

How human cytomegalovirus (HCMV) does infect dendritic cells?

with

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What is human cytomegalovirus (HCMV)?

J. Déchanet-Merville: HCMV is a betaherpesvirus widely distributed among the human population (seroprevalence 60-100%). Viral transmission between individuals results from close contact with contaminated body fluids and subsequent infection is characterized by local spread in lymphoid tissues followed by a blood cell mediated systemic dissemination toward multiple organs. In healthy individuals, HCMV infection is

asymptomatic and efficiently controlled, but the virus is never completely eliminated and persists in a latent or faintly active form during the whole host life. In sharp contrast, HCMV is frequently responsible for severe troubles in immunocompromised individuals such as allograft recipients or AIDS patients, and after in-uterine transmission. The immune system (particularly CD8 T cells) is essential to control HCMV multiplication.

Can HCMV infect dendritic cells (DC)?

F. Halary: DC were previously known to be refractory to infection by laboratory-adapted HCMV strains, but were shown to be permissive to viral replication when infected with a clinical HCMV isolate (1). HCMV infection of DC induces several phenotypic and functional changes leading to a reduced capacity to stimulate T cells (2,3). These modulations may be involved in the generalized immunosuppression observed in patients suffering from HCMV infection. We evidenced the crucial role of a lectin called DC-SIGN (DC-specific ICAM 3-grabbing nonintegrin, CD209) for the binding of HCMV to DC (4). DC-SIGN is a ligand for ICAM-2 and -3 (5,6) shown to mediate the transmission of HIV from DC to permissive CD4 T cells (7). We demonstrated that DC-SIGN is also able to bind HCMV-envelope glycoprotein gB

and is necessary for the infection of DC by HCMV clinical isolates. Furthermore, in cells weakly susceptible to HCMV infection (eg THP-1 cells), transfection of DC-SIGN cDNA confers the ability to fully replicate and produce infectious virus. This effect is notably due to an increased binding of HCMV on cell membrane, but the rapid internalization capacity of DC-SIGN (8) may also promote an easier viral entry into cells. Routing of DC-SIGN/HCMV complexes to particular intracellular compartments might then help for the transport of HCMV to the nucleus where viral DNA replication is initiated. By contrast, cells totally refractory to HCMV infection (eg HELA cells) cannot be rendered permissive by DC-SIGN transfection, suggesting that the lectin cannot replace the putative cellular entry receptor which remains to be identified.

What are the consequences of CMV binding to DC-SIGN?

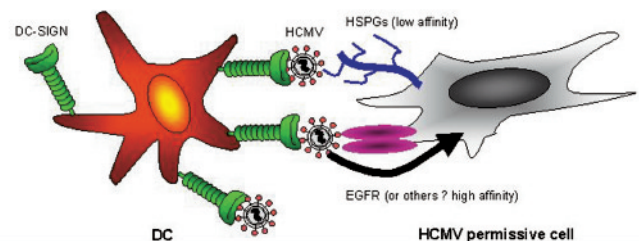
J. Déchanet-Merville: Another consequence of CMV binding to DC-SIGN is the transmission of infectious virus to permissive target cells

and therefore a wide and active body dissemination of the viral agent through the high mobility of dendritic cells. This process does

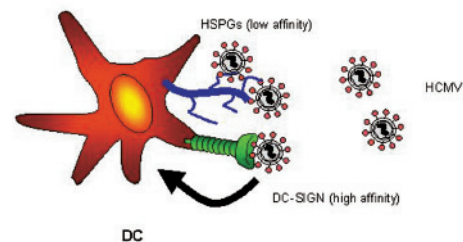
not require the CMV replication in the carrier cells but virus endocytosis is probably essential since viral transmission is strongly decreased when binding of HCMV to DC-SIGN is performed at +4°C, or when the cytoplasmic domain of

DC-SIGN containing internalization motifs is deleted. Moreover, binding to DC-SIGN enhances and preserves the infectious potential of HCMV. This phenomenon might be explained by intracellular accumulation of the virus or by pH-mediated changes of the viral particles in intracellular compartments. *In vivo*, expression of DC-SIGN on immature DC of intestinal and genital mucosae (9) is assumed to allow for infection of these primary target cells at the anatomical site of initial CMV transmission and to promote the following propagation of the virus in the periphery.

Trans infection



Cis infection



Binding to DC-SIGN serves two functions for HCMV: (i) captured virus can be conveyed safely by DC and efficiently transmitted to permissive cells and (ii) DC-SIGN is a docking HCMV receptor necessary for the infection of DC.

Any clinical perspectives in the prophylaxis of CMV infection?

F. Halary: The interaction of CMV with DC-SIGN could be of interest for future anti-CMV therapeutical strategies. Preventing this binding would lead to inhibition of HCMV transmission by DC and of infection of DC-SIGN expressing cells. Together, these effects may diminish viral dissemination into the organism and reduce the immunosuppressive pressure of HCMV onto DC. Further studies on the ability of murine CMV to bind the recently cloned murine DC-SIGN homologs should give a boost to the investigations on the actual implication of DC-SIGN in the dynamic of CMV dissemination *in vivo* and

on the clinical validity of blocking agents in an animal model. The list of pathogens able to bind to DC-SIGN is rapidly growing (HIV, Ebola, HCMV, HCV, dengue virus, Mycobacterium tuberculosis, Candida albicans) widely opening the perspectives for the applications of antagonistic drugs.

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