Review

DC-SIGN and Immunoregulation

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Dendritic cells (DCs) are known to be the most powerful professional antigen-presenting cells so far. It could activate primary immune response, and also downregulate immune response. DCs have a unique character of immunoregulation. DC-SIGN, a molecule designated as CD209, is one member of the C-type lectin superfamily. It is not only a pattern recognition receptor but implicated in immunoregulation of DCs. DC-SIGN has become hotspot of recent studies because of its important role in mediating DC adhesion, migration, inflammation, activating primary T cell, triggering immune response and participating in immune escape of pathogens and tumors. These studies on DC-SIGN involved in primary and secondary immune response and relevant mechanism will certainly provide us with a new method in treating and preventing certain diseases. *Cellular & Molecular Immunology*. 2006;3(4):279-283.

Key Words: DC, DC-SIGN, pattern recognition receptor, immunoregulation

Introduction

Dendritic cells (DCs) are known to be the most powerful professional antigen presenting cells so far. It could not only initiate primary immune response, but down-regulate immune reaction as well (1). DCs play an important role in maintaining immune homeostasis for their distinguished immune regulatory capability. Also, DCs are initial factors in auto-immune diseases, and play a key role in immune escape of pathogens and tumors. It is known that immune regulatory capability of DCs is closely related to pattern recognition and immune regulation of the receptors on DC surface. Among those receptors, C-type lectin receptors (CLR) and Toll-like receptors (TLRs) have been sufficiently studied. As a member of CLR family, DC-SIGN (DC-specific ICAM-grabbing non-intergrin) is important in immune regulation of DC. DC-SIGN is also denoted as CD209, which was first discovered by American experts who were studying human immunodeficiency viruses (HIV) in 2000 (2). As DC-SIGN could bind to gp120, promote $CD4^+$ T cell infection by DCs and thus results in immunodeficiency, it is also denoted as HIV-1 gp120 binding C-type lectin (2, 3). Because such C-type lectin mediates DC binding to ICAM-3 on T cell surface without intergrin, but with Ca^{2+} participating, it is denoted as DC-SIGN. Recent studies show that DC-SIGN is the pattern recognition receptor and adhesion receptor of DCs, and plays an important role in DC migration and adhesion, inflammatory response, activating T cells, initiating immune response and immune escape of pathogens and tumors. Also, DC-SIGN is found to participate in DC regulation of natural immunity and adaptive immunity (2, 3). Our review focuses on functions of DC-SIGN in immunoregulation.

Structure and localization of DC-SIGN

The genes encoding DC-SIGN (CD209), which contains 7 exons and 6 introns, are located on human chromosome 19p13.2-3, and are about 13 kb in length. It is connected to other CLR genes such as CD23 (4). DC-SIGN is a type II membrane protein which contains 404 amino acids and is of 44 kD in molecular weight. DC-SIGN consists of extra-cellular domain, transmembrane region and cytoplasmic region. The extracellular domain contains carbohydrate recognition domain (CRD) and neck domain or hinge domain. The CRD of DC-SIGN is a globular structure consisting of 2 α-helices, 12 β-strands, and 3 disulphide bridges. A loop protrudes from the protein surface and forms part of two Ca^{2+}-binding sites. One of such sites is essential for the conformation of the CRD, and the other is essential for direct coordination of the carbohydrate structures. Four amino acids (Glu347, Asn349, Glu354 and Asn365) interact with Ca^{2+} at this site and dictate the recognition of specific carbohydrate

