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Review

Measles virus interactions with cellular receptors: Consequences for viral pathogenesis

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Although CNS complications occuring early and late after acute measles are a serious problem and often fatal, the transient immunosuppression lasting for several weeks after the rash is the major cause of measles-related morbidity and mortality worldwide. This review is focused on the interactions of measles virus (MV) with cellular receptors on neural and lymphoid cells which are important elements in viral pathogenesis. First, the cognate MV receptors, CD46 and CD150, are important components of viral tropism by mediating binding and entry. Second, however, additional unknown cellular surface molecules may (independently of viral uptake) after interaction with the MV glycoprotein complex act as signaling molecules and thereby modulate cellular survival, proliferation, and specific functions. *Journal of NeuroVirology* (2001) **7,** 391–399.

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Introduction

Acute measles, early and late complications

After entering the upper respiratory tract, measles virus (MV) exhibits pronounced tropism for monocytic and lymphoid cells, and soon viral replication is detected in draining lymph nodes. In the course of its viremic spread, the virus remains highly cell associated and can be isolated from blood leukocytes in the early stages of infection. Only a small proportion of the patient's peripheral blood mononuclear cells (PBMC) are infected, and these include B and T cells as well as monocytes. Following extensive replication in lymphoid tissues, virus is spread through a secondary viremia, and replication continues in the epithelia of the lung and buccal cavity. Inflammatory reactions first affect the integrity of thin layer epithelia in the respiratory tract and conjunctiva to cause the inital prodromal symptoms and subsequently the thicker mucosal surfaces of the buccal cavity. The appearance of Koplik's spots marks the onset of a delayed-type hypersensitivity reaction similar to that which gives rise to the rash. Virus antigen can be detected in the skin, but it is concentrated near blood vessels and in endothelial cells of dermal capillaries where it causes accumulated damage to the vascular walls. In the immunocompetent, the virus is efficiently cleared after onset of a virus-specific immune response in the presence of a transient immunosuppression to general other antigens lasting during and several weeks after the rash (Griffin and Bellini, 1996).

In industrialised countries, main complications are pneumonia and encephalitis. In developing countries, measles is associated with high annual rates of morbidity and mortality that are caused by opportunistic infections resulting from the profound immunosuppression (Clements and Cutts, 1995). Typically, the MV patients reveal a marked lymphopenia affecting particularly the T-cell population. Mechanisms involved in T-cell depletion are not fully understood and may include disturbances in the generation of T cells from precursors, thymocyte, or T cell apoptosis, recruitment of T cells in syncytia with infected dendritic cells, or aberrant homing of highly activated T cells (Auwaerter *et al*, 1996; Fugier-Vivier *et al*, 1997; Grosjean *et al*, 1997; Nanan *et al*, 1999). It is, however, unlikely that lymphopenia is directly associated with impaired proliferative responses of bulk lymphocyte populations to polyclonal or antigen-specific stimulation, since the lymphocyte counts have returned to normal when proliferation is still reduced weeks after acute measles (Borrow and Oldstone, 1995). Several hypotheses have been put forward to explain this particular

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phenomenon, which is considered as one of the hallmarks of MV-induced immunosuppression. As evident from *in vitro* studies, infection of lymphocytes causes proliferative arrest and accumulation of the cells in the G0 or G1 phase of the cell cycle (Naniche *et al*, 1999). However, given the low abundancy of infected lymphocytes during and after acute measles, it seems unlikely that this infection-induced arrest essentially contributes to the general inhibition of lymphocyte proliferation. Rather, other mechanisms such as release of inhibitory cytokines from infected cells (Fujinami *et al*, 1998; Sun *et al*, 1998) or inhibitory signals elicited by contact between viral glycoproteins on the surface of infected cells and uninfected cells (Engelking *et al*, 1999) seem to be more important.

