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Measles virus-induced suppression of immune responses

Diane E. Griffin

W. Harry Feinstone Department of Molecular Microbiology and Immunology, Johns Hopkins
Bloomberg School of Public Health, Baltimore, MD, USA

Summary

Measles is an important cause of child mortality that has a seemingly paradoxical interaction with the immune system. In most individuals, the immune response is successful in eventually clearing measles virus (MV) infection and in establishing life-long immunity. However, infection is also associated with persistence of viral RNA and several weeks of immune suppression, including loss of delayed type hypersensitivity responses and increased susceptibility to secondary infections. The initial T-cell response includes CD8⁺ and T-helper 1 CD4⁺ T cells important for control of infectious virus. As viral RNA persists, there is a shift to a T-helper 2 CD4⁺ T-cell response that likely promotes B-cell maturation and durable antibody responses but may suppress macrophage activation and T-helper 1 responses to new infections. Suppression of mitogen-induced lymphocyte proliferation can be induced by lymphocyte infection with MV or by lymphocyte exposure to a complex of the hemagglutinin and fusion surface glycoproteins without infection. Dendritic cells are susceptible to infection and can transmit infection to lymphocytes. MV-infected dendritic cells are unable to stimulate a mixed lymphocyte reaction and can induce lymphocyte unresponsiveness through expression of MV glycoproteins. Thus, multiple factors may contribute both to measles-induced immune suppression and to the establishment of durable protective immunity.

Keywords

dendritic cells; lymphoproliferation; type 2 cytokines

Introduction

Measles is a human disease that continues to be an important cause of child morbidity and mortality in many parts of the world, despite the wide availability of a safe and effective live attenuated virus vaccine (1–5). Difficulties with control stem partly from the fact that measles virus (MV) is highly infectious and spreads efficiently to susceptible individuals and partly from difficulties with vaccine delivery.

MV infection has been of substantial interest to immunologists because of its seemingly paradoxical interactions with the immune system. Infection is initiated in the respiratory tract, spreads systemically, and results in a characteristic rash illness within 10–14 days. MV replicates in lymphoid cells and tissues as well as in epithelial and endothelial cells in multiple organs (6). Many of the manifestations of disease (fever, rash, conjunctivitis) are due to the immune response to infection. In most individuals, this immune response is successful both in clearing infection from the multiple sites of virus replication and in establishing life-long immunity to re-infection. However, infection is also associated with

several weeks of immune suppression with the consequence that the primary causes of measles deaths are secondary infections (7).

The MV vaccine is a live attenuated virus derived from a wildtype virus (Edmonston) by passage in chicken cells (8,9). Infection with the vaccine virus isolate induces long-term protective immunity but is not associated with clinically significant immunosuppression. Therefore, virus strain is an essential determinant of *in vivo* immune suppression, but the specific properties of MV important for this characteristic have not been defined.

Knowledge about the pathogenesis of measles and its interaction with the immune system comes from *in vivo* and *ex vivo* studies of samples from naturally infected humans, naturally and experimentally infected macaques, and experimentally infected cotton rats and transgenic mice, as well as several *in vitro* systems. This review focuses primarily on what is known about the suppression of immune responses by infection with wildtype strains of MV and how this may relate directly or indirectly to MV infection of dendritic cells (DCs).

Measles pathogenesis and sites of virus replication

Measles virus

MV is a non-segmented negative-strand enveloped RNA virus that encodes 8 proteins. The envelope hemagglutinin (H) and fusion (F) proteins are transmembrane proteins present on the virion surface that initiate infection of susceptible cells. Antibody to these proteins can neutralize virus infectivity. The nucleoprotein (N) forms a helical nucleocapsid around the genomic RNA to form the ribonucleocapsid. The phosphoprotein (P) and large (L) polymerase protein are associated with the ribonucleocapsid and necessary for RNA synthesis after initiation of infection. The matrix (M) protein associates with the interior surface of the viral lipid envelope and links the ribonucleoprotein complex to the envelope glycoproteins during virus assembly (10). Two nonstructural proteins, C and V, are encoded within the P gene through an alternative translation initiation site and RNA editing. Neither C nor V is necessary for MV replication in tissue culture (11,12), but both proteins, along with P, interact with cellular proteins and regulate the response to infection (13–15).

