STAT2 Is a Primary Target for Measles Virus V Protein-Mediated Alpha/Beta Interferon Signaling Inhibition

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Received 17 April 2008/Accepted 17 June 2008

Measles virus, a member of the Morbillivirus family, infects millions of people each year despite the availability of effective vaccines. The V protein of measles virus is an important virulence factor that can interfere with host innate immunity by inactivating alpha/beta interferon (IFN-α/β) and IFN-γ signaling through protein interactions with signal transducer and activator of transcription proteins STAT1 and STAT2. Here we demonstrate that although STAT1 interference results from protein interactions within a V protein N-terminal region encompassed by amino acids 110 to 130, detection of STAT1 interaction and IFN-γ signaling inhibition requires the presence of cellular STAT2. Cell-specific variability in STAT1 interference was observed to correlate with V protein expression level. A more direct target for measles virus V protein-mediated IFN-α/β evasion is STAT2. Results indicate that the widely conserved C-terminal zinc finger domain of measles virus V protein is both necessary and sufficient to bind STAT2 and disrupt IFN-α/β signal transduction. Mutagenesis and molecular modeling define a contact surface for STAT2 association that includes aspartic acid residue 248 as critical for STAT2 interference and IFN antiviral immune suppression. These findings clearly define the molecular determinants for measles virus IFN evasion and validate specific targets as candidates for therapeutic intervention.

Measles virus is a leading cause of death among young children despite the availability of a safe and effective vaccine for the past 40 years (28). Vaccination has greatly limited the spread of measles virus, and yet sufficient vaccine coverage has been difficult to achieve in developing countries. Factors such as immigration and public distrust of vaccine safety have contributed to local measles outbreaks even in developed countries, including the United States (5, 6, 29). A greater understanding of the molecular mechanisms underlying host evasion by this pathogen would facilitate the design of new therapeutic strategies by identifying targets for pharmacological inhibition that could augment or replace vaccinations in some situations.

Measles virus belongs to the Morbillivirus genus of the large Paramyxoviridae family (reviewed in reference 21). Most of these viruses share common genetic features, including a poly-cistronic gene that encodes two or more viral proteins from overlapping open reading frames (ORFs). In measles virus, a single gene encodes three proteins (C, P, and V) from a series of overlapping ORFs. The P/V/C locus of measles virus, like that of other paramyxoviruses, is associated with host immune evasion, and paramyxoviruses use these gene products for interference with the antiviral cytokines in the interferon (IFN) family. This interference includes inhibition of the critical antiviral IFN signaling (9) as well as the reported prevention of apoptosis (16, 48), cell cycle alterations (24), inhibition of double-stranded RNA signaling (16, 36), and prevention of IFN biosynthesis (16, 36, 48). In most cases, these activities are ascribed to the V protein, but specific cases of P- and C-mediated host evasion have been revealed (8, 10). The ORF encoding the P protein overlaps partially with a second ORF encoding the V protein. Access to the hidden ORF is achieved by cotranscriptional insertion of nontemplated guanine nucleotides at a precise location, or “editing site,” to generate alternate mRNAs that differ only by the presence or absence of one or two additional nucleotides. Due to this unusual coding strategy, the paramyxovirus P and V proteins share an amino terminus but have unique carboxyl termini (4, 45). Paramyxovirus V proteins are identifiable by their C-terminal domain (CTD), which codes for a conserved cysteine-rich region (21, 35, 45). The CTDs among all paramyxovirus V proteins are approximately 50% identical and invariably include one histidine and seven cysteine residues capable of binding two atoms of zinc (25, 35). Aside from this stoichiometry, which is similar to that of some cellular metalloproteins, the spacing of CTD cysteine residues is not consistent with that of known zinc-binding domains and no cellular V protein homologues have been described. Recent X-ray crystallographic studies confirm that the V protein CTD forms a unique zinc finger fold (23).

IFN family cytokines have long been recognized as fundamental mediators of innate antiviral responses (18). Alpha IFN (IFN-α) subtypes and IFN-β, referred to collectively here as IFN-α/β, are the principal antiviral cytokines produced by mammalian cells and act directly on target cells by blocking virus replication and enhancing adaptive immunity. IFNs have diverse effects on a variety of cell types, and both IFN-α/β and IFN-γ (a related but distinct cytokine) can cause diminished virus replication by using a number of mechanisms initiated by changes in gene expression upon IFN receptor stimulation (13). The principal intracellular signaling apparatus downstream of IFN-α/β receptors culminates in the assembly of an active transcription factor complex, ISGF3, which contains two
signal transducer and activator of transcription (STAT) proteins, STAT1 and STAT2, and an IFN regulatory factor, IRF9 (12, 20). ISGF3 is responsible for directing the expression of the antiviral effector gene expression program leading to an antiviral state. Similar signaling downstream of the IFN-γ receptor leads to activation of a tyrosine-phosphorylated STAT1 homodimer that regulates a distinct subset of cellular genes that help shape the IFN-γ-mediated antiviral response.