It is likely that a clinically symptomless cerebral dysfunction is common in uncomplicated measles as documented by abnormalities of the EEG in about 50% of patients and cerebrospinal fluid (CSF) pleocytosis (Ojala, 1947; Gibbs *et al*, 1959; Reinicke *et al*, 1974). In view of the wide dissemination of MV in the body, it is surprising how infrequently a nervous system disease develops as a complication of measles. Because MV-specific nucleic acids are only detected with highly sensitive methods in brain material from patients with acute postinfectious measles encephalitis (APME; Nakayama *et al*, 1995), and are absent in the majority of cases studied, CNS damage in APME is considered to result from a virus-induced cellular autoimmune response directed against CNS antigens such as myelin basic protein (Liebert *et al*, 1988). In contrast to APME, MV has been extensively documented in brain cells of patients with subacute sclerosing panencephalitis (SSPE) and measles inclusion body encephalitis (MIBE), both of which develop after a clinically latent periods of months to years after acute measles and are inevitably fatal. Whereas SSPE develops in fully immunocompetent individuals, MIBE is confined to patients with underlying cellular immunodeficiencies and may thus be considered as opportunistic infection of the CNS due to inappropriate immunological control. As a consequence, the humoral hyperimmune reaction in serum and CSF pathognomic for SSPE is not seen in MIBE (Dörries and ter Meulen, 1984).

The pathways of MV entry in the CNS have not been resolved yet, but it is likely that MV-infected lymphocytes or monocytes are important in either directly entering the CNS or as carriers to enable infection of vascular endothelial cells with subsequent spread to neural cells. It is also unknown why the host's immune system fails to control MV CNS infection at early stages in SSPE and what genetic or viral factors are decisive for the establishment of a persistent MV brain infection with subsequent viral and spread to neurons and macroglial cells. As revealed by molecular epidemiological studies, MV gene sequences obtained from autopsy material are, except from mutations accumulated in certain regions of the genome, homologous to the corresponding gene sequences of MV genotypes circulating at the time of primary exposure of the patients to MV (Rima *et al*, 1997). This strongly supports the notion that there are no MV genotypes that are particularly neurovirulent and that persistent brain infections are established by wildtype rather than vaccine strains. Mechanisms determining the inital establishment and the maintenance of a persistent MV CNS infection have not been resolved, it appears however, that MV replication in brain cells is restricted by certain host cell proteins including the type I IFN-inducible MxA protein (Schneider-Schaulies *et al*, 1994). In this context it is interesting to note that some MV isolates from SSPE brains were found to reveal a reduced sensitivity to Type I IFN in tissue culture (Carrigan and Knox, 1990). As documented by immunohistochemistry and later by sequence analyses with brain autopsies, the expression of the MV envelope proteins is largely restricted in SSPE and MIBE and transcriptional restrictions of the corresponding genes or mutations within the coding sequences were found which interfere with the synthesis of functional gene products (Rima *et al*, 1995; Schneider-Schaulies *et al*, 1999). As a consequence, expression of the viral envelope proteins is generally low or even absent in persistent brain infections, whereas the integrity of the replicative complex as indicated by the presence of nucleocapsids is apparently maintained. Given these constraints, it is not surprising that giant cell formation is not seen in SSPE and MIBE *in situ,* and reisolation of infectious virus from SSPE autopsy material is rarely successful.

MV envelope proteins

The viral envelope contains three proteins which essentially control receptor interactions and viral uptake (Figure 1). The matrix (M) protein that links the viral nucleocapsid to the envelope, is believed to interact with one or both cytoplasmic domains of the glycoproteins and to regulate the fusogenic activity of the glycoprotein complex (Cathomen *et al*, 1998a; Cathomen *et al*, 1998b). Remarkably, most mutations seen in SSPE are within the M gene (Rima *et al*, 1995). The hemagglutinin protein (H) is a type II transmembrane glycoprotein which has a dual function in mediating viral attachment to host cell receptors, and providing fusion helper function for the second viral glycoprotein, the fusion (F) protein (Wild *et al*, 1991). The latter is a type I glycoprotein and synthesised as a F0 precursor protein that needs to undergo proteolytic activation into a disulfide-bond linked F1/F2 heterodimer to be functional (Wild *et al*, 1995). Both proteins form a complex on the surface of infected cells consisting of an H tetramer and a F1/F2 trimer. Based on molecular modeling, the H protein most likely consists of membrane-distal a six-winged propeller-like structure linked via a membrane proximal stem to the cell surface, followed by a transmembrane and short cytoplasmic domain (Langedijk