MV receptors and initiation of infection

H is responsible for interaction of the virus with specific MV receptors on susceptible cells and is an important determinant of cell tropism (16,17). H is glycosylated, has a variable sequence, and is present on the surface of the virion as a homotetramer consisting of a dimer of two covalently linked homodimers (18,19). Three cellular receptors for MV are recognized: the relatively low affinity complement regulatory protein CD46 (20,21), present on all nucleated cells (22); the higher affinity signaling lymphocyte activation molecule (SLAM/CD150) (23,24), present on subsets of lymphocytes, thymocytes, macrophages, and DCs (25–27,31,32); and an unidentified receptor present on ciliated columnar respiratory epithelial cells (28–30). The H proteins of wildtype strains of MV preferentially interact with SLAM/CD150 (33,34), the primary determinant of MV tropism for immune cells. Tissue culture-adapted and vaccine strains of MV interact efficiently with CD46, as well as CD150, and exhibit decreased tropism for lymphocytes (34,35).

Determination of the structure of the ectodomain of the H glycoprotein revealed a globular head group composed of 6 antiparallel β -sheet propeller motifs stabilized by two intramonomeric disulfide bonds and partially covered with N-linked carbohydrates (36,37). Binding regions for the different cellular receptors on H are adjacent to each other in the head group and a number of amino acids critical for determining receptor-binding specificity have been identified (29,36–38). This globular head is attached to the trans-membrane region of the protein through extended α -helical stalk domains (39,40).

MV also infects endothelial cells in many organs (6,41) and infects neurons and astrocytes as part of persistent infection of the nervous system associated with subacute sclerosing panencephalitis (SSPE) (42) but less is known about the receptor(s) used for infection of these cells.

In addition to these identified and unidentified entry receptors, a variety of cell surface molecules that interact with MV proteins are recognized and may play an important role in infection but do not act as entry receptors. These include moesin (43), the substance P receptor (neurokinin-1) (44), Toll-like receptor 2 (TLR2) (45), the Fc- γ receptor II (46), and DC-SIGN (47). These accessory molecules may facilitate receptor clustering, fusion, entry, and cell-to-cell spread (48–50) or induce cytokine production and help to initiate the innate response to infection (45).

The F protein is responsible for fusion of the viral envelope and cellular plasma membrane to initiate infection. The F protein is a trimer with a globular head attached to the transmembrane domains through a helical stalk consisting of membrane-proximal heptad repeat domains (51). The fusion function of F requires prior processing of the F₀ precursor protein by furin in the late Golgi to produce a metastable structure with a membrane-spanning F₁ subunit covalently linked to a membrane-distal, glycosylated F₂ subunit. Cleavage leaves the previously internal fusion peptide at the N-terminus of F₁ ready to be exposed and inserted into the target membrane when fusion is triggered (52,53).

H and F are associated in the endoplasmic reticulum (54), most likely through the stalk region of H and the head region of F (39,55). Studies of the efficiency of MV fusion suggest that the binding of H to a receptor is the trigger that dissociates the complex and induces conformational rearrangements in the metastable prefusion F protein that lead to fusion with the cell membrane (56,57). The extent of MV-induced fusion correlates inversely with the strength of the H–F interaction (58). Thus, H proteins that interact more efficiently with F dissociate less readily and are fusion deficient.

MV buds from the plasma membrane, therefore, MV-infected cells producing virus express H and F on the cell surface. Receptor binding by cell surface H protein to neighboring cells can activate the fusion function of F resulting in formation of syncytia or giant cells, the typical MV cytopathic effect.

MV replication *in vivo*

Infection is efficiently initiated in the respiratory tract, but the type of cell that is highly susceptible to infection is unclear. Type I pneumocytes, alveolar macrophages, and respiratory epithelial cells become infected (59,60), but which, if any, of these cells is the site of initial virus replication has not been definitively determined (61). In CD150 transgenic mice, alveolar macrophages and DCs are infected within 24 h and spread infection to local lymphatic tissue (62). In macaques infected with a virus expressing green fluorescent protein, bronchoalveolar lavage fluid contains MV-infected epithelial cells, alveolar macrophages, and T cells several days after infection (63).

