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Receptors and ligands involved in viral induction of type I interferon production by plasmacytoid dendritic cells

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Abstract

Virus infection is sensed by the innate immune system which then rapidly initiates biosynthesis of type I interferon (IFN). The IFN signaling systems produce a broadly effective innate antiviral response by creating an antiviral state in both an autocrine and paracrine manner in cells and by activating innate and adaptive immunity. Plasmacytoid dendritic cells (pDCs) have the unique ability to produce very high levels of type I IFN following viral infection *in vivo*. Most recent research has focused on oligonucleotide-mediated induction of type I IFN production, implicating viral genome and replication intermediates as the stimulus for this response. However there are additional viral ligands which can potentially induce type I IFN production in pDCs, such as envelope glycoproteins, viral glycolipids, tegument, capsid or nuclear proteins. This area of viral immunology, which has been neglected in the literature, will be discussed here.

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Keywords: Plasmacytoid dendritic cells; Type I interferon; Viral glycoprotein

Introduction

Type I interferon (IFN) production can be elicited by a wide variety of stimulants, including viruses, products of bacteria, plants and fungi. Many cell types produce type I IFN following viral infection. For example, influenza virus infection of monocytes (Ronni *et al.*, 1995), macrophages (Roberts *et al.*, 1979) and dendritic cells (DCs) (Cella *et al.*, 1999b) activates the production of type I IFN in these cells and Sendai virus infection has been demonstrated to induce monocytes and macrophages to release IFN (Saksela *et al.*, 1984). It is probable that in these cells double-stranded RNA (dsRNA) synthesized during the viral replicative cycle (Jacobs and Langland, 1996) is a trigger for type I IFN production, since synthetic dsRNA, e.g. polyinosinic–polycytidylic acid (polyI:C), is known to be a potent inducer of type I IFN (De Clercq, 1981; Majde, 2000).

Abbreviations: DCs, dendritic cells; dsRNA, double-stranded RNA; HA, haemagglutinin; HCMV, human cytomegalovirus; HCV, hepatitis C virus; HEK, human embryonic kidney cells; HIV, human immunodeficiency virus; HPIV, human parainfluenza virus; HSV, herpes simplex virus; IFN, interferon; LPS, lipopolysaccharide; mAb, monoclonal antibodies; MBL, mannose-binding lectin; MCMV, mouse cytomegalovirus; Mda5, melanoma differentiation-associated protein 5; MHV, mouse hepatitis virus; MR, mannose receptor; NA, neuraminidase; NDV, Newcastle disease virus; NIPC, natural interferon producing cell; PBMC, peripheral blood mononuclear cells; pDCs, plasmacytoid dendritic cells; PKR, protein kinase R; polyI:C, polyinosinic–polycytidylic acid; PRR, pattern recognition receptor; RIG-I, retinoic acid inducible gene-I; RSV, respiratory syncytial virus; siRNA, small interfering RNA; SIV, simian immunodeficiency virus; SP, surfactant protein; SR-A, type I and type II class A scavenger receptor; ssRNA, single-stranded RNA; TGEV, transmissible gastroenteritis coronavirus; TLRs, Toll-like receptors

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Plasmacytoid dendritic cells (pDCs), also known as natural interferon producing cells, (NIPCs), are major producers of type I IFN in response to stimulation with enveloped viruses and hence are key effectors in the innate immune system. pDCs are a rare cell population found in the peripheral blood, lymphoid organs, bone marrow, thymus, liver and lung (Asselin-Paturel et al., 2003; Blasius et al., 2004; de Heer et al., 2004; Demedts et al., 2005). In addition to their functional definition as the main type I IFN producing population in response to viruses they are defined by flow cytometry as CD11c^{low}B220⁺CD11b⁻Ly6C⁺ murine cells, or lineage⁻HLA-DR^{high}CD11c⁻CD123⁺ human cells (Asselin-Paturel et al., 2001; Cella et al., 1999a; Dzionek et al., 2000; Nakano et al., 2001). More recently developed monoclonal antibodies (mAb) such as 120G8, anti-mPDCA-1 and anti-BDCA-2, specific for the pDC, will ease identification of this cell type (Asselin-Paturel et al., 2003; Dzionek et al., 2000; Krug et al., 2004a). Virally stimulated pDCs can produce other cytokines in addition to type I IFN, but the mechanism of induction of the secretion of these factors is not fully understood to date (Piqueras et al., 2005).

