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• REVIEW •

DC-SIGN: Binding receptor for HCV?

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Abstract

DC-SIGN, a dendritic Cell-specific adhesion receptor and a type II transmembrane mannose-binding C-type lectin, is very important in the function of DC, both in mediating naive T cell interactions through ICAM-3 and as a rolling receptor that mediates the DC-specific ICAM-2-dependent migration processes. It can be used by viral and bacterial pathogens including Human Immunodeficiency Virus (HIV), HCV, Ebola Virus, CMV and Mycobacterium tuberculosis to facilitate infection. Both DC-SIGN and DC-SIGNR can act either in *cis*, by concentrating virus on target cells, or in *trans*, by transmission of bound virus to a target cell expressing appropropriate entry receptors. Recent work showed that DC-SIGN are high-affinity binding receptors for HCV. Besides playing a role in entry into DC, HCV E2 interaction with DC-SIGN might also be detrimental for the interaction of DC with T cells during antigen presentation. The clinical strategies that target DC-SIGN may be successful in restricting HCV dissemination and pathogenesis as well as directing the migration of DCs to manipulate appropriate immune responses in autoimmunity and tumorigenic situations.

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INTRODUCTION

Dendritic cells and Langerhans cells are specialized for the recognition of pathogens and have a pivotal role in the control of immunity[1-7]. Recently, several C-type lectin and lectin-like receptors (DC-SIGN and DC-SIGNR) have been characterized that they are expressed abundantly on the surface of these professional antigen-presenting cells, which not only serve as antigen receptors but also regulate the migration of dendritic cells and their interaction with lymphocytes. DC-SIGN was originally defined as an intercellular adhesion molecule-3 (ICAM-3) receptor supporting DC-mediated T-cell proliferation and binding and presentation of HIV-1 virions through gp120. DC-SIGNR or L-SIGN is a homologue of DC-SIGN and expressed in lymph nodes and by liver sinusoidal endothelial cells. L-SIGN has the same ligand-binding specificities as DC-SIGN, but is not produced by DCs or LCs. Furthermore, a series of DC-SIGN-like transcripts are predicted to encode other membrane-associated and soluble isoforms. The DC-SIGN and L-SIGN genes, map to chromosome 19p13 adjacent to the type II C-type lectins CD23 (Fc_E receptor II) and activation marker CD69. DC-SIGN and L-SIGN can bind mannose residues of viral glycoproteins through a C-terminal carbohydrate recognition domain (CRD)[8].

Hepatitis C virus (HCV) is the major causative agent of non-A, non-B hepatitis throughout the world with more than 170 million people infected. The majority of infected patients are unable to clear the virus and many develop chronic liver disease, cirrhosis and hepatocellular carcinoma. Replication of the HCV genome could be demonstrated *in vivo* and *in vitro* in liver hepatocytes and hematopoietic cells including dendritic cells and B cells. However, the molecular mechanism by which the virus targets to these sites of replication, notably in the liver, is not known. Regarding the interaction with DC-SIGN it has been shown that this lectin facilitates virus entry into DC in *cis* by enhancing attachment of HCV, as well as HIV, Ebola Virus, Cytomegalovirus, and Dengue Virus to the cell, thereby increasing the likelihood of interaction with specific entry receptors[9-17].

TROJAN HORSES: DUAL ROLES FOR DC-SIGN

DCs from different anatomical sites express distinct arrays of alternative HIV receptors. Some of these subsets could represent good gatekeepers, whereas others may be "Trojan horses" that carry HIV into the lymph node[18]. Our understanding of the role of DC-SIGN has become more complicated with the discovery of other functions. First, DC-SIGN binds ICAM-2, an integrin expressed on the endothelia of blood vessels and high endothelial vessels. DC-SIGN–ICAM-2 interactions help mediate tethering and transendothelial migration of DCs and may be critical for permitting DCs or their precursors to migrate towards inflammation in peripheral tissue or to enter lymph nodes[19-22]. Second, DC-SIGN initiates interactions with naï ve T cells through contact with a third ligand, ICAM-3, which is believed to stabilize DC-T cell membrane contacts and enable efficient T cell receptor engagement. Finally, DC-SIGN can internalize soluble antigen ligands, resulting in processing and presentation of antigenic peptides to T cells[23-27].