The role of the unidentified epithelial receptor is particularly puzzling, as *in vitro* studies show that MV preferentially enters polarized respiratory epithelial cells basolaterally, suggesting the possibility that infection of these cells only occurs after systemic infection has been established (64). *In vivo*, a mutated MV unable to induce fusion of epithelial cells can cause disease in monkeys, but the viremia is 10-fold lower in titer than that of the parent strain suggesting that interaction with this receptor is important for full MV pathogenicity (29).

From the respiratory tract, MV is spread to the local secondary lymphoid tissue (Fig. 1A), most likely through uptake and transport by lung DCs or alveolar macrophages (62,65). Replication in lymphatic tissue is efficient, and infected cells enter the circulation so that MV can be detected in peripheral blood mononuclear cells (PBMCs), including T cells, B cells, and monocytes beginning about 7–9 days after infection (66,67). From the blood, infection is spread to distal lymphoid tissue and to epithelial and endothelial cells in multiple organs including the liver, brain, and skin (6,41). Lymphocytes infected with MV *in vitro* display increased adherence and can induce transmigratory cups and transmit infection to endothelial cells, but migration across an endothelial barrier is impaired by infection (68). Therefore, entry of MV into tissues may occur primarily by infection of endothelial cells or movement of other types of infected cells, such as monocytes, across blood vessel walls (69).

The innate immune response

Interaction of MV RNA or proteins with pathogen recognition receptors at the cell surface or in the cytoplasm can trigger signaling pathways in the infected cell that are cell-type specific (45,70–72). At the monocyte cell surface, interaction of H with TLR2 stimulates induction of interleukin-6 (IL-6) and increases surface expression of CD150 (45), while interaction with CD46 inhibits IL-12 production (73). MV interaction with epithelial cells induces production of IL-8 (74). The relevance of these interactions is confirmed *in vivo*, as children with measles have increased levels of mRNAs for IL-1 β , tumor necrosis factor- α (TNF α), and IL-8 in peripheral blood mononuclear cells (PBMCs) and increased levels of IL-1 β and IL-8 protein in plasma (75).

An important early response to many virus infections is production of interferon- α/β (IFN- α/β), but the role of type 1 IFN in MV infection is unclear. RNA viruses typically induce IFN- β production through interaction of viral RNA with TLR3 in the endosome or with the RNA helicases RIG-I, MDA5, or LGP2 in the cytoplasm (76). MDA5 recognizes long double-stranded RNAs, while RIG-I detects short double-stranded RNAs and single-stranded RNAs with a 5'-triphosphate residue (77,78). Both pathways result in activation of the transcription factors IFN regulatory factor-3 (IRF-3) and nuclear factor- κ B (NF κ B) and induction of IFN- β gene transcription (70,79).

MV replication is required for induction of IFN- β transcription in responsive cells (80), and mechanisms have been identified in infected epithelial cells. MV leader RNA interacts with and activates RIG-I and to a lesser extent MDA5, and, in concert with an unidentified cellular cofactor, N can interact with and activate IRF-3 (70,81–83).

In vitro, MV infection of epithelial cells and monocyte-derived DCs leads to rapid production of IFN- β and many IFN- α s followed by induction of IFN-responsive genes (72,84–86). However, MV infection of mitogen-stimulated PBMCs does not usually stimulate IFN production (87). In fact, MV suppresses type 1 IFN production and signaling in CD4⁺ T cells (72) and has a variable effect on plasmacytoid DC IFN production (88,89). In addition to being cell type dependent, IFN induction by MV is virus strain dependent, with wildtype viruses generally less able to induce IFN than tissue culture-adapted or vaccine strains (87).