Although replicative intermediates and viral genome are important for inducing type I IFN production, there is a complementary mechanism for the innate sensing of viral glycoproteins, which does not require infectious virus. In earlier work, human and porcine peripheral blood leukocytes and mouse spleen cells, and more recently human and murine pDCs specifically, have been shown to produce type I IFN in response to inactivated enveloped viruses, supporting the argument for an additional replication-independent viral recognition system. This article will focus mainly on reviewing the evidence that viral glycoproteins can mediate type I IFN induction, in a mechanism which may be independent of the well-studied genome-mediated route.

A hitherto poorly studied issue is the search for the cellular receptors involved in viral glycoprotein recognition leading to type I IFN production. Cell surface receptors regulate a range of functions, including differentiation, growth and survival, adhesion, migration, phagocytosis, activation and cytotoxicity. Identification of viral receptors is often difficult as many mediate only low affinity binding to surface viral proteins. It has been difficult to identify the receptors specifically involved in glycoprotein-mediated IFN α/β induction for both this reason and due to the rarity of pDCs. Surface receptors on DCs for microbial antigens include Toll-like receptors (TLRs), C-type lectin receptors and scavenger receptors. The full repertoire of surface-expressed pDC receptors remains to be elucidated, however the list is growing as researchers try to understand how this important cell type recognizes and responds to pathogens. In this review we highlight pattern recognition receptors (PRR) that bind or sense

viral glycoproteins. Their expression on pDCs in particular, is not known in all cases.

Evidence for genome mediated induction of type I IFN by pDCs

Viral recognition by endosomal sensors

Oligonucleotides have been proposed as type I IFN inducing ligands recognized by cytosolic and endosomal sensors in many cell types. The mechanism of discrimination between self and non-self ligands is unclear, although compartmentalization of host ligands away from these receptors has been suggested (Barton et al., 2006). Type I IFN induction by pDCs can be triggered through viral recognition via both TLR and non-TLR recognition of oligonucleotides. pDCs express high levels of TLRs 7 and 9 (Edwards et al., 2003), which have been shown to sense nucleic acids leading to type I IFN production. For example, TLR7 has been shown to mediate recognition of influenza virus genomic single-stranded RNA (ssRNA) (Diebold et al., 2004) and ssRNA from human immunodeficiency virus (HIV)-1 (Heil et al., 2004) while TLR9 senses mouse cytomegalovirus (MCMV) (Krug et al., 2004a; Tabeta et al., 2004). Purified ssRNA from influenza virus can stimulate bone marrow-derived DC cultures that contain pDCs to secrete IFN α ; this was reduced to background levels using cells from TLR7^{-/-} mice (Diebold et al., 2004). In addition, ssRNA derived from the HIV-1 genome stimulated human peripheral blood pDCs and murine bone marrow-derived pDCs to produce IFN α in a TLR7-dependent manner (Heil et al., 2004). Similarly, it has been shown that splenic pDCs produce IFN α in response to MCMV in a TLR9-dependent manner in experiments measuring IFN α secretion by in vitro and in vivo stimulated murine splenic pDCs. In this report the exact viral stimulus for TLR9 was not defined, but the double-stranded DNA genome of MCMV was implicated by studies using the TLR9 agonist unmethylated CpG DNA (Krug et al., 2004a). The in vivo relevance for TLR9 in recognizing MCMV was confirmed in the same year when Tabeta et al. (2004) showed that mice with a point mutation in TLR9, which renders this receptor insensitive to its synthetic CpG DNA agonist, have higher MCMV titers in the spleen and reduced survival compared to control mice following MCMV infection. In addition, these TLR9 mutant mice have reduced IFN α/β in their serum following MCMV infection. TLR3 senses dsRNA resulting in IFN α/β induction, however it is not essential for IFN α/β induction in virally infected cells (Honda et al., 2003) and neither human nor murine pDCs express this TLR (Colonna et al., 2004; Edwards et al., 2003). This

evidence suggests that TLRs can play an important, and often necessary, role in viral sensing leading to type I IFN production; however, they are only expressed in a subset of cells and other receptors also sense viral ligands.