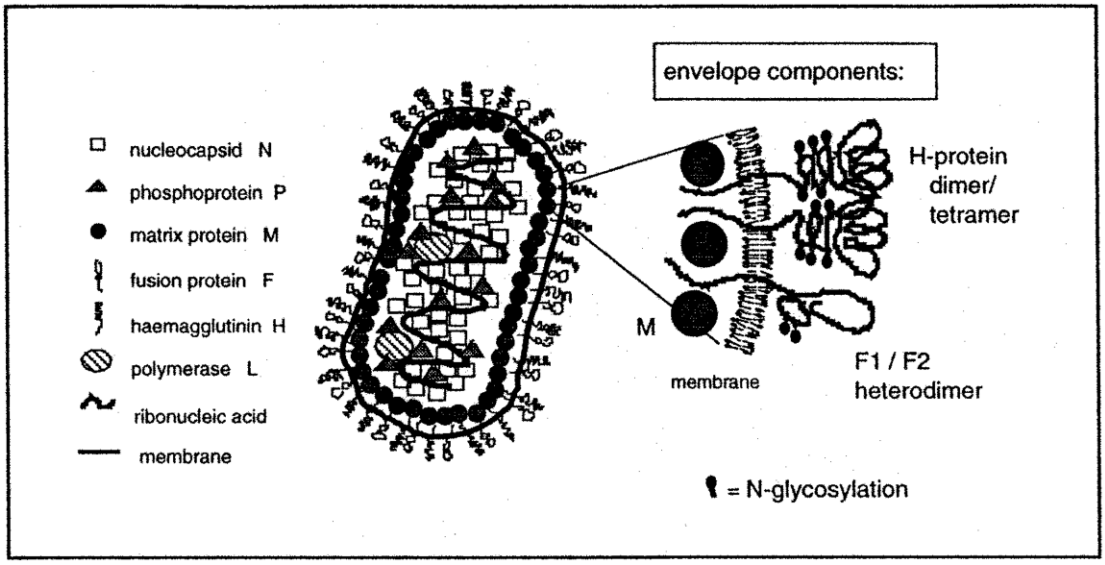

Figure 1 The measles virus particle and its envelope glycoproteins.

et al, 1997). Functional domains within the H protein are largely unknown but begin to be unraveled. In analogy to findings obtained with F proteins of closely related viruses, the MV F protein is thought to undergo conformational changes, the first of which occurring after proteolytic processing in the trans-golgi network by furin, a subtilisin-like protease (Bolt and Pedersen, 1998). As a result of this cleavage, a hydrophobic domain is exposed at the *N*-terminus of the F1 subunit the sequence of which is highly conserved among the paramyxoviruses (Lambert *et al*, 1996; Baker *et al*, 1999). A second conformational change is believed to occur within the F1/F2 molecule after binding of the H protein to the receptor on the host cell, thereby juxtaposing the two amphipatic α-helical domains and enabling the insertion of the fusion domain into the target cell membrane (Lamb, 1993). In support of this model, peptides interfering with the insertion of the fusion domain or preventing the interaction of the amphipatic α-helical domains efficiently abolish viral membrane fusion (Wild and Buckland, 1997).

MV tropism and receptor usage

The interaction of particularly the MV H protein with its cellular surface receptor(s) is an essential determinant of MV tropism. CD46 (membrane cofactor protein, MCP, Figure 2) has been identified as MV receptor (Dörig *et al*, 1993; Naniche *et al*, 1993a), which is ubiquitously expressed on most human nucleated cells, although little in the brain (Ogata *et al*, 1997). Various isoforms were shown to support uptake of MV vaccine and some wild-type strains (Gerlier *et al*, 1994; Manchester *et al*, 1994). Transgenic expression of CD46 can confer susceptibility to MV infection in rodent cells *in vitro*, and this is associated with an enhancement of fusion between viral and host cell membranes (Horvat *et al*, 1996). Binding sites for the H protein of certain MV strains have been mapped in both membrane distal domains of CD46 (Buchholz *et al*, 1997; Casasnovas *et al*, 1999), which are also essential for downregulation from the cell surface after contact with the H protein with these strains (Firsching *et al*, 1999). Because particularly MV wild-type strains isolated and passed on lymphocytic cells failed to bind to or to downregulate CD46, it became clear that additional receptors mediating MV entry should exist (Schneider-Schaulies *et al*, 1995b; Bartz *et al*, 1998; Hsu *et al*, 1998; Tanaka