Strain dependence may be due in part to sequence differences in the C and V proteins, the MV proteins that regulate IFN responses, but this has not been clearly defined (90,91). C inhibits IFN induction and signaling, in part by decreasing viral RNA synthesis, and has been implicated in prevention of cell death (92–96). Deletion of C decreases MV replication in PBMCs, thymic epithelial cells, and infected monkeys and decreases neurovirulence for CD46 transgenic mice, suggesting an important *in vivo* role (93,97–99).

V is phosphorylated, diffusely distributed in the cytoplasm of infected cells, and affects N–P interaction (13). Plasmid-expressed V interacts with IKK α and prevents phosphorylation and activation of IRF-7 and also binds to MDA5 and LGP2, disrupting adenosine triphosphatase (ATPase) activity and preventing activation of the IFN- β promoter through the RNA helicase pathway (100–103). In addition to disrupting IFN production, V also interferes with IFN signaling in MV-infected cells in a strain-specific fashion (104–106). Deletion of V decreases the amount of virus released from glioblastoma cells, delays and prolongs MV replication in human thymic epithelial cells, and decreases MV replication in the lungs of cotton rats and in the brains of CD46 transgenic mice (13,98,99). Overexpression of V is associated with more rapid replication but decreased cytopathic effect in Vero cells (12,98).

MV induction of IFN inhibits differentiation and development of DCs but stimulates maturation of immature DCs and terminal differentiation of cortical thymic epithelial cells (107,108). IFN decreases MV replication and increases expression of MHC class I antigen and TLR3 on infected cells (84,109). MV replication is sensitive to inhibition by the IFN-inducible protein MxA, but other IFN-induced regulators of MV replication have not been identified (110).

In vivo, there is little evidence of IFN production in response to infection, and IFN-stimulated genes are not represented among the mRNAs that are increased in PBMCs of children with measles (75,111). However, most human measles studies reflect the immune state at the time of the rash when disease is recognized and may miss production of type 1 IFN early after infection (112,113).

The adaptive immune response

Fever, conjunctivitis, and the characteristic morbilliform rash appear 10–14 days after infection, coincident with the appearance of the adaptive antiviral immune response (Fig. 1B). At the time of the rash, both MV-specific antibody and activated T cells are detectable in circulation (114–122) (Fig. 1C). Biopsy of the rash shows infiltration of CD4⁺ and CD8⁺ T cells in areas of MV-infected epithelial cells (123). Within a few days after the appearance of the rash, the viremia is cleared and MV can no longer be recovered from PBMCs by co-cultivation (Fig. 1A). Depletion of CD8⁺ T cells from infected macaques leads to higher and more prolonged viremia (123), indicating the importance of CD8⁺ T cells for virus control. Numbers of activated CD8⁺ T cells in circulation and plasma levels of IFN- γ and soluble CD8 decrease rapidly after clearance of infectious virus (121,124–128). However, numbers of activated CD4⁺ T cells in circulation decrease much more slowly (127) (Fig. 1C). Early in the immune response, CD4⁺ T cells produce IFN- γ and IL-2 but later switch from this type 1 cytokine profile to the production of type 2 cytokines IL-4, IL-10, and IL-13 for several weeks after clearance of infectious virus and resolution of the rash (121,124,127,129) (Fig. 1D). The early patterns of cytokine production (i.e. several days of increased IFN- γ , IL-2, and neopterin at the time of acute disease) are consistent with activation of CD8⁺ T cells and type 1 CD4⁺ T cells prior to and during the rash. The rapid decline in these immune mediators is consistent with subsequent contraction of these cell populations as infectious virus is cleared and memory is established (121,124,125). This period of initial virus clearance is followed by patterns of cytokine production that suggest activation of type 2 and regulatory CD4⁺ T cells during recovery (121,129).

In the absence of a robust cellular immune response, there is no rash, and progressive infection of the lungs or nervous system may result in fatal giant cell pneumonia or inclusion body encephalitis (131,132). In rare instances, immunologically normal children infected at a young age can also develop persistent infection of the nervous system leading to SSPE (133–135).