Viral recognition by cytosolic sensors

In addition to endosomal TLR-mediated virus recognition, cytosolic pathways are also present. The cytoplasm of both innate immune cells and non-immune cells contains retinoic acid inducible gene-I (RIG-I) and melanoma differentiation-associated protein 5 (Mda5), which sense cytosolic virus-associated dsRNA leading to type I IFN production (Yoneyama et al., 2004, 2005). Interestingly, studies comparing pDCs from RIG-I^{-/-} and MyD88^{-/-}TRIF^{-/-} mice (which lack all known TLR-mediated activation signaling pathways) by Kato et al. (2005) demonstrated that the use of RIG-I or TLRs was cell type specific. While RIG-I seems to be required for IFN α/β production in several cell types, TLRs remain the key pathway for innate recognition of RNA viruses in pDCs. Hence, pDCs from RIG-I^{-/-} mice showed equivalent IFN- α production following Newcastle Disease virus (NDV) infection to that by wild-type mice, whereas pDCs from MyD88^{-/-} mice had a 4-fold reduction in IFN- α production. These two pathways of cytosolic dsRNA detection may have complementary functions; perhaps RIG-I sensing of cytosolic dsRNA may be important for an immediate detection of viral infection while TLR sensing of dsRNA in endosomal compartments may be more important for the systemic response to virus (Benedict and Ware, 2005; Levy and Marie, 2004). Cells can also detect dsRNA through the dsRNA-dependent protein kinase R (PKR), which in response, inhibits host translation by phosphorylating the translation initiation factor eIF2 α and activates NF- κ B (Saunders and Barber, 2003). Whether cells also have a mechanism for cytosolic recognition of ssRNA remains to be discovered. Recently, a pathway by which the recognition of foreign cytosolic DNA leads to the production of type I IFN has been investigated in macrophages and DCs; however, the identity of the DNA sensor is not yet known, nor is whether DNA viruses may activate this pathway (Ishii et al., 2006; Stetson and Medzhitov, 2006). Stetson and Medzhitov (2006) used infection by the intracellular bacterium *Listeria monocytogenes* as a source of cytosolic DNA, as well as DNA that lacks CpG motifs, to induce type I IFN production and this second source of DNA also induced potent induction of type I IFN when transfected into pDCs. Clearly, there is still more to learn about the cytosolic recognition of viral nucleic acids.

The exact viral ligand binding to these receptors has not been unambiguously identified, although viral

genome has been strongly implicated by the discovery of agonists of these receptors. It is conceivable that the viral ligand, such as dsRNA, ssRNA or DNA (whether it contains CpG or not), is recognized through another unidentified receptor and this brings the proposed ligand in contact with the known PRR (for example TLR) either by directing it to the correct cellular compartment or clustering the ligand in the vicinity of PRR, leading to the presentation of an array of ligands. Alternatively, signaling via an additional co-receptor may be required or another ligand associated with the oligonucleotide may mediate binding to the PRR.

Evidence for glycoprotein mediated induction of type I IFN

In the 1980s and 1990s there were a number of reports describing viral glycoprotein-stimulated induction of type I IFN by a population of peripheral blood mononuclear cells (PBMC) or splenocytes involving a mechanism which does not require viral entry into the IFN producing cell. At this time, the pDC had not been identified and when researchers attempted to define the cell type responsible for this induction of type I IFN production they described a cell with plasmacytoid morphology. These were negative for lineage markers of T cells, B cells, NK cells and monocytes, and were termed NIPCs, consistent with the phenotype of pDCs. Now that we have improved tools for identifying and isolating pDCs it is an opportune moment to clarify what role viral glycoproteins play in the induction of type I IFN by this cell type.

Fixed virus-infected cells can stimulate IFN production

Studies using fixed virus-infected cells as stimuli for type I IFN induction suggest that IFN production is independent of virus entry into the producer cells. This has been demonstrated using fixed cells infected with herpes simplex virus (HSV)-1 (Capobianchi et al., 1985; Lebon, 1985), dengue virus (Kurane et al., 1986), transmissible gastroenteritis coronavirus (TGEV) (Charley and Laude, 1988), human parainfluenza virus (HPIV)-4A (Ito et al., 1994); and influenza virus (Miller and Anders, 2003). These fixed virus-infected cells are thought to present arrays of viral glycoproteins at their surface, which would presumably be able to interact with receptors on the NIPC. A number of these studies also implicated specific viral glycoproteins as necessary for IFN induction since mAb specific for the viral glycoprotein could block IFN induction. For example, in experiments by Charley et al. IFN induction by fixed TGEV-infected cells could be blocked by antibodies