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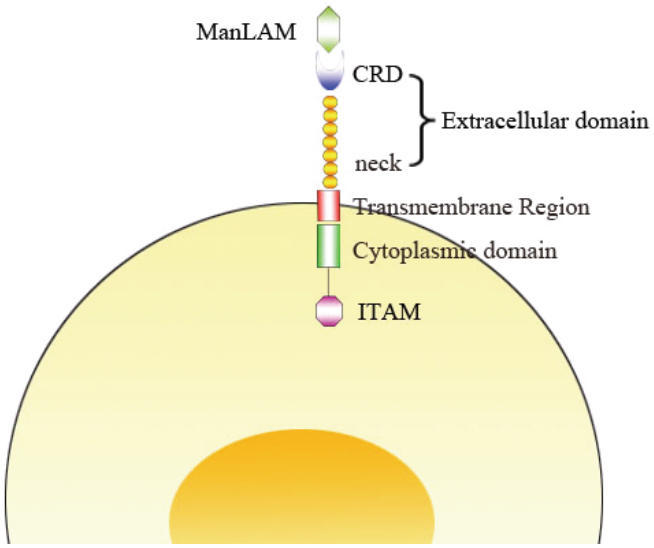

Figure 1. Structure of DC-SIGN. Cytoplasmic domain, transmembrane region (TM) and extracellular domain are the three parts of DC-SIGN. The extracellular domain contains carbohydrate recognition domain (CRD) and neck domain. Cytoplasmic domain contains LL (di-leucine), EEE (tri-acidic clusters) and other internalization motifs and is connected to an incomplete ITAM. CRD recognizes certain carbohydrate-contained antigens like ManLAM and Lewis^x by four amino acids (Glu347, Asn349, Glu354 and Asn365) and one Ca^{2+}-binding site in it.

structures. CRD could recognize certain carbohydrate-containing antigens like ManLAM and Lewis^x. The neck domain contains 7 or 8 complete tandem repeats and 1 incomplete repetitive sequence. It is required for oligo-merization, which regulates carbohydrate specificity. Transmembrane region is essential in localization of DC-SIGN on cell surface. The cytoplasmic region contains internalization motifs, such as di-leucine (LL) motif, tri-acidic (EEE) clusters and an incomplete immunoreceptor tyrosine-based activation motif (ITAM). The LL motif participates in antigen internalization and EEE clusters participate in signal transduction (Figure 1) (5-7). DC-SIGNR is homologous to DC-SIGN and is also denoted DC-related protein (L-SIGN), which has a similar structure to DC-SIGN. The genes encoding DC-SIGNR are similar to those of DC-SIGN (8).

DC-SIGN is exclusively expressed by both immature and mature DCs (9). DC-SIGN is not expressed by monocytes, activated monocytes, T cells, activated T cells, B cells, activated B cells, thymocytes and $CD34^+$ bone marrow cells. DC-SIGN expressing cells are present in the T cell area of lymph nodes, tonsils and spleens. In skin sections, DC-SIGN is only expressed on dermal DCs, and CD1a Langerhans cells in the epidermis don't express DC-SIGN. Also, DC-SIGN is expressed on DC-like cells present in the mucosal tissues, such as rectum, cervix and uterus (2). Recent studies show DC-SIGN could also be expressed by the macrophages in fetus tissues, such as Hofbauer cells in the chorion (10). DC-SIGN is expressed on the endothelial cells in hepatic sinusoid and lymphatic sinus (9).