Although infectious virus is no longer detectable after resolution of the rash, viral RNA continues to be present in PBMCs as well as in respiratory secretions and urine for several weeks after apparent recovery (130,136,137). The continued presence of infected cells may be responsible for the continued activation of CD4⁺ T cells and contribute to the establishment of lifelong protective immunity. The mechanism by which MV is eventually cleared from its many sites of replication and the relationship of viral infection and immune-mediated clearance to immunosuppression are not understood. Many aspects of the interactions of the immune system with MV-infected cells *in vitro* and *in vivo* have been characterized and provide clues to this complicated disease process.

Measles virus-induced immunosuppression

Measles was the first disease recognized to increase susceptibility to other infections, and it is now recognized that most measles deaths are due to pneumonia or diarrhea caused by other infectious agents (7). The immunosuppressive effects of measles were recognized in the 19th century and first quantified by von Pirquet in his study of delayed type hypersensitivity skin test responses during a measles outbreak in a tuberculosis sanitarium (138). The tuberculin response is suppressed for weeks after the rash has cleared and recovery appears complete (139) (Fig. 2A). Other *in vivo* manifestations of immune suppression that last several weeks after recovery from the acute rash illness include increased susceptibility to other infections (2) and decreased *in vitro* proliferation of T cells in response to mitogens (140,141) (Fig. 2B). Evidence of immunosuppression begins during a period of intense immune activation associated with the onset of the measles rash and generation of the immune response to MV (Fig. 1) that eventually results in virus clearance and in lifelong immunity to re-infection. A number of different potential indirect and direct mechanisms for MV-induced immunosuppression have been proposed, including lymphopenia, type 2 skewing of cytokine responses, and suppression of lymphocyte proliferation.

Lymphopenia

Infection is associated with lymphopenia with decreased numbers of T cells and B cells in circulation during the rash (127,142–144). Altered trafficking and an increased susceptibility to cell death are likely contributors to this decrease (127,145). Ligation of CD150 favors CD95-mediated apoptosis (32,151), and MV-infected cells can induce bystander lymphocyte apoptosis (146–150), processes that may contribute to lymphocyte loss. However, numbers of lymphocytes in circulation rapidly return to normal as the rash resolves, while immunologic abnormalities persist (66,127,141,152).

Type 2 cytokine responses

Indirect mechanisms of immune suppression have been related to the nature of the immune response during recovery, particularly type 2 skewing of CD4⁺ T-cell cytokine production and induction of regulatory T cells (129,153). During measles, there is suppression of IL-12 production, lymphocyte expression of CD30, and elevation of IL-4, IL-10, and IL-13, all of which persist after resolution of the rash (129,154–156) (Fig. 1D).

IL-12 production by antigen-presenting cells (APCs) is important for T-cell production of type 1 cytokines, particularly IFN- γ . The role of MV interaction with CD46 in the predominance of type 2 cytokine production is intriguing but unclear. As with most cellular receptors for viruses, the normal function of the receptor includes ligand binding that can result in activation of signaling cascades that modify cell function. MV receptor CD46 is no exception. CD46 is a complement regulatory molecule with isoforms that feature two different intracellular cytoplasmic domains that can influence innate immunity and

downregulate receptor expression in a cell type-specific fashion (157–163). Decreased expression of CD46 could increase the susceptibility of the infected cell to complement-mediated lysis (165). Interaction of MV with CD46 on APCs decreases production of IL-12 by both activated macrophages (73) and DCs (164). Most interestingly, CD46 crosslinking on T cells also induces proliferation of regulatory CD4⁺ T cells and production of large amounts of IL-10 (166). Thus, the interaction of MV with CD46 could be a major factor driving the stimulation of type 2 cytokines and regulatory T cells during the later phases of recovery from measles when immune suppression is prominent. However, the importance of these MV H-CD46 interactions during measles is unclear, because wildtype strains of MV do not interact efficiently with CD46 (33,34).

