Dendritic cells and lymphotropic viruses

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Section 3: Dendritic cells have a dual role in the pathogenesis of measles
Chapter 3.1

Measles virus: Structure, pathogenesis and interaction with DCs

Bridge

In Section 2 we have demonstrated that DC-SIGN⁺ DCs mediate transmission of HIV-1 to CD4⁺ T cells. This mechanism might be widely used by lymphotropic viruses to enter the lymphoid tissues from the site of entry. In Section 3 we have investigated whether DC-SIGN⁺ DCs mediate transmission of the lymphotropic measles virus and whether the same receptors and pathways are involved as for HIV-1. Moreover, we determined whether the interaction of viruses and DC-SIGN⁺ DCs results in antigen presentation of virus-derived peptides in the context of MHC class-II molecules, inducing a MV-specific immune response. Furthermore, we expanded our studies on DCs and viruses with an in vivo model. Using a recombinant MV strain expressing EGFP we investigated the target cells for MV in macaques, since the target cells for the virus at the site of entry and during the systemic phase are debated.
Measles

Measles is an acute severe illness caused by measles virus (MV). MV is spread through aerosolized droplets or direct contact. MV is one of the most contagious viruses that affect humans and is stable in the air for up to two hours. Before the introduction of MV vaccination almost everyone caught measles during childhood. After an incubation period of 10 to 14 days, the first clinical signs of measles are usually high fever, a runny nose, cough, conjunctivitis and small white spots on the buccal mucosa (Koplik spots). This prodromal phase is followed by the appearance of a maculopapular skin rash. The rash lasts for five to six days, and then fades. Complications of measles include blindness, encephalitis, diarrhoea and a transient but profound immune suppression that might result in severe opportunistic infections. A curative treatment for MV infection is not available; however survival is improved by nutritional support, management of dehydration, and treatment of secondary infections²⁵,¹³.

Measles epidemic and vaccination

Measles remains a major cause of childhood mortality, particularly in countries with inadequate medical care, malnutrition and/or low vaccination coverage. According to the World Health Organisation²⁶ more than 20 million people are affected with measles each year and in 2006, measles caused approximately 242,000 deaths. Immunization with the live-attenuated measles vaccine is safe, effective and inexpensive, and induces long lasting humoral and cellular immunity. Vaccination and economic development has had a major impact on measles deaths. Prior to the introduction of MV vaccinations in 1963, measles was estimated to result in 5-8 million deaths each year¹⁰. However, to completely eradicate measles, high levels of population immunity and a rapid response to outbreaks would be required¹⁰.

The high infectivity of MV is underlined by the fact that measles still causes outbreaks in countries with excellent vaccine coverage. In the Netherlands more than 95% of the children are immunized⁸. However, the country experiences a MV epidemic every 5-7 years. In the winter of 1999-2000, a measles epidemic started in an orthodox reformed primary school with only 7% vaccine coverage. A total of 3292 measles cases were reported, 16% suffered from serious complications, resulting in 3 deaths²⁴.

Measles virus structure and life cycle

Measles virus (MV) is a member of the family Paramyxoviridae, genus Morbillivirus. MV has a non-segmented RNA genome of negative polarity and is surrounded by a host cell-derived envelope (Figure 3.1.1). The MV genome consists of six genes (N, P/C/V, M, F, H and L) coding for six structural (N, P, M, H, H and L) and two non-structural proteins (C and V). The nucleocapsid protein (N) interacts with the viral RNA. The matrix protein (M) is involved in viral budding and links the nucleocapsid to the envelope. The envelope carries two envelope transmembrane glycoproteins: the fusion protein (F) and haemagglutinin (H). H mediates attachment of the virus to the entry receptor CD150 (or CD46 for attenuated MV strains). Subsequently, F mediates fusion of the viral and cell membrane. Upon viral entry mRNA is transcribed directly from the viral genome and viral structural and non-structural proteins are translated. The viral polymerase complex consists of large protein (L) and phosphoprotein (P). To generate new genomic RNA, the viral polymerase complex mediates the synthesis of antigenomic RNA, which is subsequently transcribed in genomic RNA. The virus exits the cell by budding from the cell membrane. Infection of new cells occurs through binding of de novo synthesized virus or fusion with uninfected neighbouring cells, resulting in typical syncytium formation. The non-structural proteins C and V have a role in pathogenesis and can affect IFN signaling⁵,¹³,¹⁵.
Measles virus receptors and tropism
The entry receptor for MV is CD150 or signaling lymphocyte activation molecule (SLAM)\textsuperscript{23}. CD150 is a member of the immunoglobulin-superfamily glycoprotein and is involved in T-cell receptor signaling and macrophage activation\textsuperscript{25}. It is expressed on a proportion of B cells, T cells, macrophages, mature DCs and immature thymocytes\textsuperscript{27}. In addition to CD150, laboratory-adapted MV strains, such as the live-attenuated vaccine strains, may also use CD46 for entry. Since MV has been described to infect CD150\textsuperscript{+} epithelial, endothelial and neuronal cells, it is thought that MV can use at least one additional entry receptor\textsuperscript{5,27}.