All of the above functions are consistent with a general model in which DCs in mucosa encounter HIV-1, internalize particles *via* DC-SIGN and become "Trojan horses", traveling to lymph nodes to release infectious particles into the midst of activated T cells. The concept that DC-SIGN is the primary receptor mediating this sequence of events came mostly from studies of DCs derived *in vitro* from monocytes. To address this problem, Turville *et al*[28] isolated resident DC subsets from skin, tonsils and blood and analyzed DC-SIGN expression and the gp120 binding capacity of these cell types directly *ex vivo*. Their results showed DC-SIGN has been detected on immature DCs in the lamina propria of mucosal tissues as well as on macrophages in decidua and placenta. DC-SIGN supports tethering and rolling of DC-SIGN–positive cells on the vascular ligand ICAM-2 under shear flow. The DC-SIGN-ICAM-2 interaction regulates chemokine induced transmigration of DCs across both resting and activated endothelium. Thus, DC-SIGN is central to the unusual trafficking capacity of DCs, further supported by the expression of DC-SIGN on precursors in blood and on immature and mature DCs in both peripheral

and lymphoid tissues. DC-SIGN- and DC-SIGNR-gp120 interactions represent a potential target for anti-HIV therapy aimed at disrupting the DC-virus interaction at primary sites of infection, in order to lower the efficiency of T cell infection. Lastly, these studies[29-31] suggest that the interaction of DC-SIGN and DC-SIGNR with endogenous ligands may not be restricted to ICAMs that have been studied to date, but may include other cell surface or soluble glycoproteins with appropriately displayed high mannose oligosaccharides. The mechanism of DC SIGN-mediated *trans*-infection is not completely understood, but it involves the internalization of HIV particles into an early endosome, where they appear to undergo pH-dependent changes that make them more infectious. When DCs contact $CD4^+$ T cells, virus is released and T cells become infected. Evidence is accumulating that DC-SIGN may also facilitate infection in *cis*. *Cis* infection occurs when virus directly infects the DC-SIGN–expressing cell. Because DC-SIGN also binds HIV-2 and SIV, it has been dubbed the "universal receptor" for primate lentiviruses. All of the above functions are consistent with a general model in which DCs in mucosa encounter HIV-1, internalize particles *via* DC-SIGN and become "Trojan horses", traveling to lymph nodes to release infectious particles into the midst of activated T cells. Another example is *M. tuberculosis*. Dendritic cells (DCs) are important mediators of immune responses against *M. tuberculosis*. The interaction of mycobacteria with DC-SIGN also results in production of IL-10, which can modify the immune response, and might promote survival of mycobacteria. These results[11] indicate that M. tuberculosis infects DCs and interferes with DC-mediated immune responses by targeting DC-SIGN. So, DC-SIGN is a Trojan horse for *M. tuberculosis* as has been shown previously for HIV-1.

DC-SIGN also binds HIV gp120 to facilitate HIV transmission from DCs to T cells. Engering *et al*[32] showed DC-SIGN underwent rapid ligand-specific internalization to deliver its cargo to the acidic late endosome-lysosome compartments, where subsequent antigen-processing and presentation to T cells could occur. Internalization of soluble DC-SIGN ligands triggered antigen-specific T cell activation[33,34]. Importantly, such ligand internalization points to a mechanism by which HIV may cloak itself for delivery to T cell–rich areas in peripheral lymphoid tissues. There was high expression of DC-SIGN on MDDCs and in gp120 binding assays, DC-SIGN mediated all gp120 binding on MDDC. Recently Pohlmann *et al*[35] discovered DC-SIGNR, which can also act as a similar HIV ' trans-infection,' receptor in a 293T transfectant background. Furthermore, DC-SIGNR is expressed predominantly in the liver and lymph node tissue and MDDCs do not appear to express this receptor at high levels, suggesting it has a less important role in HIV binding. Therefore in addition to DC-SIGN, CD4, MMR, and as yet unknown trypsin resistant DC-SIGN and, possibly, DC-SIGNR, on DCs seems likely to have the capacity to bind gp120. This work supports intraepithelial DC as the first target for HIV but the original SIV tracking work suggested deeper tissue DC within the lamina propria were the first to be infected. Trauma during sexual transmission or genital ulceration would favour the latter. These data suggest that skin and probably other tissue DCs bind gp120 and/or HIV via both DC-SIGN and CD4/CCR5. HIV gp120 saccharide-DC-SIGN binding may provide constant high affinity virion binding to DC for any HIV strain, facilitating subsequent CD4/chemokine receptor binding and fusion. Therefore DC-SIGN may enhance DC infection and mucosal transmission. Furthermore mucosal DCs may provide the selection event which results in the predominance of R5 isolates[36].