DC migration, inflammatory reaction and DC-SIGN

Cellular adhesion between neutrophils and endothelial vessel wall together with cellular interaction by shear stress will result in transendothelial migration of neutrophils (11). This step slows down the speed of the cells in the blood stream by tethering and rolling on the endothelium. In such process, selectin plays an important role in mediating neutrophils recruiting and adhesion. For example, neutrophils could roll on endothelial cells and then migrate to local tissues by selectin on them. It has been known that progenitor DCs, immature DCs and mature DCs could be mediated by interaction of DC-SIGN and ICAM-2 on endothelial cells together with IL-8, MIP-1 and other cytokines. Then they migrate from blood to peripherals and initiate immune response (12). ICAM-2 is highly expressed on endothelial cells, and the binding of DC-SIGN to ICAM-2 can resist shear stress. The glycosylation of ICAM-2 contributes to its recognition of DC-SIGN. Both DC-SIGN and the selectins contain lectin domains that bind to carbohydrate structures on the endothelium. Other antigen presenting cells could also be recruited by adhesion molecules and chemokines from the blood. Selectin-DC-SIGN-ICAM-2 and chemokine could activate intergrin, such as LFA-1, recruit DCs and induce adhesion. Meanwhile, up-regulated ICAM-1 by inflammatory mediators could strengthen such adhesion *via* LFA-1-ICAM-1 interaction. Studies show interaction between DC-SIGN-ICAM-2 and LFA-1-ICAM-1 is required in mediating transendothelial migration of DCs. Among such process, DC-SIGN-ICAM-2 interaction induces initial adhesion of DC and its effects are short and reversible, while LFA-1-ICAM-1 interaction promotes transendothelial migration of DC (13). Local chemokines will attract only DCs that express the appropriate chemokine receptors and DC-restricted expression of DC-SIGN makes it possible for DCs to migrate specifically and perform their immunological function. Thus, DC-SIGN$^+$ DCs could participate in local inflammation (3, 9). Caparros et al. discovered that engagement of DC-SIGN by specific antibodies does not promote dendritic cell maturation but induces ERK1/2 and Akt phosphorylation without concomitant p38 MAPK activation (14). DC-SIGN ligation also triggers PLCγ phosphorylation and transient increases in intracellular calcium in dendritic cells. Such results suggest that DC-SIGN triggered intracellular signals such as ERK1/2, tyrosine kinases Lyn and Syk etc., modulate DC maturation and take part in inflammation. And DC-SIGN together with PU.1, the most divergent member of the Ets family of transcription factors, takes part in macrophage and DC maturation (15). Our studies showed that P-selectin expression was up-regulated in the early stage of nephritises. At the same time, recruitment of DC-SIGN$^+$ DCs also increases, which is related to the progression and prognosis of the disease (16). Further studies show that tubular

endothelial cells could express DC-SIGN in nephritises. Such results suggest tubular endothelial cells could trans-differentiate and then participate in kidney repairing and inflammatory reaction (17). Furthermore work is needed to investigate the role of DC-SIGN in regulating tubular endothelial cells transdifferentiation.

After migrating to lymphoid tissues, DCs could induce initial immune response. Once in the lymph node, DCs present their antigens in the form of peptide-MHC complexes to the resting T cells (12, 13). The full activation of T cells is provided by costimulatory molecules presenting on the DCs. The organization of the immunological contact site plays an important role in the control of immunity. TCR-MHC complex, together with CD2-LFA-3 interaction, is situated in the center of the immunological synapse, while LFA-1-ICAM-1 interactions form the outer ring of the synapse (18, 19). Whether DC-SIGN is situated in the synapse is not certain. It is clear that DC-SIGN-ICAM-3 interaction binds DCs to resting T cells. Following such interaction, LFA-1 on T cells is activated and then stabilizes the immunological junction through the high avidity of LFA-1-ICAM-1 and CD2-LFA-3 interactions (9).

DC-SIGN and immune reaction

DC-SIGN supports initial immune response

DCs could activate arrest T cells in the lymph node, but the mechanism is poorly understood. Recent studies showed that binding of DC-SIGN to both CEA-related cell adhesion molecule 1 (CEACAM1) and Mac1 was required to establish cellular interaction between DCs and neutrophils, and such interaction could promote T cell proliferation and transforming to Th1 cells (20). Such results suggest DCs participate in the contact between itself and resting T cells, also in T cell activation. And such effect is related to its cytoplasmic ITAM signal transduction (21). Martinez et al. discovered DC-SIGN could promote CD3-activated T cells to produce IL-2 and receive a strong TCR signal, thus strengthens TCR-APC interaction and enhances immune response (22). Our study discovered that inhibiting DC-SIGN on DCs could reduce T cell proliferation and inhibit co-stimulator CD11c, CD83, CD80 and CD86 expression. Such effects are achieved by NF-κB signaling pathway (27).