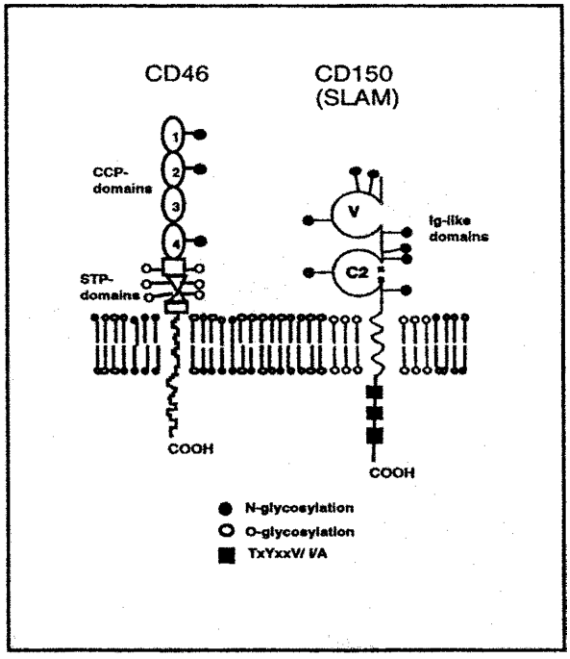

Figure 2 Structure of the measles virus receptor CD46 and CD150 (SLAM).

et al, 1998). Involvement of proteins such as moesin or substance P receptor in MV binding and/or entry in certain cell types has been proposed, their exact function for these processes has not been unraveled (Harrowe *et al*, 1992, Schneider-Schaulies *et al*, 1995a). More recently, CD150 (signaling lymphocyte activation molecule, SLAM, Figure 2) was identified as a cellular receptor for MV vaccine and wild-type strains (Tatsuo *et al*, 2000; Erlenhoefer *et al*, 2001; Hsu *et al*, 2001). The costimulatory molecule CD150 is expressed on activated T and B lymphocytes, memory cells, and dendritic cells (Cocks *et al*, 1995; Polacino *et al*, 1996; Punnonen *et al*, 1997; Ohgimoto *et al*, 2001). As found for CD46, CD150 is very efficiently downregulated from the cell surface after infection or contact with MV, which might contribute to the immunosuppressive capacity of the virus (Erlenhoefer *et al*, 2001). It is not clear yet whether MV wild-types do interact with CD46 at all, or may use it as a low affinity receptor (Manchester *et al*, 2000; Ono *et al*, 2001). Because CD150 is expressed on subsets of T and B cells and dendritic cells, but has not been reported on monocytes, epithelial cells, endothelial cells, and various brain cell types, wild-type MV might use additional molecule(s) as receptor on these cells.

MV receptor interactions with CNS cells

It has not been resolved as yet which cellular receptors essentially mediate MV entry in brain cells. Whereas CD150 expression has been reported exclusively for lymphoid and dendritic cells, CD46 has been found to be expressed also, albeit at relatively low levels, by neurons and astrocytes in normal brains. Within heavily infected MV-positive brain lesions of SSPE patients, CD46 was undetectable, independent of whether MV antigens were present in these individual cells. In contrast, normal levels of CD46 were found in SSPE brain tissue distant from the lesion suggesting that CD46 expression was reduced by the MV infection (Ogata *et al*, 1997). However, because only little CD46 is expressed by a proportion of neural cells, it is questionable whether MV in SSPE could spread via usage of this receptor in the human brain. Two further facts mentioned above argue against a role of CD46 as MV-receptor in the human brain: (1) MV strains causatively linked to SSPE are wild-type strains which may not interact with CD46, and (2) the viral RNP complex is spreading in the brain in the virtual absence of viral envelope proteins. Alternative mechanisms of cell-to-cell spread in neural tissue, such as usage of synaptic vesicles, have been discussed and described (Meissner and Koschel, 1995; Allen *et al*, 1996; Duprex *et al*, 1999b; Urbanska *et al*, 1997; Lawrence *et al*, 2000). MV spreads in differentiated human neuronal cells lacking CD46 from cell to cell by an intracellular route most likely involving local microfusion events at cell contact points (McQuaid *et al*, 1998).

