seminars in **VIROLOGY**, Vol 5, 1994 : pp 273-280

The role of host factors in measles virus persistence

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As critical steps in the life cycle of measles virus (MV), the efficiency of uptake into and replication in susceptible host cells are governed by cellular determinants. Measles virus infections of cells of the human CNS are characterized by particular constraints imposed on viral transcription and translation attenuating viral gene functions and thus contributing to the pathogenesis of MV persistence in these cells.

Key words: CNS infection / MV receptor / MV transcription / unwindase

COMPLICATIONS OF acute measles are frequent, most of them are linked to virus-mediated cytolysis of the primary target cells, the peripheral blood mononuclear cells (PBMCs), and indirect mechanisms based on the temporary virus-induced immunosuppression as well as virus-induced autoimmune reactions.[1-3] Although not convincingly confirmed experimentally, persistent infection of lymphocytes or monocytes has been suggested for the pathogenesis of MV associated disease processes including CNS complications.[4,5] Subacute sclerosing panencephalitis (SSPE) and, in immunocompromised hosts, measles inclusion body encephalitis (MIBE) develop on rare occasions months or years after primary infection based on persistence of virus in neuronal and glial cells.[6] Both lethal conditions are characterized by the absence of free infectious virus in brain tissue due to a defective intracellular replication cycle which allows the virus to survive in a cell associated form and inaccessible to the host immune surveillance.[1] This is generally achieved by maintaining the integrity of the viral protein functions associated with ongoing transcription and intracellular replication and attenuating or abolishing the expression of the viral envelope proteins. The restrictions of the latter have been linked to a generally low abundance of the corresponding mRNAs in brain tissue and to the fact that many of the envelope gene sequences known today harbor mutations interfering with functional expression of the gene products[6,7] (Table 1).

Although mutations within the envelope gene sequences are undoubtedly important for controlling viral gene functions in persistent MV CNS infections, the presence of MV wild-type-like sequences in SSPE brain material provided a strong argument for a nondefective virus initially infecting the CNS.[8] Thus, the primary virus-host cell interaction probably is governed by host cell factors attenuating viral gene functions thereby abolishing a lytic, productive replication and enabling the establishment of a persistent infection.

In this review we will focus on basically two distinct events in the viral replication cycle which are determined to a major extent on host cell dependent factors, namely the interaction of MV with its cellular receptors and intracellular regulatory events interfering with the synthesis and functionality of virus-specific transcripts.

MV receptor interactions

The first events determining the cell tropism of MV *in vivo* are receptor mediated entry of the virus, subdivided into specific attachment, close binding and subsequent fusion between viral and host cell membrane and ultimately, the release of the viral genetic material into the cytoplasm (shown schematically in Figure 1). It was not until recently that two different cell surface molecules have been identified on tissue culture cells that are functionally associated with infectivity of the cell with MV. Antibodies raised against CD46 (membrane cofactor protein, expressed on the surface of most human cells)[9] were able to interfere with MV infection.[10,11] Upon stable transfection of CD46, certain mouse cell lines were capable of supporting productive MV replication, whereas others were not,[10] indicating that CD46 would be necessary but not sufficient to confer susceptibility to MV infection.[10,11] More recently, as a second

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1044-5773/94/040273 + 08$8.00/0

Table 1. Alterations of MV gene functions in persistent brain infections

Replication step	Alterations in persistent infections	Consequences
Transcription	Highly polar expression gradients for monocistronic mRNAs	Low abundance of the envelope and polymerase proteins
	Increased frequency of bicistronic mRNAs	Inefficient translation of the second reading frame
Function of viral mRNAs and proteins	**N, P, L *proteins:***	*Alterations of the polymerase activity?*
	few expressed point mutations over the entire genes	Altered protein/protein interactions?
		Antigenic changes
	M proteins:	M proteins absent, truncated or instable
	point mutations and hypermutations over the entire coding sequence	Defective budding?
		Alterations of NC binding?
	F proteins:	Truncation, distortion of the C-terminal domain
	C-terminal point mutations	
	H proteins:	Loss of glycosylation sites
	point and hypermutations	Impaired dimerization and membrane transport
		Reduced hemadsorption activity
		Antigenic changes