Crosstalk between DC-SIGN and TLR

Recent studies suggest that there is a crosstalk between DC-SIGN together with its CLRs family members and TLRs, and such crosstalk could lead to immune activation or T cells depression (23, 24). DC-SIGN and members of CLR family could mediate antigen presenting capability of DCs *via* capturing and internalizing pathogen cell wall components or glycoprotein of self-antigen. TLRs could activate T cells and stimulate DC maturating by recognizing LPS, HSP70, nucleic acid, etc. The signal transduction by such pattern recognition could stimulate DCs to express multiple pro-inflammatory or anti-inflammatory mediators, active oxygen, active nitrogen to up-regulate expression of costimulators and even trigger acquired immune response (25). In the study of leprosy, Krutzik et al. found TLR could induce differentiation of monocytes into either macrophages or DCs and seemed to crucially influence effective host defenses in human infectious diseases (26). In physiological conditions, pattern recognition and immunoregulation mentioned could maintain homeostasis. But in pathological conditions, activated CLRs and TLRs could stimulate DC maturation, proinflammatory mediators secreting and regulate DC activation in immune response, which might be contributed to certain autoimmune diseases or inflammatory diseases (23, 24).

DC-SIGN and immune escape

DC-SIGN plays an important role in innate immunity. During the interaction between body and pathogens or tumors, the latter could escape immune surveillance and survive. Such mechanism is related to suppressions of DCs by DC-SIGN. As mentioned, Ebola virus, hepatitis C virus, Dengue virus, cytomegalovirus (CMV), HIV-1, measles virus (MV), human herpesvirus 8 (HHV-8), SARS coronavirus, *Mycobacterium tuberculosis*, *helicobacter pylori*, *Streptococcus pneumoniae*, fungi, some parasites and tumors all interact with DC-SIGN (28-31). Recent studies discovered that SARS coronavirus could bind to DC-SIGN by its glycosylated S protein and takes part in the inflammation response of DCs (32-34). Such process is recognized by CRD of DC-SIGN. The mechanism of immune escape mediated by DC-SIGN remains poorly understood. The possible explanation might be antigen internalizing or crosstalk between CLRs and TLRs, etc.

DC-SIGN and HIV-1

Previous studies showed that DC-SIGN has high avidity to gp120 (2). DCs are thought to capture HIV-1 at entry sites and transport the virus to lymphoid tissues, in which DC-bound HIV-1 is efficiently transmitted to $CD4^+$ T cells. DC-SIGN does not facilitate HIV-1 processing by DCs but protects the virus from intracellular degradation. There is no DC-SIGN and ICAM-3 interaction in such process, but other adhesive molecules such as LFA-1, ICAM-1 do take part in it (2, 3). The mechanism of DC-SIGN and HIV-1 interaction remains unclear. Possible explanation might be as follows: binding of the viral envelope glycoprotein to DC-SIGN may induce a conformational change that enables a more efficient interaction with CD4 and/or the chemokine receptor. And the binding of DC-SIGN to gp120 may facilitate or stabilize one of these transitions. Also, binding of viral particles to DC-SIGN may focus or concentrate them at the surface of the DC and thus increase the probability that entry will occur after they bind to the receptor complex on target cells (2, 3).

Further studies found that HIV-1 would lose its activity if it is kept *in vitro* for 24 hours, but DC-SIGN-bound HIV-1 could be kept within DCs for more than 4 days, allowing incoming virus to persist for 25 days before infecting target. *In vivo*, HIV-1 could be transported from peripherals to lymph nodes after 2 days of infection, while DC-SIGN-

bound HIV-1 could still infect target cells after 5 days (10, 16). The mechanism of DC-SIGN prolongating viral infectivity is still poorly understood. A possible explanation might lie in antigen internalization. However recent study shows that DC-SIGN-mediated HIV internalization is dispensable for DCs capturing HIV particles and enhancing the infection of $CD4^+$ T cells, which is known as trans-enhancement (35). After binding with DC-SIGN, HIV-1 was transported to cytoplasm. Because DC-SIGN has high avidity to HIV-1 in neutral pH environment, but loses such avidity in acid environment of pH 5, HIV-1 could be released from phagosomal compartments in acid environment and then infects target cells (10, 36). Similar pH-dependent fusion into DC was also observed during the study of Dengue virus (DV) infection (37).

