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Cells in Focus

Dendritic cell subsets involved in type I IFN induction in mouse measles virus infection models

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Running title: IFN induction in MV mouse models

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Abstract

Measles caused by measles virus (MV) infection remains important in child mortality. Although the natural host of MV is human, mouse models expressing MV entry receptors (human CD46, CD150) and disrupting the interferon (IFN) pathways work for investigating immune responses during early MV infection *in vivo*. Dendritic cells (DCs) are primary targets for MV in the mouse models and are efficiently infected with several MV strains in the respiratory tract *in vivo*. However, questions remain about what kind of DC in a variety of DC subsets is involved in initial MV infection and how the RNA sensors evoke circumventing signals against MV in infected DCs. Since type I IFN-inducing pathways are a pivotal defense system that leads to the restriction of systemic viral infection, we have generated CD150-transgenic mice with disrupting each of the IFN-inducing pathway, and clarified that DC subsets had subset-specific IFN-inducing systems, which critically determined the DC's differential susceptibility to MV.

Key words: dendritic cells; measles virus; mouse model; type I interferon (IFN); immune suppression.

Introduction

The pathogenic measles virus (MV) causes measles in infants. The MV genome is a nonsegmented negative single-stranded RNA consisting of six genes that encode the nucleocapsid (N), phosphoprotein (P), matrix (M), fusion (F), hemagglutinin (H), and large (L) proteins. The P gene encodes P protein and the nonstructural V and C proteins. Although the nonstructural V and C proteins of wild type (WT) strains of MV are important in suppressing the host interferon (IFN) response in human cells (Gerlier and Valentin, 2009), WT strains of MV are less able to suppress type I IFN production in murine cells than in human cells (Shingai et al., 2005), suggesting that V and C proteins are relatively ineffective suppressors for IFN response in murine cells.

CD46 (also called MCP) was first identified as an MV entry receptor for laboratory-adapted and vaccine strains of MV. CD46 is expressed in all human nucleated cells including epithelial cells (Gerlier and Valentin, 2009). In 2000, human CD150, a signaling lymphocyte activation molecule (SLAM), was identified as the second MV entry receptor for all MV strains including WT (Tatsuo et al., 2000). Expression of CD150 is restricted to activated lymphocytes, dendritic cells (DCs), and macrophages (Delpout et al., 2012), consistent with the lymphotropism of MV. However, the expression pattern of CD150 does not explain why WT strains of MV infect epithelial cells that do not express CD150. Recently, human nectin-4 (also called poliovirus receptor-related 4, PVRL4) was identified as the third entry receptor for WT strains of MV (Mühlebach et al., 2011, Noyce et al., 2011). Expression of nectin-4 is restricted to the basolateral surface of epithelial cells (Delpout et al., 2012). Thus, laboratory-adapted and vaccine strains of MV use CD46 and CD150 as entry receptors, and WT strains of MV use CD150 and nectin-4. Initial infection with WT strains of MV via CD150 occurs in DCs and alveolar macrophages (AMs) and secondary spreading of MV infection is established in lymphocytes through infected DCs and AMs. Ultimately, MV-infected lymphocytes systemically spread to distal sites including the respiratory tract and then MV infects epithelial cells via nectin-4, resulting in release of MV into the airway lumen of the infected lung (Delpout et al., 2012).

C-type lectin DC-SIGN (also called CD209) has an important role for infection of DCs by laboratory-adapted and WT strains of MV (de Witte et al., 2006), although DC-SIGN is dispensable for MV entry. Both attachment and infection of immature DCs with MV are blocked by DC-SIGN inhibitors, suggesting that DC-SIGN is critical for enhancement of CD46/CD150-mediated infection of DCs (de Witte et al., 2006).