Th2 cytokine predominance after resolution of the rash produces an environment favoring B-cell maturation that facilitates the establishment of humoral memory important for lifelong protection from reinfection, while depressing macrophage activation and induction of type 1 responses that may be required for combating new pathogens. *In vivo* IL-12 supplementation during MV infection of monkeys with an IL-12-producing recombinant MV increased production of IFN- γ and suppressed production of MV-specific antibody but did not improve lymphocyte proliferation (167). Similarly, infection of cotton rats with an IL-4-producing recombinant MV did not affect mitogen-induced lymphocyte proliferation (154). These data suggest that the MV-induced Th2 cytokine milieu may alter responses to other pathogens and thus contribute to increased susceptibility to infection but that these cytokine changes do not explain the characteristic measles-induced defect in lymphoproliferation.

The relative importance for suppression of delayed type hypersensitivity skin test responses is more difficult to assess. These reactions require the attraction and infiltration of CD4⁺ T cells into the site of antigen inoculation and are generally considered a measure of Th1 immunity. Therefore, the Th2 bias of CD4⁺ T cells may also account for this defect.

Suppression of lymphocyte proliferation

The proliferation of PBMCs from children and monkeys with measles in response to stimulation with mitogens is suppressed for several weeks after infection (66,140) (Fig. 2B). Proliferation can be improved but not completely restored by supplementation of the cultures with IL-2, suggesting that failure to produce IL-2 in response to mitogen stimulation is at least part of the proliferative defect (168).

Direct mechanisms for decreased lymphoproliferation have focused on the effect of MV on cells of the immune system through receptor interaction and infection. Inhibition of lymphocyte cell cycle progression associated with G1 arrest after *in vitro* infection with MV has long been recognized (171–175). The recent recognition that MV RNA can persist in PBMCs for months after clearance of infectious virus (136,137) suggests that renewed MV replication in cultured cells may contribute to suppressed proliferation. This possibility has not yet been examined.

CD150, the receptor used by wildtype strains of MV to infect lymphocytes and macrophages, is a dual function co-receptor for lymphocyte activation. The cytoplasmic domain has 2 copies of an immunoreceptor tyrosine-based switch motif (ITSM) that mediates different functions depending on the availability of downstream molecules in the signal transduction pathway (32). The normal function of CD150 is to enhance T-cell proliferation and cytokine, particularly IFN- γ , production (27,31,170). MV interaction with CD150 downregulates receptor expression (24,169), but other functional consequences for lymphocytes of MV binding to CD150 have not been described but could play a role in suppression of proliferation.

Suppression of T-cell proliferation can also be induced without infection through direct inhibitory signaling to T cells by the viral glycoprotein complex of H and F₁-F₂ in the membrane of virions or infected cells (176–180). This cell surface contact-dependent inhibitory signal prevents S phase entry of T cells for several days (176,180,181) and is not dependent on cell death, membrane fusion, production of soluble inhibitors, or T-cell infection (174,177,182–184). This inhibitory signaling results in a reduction in cyclin-dependent kinase complexes and delayed degradation of p27^{Kip} leading to cell cycle retardation and accumulation of cells in the G₀/G₁ phase (174,183,184). Antibody to H or F can reverse the inhibition (177), but this effect is not induced by the interaction of H with CD150 or CD46, because antibodies to these receptor molecules do not interfere with the ability of MV to suppress lymphocyte proliferation (24). It is possible that ongoing interactions of T cells in lymphatic tissue or in circulation with MV-infected cells induce this refractory state *in vivo* and result in suppressed proliferation in response to stimulation *ex vivo*.

The mechanism by which H/F₁-F₂ suppresses mitogen-induced proliferation is an area of active study and appears to be associated with MV-induced interference with the T-cell activation of phosphoinositide 3-kinase (PI3K) in response either to ligation of the T-cell receptor or the IL-2 receptor (185,186). In response to IL-2, MV-treated cells activate signal transducer and activator of transcription 3 (Stat3) but cannot activate Akt kinase necessary for cell cycle progression (186). Current data suggest that the MV glycoprotein complex induces this unresponsiveness by binding to lipid rafts on resting T cells (185). Binding inhibits degradation of the cytoplasmic inhibitory protein Cbl-b, resulting in a lack of recruitment of the PI3K regulatory subunit p85 to lipid rafts (185). This then alters recruitment of Akt kinase and Vav to the membrane. In addition, induction of the SHIP isoform SIP110 phosphatase decreases availability of PIP3 needed for phospholipid signaling (187). Determination of the relevance of this process to *in vivo* suppression of lymphoproliferation requires further study.