DC-SIGN and tubercle bacillus

For DCs, DC-SIGN is the main receptor for mycobacteria. Although immature DCs also express high levels of the mannose receptor, CD11b and CD11c, DC-SIGN-specific antibodies, in contrast to mannose-receptor-specific antibodies, inhibit the interaction of DCs with both *M. bovis* BCG and ManLAM by more than 80% (38, 39). However, study showed DC-SIGN couldn't be considered as the unique DC receptor for BCG internalization as some other receptors take part in the mycobacteria-induced immunosuppression (40). It is possible that mycobacteria-containing phagosomes mature to late endosomes/lysosomes in DCs, resulting in degradation, whereas in macrophages, mycobacteria arrest the phagosome maturation at an early endosomal stage, thereby promoting the growth of mycobacteria (39).

Interaction between DCs and mycobacteria is related to crosstalk between TLRs and CLRs. Targeting of DC-SIGN by ManLAM results in an altered immune response through signaling between C-type lectins and TLRs. Recent studies show that ManLAM inhibits LPS-induced DC maturation by interacting with DC-SIGN, as LPS-induced DC maturation in the presence of ManLAM is fully restored by inhibiting the DC-SIGN-ManLAM interaction with specific antibodies (39). This illustrates that DC-SIGN, after binding ManLAM, delivers a signal that interferes with the *M. bovis* BCG-induced DC-maturation signals presumably generated by TLR4. The mechanism of TLR suppression by DC-SIGN is still unclear. A possible explanation is that such suppression is related to ITAM of DC-SIGN. Further work shows that other CLRs, such as dectin-1 also participate in pathogen recognition and TLRs crosstalk. It could enhance expression of TNF-α and IL-12 of DC together with TLR2, and promote Th1 response (24). Such result is also correlated to ITAM of dectin-1. The results mentioned suggest different TLRs and CLRs crosstalk and signal transduction could induce proinflammatory or anti-inflammatory effects and thus lead to immune activation or suppression.

DC-SIGN and tumor

Recent work shows DC-SIGN is also related to immune escape of tumor (41). Immature dendritic cells are located intratumorally within colorectal cancer and intimately interact with tumor cells, while mature dendritic cells are present peripheral to the tumor. The majority of colorectal cancers overexpress carcinoembryonic antigen (CEA), and malignant transformation changes the glycosylation of CEA on colon epithelial cells, resulting in higher levels of $Lewis^x$ and *de novo* expression of $Lewis^y$ on tumor-associated CEA (41). Also, DC-SIGN does not bind to normal colon epithelial cells which express Lewis antigen on CEA. Other studies show there are CEA specific T cells in colorectal cancer patients which have anti-tumor effects (42). Such results suggest DCs could recognize and bind to colorectal tumor cells by DC-SIGN and participate in anti-tumor immune response. At the same time, tumor cells could suppress DC maturation by DC-SIGN and escape immune surveillance. Other study shows that CEACAM1 selectively attaches and specifically interacts with DC-SIGN, and participates in cancer development (43). Further studies are required to study the mechanism of such findings.

Conclusion

DC-SIGN is a kind of newly discovered immune molecule with many functions: on one hand, it could mediate DC migration, antigen internalization, T cell activation; on the other hand, it could be the target of certain pathogens or tumor cells which may lead to escape of immune surveillance or immune suppression. Its function could serve as the basis of our future studies on immune regulation of DCs. What's more, vaccine and agents based on DC-SIGN could provide us with new ways to treat and prevent certain immune disorders and inflammatory diseases.

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