Measles virus has been demonstrated to antagonize IFN-α/β and IFN-γ responses by V protein interference with STAT signal transduction. Prior investigations of measles virus V protein-mediated IFN signaling evasion produced several reports confirming IFN-α/β interference, but IFN-γ signaling interference was not always observed (3, 8, 10, 33). This apparent discrepancy was attributed to differences in the virus strains or passage histories, host cell lines tested, or procedures used. The finding that measles virus can interfere with dendritic cell development and expansion by altering IFN-α/β responses that are STAT2 dependent and STAT1 independent (15) suggested that STAT2 may be an important target for measles virus-induced immune suppression (32).

Like other paramyxovirus V proteins, measles virus V protein can inhibit IFN antiviral responses at least in part through associations with both STAT1 and STAT2 (3, 33). Despite the importance of these protein interactions in determining measles virus virulence, little mechanistic information has been obtained regarding the nature of V protein interactions with STATs. Here, we resolve in molecular detail the biochemical basis for measles virus V protein engagement of STAT1 and STAT2. Detection of STAT1 association was found to be influenced by the V protein expression level and was highly stabilized by the presence of cellular STAT2. The STAT1 contact site was mapped to amino acids 110 to 130, in general agreement with prior reports of P and V protein interference (VSV-GFP) (9).

RESULTS

STAT2 is a primary target for measles virus V protein. To better understand the diverse observations regarding measles virus V protein host interference, IFN signaling evasion assays were carried out using a variety of mammalian cell lines, including the human cell lines 2fTGH and HEK293T. Uniform IFN-α/β interference was observed for all lines tested, but the degree of IFN-γ signaling interference varied in a fashion that correlated with the intrinsic susceptibility of the cell line to plasmid transfection and the expressed V protein accumulation level. For example, our estimates indicate that transient transfection of equal amounts of plasmid vector into a confluent monolayer of 2fTGH or HEK293T cells results at least fourfold more protein for the HEK293T than for the 2fTGH cell line per microgram of total protein in a 24-h period (data not shown). We routinely observed modest IFN-γ signaling interference in the 2fTGH cells compared to a high degree of interference in the HEK293T cells (Fig. 1A and B).

Luciferase reporter gene assays were performed using HEK293T or 2fTGH cells as described previously (47). Briefly, the cells were transfected with a reporter gene, Renilla luciferase, and either empty vector or the cDNA expression plasmids. For IFN-γ response determinations, the reporter gene used contained four copies of m67-SIE (GAS) linked to a TATA box and the firefly luciferase ORF. The IFN-α/β-responsive reporter gene contains five copies of the ISG54 IFN-stimulated response element (ISRE) upstream of the TATA box and the firefly luciferase ORF. After 24 h, transfection medium was replaced with fresh medium or medium supplemented with 1,000 U of IFN-α/ml or 5 ng of IFN-γ/ml. At 14 h after IFN treatment, the cells were harvested and assayed for firefly and Renilla luciferase activity (dual luciferase reporter assay system; Promega). Relative expression levels were calculated by dividing the firefly luciferase values by those obtained with Renilla luciferase.

For MDA5 signaling assays, cells were transfected with myc-tagged MDA5 construct, MDS, −110 IFN-β luciferase reporter gene, and Renilla luciferase. After 24 h of transfection, the cells were stimulated with 5 μg of poly (I:C)/ml (Amersham Pharmacia) by transfection with Lipofectamine or Lipofectamine 2000 (Invitrogen). The cells were harvested after 6 h and assayed for firefly and Renilla luciferase activity. The data are graphed to represent the average values for triplicate samples normalized to cotransfected Renilla luciferase activity (expressed as a percentage of the value for the control stimulated sample).