Intracerebral infection of the rodent brain adapted CAM strain of MV has been extensively used to study the pathogenesis of acute and persistent MV CNS infections (Liebert and Finke, 1995). Because neither CD46 nor CD150 are expressed on rodent brain cells, it remains undefined which receptor(s) are involved in uptake and spread of MV in these animals. The role of the viral H protein on neurovirulence was investigated using a recombinant MV in which the H of MV Edmonston had been replaced by the H of the neurovirulent rat brain adapted CAM strain (Duprex *et al*, 1999a). After intracerebral injection into suckling C57/BL/6 mice this recombinant virus (EdtagCAMH) induced neurological disease, and MV antigen was found in neurons and neuronal processes of the hippocampus, frontal and olfactory cortices, and neostriatum. However, the neurovirulence of EdtagCAMH was reduced compared to the neurovirulent parental strain CAM indicating that not only the H, but also other viral genes, most likely the polymerase, contribute to the CAM-induced CNS disease. To investigate the molecular basis of the neurovirulence mediated by the CAM-H protein, a panel of recombinant MVs expressing mutant CAM-H proteins was generated. Replacement of only two amino acids in the CAM-H at positions 195 G $\rightarrow$ R and 200 S $\rightarrow$ N, caused a change in neurovirulence (Moeller *et al*, 2001). With the availability of mouse strains transgenic for CD46, it became recently possible just to use MV Edmonston or related strains for intracerebral infections (Rall *et al*, 1997; Mrkic *et al*, 1998).

MV interaction with cellular receptors in lymphocytic and monocytic cells

Both CD46 and CD150 are expressed on human primary peripheral blood lymphocytes (PBL) and monocyte-derived dendritic cells (DC), and particularly CD150 was found to support binding and entry of both MV vaccine and wild-type strains in these cells (Tatsuo *et al*, 2000; Erlenhoefer *et al*, 2001; Ohgimoto *et al*, 2001). Because CD150 was not found on monocytes, the infection of these cells with MV wild-type strains seems less clear. It remains to be resolved whether CD150 is expressed by monocytes/macrophages at low copy numbers and might not have been detected so far, or, what is more likely, given the fact that it is detectable on myeloid DC generated from monocytes *in vitro* (Ohgimoto *et al*, 2001), is that it might be expressed after activation/differentiation of monocytes by inflammatory signals. Using recombinant MV in which the authentic Edmonston-strain glycoproteins were singly or doubly exchanged for those of a lymphotropic wild-type strain, WTF, we recently found that the H protein essentially determines the tropism of the virus for lymphocytes or DC, respectively (Ohgimoto *et al*, 2001). Whereas binding, uptake, and spread in primary human PBL cultures is more efficient with viruses expressing the vaccine strain-derived H protein, cellular fusion, viral uptake, and spread

in DC was significantly enhanced with viruses expressing the H protein of wild-type MV. Importantly both, replication in secondary lymphoid tissues, and the induction of immunosuppression as determined by impaired proliferative responses of lymphocytes *ex vivo* were observed after intranasal infection of cotton rats (Sigmodon hispidus) with MVs expressing the wild-type H protein, but not those expressing the vaccine H protein (Ohgimoto *et al*, 2001). Although not directly shown *in vivo* as yet, it appears that wild-type MV strains reveal a tropism for professional antigen-presenting cells that may favor uptake in DC and transport to secondary lymphoid tissues, and that the H protein plays an important role in this process.

A plethora of alterations of lymphocyte, monocyte, and DC functions and viability has been described related to MV infection in these cell populations, and these were extensively discussed in the context of immune activation and suppression (Schneider-Schaulies *et al*, 2001). Here we focus on those events that have been clearly attributed to MV surface interactions with the respective host cells. As outlined above, downregulation of both CD46 and CD150 was observed after contact with MV H proteins (Naniche *et al*, 1993b; Krantic *et al*, 1995; Schneider-Schaulies *et al*, 1996; Erlenhoefer *et al*, 2001). Whereas functional consequences of CD150 downregulation by MV have not been assessed, it became essentially clear that MV H-mediated downregulation of CD46, in accordance with the natural function of this protein, is associated with an enhanced sensitivity to complement-mediated lysis of both infected and uninfected cells (Schnorr *et al*, 1995). Because CD46 modulation and subsequent elimination of virus together with infected cells is mainly observed with MV vaccine strains, this finding is likely to reflect an attenuation marker. Examples of signaling events elicited after surface contact with MV H protein include upregulation of LFA-1 on leukocytes (Nagendra *et al*, 1995) and the induction of type I IFN and NO in the presence of type II IFN in mouse macrophages stably expressing human CD46 (Hirano *et al*, 1999; Katayama *et al*, 2000). In this study, tyrosine phosphorylation of CD46 cytoplasmic domain 2 did occur after CD46 ligation in a src family-dependent manner. Moreover, CD46 ligation by MV- or CD46-specific antibodies interfered with induction of IL-12 synthesis in monocyte cultures (Karp *et al*, 1996, Kurita-Taniguchi *et al*, 2000), which could explain why Th1 responses might be inadequately generated during measles (Griffin and Ward, 1993). The role of signaling via CD46 for immunosuppression is unclear because many wild-type strains appear not to interact with this molecule. In T cells, cross-linking of CD46 was even found to confer a costimulatory signal in promoting T cell proliferation (Astier *et al*, 2000). Because the antibody used for CD46 crosslinking in this study was identical to that which blocks MV binding, this suggests that signaling elicited by MV via CD46 should rather stimulate than inhibit T-cell proliferation. Similarly, CD150 ligation by monoclonal antibodies was linked to T-cell stimulation rather than inhibition (Cocks *et al*, 1995).