Summarized are alterations of MV gene functions defined directly in brain material of patients with persistent CNS infections or by analyzing MVs isolated from brain tissue by cocultivation and propagated as 'SSPE isolates' in persistently infected tissue culture cells. Transcriptional attenuation has generally been observed affecting both overall MV transcription levels (as determined as copy numbers/10 pg of total RNA) as well as the formation of highly polar expression gradients for the downstream mRNAs.[19,20] Functional impairments of these mRNAs, mainly due to point and hypermutations, alter, truncate, destabilize or completely abolish the corresponding translation products.[6,7] While functional consequences for the alterations within the N, P and L proteins are anticipated, they have been experimentally addressed for the envelope proteins recently.[73-75]

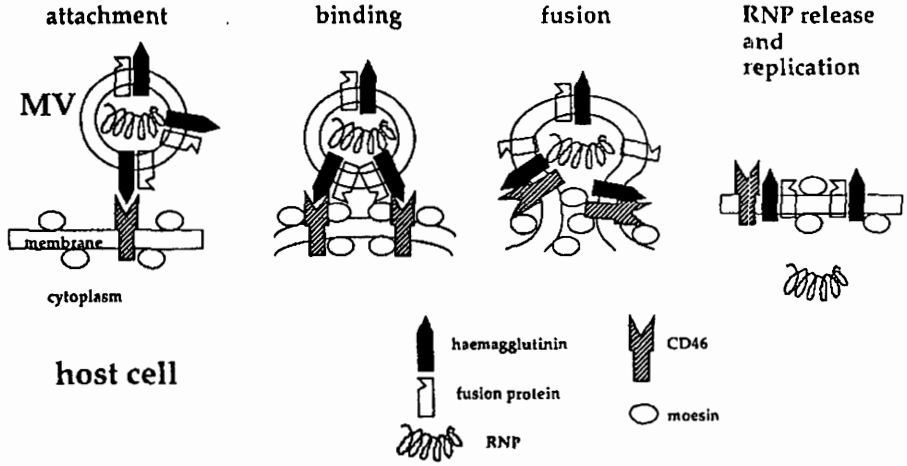

Figure 1. Steps in measles virus-cell interactions. Binding of enveloped viruses to cells and subsequent fusion is a multistep mechanism not well understood. The model predicts that complexes of CD46 and moesin and MV-H and F are required for efficient uptake of MV by cells. While the interaction of MV-H protein with CD46 is strongly suggested,[10] the interaction of the F protein with one of these components has not been established. Note also, that CD46 is a classical transmembrane glycoprotein,[9] whereas moesin is associated with both surfaces of the cellular membrane, however, has no typical transmembrane domain.[12] Following release of the viral RNP, factors within the cytoplasmic compartment determine the susceptibility of the host cell.

molecule, moesin (membrane, organizing external spike protein, widely expressed on eucaryotic cells)[12] could be linked to MV susceptibility in a variety of tissue culture cells.[13] Monoclonal antibodies against both constituents efficiently blocked infection with MV, but not with viruses as closely related as CDV in tissue culture[10,13] and recently, data accumulated suggesting that both molecules are part of the functional receptor complex for MV (J. Schneider-Schaulies, unpublished). Both molecules reveal a wide tissue distribution *in vivo*,[9,12] but only certain isoforms of CD46 have been detected on the surface of brain cells.[14]

A role of the receptor in determining the outcome of a viral infection has also been suggested. For HPIV 3, removal of the receptor during infection has been linked to a persistent state by preventing cell-cell fusion.[15] The establishment of persistence upon limitation of the receptor has also been observed for HIV.[16] In a cell line persistently infected with MV, cell-cell fusion did not occur unless fresh cells were added to the culture[17] and recently it was shown that infection with MV or a recombinant vaccinia virus expressing the MV H protein led to a down-regulation of CD46 molecules at the cell surface[10] and, in fact, significantly reduced amounts of CD46 and moesin were detected on the surface of persistently MV-infected human monocytes (ref 13; L.M. Dunster, unpublished). Functional consequences of removal of CD46 proteins from the cell surface may include an increased vulnerability of the infected cells to complement lysis (J.-J. Schnorr, in preparation). On the other hand, their reduced fusability could favor the establishment of viral persistence. Since, however, a strict correlation was found between the degree of down-regulation of CD46 and the amount of the H protein, the latter hypothesis will probably not refer to brain cells where the expression of the envelope proteins is generally restricted (see below).