Figure 3.1.1. Measles virus structure and replication (adapted from\textsuperscript{15}). (a) MV (100-300 nm size) consists of one RNA molecule of negative polarity and structural proteins, surrounded by a host cell-derived envelope. The RNA interacts with the nucleocapsid protein (N) which is attached to the envelope by the matrix protein (M). The envelope carries two glycoproteins: the fusion protein (F) and haemagglutinin (H). (b) F and H mediate attachment of the virus to the entry receptor CD150 and fusion with the cell membrane, respectively. Upon viral entry mRNA is transcribed directly from the viral genome and viral structural and non-structural proteins are translated. The virus exits the cell by budding from the cell membrane.

Measles virus transmission, pathogenesis and immunity
The entry site for MV is the respiratory tract; however the events establishing systemic disease are debated. In human necropsy samples MV antigen was detected in respiratory epithelial cells, suggesting initial MV replication in the respiratory epithelium prior to systemic dissemination\textsuperscript{5} (Figure 3.1.2). However, later reports demonstrated that CD150 is not expressed on epithelial cells\textsuperscript{23}, and therefore this route of transmission might be inefficient. In this section, we have investigated capture via DCs as an alternative route for transmission (Figure 3.1.2).
After entry in the respiratory tract, MV first replicates in the regional lymph nodes and subsequently spreads throughout the body by a cell-associated viraemia (Figure 3.1.2). MV infection is then observed in lymphoid tissues, including thymus, spleen, lymph nodes, and tonsils, but also other organs such as
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Skin, lung and the gastrointestinal tract. In chapter 3.2 we will further illustrate the extensive organ infiltration by MV in infected macaques. During the appearance of the rash, MV RNA is detected in plasma, which may last until weeks after the rash has faded. At the same time a virus-specific immune response is observed, including MV-specific antibodies and CTLs in blood. This MV-specific response is robust, resulting in viral clearance and life-long protection.

**Figure 3.1.2 Transmission of measles virus.**

1. Approach (aerosols)
2a. Primary replication? (CD150 independent)
2b. DC capture of virus?
3. Dissemination through DCs
4. First lymphoid site of infection
5. Viraemia

Blood
Lymphoid organs

Regional lymph node

(A) MV enters the body via the respiratory tract; however the events establishing systemic disease are debated. (2a) The dogma states that MV initially replicates in the respiratory epithelium prior to systemic dissemination. However epithelial cells do not express CD150, the entry receptor for MV. (2b) Alternatively, DCs might capture MV in the respiratory tract, migrate to the lymphoid tissues, where the virus is transmitted to lymphocytes.

**The role of DCs in MV-induced immune suppression**

Although MV infection results in an efficient specific immune response, it also induces a transient generalised immune suppression. This may last for weeks to months after the onset of the rash, and can lead to severe secondary infections. Suppression of the delayed type hypersensitivity to recall antigens and impaired cellular and humoral responses to antigens are observed. Moreover, a cytokine imbalance has been reported, with similarities to a Th2 response, suppressing cellular immune responses. The underlying mechanism for this immune suppression is thought to be multifactorial,
including reduced levels of T cells, decreased CD4:CD8 T cell ratios and dysfunction of a variety of leukocytes, including T cells, monocytes, macrophages, B cells, and due to their regulatory role in the immune system, also DCs. Different studies have addressed the role of DCs in MV-induced immune suppression and revealed different mechanisms that might be involved. MV productively infects DCs in vitro. Susceptibility for MV infection is increased upon DC maturation, probably due to upregulation of CD150. DC infection results in Fas-mediated apoptosis of DCs and Fas-independent apoptosis of co-cultured T cells. MV-infection and interaction induces DC maturation via TLR-2 but also production of the anti-inflammatory cytokine IL-10; however the terminal maturation upon CD40 ligation is inhibited, including the production of IL-12, which is also observed in macaques and infected patients. Although infected DCs up-regulate co-stimulatory molecules and cytokine production, they suppress T cell responses in a mixed leukocyte reaction, indicating that their allo-stimulatory capacity is lost. Moreover, the synapse between DC and T cells is unstable and MV infection interferes with the interferon production in plasmacytoid DCs. Most of these mechanisms have been unravelled in vitro or in CD150-transgenic mice. It is now essential to assess the relevance of these mechanisms for human disease.

References