Measles virus infection of dendritic cells

Susceptibility to infection

In vivo, DC infection has been observed in experimentally infected cotton rats (188), transgenic mice (189), and macaques (63), and the effects of MV infection on DC function have been extensively studied *in vitro*. As the primary professional APC for initiation of the immune response to MV, as well as to other infections, the effect of MV infection on DC function and T-cell activation has been of substantial interest. *In vitro* studies have used a variety of sources for DCs (i.e. CD34⁺ cord blood cells, Langerhans cells, peripheral blood monocytes) and infection with wildtype, tissue culture-adapted, and vaccine strains of MV.

Undifferentiated monocytes express CD46 but are relatively resistant to MV replication (4,146,190,191). Monocytes upregulate MHC class II molecules in response to infection with a tissue culture-adapted strain of MV and are able to present MV antigens but not unrelated antigens to cocultured virus-specific T cells, due to a failure in antigen processing (192,193). In cultures of PBMCs, infected monocytes can induce apoptosis in uninfected T cells (147).

In vitro differentiation of monocytes into immature DCs with granulocyte/macrophage colony-stimulating factor (GM-CSF) and IL-4 is associated with expression of CD150 and increased susceptibility to MV infection (4,188,191). In CD150 transgenic mice, MV infection inhibits differentiation of DCs (108). Infection of immature DCs is enhanced *in vitro* by interaction of the H and F surface glycoproteins with the C-type lectin DC-SIGN

(47). Immature DCs matured with TLR2 and TLR4 ligands further increase expression of CD150 with a concomitant increase in susceptibility to MV infection (191).

The H protein determines tropism of MV for monocyte-derived DCs (moDCs) so that replication and syncytia formation in moDCs is strain dependent with efficient infection by wildtype strains of MV (188,191). Vaccine strains infect and replicate but produce little infectious virus, due to instability of the M protein (4). Infection of immature moDCs with MV induces maturation with upregulated expression of CD80, CD83, CD86, and HLA-DR and decreased expression of CD1a (86,179,194). Infection also alters moDC expression of chemokines, chemokine receptors, and chemotaxis (195) and results in rapid induction of IFN- β mRNA and protein and multiple IFN- α mRNAs and proteins that contribute to maturation of cultured DCs (86,177). Infected DCs respond to IFN with induction of a variety of IFN-responsive genes, e.g. 2'5'-oligoadenylate synthetase, MxA, guanylate-binding protein, ISG-12, ISG-15, and APOBEC3B (86,178).

MV-exposed moDCs expressing either CD150 or DC-SIGN can transmit MV to co-cultured T cells (197). Infection spreads in DC cultures, but release of infectious virus is minimal unless the cells are activated (146,164). Addition of lymphocytes to MV-infected DCs results in lymphocyte infection, moDC activation, and enhanced MV replication, leading to DC death (146,191,196). Death in the cultures has been associated with expression of Fas/Fas ligand and TNF-related apoptosis inducing ligand (TRAIL) (196,198).

Effects of infection on cytokine production

Monocyte lineage cells, including moDCs, exposed to MV are impaired in production of IL-12 *in vitro* (73,146,194,199) and *in vivo* (155,200,201). Suppression of IL-12 production by DCs from CD150 transgenic mice in response to TLR4 ligation is facilitated by H interaction with CD150 (199). MV interaction with DC-SIGN during infection of moDCs increases IL-10 transcription by inducing acetylation of the TLR-activated NF κ B subunit p65 (202). Infected moDCs also produce more IL-10 in response to CD40 ligand than uninfected moDCs (194). Suppression of IL-12 production and induction of IL-10 probably contribute to the type 2 cytokine responses that develop during recovery from measles (121,129).