Human CD150 transgenic (Tg) and CD150 knock-in mice were generated as

MV infection models to study receptor tropism and the immune dynamics of MV (Hahm et al., 2003, Hahm et al., 2004, Ohno et al., 2007, Sellin et al., 2006, Shingai et al., 2005, Welstead et al., 2005) and these mice were somehow permissive to MV *in vivo*. Systemic infection by WT strains of MV *in vivo* was observed in CD150Tg/*Ifnar*^{-/-} mice, generated by crossing CD150Tg mice with mice having the disrupted IFN receptor 1 (*Ifnar*) gene; the other is CD150Tg/*Stat1*^{-/-} mice, generated by crossing CD150Tg mice with mice knocked out for the signal transduction and activator of transcription 1 (*Stat1*) gene, which is a major signaling molecule for the IFN receptor (Shingai et al., 2005, Welstead et al., 2005). Both models indicate the importance of the IFNAR pathway for restricting MV *in vivo* infection in mice. DCs and AMs are primary targets for MV intranasally inoculated into CD150Tg models (Ferreira et al., 2010), since these cells express CD150 and are located in the lung where host cells firstly encounter MV. Results from mouse models for MV *in vivo* infection reflect *in vitro* high susceptibility of human monocyte-derived DCs (moDCs) to MV. DCs and AMs are the first target cells during early MV infection in monkeys (de Swart et al., 2007, Lemon et al., 2011). All these data indicate that type I IFN produced by DCs and AMs primarily protects hosts from systemic MV infection.

In this review, we summarized the mouse model studies on the host antiviral response to MV infection, which involves both Toll-like receptors (TLRs) and retinoic acid-inducible gene (RIG)-I-like receptors (RLRs) in specific DC subsets.

Type I IFN-inducing pathways respond to viral RNA

The IFN response, which is the induction of type I IFN- α/β , is a major antiviral defense pathway that confers virus resistance to neighboring cells. Previous reports showed that viral RNA is detected by cytoplasmic pattern recognition receptors (PRRs) such as RIG-I and the melanoma differentiation-associated gene 5 (MDA5) (Kawai and Akira, 2009). MDA5 and RIG-I detect long and short dsRNA, respectively (Kato et al., 2008). TLR3 recognizes extracellular double-stranded RNA (dsRNA) in the endosome whereas RIG-I and MDA5 sense cytoplasmic dsRNA (Figure 1). TLR3 recruits the adaptor, Toll/interleukin-1 receptor (TIR) homology domain-containing adaptor molecule 1 (TICAM-1, also called TRIF) in response to dsRNA and induces type I IFN production. Activation of RLRs is regulated by multiple consecutive processes including dephosphorylation, ubiquitination and oligomerization of RLR (Gack et al., 2007, Wies et al., 2013). The CARD domain of RLRs is phosphorylated by unknown kinases in steady state, prohibiting RLR activation (Wies et al., 2013). Viral infection activates RLRs via dephosphorylation by serine-threonine phosphatases PP1 α and PP1 γ

(Wies et al., 2013). The dephosphorylated RLRs provide signals through the mitochondrial antiviral signaling protein (MAVS; also called VISA, Cardif, or IPS-1) to induce type I IFN. Disrupting these adaptor genes results in failure to activate IFN regulatory factor (IRF)-3 and IRF-7, abrogating type I IFN production and antiviral host defense. Virus-derived single-stranded RNA (ssRNA) is recognized by TLR7 and TLR8 which are in the endosome. MyD88-dependent signaling is activated upon viral RNA recognition by TLR7 to induce type I IFNs (Kawai and Akira, 2009). Unlike ubiquitous RLRs, TLR expression is restricted to particular cell types with a different set of TLRs (Table I) (Edwards et al., 2003). This differential expression pattern of TLRs directs specific sets of cells to respond to particular TLR ligands, which enhance a variety of immune responses.

Type I IFN induction in MV-infected murine DCs

Studies in mice with targeted gene deletions provide insight into the mechanisms of type I IFN induction in response to MV infection *in vivo* and *in vitro*. Bone marrow-derived DCs (BMDCs) were used to study MV permissiveness of DCs, initially in CD150Tg mice (Ohno et al., 2007, Shingai et al., 2005, Welstead et al., 2005). Studies using BMDCs from CD150Tg mice in combination with *Mavs*^{-/-}, *Irf3*^{-/-}/*Irf7*^{-/-}, *Ticam1*^{-/-} and *Myd88*^{-/-} mice showed that type I IFN expression in BMDCs completely relied on MAVS but not TICAM-1 and MyD88 (Takaki et al., 2014). Surprisingly, BMDCs derived from CD150Tg/*Irf3*^{-/-}/*Irf7*^{-/-} mice produce a detectable IFN- β in response to MV infection, which confers nonpermissiveness to CD150Tg/*Irf3*^{-/-}/*Irf7*^{-/-} BMDCs (Takaki et al., 2014). A pharmacological study indicated that MV-derived IFN- β expression partially depended on NF- κ B (Takaki et al., 2014). A recent study using West Nile virus showed that IRF3/IRF7 and IRF5 coordinately regulate the type I IFN response in DCs (Lazear et al., 2013). For MV, IRF5 might be a transcription factor for MAVS-dependent and IRF3/IRF7-independent type I IFN induction in BMDCs (Figure 2).