Two papers in <<Immunity>> show that the HIV-1 protein Nef up-regulates DC-SIGN expression on DCs and that binding of DC-SIGN mediates internalization of virus particles into a non-lysosomal compartment, which enhances infectivity. The study from Sol-Foulon *et al*[37] examined the role of HIV-1 Nef in viral infectivity. DC-SIGN was found to be upregulated at the surface of infected cells. Up-regulation was dependent on Nef, given that DCs infected with Nef-deficient virus showed DC-SIGN staining patterns similar to uninfected cells. Two putative internalization signals - a tyrosine-based motif and a dileucine motif - are located in the cytoplasmic tail of DC-SIGN. The role of these motifs was examined using DC-SIGN-negative HeLa cells transfected with plasmids encoding DC-SIGN or Nef, or both. HeLa cells expressing wild-type DC-SIGN had very little surface expression but a high rate of endocytosis. By contrast, dileucine mutants of DC-SIGN showed high levels of surface expression with little or no internalization. Co-transfection with wild-type DC-SIGN and Nef resulted in stable expression of DC-SIGN at the plasma membrane. These results show that Nef up-regulates DC-SIGN surface expression by preventing internalization, which enhances the ability of DCs to form clusters with lymphocytes and facilitates viral transmission. The study from Baribaud *et al*[36] focused on the role of DC-SIGN in internalization and infectivity of HIV-1. DC-SIGN was shown to mediate the internalization of gp120 in a monocyte cell line transduced with a DC-SIGN-encoding virus. Fluorescence confocal microscopy showed that whole viral particles could be internalized by human DCs. After 45 min, most of the viral particles were localized in a non-lysosomal compartment, and these could be transmitted to a second target cell. Low pH in this compartment was important for maintenance of infectivity, given that neutralization of pH abolished the ability of DC-SIGN-positive cells to enhance infection of T cells. Although several questions - such as how HIV returns to the cell surface and what regulates this process - remain to be answered, this new work has implications for our understanding of HIV pathogenesis. Finally, DC-SIGN is up-regulated on monocytes exposed to inflammatory cytokines or undergoing differentiation into DCs, which suggests that expression on cells can be modulated by the microenvironment[38-41]. More definitive experiments will be required to determine actual amounts of expression in the blood and lymph nodes of both healthy and HIV-infected subjects. They suggest that DC-SIGN-mediated *cis*-infection of DCs could play a key role in viral dissemination[42-46]. This diversity may pose additional challenges for those who wish to block HIV infection by targeting DC-SIGN.

BINDING RECEPTORS FOR HCV

HCV is a small, enveloped, plus-strand RNA virus belonging to the family flaviviridae and genus hepacivirus. The HCV RNA genome is 9 600 nucleotides in length and encodes a single polyprotein that is post-translationally cleaved into up to 10 polypeptides including three structural proteins (core, E1 and E2), located at the N-terminus, and five nonstructural proteins. Shortly after translocation into the endoplasmic reticulum (ER), oligosaccharidetransferase catalyzes addition of Glc3Man9GlcNAc2 complexes at up to 6 (E1) and 11 (E2) Nglycosylation sites. Glucose residues are removed by glucosidases I and II and correctly folded proteins are released from ER chaperones calnexin and calreticulin. The transmembrane domains of E1 and E2 are responsible for both heterodimerization and retention of the glycoproteins in a high mannose EndoH sensitive glycoform in the ER. By analogy to other flaviviruses it is assumed that HCV capsids bud from the cytoplasm into the ER and that enveloped particles follow the secretion pathway through the Golgi. However, attempts to produce secreted HCV particles *in vitro* have not been successful so far and it is not known if E1 and E2 on mature

infectious virions possess a high-mannose, complex or mixed glycosylation.