Microarray analysis of the transcriptional changes in moDCs infected with MV compared these responses to those of moDCs infected with other pathogens, including influenza virus, a bacteria, and yeast. These studies revealed that many of the changes postulated to be responsible for DC-mediated MV-induced immune suppression were common to moDC responses to pathogens that are not associated with immune suppression (86). Core moDC responses to all pathogens include upregulation of genes associated with DC maturation, such as CCR7, CXCR4, and CCRL2, IL-6, and TNF superfamily members TNF, CD27L, 41BBL, and TRAIL (204). Features unique to MV included a rapid upregulation of the expression of IFN- β and almost all IFN- α s within 12 h and increased transcription of CCL1/I-309, TNFSF8/CD30L, IL-12B, and IL-15. More genes were downregulated than upregulated within 24 h after moDC infection. These included many genes associated with oxidative phosphorylation, protein synthesis, and chromatin regulation, but the importance of any of these changes has not yet been defined.

Effects of infection on APC function

DC antigen-presenting function after MV infection has been assessed in several ways. Antigen uptake, as measured by mannose receptor-mediated endocytosis, is not affected (164). However, MV-infected DCs are deficient in stimulation of a mixed leukocyte reaction

(MLR) that measures the ability of DCs to stimulate proliferation of heterologous CD4⁺ T cells, a property that does not require release of infectious virus (164,179,203).

The effect of DC infection with MV on T-cell function has been also been assessed by co-cultivation of infected moDCs with mitogen-stimulated peripheral blood lymphocytes. MV-exposed T cells are recruited into conjugates with DCs *in vitro* but have impaired clustering of receptors needed for sustained T-cell activation, in part due to accumulation of ceramide (50,205). Because T-cell conjugation with DCs is unstable and cannot be sustained, full T-cell activation does not occur (206).

The importance of the deficiencies identified in DC function *in vitro* is unclear. Analysis of antigen-presenting function of MV-infected monocytes has shown that these cells can present MV but not an unrelated antigen to T-cell clones (193). *In vivo*, a vigorous MV-specific cellular and humoral immune response is mounted to infection. This response results in rapid clearance of infectious virus, gradual clearance of viral RNA, and establishment of life-long protective immunity.

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Fig. 1. Schematic diagram outlining an overview of the pathogenesis of measles from the time of virus infection through recovery

(A) Virus infection is initiated in the respiratory tract and then spread systemically to infect multiple organs including lymphoid tissue, liver, lungs, and skin. The types of cells infected include epithelial cells, endothelial cells, B and T lymphocytes, monocytes/macrophages, and dendritic cells. Virus clearance begins with the onset of the rash. Clearance of infectious virus is complete 20 days after infection, but viral RNA (represented by the dashed line) persists at multiple sites. (B) Clinical signs and symptoms begin approximately 10 days after infection with prodromal symptoms of fever, conjunctivitis, and appearance of Koplik's spots followed by the maculopapular rash that lasts 3–5 days. (C) The rash is a manifestation of the adaptive immune response with infiltration of CD4⁺ and CD8⁺ T cells into sites of virus replication and initiation of virus clearance. There is a rapid activation, expansion, and then contraction of virus-specific CD8⁺ T cells. The CD4⁺ T-cell response appears at the same time, but activation is prolonged. MV-specific IgM appears with the rash and is commonly used to confirm the diagnosis of measles. This is followed by the sustained synthesis of MV-specific IgG. Immune suppression is evident during acute disease and for many weeks after recovery. (D) Cytokines and chemokines that are produced during infection in sufficient quantities to be found in plasma in elevated amounts are of several distinct types. Early, the chemokine IL-8 is increased. During the rash, IFN- γ and IL-2 are produced by activated type 1 CD4⁺ T cells and by CD8⁺ T cells. After resolution of the rash, type 2 and regulatory CD4⁺ T cells produce IL-4, IL-10, and IL-13.

Fig. 2. Manifestations of immune suppression during measles

(A) Delayed type hypersensitivity skin test responses to tuberculin in Peruvian children before (control) and after the onset of measles (139). (B) Proliferation in response to stimulation with phytohemagglutinin of PBMCs from rhesus macaques during a primate center outbreak of measles (66).