An *in vivo* MV infection study using a CD150Tg mouse model revealed that MAVS disruption scarcely led MV permissiveness or type I IFN gene expression in the spleen compared to CD150Tg mice (Takaki et al., 2013). *In vitro* infection assays showed that isolated cell subsets of CD11c⁺ DCs, but not T or B cells, mainly produced type I IFN in response to MV infection through a MAVS-independent pathway. Various types of DCs have been identified in mouse secondary lymphoid tissues, including three CD11c^{high} subsets of conventional DCs (cDCs): CD8 α ⁺, CD4⁺ and CD4⁻CD8 α ⁻ double negative (DN) DCs (Vremec et al., 2000), and one subset of CD11c^{low} plasmacytoid

DCs (pDCs) (Asselin-Paturel et al., 2001). These DC subsets express different sets of TLR genes and have distinct functions (Table I) (Edwards et al., 2003, Luber et al., 2010). Mouse pDCs express most TLRs except TLR3 and therefore respond to a wide range of pathogen-associated molecular patterns including TLR7 ligand (Boonstra et al., 2003, Edwards et al., 2003). CD8 α ⁺ DCs express high amounts of TLR3, but not TLR7 (Edwards et al., 2003) and mainly participate in poly I:C-induced cross-presentation. Although a CD4⁺ and DN DCs have a similar TLR expression pattern (Edwards et al., 2003), CD4⁺ DCs but not DN DCs express TLR7 protein at low levels (Takaki et al., 2013). Type I IFN expression is induced in CD4⁺ DCs and pDCs, but not CD8 α ⁺ and DN DCs that are isolated from MAVS-disrupted mice during *in vitro* MV infection (Takaki et al., 2013). This result indicates that type I IFN-inducing pathways in pDC and CD4⁺ DCs are independent of the MAVS pathway. A pharmacological study showed that the MyD88 pathway is involved in a MAVS-independent type I IFN-inducing pathway (Takaki et al., 2013). This result was confirmed using CD150Tg/*Myd88*^{-/-} pDCs, suggesting that TLR7 is responsible for recognition of MV RNA in CD4⁺ and pDCs. Since the RLR-MAVS pathway usually senses endogenous viral RNA in CD4⁺ DCs (Luber et al., 2010), MAVS disruption highlights that the MyD88 pathway participates in initial type I IFN induction in CD4⁺ DCs in MV infection (Figure 2). However, CD150Tg/*Myd88*^{-/-} mice are not permissive to MV infection *in vivo*, both MyD88 in pDCs and CD4⁺ DCs and MAVS in other cells contribute to protection against systemic MV infection.

Since TLR7 is in the endosome, viral RNA transport to the endosome is required to activate the TLR7/MyD88 pathway. Autophagy is required for the recognition of vesicular stomatitis virus by TLR7 to transport cytosolic viral replication intermediates into the lysosome, leading to type I IFN production in pDCs (Lee et al., 2007) IFN- β mRNA expression is induced in UV-irradiated MV-infected CD150Tg/*Mavs*^{-/-} DCs; however, treatment with an autophagy inhibitor prevented this IFN- β induction (unpublished data). These data suggest that autophagy but not viral replication is required for MV-mediated type I IFN induction via TLR7 in MAVS-disrupted murine DCs.

In contrast to BMDCs, type I IFN gene expression is observed in DCs and splenocytes derived from MV-infected CD150Tg/*Mavs*^{-/-} mice, which prevents DCs from MV infection *in vivo* in these mice (Takaki et al., 2013, 2014). RIG-I/MAVS but not TLR7/MyD88 mediates the antiviral response to RNA virus in conventional DCs. The studies using reporter mouse that expresses green fluorescence protein (GFP) under the control of the *Ifn- α 6* promoter show that intranasal infection with newcastle disease

virus (NDV) induces GFP expression in AMs and cDCs in lung as an initial defense via the RLR pathway (Kumagai et al., 2007). Although systemic NDV infection leads to GFP expression in not only pDCs but also cDCs and AMs, the frequency of GFP positive cells is higher in pDCs than in other cells. Thus, the activation of different subsets of DCs would be important to produce type I IFNs in systemic and local RNA virus infection.