Further characterization of the MV/cell receptor-interactions and the establishment of stably transfected cell lines or transgenic mouse lines will, however, contribute not only to the understanding of the pathogenesis of MV, but also to evaluate the role of intracellular factors controlling the permissiveness of the host cell. In fact, although extensive formation of syncytia was observed after infection with a vaccinia virus recombinant encoding both MV F and H, mouse L cells constitutively expressing CD46 were not permissive for MV indicating a block of MV replication later than at the level of entry.[10]

Control of intracellular MV gene expression in brain cells

Alterations of MV gene expression have mainly been characterized directly using autopsy brain material of SSPE and MIBE patients and cell lines persistently infected with MV isolates obtained by cocultivation from brain tissue.[18] To investigate the particular virus-host interactions governing the primary infection as experimental systems, an animal model for experimentally induced MV-CNS infections in rats and tissue culture systems with primary and permanent cell lines of neural origin have been used.

Regulation of MV transcription

Transcription of viral subgenomic mRNAs is initiated by the transcriptase complex at a promoter site within the 3′ noncoding region and subsequently the individual mRNAs are synthesized. The polymerase tends to detach from the template at the intergenic regions with increasing frequency to the 5′ end of the genome leading to a polar accumulation of viral mRNA transcripts *in vivo* and *in vitro*.[19-21] In SSPE brain material, this gradient appears to be 40-fold steeper[19,20] leading to a considerable reduction in M, F and H protein expression which has been directly documented[22] (Table 1).

In analyzing potential host factors it became evident that in brain cells the overall MV specific transcription is substantially reduced as indicated by the steady-state levels of the N-specific transcripts per infected cell. In MV-infected human neural tissue culture cells and primary rat astroglial cells, these transcripts were up to tenfold less abundant compared to nonneural cells under identical conditions.[23,24] A further reduction of the overall MV transcription has been linked to the differentiation state of the infected cells in brain material of both experimentally infected animals and in tissue culture of human neuroblastoma cells treated with differentiating compounds.[25,26] Concomitant with the overall reduction observed, the progressive decrease of the mRNA frequency along the gene order, typical for SSPE, could also be detected in tissue culture systems using neural cells

and in brain tissue of experimentally infected animals.[24,27]

Antibody-induced antigenic modulation

Transcriptional attenuation of MV in brain cells may also be supported by exogenous factors such as virus-neutralizing antibodies. A significant down-regulation of MV transcription was observed in experimentally infected newborn animals compared to naive controls after passive transfer of neutralizing anti-H-antibodies.[25] In the presence of neutralizing antibodies, a pronounced reduction of the expression of all MV structural proteins within few days was observed in persistently MV-infected rodent neural cells, but not in Vero cells or human lung fibroblasts.[28-30] RNA analyses revealed that 24 h after the application of antibodies, total MV transcriptional efficiency was reduced up to tenfold whereas the relative frequencies of the 5′ mRNAs were substantially unaffected.[30] Although 'antibody induced antigenic modulation (AIAM)' has recently been shown to account also for restrictions of other viruses,[31] the signal transduction pathways involved have not been investigated. An immediate, temporary increase in phosphoinositol breakdown and stimulation of the protein kinase C has been described following addition of an anti-H antibody to persistently MV-infected rat glioma cells,[32] whereas other investigators observed a down-regulation of protein kinase C activity upon treatment of a persistently infected mouse neuroblastoma cell line with MV hyperimmuneserum.[33] Protein kinase C mediated alterations of MV gene expression in neural cells have not been investigated so far. In PBMCs, stimulation of protein kinase C by TPA (phorbol myristate acetate) or the Ca ionophore 23187 led to the activation of MV replication.[34]

