferon in a cell-dependent fashion [3][4][21]. In the case of pro-inflammatory cytokines, TLR7 induces more IL-1β, IL-6, IP-10 and IL-23, whereas TLR8 agonists induce more IL-1α/β, IL-6, IL-8, TNF-α, IL-12β, IL-27 and MIP-1α in myeloid dendritic cells [21][44][50]. Moreover, TLR7 agonist stimulation in monocytes fails to induce a robust NF-kB. However, it induces the activation of AP-1, which may explain the

differential cytokine profile elicited by TLR8 and TLR7 agonists [21]. A similar phenomenon is observed in the production of IFN by the activation of these two receptors. While TLR7 activation induces the expression of IFN-α1 and IFN-α2 in monocytes and pDCs [50][51], TLR8 activation in monocytes and myeloid DCs expresses more IFN-β1 [3][4][21][50]. After TLR7 ligand activation, the adaptor molecule MyD88 can stimulate IRF through two different mechanisms. First, MyD88 can phosphorylate IRF7, forming a complex that promotes the IFN response. Second, MyD88 activates TRAF6, which binds to IRF7, inducing the expression of IFN-α [52]. This experimental evidence illustrates the unique characteristics of TLR8 in triggering the inflammatory and antiviral host responses.

4. Future Perspectives for Therapeutics with TLR8 Agonist for Viral Infections

Commercially available TLR8 agonists have demonstrated the capability to selectively activate TLR8. There are many properties of these molecules that make them attractive candidates for use as vaccine adjuvants or antiviral activity [2][53]. These molecules can be administered through multiple methods including intravenously, oral [40], inhaled, or topically applied, which make them good candidates as therapeutical options for the future. Currently, TLR8 agonists are being investigated as vaccine adjuvants and in some other ailments such as allergy or asthma [54]. One example is that of HIV Gag protein, which was conjugated to TLR7/8 agonists as an effective way to elicit a broad-based adaptive immunity in nonhuman primates [55]. Moreover, recent work has demonstrated that the TLR7/8 agonist imidazoquinoline coupled to a novel amphiphilic carrier enhances vaccine efficiency by inducing a robust Th1 skewed antibody response in mice treated with a single shot with spike protein for SARS-CoV-2 or seasonal quadrivalent inactivated influenza virus vaccine [56]. Selgantolimod (GS-9688), also known as oral (R)-7, is a TLR8 agonist that has a good absorption properties, and is currently in phase 2 clinical trial (NCT04891770) for the treatment of chronic hepatitis B [40]. Some progress has also been done on the use of TLR8 agonists in HIV infection, where it is shown that T CD4+ TLR8 promoted Tfh differentiation towards Tfh1 and Tfh17 during HIV infection. Such differentiation and the cytokine secretion from TCD4+ via TLR8 could be exploited as a potential therapeutic target and vaccine development [46].

TLR8 agonists in combination with other ligands such as fms-like tyrosine kinase (Flt3L) have demonstrated to prime Ag-specific CD8+ T cells, suggesting that TLR8 ligands could also be used as potent adjuvants to prime functionally superior Ag-specific human CD8+ T cells and improve the response to viral infections [57].

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