Cell extracts, immunoblotting, and immunoprecipitation. For preparation of cell extracts, samples were washed once with ice-cold phosphate-buffered saline and subsequently lysed with whole-cell-extract buffer (WCEB) as described previously (34, 46). For immunoblotting, proteins were separated, transferred to nitrocellulose, probed with antibodies, and visualized by chemiluminescence (NEL Life Sciences). For immunoprecipitation, lysates were prepared in WCEB and preclutted with Sepharose beads. Antibody-protein complexes were purified with FLAG M2 (Sigma) or glutathione beads (GE Healthcare) and washed with WCEB. After elution with sodium dodecyl sulfate, proteins were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and processed for immunoblotting. The antibodies used were STAT1 (Santa Cruz C20), STAT2 (Santa Cruz, C24), FLAG (Sigma), and glutathione S-transferase (GST) (Sigma).

Indirect immunofluorescence. For immunofluorescence, 2fTGH cells were grown on Permanox chamber slides (Nalgene Nunc) and transfected and stained exactly as described previously (40). Images were obtained using a Leica TCSSP confocal microscope, and representative fields with both transfected and untransfected cells in the same field are shown wherever possible for direct comparison.

Antiviral assays. Antiviral responses measured by green fluorescent protein (GFP) reporter virus assays were conducted as reported previously (11, 17). Briefly, 2fTGH stable cell lines expressing empty vector, wild-type (WT) V protein, and mutant V protein were pretreated with IFN for 8 h. Cells were washed with serum-free medium and infected with vesicular stomatitis virus-GFP (VSV-GFP) (9 × 10^4 PFU/ml) for 1 h and cultured for 22 h in the presence of 2% serum-containing media. After 22 h, the cells were photographed and harvested for analysis by flow cytometry.
The ability of V proteins to interfere with STAT function generally relies on formation of stable protein interactions. To test the specificity of measles virus V protein interactions with STAT1 and STAT2 under moderate expression conditions, a V protein coimmunoprecipitation assay was carried out with transfected 2fTGH- or 2fTGH-derived cell lines harboring single gene defects in STAT1 (U3A) or STAT2 (U6A) (22, 30). Expressed FLAG-tagged measles virus V protein was immuno-noprecipitated using FLAG-M2 agarose beads and tested for coprecipitation of endogenous STATs. Results indicate that 2fTGH cells can support both STAT1 and STAT2 copurification with the expressed FLAG-tagged V protein (Fig. 1C). In the absence of STAT1 expression (U3A cells), the V protein association with STAT2 was retained. The converse was not true: in the absence of STAT2 (U6A cells), greatly reduced STAT1 association was observed. The defect in STAT1 coprecipitation could be rescued by complementing the cells with stable STAT2 expression. These data indicate that genetic deficiency in STAT2 can influence the association with STAT1. Apparently, STAT2 is a primary target for measles virus V-mediated IFN evasion, but STAT1 interference requires the presence of cellular STAT2 and was observed to correlate with V protein expression levels.

The measles virus V protein CTD is necessary and sufficient for STAT2 binding. To guide the mapping of the V protein-STAT interaction sites, two FLAG-tagged measles virus V protein fragments were expressed. One of these encompassed the N-terminal 231 amino acids that are shared between measles virus V and P proteins, and the other was the isolated cysteine-rich CTD, consisting of residues 232 to 299 (Fig. 2A). While the N-terminal fragment accumulates to steady-state levels similar to those seen with the WT protein, the much smaller CTD (68 amino acids) was difficult to detect in the transfected cells. FLAG immunoprecipitation revealed that the full-length measles virus V protein coprecipitated both STAT1 and STAT2, but both fragments were greatly incapacitated for STAT1 interaction (Fig. 2B). A small amount of STAT1 coprecipitated with the N-terminal fragment, but STAT2 was readily detected in association with the CTD fragment despite its low level of accumulation. Therefore, the CTD is both necessary and sufficient to mediate STAT2 association. This result stands in contrast with those seen with other paramyxovirus V proteins for which CTD is not sufficient to mediate STAT interaction (see, e.g., references 38 and 46).

To verify this result, GST fusions were constructed to help stabilize the CTD fragment. Glutathione purification of the expressed fusions confirmed that the measles virus V protein N terminus did not associate with STAT2. STAT2 bound specifically to the measles virus V CTD but not to the control mumps virus V protein CTD (Fig. 2C). The ability of the V protein fragments to interfere with IFN signaling was tested in an IFN-responsive luciferase reporter gene assay. Only the measles virus V CTD disengaged IFN-induced ISRE luciferase reporter gene activity, but neither the measles N-terminal domain nor the mumps virus V protein CTD inhibited reporter gene activity (Fig. 2D). It has been demonstrated that the V protein interacts with MDA5 via the intact zinc finger domain (1). To verify the proper folding of both CTD fusions, their ability to disrupt signaling by the RNA signaling-helicase protein MDA5 was tested. Both measles virus and mumps virus CTD fusions were capable of disrupting MDA5-dependent signaling to the IFN-β promoter reporter gene (Fig. 2E). Based on these experiments, we conclude that the CTD interaction with STAT2 is a specific and unique adaptation of measles virus for overcoming IFN antiviral signal transduction.