Since the genomic sequence of HCV was determined, significant progress has been made towards understanding the functions of the HCV-encoded proteins, despite the lack of an efficient in-vitro replication system or convenient small-animal model. The identity of the receptor for HCV remains elusive, however. Several receptors have been proposed that could play a role in HCV entry into hepatocytes. Low-density lipoprotein receptor, CD81 and GAGs may all act as receptors for HCV, either sequentially or by different viral quasispecies The low density lipoprotein (LDL) receptor (LDLR) has been shown to mediate HCV internalization via binding to virus associated LDL particles. A second putative HCV receptor, the tetraspanin CD81, has been identified as a high affinity binding receptor for soluble recombinant E2 from HCV genotype 1a. CD81 and LDLR are expressed in most cell types and thus not likely account for the hepatic tropism of the virus. Recent work using pseudotypic VSV bearing E1 or E2 chimeric molecules showed that entry of the E1 pseudotype can be inhibited by recombinant LDLr, whereas the E2 pseudotype is more sensitive to inhibition by recombinant CD81 or heparin. These results suggest that E1 and E2 may be responsible for interactions with different cellular molecules. It is also conceivable that additional, yet unidentified, cellular proteins are involved in viral binding and entry. Intriguingly, the reports of HCV-RNA associated with PBMC suggest that HCV infection may not be restricted to hepatocytes. Thus, separate reservoirs of virus may exist, and HCV may use different receptors to access these different cell types. The lack of an efficient cell culture model has precluded functional confirmation of these receptor candidates at the level of virus entry. Recently Lozach *et al*[9] found that DC-SIGN and L-SIGN are two novel HCV envelope binding receptors and the HCV envelope glycoprotein E2 binds DC-SIGN and L-SIGN through high-mannose N-glycans. Competing ligands such as mannan and an antibody directed against the carbohydrate recognition domains (CRD) abrogated binding. The highest affinity is seen for plasma membrane expressed DC-SIGN and L-SIGN. These results indicate that several high-mannose N-glycans in a structurally defined cluster on E2 bind to several subunits of the oligomeric lectin CRD. Its localization on the endothelium lining hepatic sinusoids makes it an interesting candidate for the capture of HCV. Productive infection of endothelial cells by HCV has not been demonstrated, but L-SIGN could be responsible for the transmission of bound virus to neighbouring hepatocytes. This kind of mechanism of *trans*-enhancement has been demonstrated more than a decade ago for HIV transmission from DC to T cells and can be attributed to DC-SIGN. In the case of HCV, it is tempting to speculate that subsequent to interaction with L-SIGN on endothelial cells, the virus could be transmitted to hepatocytes where it uses a specific receptor for entry. In conclusion,the results show that HCV envelope glycoprotein E2 strongly binds to oligomeric C-type lectins in a high-mannose *N*-glycan dependent fashion. High affinity interaction of viral glycoproteins with lectins might represent a strategy by which enveloped viruses target to the site of replication and represents an interesting novel target for antiviral drug development.

In another, Pohlmann *et al*[47] found that soluble versions of the hepatitis C virus (HCV) E2 glycoprotein and retrovirus pseudotypes expressing chimeric forms of both HCV E1 and E2 glycoproteins bound efficiently to DC-SIGN and DC-SIGNR expressed on cell lines and primary human endothelial cells but not to other C-type lectins tested. Soluble E2 bound to immature and mature human monocyte-derived dendritic cells (MDDCs). Binding of E2 to immature MDDCs was dependent on DC-SIGN interactions, while binding to mature MDDCs was partly independent of DC-SIGN, suggesting that other cell surface molecules may mediate HCV glycoprotein interactions. HCV interactions with DC-SIGN and DC-SIGNR may contribute to the establishment or persistence of infection both by the capture and delivery of virus to the liver and by modulating dendritic cell function[48].

QUESTIONS TO BE ANSWERED

DC-SIGN and DC-SIGNR are two closely related membrane-associated C-type lectins that bind human immunodeficiency virus (HIV) envelope glycoprotein with high affinity. Binding of HIV to cells expressing DC-SIGN or DC-SIGNR can enhance the efficiency of infection of cells coexpressing the specific HIV receptors[49-51]. DC-SIGN is expressed on some dendritic cells, while DC-SIGNR is localized to certain endothelial cell populations, including hepatic sinusoidal endothelial cells. The pattern of cellular expression of DC-SIGN is somewhat controversial. The term "DC-specific" DC-SIGN is also expressed on brain microvascular endothelial cells, certain tissue macrophages, can be induced on monocyte-derived macrophages under certain conditions and can even be found on rare $CD14^+$ cells, resembling monocytes in blood[52-55]. Pathogenic microbes have evolved means to bypass these sentinels[56-67]. For example, human immunodeficiency virus binds to DC-SIGN and hides directly beneath the cell surface until the DC encounters a T cell, that which the virus can then infect. The measles virus seems to induce death and/or fusion of the DC, thereby preventing immune responses. Wu *et al*[68] demonstrated that Dengue virus (DV), an RNA virus with a peculiar pathogenesis, preferentially targets DCs. They have demonstrated that immature monocyte-derived DCs, generated *in vitro*, were 10-fold more permissive for DV infection than either monocytes or macrophages. Several avenues are now open for investigation. How does the infection affect DCs function and the ensuing T-cell responses? Although the authors did not explore the effects of DV on DCs, a block in LC function could explain the lack of cytotoxic T-lymphocyte immunity in response to Dengue infection. Would the targeting of different DC subsets explain why some patients develop protective immunity whereas others develop non-protective responses? Indeed, targeting of interstitial DCs could skew the immune responses toward the production of DV-specific antibodies, which may result in enhanced viral load through increased entry into macrophages. Another important question is which of the DC-specific molecules DV uses as a receptor for entry. Answering this could provide a target for the design of an anti-DV compound. Furthermore, receptor polymorphisms might explain why some patients mount protective immunity whereas others do not. Finally, would the targeting of appropriate DC subset permit us to develop a successful vaccine? All these questions represent exciting areas of experimentation and are likely to keep the DC experts busy and DC researchers eager to follow their work[69-71].

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