Role of the human IFN-inducible MxA-protein in regulating MV gene expression

Cytokines released from MV-infected brain cells may interfere additionally with viral as well as cellular gene expression.[35] Amongst those, the antiviral potential of type I IFN and the well characterized IFN-inducible proteins has been a matter of more detailed investigations.[36-39] One of the latter, the type I IFN-inducible MxA protein, has recently been linked to transcriptional attenuation of MV brain cells, but not in nonneural cells.[39] MxA-dependent downregulation of MV transcription affected both overall efficiency and the relative frequencies of the 5′ mRNAs, whereas the same protein expressed in the human monocytic cell line U-937 specifically inhibited the synthesis of the MV glycoproteins in the absence of any detectable transcriptional control.[40] It is quite remarkable that the antiviral activity of the MxA protein seems to be quite complex, as previous studies revealed a host cell independent MxA-mediated inhibition of VSV RNA synthesis.[40,41] Since, however, high levels of MxA are detected in monocytes and brain cells during primary or persistent MV infection respectively, this protein apparently bears a high potential to act as a host cell specific factor attenuating MV gene expression.

Potential mechanisms and targets of MV transcriptional regulation

As appropriate experimental systems are not at hand, mechanisms contributing to MV transcriptional regulation are still largely unknown. For MV and related viral systems, evidence for a role of cytoskeletal components like tubulin for efficient replication has been provided *in vitro*.[21,42,43] Due to their ubiquitous expression, the linkage of these proteins to host cell dependent transcriptional regulation is not obvious. More recently, uncharacterized host proteins directly binding to the leader RNA of MV have been proposed to play a role in determining permissivity for MV on a transcriptional level.[44] Alternatively, host cell specific modifications of viral proteins essential for transcription and replication could be envisaged. As shown for vesicular stomatitis virus (VSV), at least one of the functionally required phosphorylation events of the viral P protein is due to the action of a cellular kinase and an inhibition of that kinase activity directly correlates with transcriptional inhibition *in vitro*.[45,46] It is well established that at least three MV proteins (N, P and the nonstructural V protein) are phosphorylated, exact phosphorylation sites, however, and their functional importance have not been defined.[47-49]

Although the polymerase protein L, is probably just required in catalytic amounts, its low abundancy due to the under-representation of the corresponding transcript, may be limiting for transcriptional efficiency in brain cells. A certain stoichiometry of N, P and L proteins for the formation of functional complexes has been shown to be required for the related Sendai virus system.[50] In addition, an inhibitory capacity of the Sendai virus V protein on

viral RNA replication was found *in vitro* with the L protein being limited. In the presence of strongly polar expression gradients for the corresponding transcripts, V protein may exert a negative effect on replication in infections where the concentration of L is relatively low, such as in brain cells.[51] Thus, although editing required for the synthesis of the V protein is most presumably an activity intrinsic to the viral polymerase and independent of host cell factors,[52] the gene function(s) of the editing product may be regulated by the host background.

Biological activity of virus-specific transcripts

Mutational alterations

In addition to altering the relative frequencies of virus-specific transcripts, their translational activity provides an important site of control for viral gene functions. From the analyses of envelope gene specific mRNAs from persistent brain infections it became apparent that most of the restrictions on translational level are based on sequence mutations leading to premature termination or complete abolishment of the corresponding reading frames.[7,18] An exception is provided by the M-specific mRNAs isolated from the brain of experimentally infected Lewis rats with SAME, that were not translated *in vivo* and *in vitro*, independent of detectable sequence alterations.[27]

In addition to point mutations as introduced by the viral polymerase during the long lasting virus-host interactions, a second type of mutations involving simultaneous clustered transitions of several uridine (U) to cytidine (C), or, less frequent, adenosine (A) to guanosine (G) residues, specified in the plus strand sense, has been encountered predominantly in the M genes of SSPE and MIBE cases and persistently infected tissue culture cells.[8,53-55] These hypermutation events have been ascribed to the activity of a double-strand (ds) RNA dependent unwinding/modifying enzyme, now referred to as DRADA (double-strand RNA specific adenosine desaminase) intrinsic to the host cell.[54,56,57] The model predicts that A residues would be desaminated to yield inosine (I) in MV-specific dsRNAs during transcription. Subsequently, within the first round of replication, the modified I residues would base pair with C replacing the primary A/U pairing.