Measles virus V IFN-α/β evasion is independent of the STAT1 binding site. STAT1 can readily coprecipitate with full-length measles virus V protein in a STAT2-dependent
manner but does not associate well with either the N terminus or the C terminus in isolation. In order to determine the protein interaction site for STAT1, a series of engineered overlapping deletions were screened for STAT1 coimmunoprecipitation and IFN-γ signaling interference (data not shown). The results implicated amino acids 110 to 130 as a potential STAT1 contact site (Fig. 2A). Deletion of this segment resulted in a failure to coprecipitate STAT1 but not STAT2 (Fig. 2F). This region coincides with a subset of residues common to the P and V proteins previously noted for extensive sequence conservation among members of the *Morbillivirus* family (8). Specifically, tyrosine residue 110 (Y110) of the P protein was implicated as important in regulating STAT1 activity in cells infected with V-deficient measles virus (8) and mutation of Y110 to histidine decreased V protein binding to overexpressed STAT1 (3). This mutant, Y110H, was defective for interaction with endogenous STAT1 in our assay, but STAT2 interaction remained intact (Fig. 2F). Importantly, these mutant V proteins remained potent antagonists of IFN-α-induced transcription (Fig. 2G). While residues 110 to 130 and, specifically, Y110 are required for STAT1 association, they are not required for STAT2 binding and IFN-α/β signal interference.

**CTD structure and amino acid sequence specify STAT2 interaction.** The paramyxovirus V protein CTD is highly conserved in amino acid sequence and has been characterized biochemically and structurally as a cysteine-rich zinc binding domain (25, 35). The crystal structure of SV5 V protein revealed that the conserved CTD forms a unique zinc finger fold as the result of the presence of the invariant histidine and seven cysteine residues coordinating two zinc atoms. The zinc binding produces a first finger that is 20 amino acids long and consists of two antiparallel β strands and a second finger of 12 residues (23). Amino acid sequence comparison of measles virus and mumps virus CTDs (Fig. 3A) revealed three non-conserved regions, referred to as Box1, Box2, and Box3, that we hypothesized may contribute to the specific STAT2 association. Box1 and Box2 are embedded in the first and second zinc fingers, respectively, and Box3 is a unique C-terminal extension found only in the measles virus V protein.

To test the importance of these three regions in STAT2 antagonism, three measles virus V variants were constructed to remove Box3 or to replace Box1 and Box2 with the analogous residues of mumps virus V protein. This swapping strategy was used to preserve the overall zinc finger structure of the CTD but to replace the variable sequences from the STAT2-binding measles virus V protein CTD with those of the non-STAT2-binding mumps virus V protein CTD. In order to test the importance of the finger structure itself, alanine substitution mutations were engineered for the histidine (H232A) or the histidine plus the first two cysteines (H232A/C251A/C255A) in order to disrupt the zinc coordination (Fig. 3A).

The WT and variant V proteins were expressed in HEK293T cells, and FLAG immunoprecipitation was carried out to test for STAT2 binding (Fig. 3B). The WT protein bound well to STAT2, and deletion of Box3 had little effect. In contrast, both substitutions for Box1 and Box2 and the point mutations resulted in proteins that failed to precipitate STAT1 but not STAT2 (Fig. 2F). This region coincides with a subset of residues common to the P and V proteins previously noted for extensive sequence conservation among members of the *Morbillivirus* family (8). Specifically, tyrosine residue 110 (Y110) of the P protein was implicated as important in regulating STAT1 activity in cells infected with V-deficient measles virus (8) and mutation of Y110 to histidine decreased V protein binding to overexpressed STAT1 (3). This mutant, Y110H, was defective for interaction with endogenous STAT1 in our assay, but STAT2 interaction remained intact (Fig. 2F). Importantly, these mutant V proteins remained potent antagonists of IFN-α-induced transcription (Fig. 2G). While residues 110 to 130 and, specifically, Y110 are required for STAT1 association, they are not required for STAT2 binding and IFN-α/β signal interference.