against the M (also known as E1) surface glycoprotein of TGEV (Charley and Laude, 1988). Similarly, fixed HSV-1-infected cells induced IFN secretion by human PBMC, which was inhibited by the addition of mAb against HSV-1 envelope glycoprotein gD (Lebon, 1985). Fixed HPIV-4A-infected cells induced IFN production by mouse splenocytes and this could be inhibited by anti-HPIV-4A antiserum and mixtures of mAb against multiple epitopes on the HN glycoprotein (Ito et al., 1994). Such systems of fixed virus infected-cells presumably have few or no free virions hence their ability to induce type I IFN is thought to be a consequence of interactions between viral envelope glycoproteins expressed on the surface membrane of the infected cells and receptors on the NIPC. Alternatively the NIPC could recognize a cellular stress ligand induced upon viral infection.

Cells transfected with viral glycoproteins can stimulate IFN production

The use of cells transfected with viral glycoproteins allows researchers to ask whether induction is triggered by one or several viral glycoproteins, whether other viral components are necessary, or whether a cellular stress response to viral infection was also important. In addition, systems using inactivated virus, or even virus-infected cells, as stimuli for type I IFN induction cannot rule out that viral nucleic acid may be present and capable of triggering type I IFN production. Experiments where no viral genome is present most strongly suggest there is a genome-independent pathway of type I IFN induction, in which viral glycoproteins are recognized as the stimuli triggering IFN production. An example of this was seen when fixed insect cells transfected with the HSV-1 envelope glycoprotein gD, but not other HSV-1 glycoproteins (gB, gC, gE, gG and gI), induced strong type I IFN secretion by human PBMC (Ankel et al., 1998). IFN induction could be inhibited by mAb against gD, strengthening the argument for a role for gD in the induction of IFN α . In addition, Ito et al. showed that mouse spleen cells produced type I IFN when co-cultured with COS7 cells transfected with HPIV-4A virus HN glycoprotein, but not with COS7 transfected with vector alone (Ito et al., 1994). Thus, in the absence of any viral nucleic acid, viral glycoproteins expressed on the cell surface are sufficient for IFN induction to occur.

Soluble viral glycoproteins can stimulate IFN production and other immune responses

Soluble viral glycoproteins can induce IFN α / β production. For example, the recombinant extramembrane fragment of HSV-1 gD was sufficient to induce

IFN α production by human PBMC to a level comparable to that of intact virus (Ankel et al., 1998). In addition, soluble HN glycoprotein of HPIV-4A induced IFN production by murine splenocytes (Ito et al., 1994). Since this work was done, pDCs have emerged as a cell type found in peripheral blood and spleen which produces the majority of type I IFN in response to viral stimulation. To our knowledge only one study to date has shown direct evidence that viral glycoproteins can stimulate pDCs to secrete type I IFN. In the study by del Corno et al. recombinant gp120 from R5 and X4 strains of HIV-1 stimulated pDCs enriched from human PBMC to secrete IFN α (Del Corno et al., 2005). Assuming there is no contamination of the glycoprotein samples with oligonucleotides, this work demonstrates a direct role of a viral glycoprotein in IFN α induction by a purified pDC population.

In support of the argument that viral glycoproteins have a role in directly activating immune responses, viral glycoproteins have been shown to induce innate immune responses in B cells. It has been shown that ultraviolet radiation-inactivated influenza virus of the H2 subtype and its purified haemagglutinin (HA) induced potent proliferation and upregulation of costimulatory molecules in human and murine B cells (Marshall-Clarke et al., 2006; Pountourios et al., 1987). The induction of this response was dependent on cell surface MHC class II glycoprotein I-E expression by the B cells and was MyD88 dependent. The identity of the molecule involved in sensing the H2 HA is not known, but this study demonstrates that viral glycoproteins can be sensed by immune cells.