The potential importance of this cellular activity in silencing MV gene functions has been recently supported by the characterization of several evolved hypermutated sequences within different brain areas of a case of SSPE.[8] As obvious from that study, a wild-type like M sequence was actively modified in the course of the infection by several discrete, consecutive hypermutation events. Moreover, evidence for hypermutation of viral genes has been provided for viral systems other than MV.[58-60] *In vitro*, the activity could be detected in a variety of mammalian tissue culture cells without an apparent template specificity.[61-63] The intracellular localization of the activity has been shown to be dependent on the cell cycle[61,62] usually being extremely low under growth arresting conditions.[61] An MV M specific subgenic fragment has been successfully modified *in vitro* in nuclear extracts of a human neuroblastoma cell line (IMR-32) but not of Vero cells.[64] More recently, the presence and activity of the enzyme in cytoplasmic extracts of *in vitro* differentiated brain cells has been confirmed.[65] Thus, although the further propagation of the mutated viral sequence is completely dependent on their impact on viral gene functions, the basic attenuation is dependent on host cell rather than viral determinants.

Translational control independent of mutations

Apart from mutational events discussed above, translational efficiency may depend on 5′ and 3′ noncoding sequences of a mRNA interacting with common or host cell specific cellular RNA binding proteins.[66] A temperature shift of persistently infected rat glioma cells led to a selective and reversible translation inhibition of MV M and F-specific mRNAs arguing strongly for the involvement of cellular determinants in controlling viral gene functions.[67] Similar observations of translational inhibition affecting partial as well as complete, MV protein synthesis have been described as a consequence of *in vitro* differentiation of tissue culture cells of neural origin.[24,26,68] In one of these studies, *in vitro* differentiation of human glial cell lines prior to MV infection led to an almost complete block of viral protein synthesis *in vivo*, whereas the synthesis of the corresponding mRNAs and their ability to direct the synthesis of translation product *in vitro* were apparently unaffected.[24] In addition, the overall protein synthesis of the infected cells was not inhibited. The obvious specific inhibition of viral rather than cellular gene expression is reminiscent of that described for the antiviral activity of certain IFN-induced proteins.[69] Although as a consequence

of MV infection the induction of IFN is indicated by the expression of human MxA in these cell lines,[35] *in vitro* differentiation did not lead to a detectable stimulation of IFN synthesis arguing against a pronounced inhibitory effect brought about by P1 kinase.[24] The sensitivity of MV specific protein expression to exogenous treatment with IFN-α independent of viral mRNA down-regulation was shown in PBMCs.[70]

Conclusions and future perspectives

As outlined above, host cell dependent attenuation of MV gene expression and functions on different levels may be of crucial relevance in favoring the establishment of persistent infections. An additional role for viral constituents in this process cannot, however, be excluded. Recently, the clonal expansion of a MV identified by a hypermutated M sequence in the brain of one SSPE patient has been suggested to be based on a selective advantage of this particular isolate.[8] To evaluate and characterize the role of viral and cellular determinants in the pathogenesis of human CNS infections, a precise definition of functional domains within the viral structural proteins required for intracellular amplification of viral genetic material and the maturation and release of viral particles will be indispensable. So far, the C-terminal domain of the MV P protein has been identified as necessary for complex formation of MV N and P proteins *in vivo*,[71] and the binding of MV M protein to MV RNP complexes has been investigated *in vitro*.[72,73] As for influenza virus and VSV, a role for that protein has been proposed in regulating MV transcription.[74] Ultimately, the MV-glycoprotein-dependent membrane fusion has been investigated in tissue culture.[75] Understanding of MV protein functions and the relevant domains will allow the evaluation of alterations within these proteins sequences encountered in persistent infections and their potential contribution to this particular virus-host interaction.

Acknowledgements

The authors thank the Deutsche Forschungsgemeinschaft, the Humboldt-Stiftung and the Bundesministerium für Forschung und Technologie for generously supporting their laboratory work.

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