Similar to murine DCs, PRRs expression differs with subsets of human DCs (Table I) (Jarrossay et al., 2001, Kadowaki et al., 2001). In cDCs, MV transcription is required to activate type I IFN response, since UV-irradiated MV is unable to promote IFN- β production (Duhen et al., 2010). Type I IFN induction by pDCs depends on the recognition of MV RNA via the endosomal pathway, since UV-irradiated MV infection induces IFN- α production and this induction is cancelled by an endosomal acidification inhibitor in pDCs (Duhen et al., 2010). Although MV can inhibit TLR7 and TLR9-mediated type I IFN induction by MV-V and MV-C proteins in human pDCs (Pfaller and Conzelmann, 2008, Schlender et al., 2005, Yamaguchi et al., 2014), it remains unknown whether MV proteins act as suppressors in murine DCs. Moreover, MV interacts with human DC-SIGN to enhance infection of human DCs (de Witte et al., 2006). However, how MV-H protein binds murine CIRE/DC-SIGN is unknown. The findings in murine DCs may differ from those in human DCs when infected with MV.

Type I IFN and cytokines in the context of MV immunosuppression

DCs contribute to MV-induced immunosuppression, including downregulation of costimulatory molecules and inhibition of IL-12 production following lipopolysaccharide stimulation (Coughlin et al., 2013, Hahm et al., 2004, Hahm et al., 2007). [MV infection suppressed BMDCs development via type I IFN that acts through STAT2-dependent signaling but independent of the STAT1 signaling \(Hahm et al., 2005\).](#) Furthermore, *in vivo* MV infection induces a T helper type 2 response, enhances apoptosis, and induces regulatory T cells (Koga et al., 2010, Sellin et al., 2009). Blocking IL-10 signaling prevents MV-induced immunosuppression in CD150 knock-in mice, indicating that IL-10 participates in immunosuppression (Koga et al., 2010). In addition, high amounts of IL-10 are produced in CD4⁺ T cells obtained from MV-infected CD150Tg mice (Takaki et al., 2014). In early infection by lymphocytic choriomeningitis virus (LCMV), type I IFN is produced via the TLR7/MyD88 pathway in pDCs. MDA5/MAVS-mediated type I IFN induction in other cells is required for sustained type I IFN responses to acute and chronic LCMV infection (Wang et al., 2012). Thus, different sources of type I IFN and signaling pathways affect immune

responses to viral infection. Besides IL-10, IL-12 and type I IFN, other cytokines and signaling molecules affect MV-mediated immunomodulation. Further analysis is needed to clarify the function of DCs that modulate MV-induced immunosuppression.

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Figure legends

Figure 1. Recognition of RNA by RLRs and TLRs

Double-stranded RNA (dsRNA) synthesized by RNA virus replication in infected cells is recognized by endosomal TLR3 and cytosolic RIG-I like receptors (RLRs), RIG-I and MDA5. They differentially recognize viral dsRNA products such that long dsRNA chains fit in MDA5, 5'-triphosphates short dsRNA couple with RIG-I and structured RNA activate TLR3 (Tatematsu et al., 2013). The outline of their signaling cascades that lead to the activation of IRF3 and NF- κ B is overviewed (Kawai and Akira, 2009). Single-stranded RNA (ssRNA) is recognized by endosomal TLR7, leading to the activation of NF- κ B and IKK α/β via adaptor protein MyD88. Transcription factor activation results in expression of type I IFN and inflammatory cytokines. NDV, newcastle disease virus; SeV, sendai virus; HCV, hepatitis C; EMCV, encephalomyocarditis virus

Figure 2. Recognition of MV RNA in mouse DC subsets

DC subsets have their own viral RNA sensors to induce type I IFN. MV specifically infects these DC subsets. The ways for IFN induction in each DC subset are shown schematically. UV-MV; UV-irradiated MV