Glycosylation on viral glycoproteins may be important in the induction of IFN

Further investigations into identifying common patterns present on the many different viral glycoproteins that can induce type I IFN production have led to the suggestion that sugar residues on viral glycoproteins can be recognized. Using genetically modified mouse hepatitis viruses (MHV) in which the abundant envelope glycoprotein, M, was either *O*- or *N*-glycosylated or not glycosylated at all, de Haan et al. (2003) studied the influence of M protein glycosylation on the IFN inducing capacity of the virus. In this study, the differentially glycosylated M proteins were all expressed at similar levels on fixed cells infected with MHV, however, IFN induction by peripheral blood lymphocytes incubated with these infected cells was inhibited 30–200-fold if virus lacked all glycosylation of its M glycoprotein. In addition, cells infected with mutant TGEV expressing partially or totally deglycosylated M were reduced in their ability to induce type I IFN production by PBMC in comparison with the parental

virus, which again, suggested that glycosylation may be important in the induction of IFN (Laude et al., 1992). In a system of type I IFN induction in murine splenocytes by inactivated influenza virus where the main cell producing type I IFN was the pDC, mannan, known to block recognition of ligands by receptors with specificity for mannose, such as mannose receptor and DC-SIGN, inhibited the induction of IFN by inactivated influenza virus ((Miller and Anders, 2003) and unpublished data R.S and J.M). Studies such as these implicate, but do not prove, the involvement of viral glycoproteins in IFN α / β induction and suggest recognition by a lectin-like receptor on the NIPC.

Receptors recognizing viral envelope glycoproteins

While recognition of viral nucleic acid is mainly mediated through TLRs in pDCs, the cellular receptors for virus glycoproteins required for type I IFN production have not been characterized. Some preliminary experiments have been performed to investigate potential cellular recognition components. In one study, PBMC were inhibited in their ability to induce IFN α production in response to three sources of HSV-1 glycoprotein (live HSV-1, cells transfected with HSV-1 gD or soluble gD) when preincubated with mAb against sulphatides (prominent lipid components of membranes) and the galactosyl–sphingosine moieties of galactosyl cerebrosides (Ankel et al., 1998). Such an agonistic effect suggests a function for these glycolipids during induction, although what this might be is not known. Furthermore, pretreatment of PBMC with antibodies against the chemokine receptors CCR3 or CXCR4 also suppressed IFN α induction by HSV-1, gD transfected cells or soluble gD. Thus, these chemokine receptors could participate in induction of IFN α by HSV-1 glycoproteins. Given the recent development of more precise tools to identify and work with pDCs, we think this is a suitable time to re-address the issue of identifying receptors on pDCs for viral glycoproteins.

Viral glycoproteins can be recognized by both TLRs and through lectin and scavenger PRRs and, although any role of these receptors in IFN induction has not been demonstrated, we will discuss these further here as an example of glycoprotein recognition by specific receptors. Table 1 summarizes PRRs involved in sensing viruses.

TLRs sensing viral glycoproteins

In addition to activating the response to nucleic acids, some TLRs can mediate responses to viral proteins. Respiratory syncytial virus (RSV) F protein is an

example of a viral envelope glycoprotein which can be sensed by TLR4 and CD14 (Kurt-Jones et al., 2000). F protein can induce IL-6 secretion from purified human monocytes in a manner that could be blocked by anti-CD14 mAb. In addition, F protein could not stimulate macrophages from CD14^{-/-} or TLR4^{-/-} mice to produce IL-6. The envelope proteins of murine retroviruses also activate TLR4 (Rassa et al., 2002). Similarly, TLR2 and CD14 can recognize an undefined human cytomegalovirus (HCMV) structure, likely to be an envelope glycoprotein (Compton et al., 2003). HCMV dense bodies (which contain envelope and tegument, but lack capsid and nucleic acid) can induce human PBMC to secrete IL-8 and IL-6 in a manner that could be inhibited by antibodies against CD14. Human embryonic kidney (HEK) cells transfected with TLR2 produced IL-8 in response to inactivated virus and inactivated HCMV could stimulate NF- κ B driven reporter gene expression in these cells. The levels of IL-8 secreted and NF- κ B driven gene expression by TLR2 expressing HEK were enhanced when CD14 was co-expressed. In addition, thioglycolate-elicited macrophages from TLR2^{-/-} mice did not secrete IL-6 in response to HCMV. The haemagglutinin (H) protein of measles virus wild-type strains also triggers TLR2 activation in a way that is enhanced by CD14 expression but independent of the measles virus receptors CD46 and CD150 (Bieback et al., 2002). This demonstrates that TLRs can sense not only viral genome, but also viral glycoproteins leading to responses including cytokine secretion. It is interesting to note that in much of the work implicating viral nucleic acid as being sensed by the TLR, viral glycoprotein is also present.