MV glycoproteins can, however, provide a surface contact mediated signal that directly inhibits lymphocyte proliferation. This was first seen in MV-infected T-cell cultures where proliferative inhibition did also occur in uninfected cells (Yanagi *et al*, 1992), and inactivated MV-infected cells actively inhibited the mitogen-dependent proliferation of autologous T cells in a dose-dependent manner. This was sensitive to anti-MV hyperimmune serum suggesting that MV components were directly involved (Sanchez-Lanier *et al*, 1988). Pursuing these studies we found that the coexpression of MV H and proteolytically activated F protein on the surface of viral particles, infected cells, or cells transfected to express these proteins was necessary and sufficient to suppress by surface contact the proliferative activity of uninfected human lymphocytes (Schlender *et al*, 1996; Weidmann *et al*, 2000b). Importantly, cells transfected to express the viral glycoprotein complex also induced immunosuppression in cotton rats (Niewiesk *et al*, 1997). Further *in vitro* experiments revealed that soluble mediators and fusion were not involved in this proliferative inhibition of lymphocytes (Weidmann *et al*, 2000a). Including fusion inhibitory peptides in this assay we established that structural requirements of the glycoprotein complex for the induction of immunosuppression and fusion are different. Inhibition of proliferation can occur in the absence of CD46 and CD150, and neither CD46- nor CD150-specific antibodies block the induction of this proliferative inhibition (Erlenhoefer *et al*, 2001). Thus, putative receptor(s) engaged in contact-mediated proliferation inhibition are still unknown.

Studying the molecular basis of this contact-mediated inhibition of lymphocytes we found that apoptosis is not induced. Rather, the cells accumulate in the G1 phase of the cell cycle that, on a molecular level, is characterised by a marked inhibition of the activity of G1 cyclin-CDK complexes and the accumulation of their subunits as well as a delayed degradation of $p27^{kip1}$ after mitogenic stimulation (Schnorr *et al*, 1997; Engelking *et al*, 1999; Niewiesk *et al*, 1999). As revealed by more recent studies, the IL-2-dependent activation of the JAK1/3/STAT3/5 pathway is unaffected in both primary human T cells and an IL-2-dependent T-cell line, whereas activation of the protein kinase B/Akt pathway by IL-2 is essentially blocked (Avota *et al*, 2001). The importance of these findings for MV-induced immunousppression was supported by the findings that (1) inhibition of Akt activation was also observed *in vivo* after MV infection of cotton rats, and (2) transgenic expression of a constitutively active myr-Akt kinase efficiently interfered with the induction of T-cell proliferation by MV (Avota *et al*, 2001). This is the first example

for inhibition of this particular pathway which is essential for transmitting both survival and S phase entry signals by a pathogen, and is apparently a completely new concept for viral modulation of gene functions.

Concluding remarks

Viral suppression of the Akt kinase might also play a role in the pathogenesis of CNS complications, since Akt is involved in the regulation of the survival of cells such as neurons and endothelial cells.

The interaction of viral envelope proteins with cell surface receptors, which means not only high affinity binding to the H protein, but also the interaction with viral fusion proteins, and the resulting signal transduction may impair cell functions of the immune and nervous system. These findings demonstrate the complexity of the interplay between the pathogen and the host, and may open new ways for therapeutic strategies. Certainly this research topic will stay on the list for the following years.

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