Table I. Expression of TLRs in murine and human DC subsets

			TLR1	TLR2	TLR3	TLR4	TLR5	TLR6	TLR7	TLR8	TLR9	TLR10
Mouse	Conventional DCs (CD11c ^{high} B220 ⁻)	CD4 ⁺	+	+	-	+	+	+	+	-	+	-
		CD4 ⁻ CD8α ⁻	+	+	+/-	+	+	+	+/-	-	+	-
		CD8α ⁺	+	+	+	+	-	+	-	-	+	-
	Plasmacytoid DCs (CD11c ^{low} B220 ⁺ PDCA-1 ⁺)		+	+	-	+	+/-	+	+	-	+	-
Human	Myeloid DCs (CD11c ⁺)		+	+	+	+	+	+	+	+/-	-	+
	Monocyte-derived DCs (moDCs)		+	+	+	+	+	+/-	+/-	+	-	-
	Plasmacytoid DCs (CD11c ⁻ BDCA2 ⁺ BDCA4 ⁺)		+/-	-	-	-	-	-	+	-	+	+

TLR expression in mouse and human DC subset is described in refs [Jarrossay et al., 2001, Kadowaki et al., 2001, Edwards et al., 2003, Luber et al., 2010]

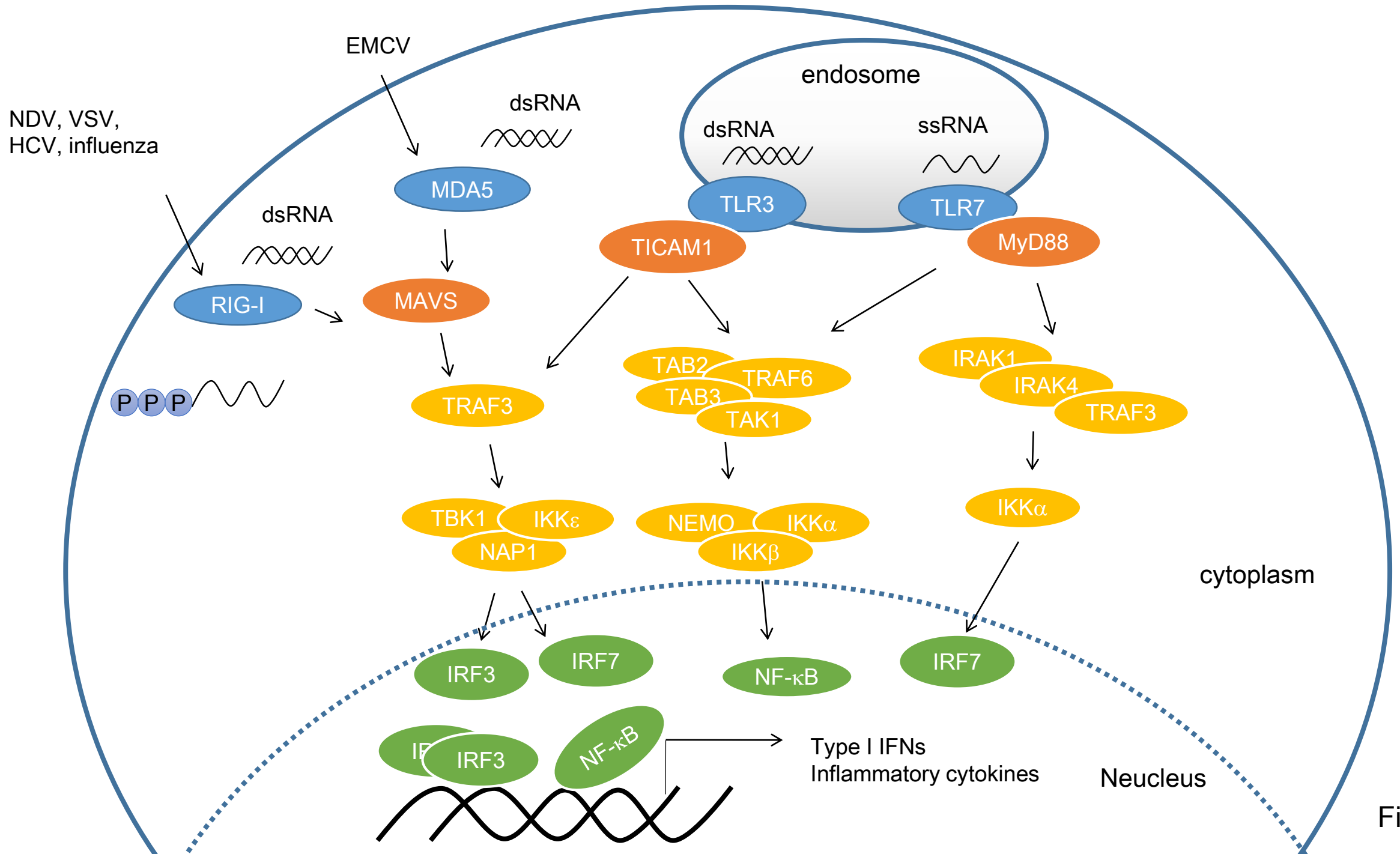


Figure 1

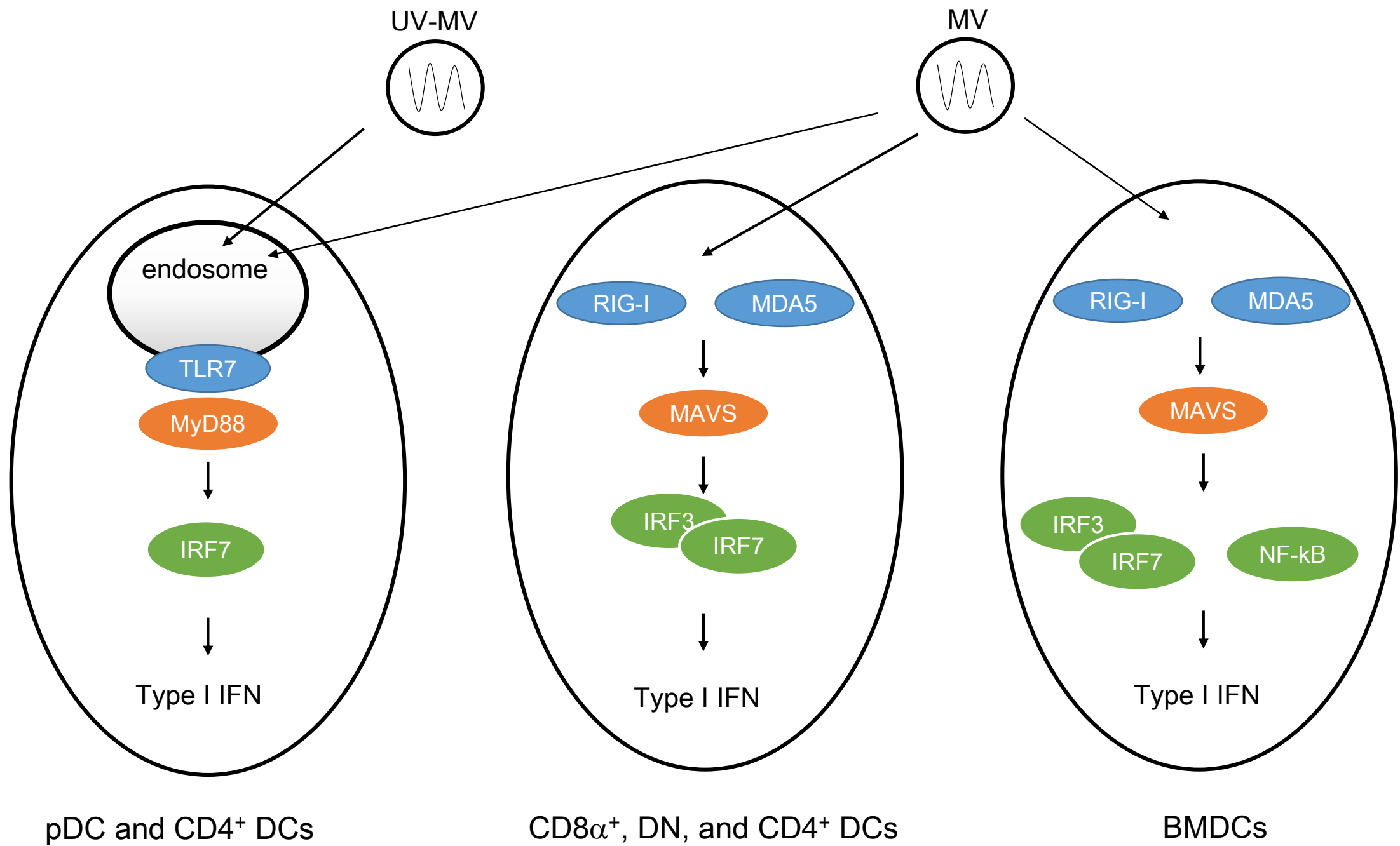


Figure 2