C-type lectins sensing viral glycoproteins

A number of C-type lectin receptors, including DC-SIGN, Langerin and the mannose receptor (MR) are important for the binding of HIV-1 envelope proteins to epithelial DCs and macrophages which express these molecules (Turville et al., 2003). The extent of glycosylation of gp120 allows HIV-1 to bind to at least three different C-type lectin receptors on cells within the stratified squamous epithelium in what is often a mannose-specific manner (Turville et al., 2002). HIV-1 whole virus particle binding to monocyte-derived macrophages can be inhibited by mannan, EDTA, D-mannose or mannose-binding lectin (MBL) (Nguyen and Hildreth, 2003) and binding of gp120 to some DC subsets can be inhibited by mannan (Turville et al., 2002). In addition gp120 also binds to an astroglial cell line expressing MR more than an untransfected control and this can be inhibited by deglycosylation of gp120 and addition of EGTA (Liu et al., 2004). A functional role for MR in HIV-1 infection is suggested by findings

Table 1. Examples of PRR involved in viral recognition

Receptor/location	Example of ligand	Viral ligand ^a	Reference
<i>Cell surface</i>			
TLR4/CD14	Lipopolysaccharide (LPS), lipid A	RSV (F)	Kurt-Jones et al. (2000)
TLR4	LPS, lipid A	Mouse mammary tumor virus envelope proteins	Rassa et al., (2002)
TLR2/CD14	Lipoteichoic acid, peptidoglycan	HCMV	Compton et al. (2003)
TLR2	Lipoteichoic acid, peptidoglycan	Measles virus (H), HSV-1	Bieback et al. (2002), Kurt-Jones et al. (2004)
DC-SIGN	Mannose containing oligosaccharides	HIV-1 (gp120), HIV-2, SIV, Ebola virus, dengue virus, HCMV (gB), HCV (E2)	Alvarez et al. (2002), Curtis et al. (1992), Dakappagari et al. (2006), Geijtenbeek et al. (2000), Halary et al. (2002), Lozach et al. (2003), Navarro-Sanchez et al. (2003), Pohlmann et al. (2001a), Tassanetrithep et al. (2003)
DC-SIGNR	Mannose containing oligosaccharides	HIV-1 (gp120), HIV-2, Ebola virus, HCMV, HCV (E2)	Alvarez et al. (2002), Bashirova et al. (2001), Dakappagari et al. (2006), Halary et al. (2002), Lozach et al. (2003), Pohlmann et al. (2001a)
SR-BI	High-density lipoprotein	Hepatitis C virus (E2)	Scarselli et al. (2002)
<i>Recycling between surface and endosome</i>			
MR	Terminal mannose and fucose residues	HIV-1 (gp120)	Liu et al. (2004)
<i>Intracellular</i>			
TLR7	ssRNA	Influenza virus (ssRNA), HIV-1 (ssRNA)	Diebold et al. (2004), Heil et al. (2004)
TLR9	CpG DNA	MCMV, HSV-1, HSV-2	Hochrein et al. (2004), Krug et al. (2004a), Krug et al. (2004b), Lund et al. (2003), Tabeta et al. (2004)
TLR3	dsRNA (polyI:C)	RSV	Rudd et al. (2005)
<i>Cytosolic</i>			
RIG-I	dsRNA	Sendai virus, NDV	Melchjorsen et al. (2005), Yoneyama et al. (2004)
Mda5	dsRNA	NDV	Yoneyama et al. (2005)
PKR	dsRNA	Reovirus (s1 mRNA)	Bischoff and Samuel (1989)
<i>Soluble</i>			
SP-D	Maltose, glucose, mannose	Influenza virus (HA and NA), RSV (G)	Hartshorn et al. (2000), Hickling et al. (1999), Reading et al. (1997)
SP-A	Maltose, glucose, mannose	Influenza virus, RSV (F)	Ghildyal et al. (1999), Malhotra et al. (1994)
MBL	Mannose, fucose, <i>N</i> -acetylglucosamine	Influenza virus, HIV-1 (gp120)	Malhotra et al. (1994), Meschi et al. (2005)
Salivary gland agglutinin gp340	SP-A and SP-D	HIV-1 (gp120)	Wu et al. (2003)

^aIf known, the specific viral component recognized by the PRR is given in brackets. Abbreviations are as in text.

that expression of MR in astroglial cells increased their infectivity by HIV-1. This effect could be inhibited by anti-MR serum, mannan and mannose. In the same way the infection of primary human astrocytes by HIV-1 was inhibited by anti-MR serum and small interfering RNA (siRNA) against MR. Together this research defines a

mannose-dependent binding mechanism of HIV-1 to some cell types and suggests a role for MR in infection. Interestingly, MR has also been reported as being important for the induction of IFN α in response to several viruses including HIV-1 (Milone and Fitzgerald-Bocarsly, 1998).

These studies with HIV-1 do not demonstrate direct binding of viral glycoproteins to a defined PRR. Although other PRR have been shown to bind viral glycoproteins, conclusive evidence is often lacking for a functional response to recognition. For example, DC-SIGN and DC-SIGNR have been shown to recognize several viruses including; HIV-1, HIV-2, simian immunodeficiency virus (SIV), Ebola virus and dengue virus (Alvarez et al., 2002; Curtis et al., 1992; Geijtenbeek et al., 2000; Navarro-Sanchez et al., 2003; Pohlmann et al., 2001a, b; Tassaneetrithep et al., 2003). In another example, a cell line expressing either DC-SIGN or DC-SIGNR bound more beads coated with gp120 of HIV-1 than the untransfected control. This binding could be partially inhibited by Fab fragments against DC-SIGN or DC-SIGNR (Dakappagari et al., 2006) or anti-DC-SIGN and DC-SIGNR mAb, mannan and EDTA (Bashirova et al., 2001). This demonstrates that viral glycoproteins can bind PRR, although evidence linking this to a functional response is limited.

Collectins sensing viral glycoproteins

Collectins are a group of soluble collagenous lectins which have a carbohydrate recognition domain that binds mannose residues. Several human collectins have been implicated in viral recognition, including surfactant protein (SP)-D, SP-A and MBL. For example SP-D binds HA and neuraminidase (NA) of influenza virus and binding was destroyed when influenza virus was deglycosylated (Hartshorn et al., 2000; Reading et al., 1997). SP-A and MBL bind influenza virus and can inhibit the haemagglutination activity of influenza virus (Malhotra et al., 1994). Collectins are soluble proteins thought to opsonise viral particles to aid their uptake by phagocytes though binding to a cellular receptor. The binding of SP-D, SP-A and MBL to influenza virus demonstrates the recognition of viral carbohydrate by soluble PRR; this could bring the virus particle closer to an innate immune cell and by clustering cellular receptors could initiate signaling.

Scavenger receptors sensing viral glycoproteins

In addition to C-type lectins, scavenger receptors have been shown to bind viruses. For example, the human class B scavenger receptor SR-BI, also known as CLA-1, binds hepatitis C virus (HCV) glycoprotein E2 (Scarselli et al., 2002). Similarly, the salivary agglutinin gp340 binds gp120 of HIV-1 and inhibits HIV-1 infectivity (Wu et al., 2003). In an *in vivo* study, Suzuki et al. (1997) showed that types I and II class A scavenger receptor (SR-A) knock-out mice display an increased susceptibility to HSV-1 infection, suggesting a role for SR-A in the development of the immune response

against HSV-1. This work demonstrates that different families of PRR can interact with viral glycoproteins.

Conclusions

The exact molecular basis for the induction of type I IFN by viruses remains to be determined, although in addition to the recognition of viral genome, viral glycoproteins are clearly sensed in a manner that can depend on glycosylation. Nucleic acid or viral glycoproteins are unlikely to be sensed in isolation; therefore it is more likely that recognition of several viral components occurs sequentially or simultaneously in a redundant manner reminiscent of the innate recognition of bacterial and fungal pathogens. Hence, the receptors for both viral oligonucleotides and glycoproteins are likely to contribute to detection of viral infection and may contribute synergistically to the subsequent induction of the innate immune response.

Although receptors mediating viral genome recognition have been proposed, good candidate receptors for signaling by viral glycoproteins have yet to emerge. Viral glycoproteins interact with PRR from a range of families (e.g. TLRs, C-type lectins, scavenger receptors and collectins); however, PRR expression on pDCs has yet to be extensively characterized. Nevertheless, pDCs do express BDCA-2 and Siglec-H, members of the C-type lectin and siglec families, and although the exact function of these proteins has yet to be elucidated, these receptor families contain members involved in pathogen recognition. It will be interesting in the future to see what PRR pDCs express and whether these play a role in viral recognition and the induction of type I IFN.

The identification of the specific cellular and viral molecules responsible for induction of type I IFN production by both viral genome and glycoprotein will be of value in the development of antiviral therapies and design of effective vaccines as we learn how to stimulate the innate immune system.

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