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The ability of these V proteins to disrupt IFN-α/β signal transduction was tested with an ISRE luciferase reporter gene assay. All of the proteins that bound STAT2 also retained the ability to inhibit IFN-α/β signaling (Fig. 3C). Importantly, despite the loss of STAT2 binding, V proteins with Box1 and Box2 substitutions retained the ability to inhibit MDA5 signaling, indicating that the overall CTD structure remained intact irrespective of the substitutions (Fig. 3D). In addition, all the
mutants also retained the ability to inhibit IFN-γ/STAT1 signaling in HEK293T cells (Fig. 3E). Together, these data indicate that both the zinc finger structure and the specific amino acids within the fingers are required for measles virus V to engage STAT2.

**Point mutations disengage V-STAT2 association.** Alignment of V protein CTDs revealed several measles-specific residues within Box1 and Box2 that could account for the ability to associate with STAT2. To further examine the amino acids important for STAT2 association, point mutations were designed to replace measles virus amino acids within Box1 and Box2 with the respective mumps virus residues (Fig. 4A). The mutant V proteins were tested for STAT2 coimmunoprecipitation (Fig. 4B) and IFN-γ/H9251/H9252 (Fig. 4C) or IFN-γ/H9253 (Fig. 4D) signaling inhibition. These parameters differed greatly among the six Box1 and six Box2 mutations tested. Based on the ISRE luciferase reporter gene assay results, mutations N241V, I247V, and L260A retained more than 80% of the WT level of activity whereas others exhibited from 30% to 70% of WT activity (Fig. 4C). One mutation, D248F, produced the strongest defect in STAT2 binding and failed to disrupt IFN signaling, and a second, F246R, was severely compromised. Despite the differential effects on STAT2, all these mutant V proteins retained the ability to disengage IFN-γ/STAT1 signaling in HEK293T cells (Fig. 4D).

**D248F disrupts V-mediated STAT2 cytoplasmic retention and antiviral signaling evasion.** The disruption of measles virus V protein function by D248F mutation was characterized further in sensitive biological assays for IFN antiviral signaling. Measles virus V protein is known to prevent IFN-induced STAT2 nuclear translocation (33) and thereby to interfere with formation of the antiviral state. Indirect immunofluorescence was used to visualize the subcellular localization of STAT2 in the presence of measles virus V proteins (Fig. 5). STAT2 is found in the cytoplasm of unstimulated cells, but IFN stimulation induces rapid translocation and nuclear accumulation (41). In the presence of measles virus V protein, IFN fails to induce STAT2 nuclear accumulation (33). The D248F mutant did not retain STAT2 in the cytoplasm, but a control mutant, N241V (which binds to STAT2), functioned like the WT V protein.

To verify the defective IFN evasion activity of the D248F mutant V protein in a biologically relevant context, a standard cytopathic effect assay was used to evaluate IFN antiviral responses. Stable cell lines expressing measles virus V protein or a D248F mutant were generated, and cell lines with similar levels of V protein abundance (Fig. 6B) were treated with IFN-α for 8 h followed by infection with a reporter virus containing a GFP transgene (VSV-GFP). Control cells with no expressed V protein were highly susceptible to infection, but IFN treatment dramatically reduced the number of fluorescent cells. Expression of WT measles virus V protein disrupted protection by IFN, resulting in uniformly higher GFP expression. In contrast, cells expressing the D248F V protein were unhindered in establishing an IFN-induced antiviral state, protecting the cells from VSV-GFP replication (Fig. 6A and C).
Together, these findings confirm that aspartic acid residue 248 of measles virus V protein CTD is a critical determinant of host immune suppression.

DISCUSSION

Host immune responses provide a strong selective pressure for the evolution of viral evasion tactics. The ability to overcome host defenses enables the pathogen to succeed, allowing further diversification of the viral armamentarium. The results presented here demonstrate that measles virus has developed distinct mechanisms for disengaging the IFN-γ and IFN-α/β signal transduction machinery through separate associations with STAT1 and STAT2.

STAT2 appears to be a primary target for V protein-mediated IFN-α/β evasion and is engaged in the absence of STAT1 or the V protein’s STAT1 binding site. Mapping the protein interaction domain for STAT2 revealed that the V protein CTD is necessary and sufficient for this interaction. This finding is unique to measles virus V protein and differs from the results obtained with other paramyxoviruses described to date. For example, members of the Rubulavirus family require both the N- and C-terminal domains for their STAT-directed evasion properties (34), and the V protein CTD is totally dispens-
able for STAT binding and IFN evasion for members of the *Henipavirus* family (38). Results demonstrate that despite the high degree of conservation in the paramyxovirus V protein CTD, sufficient differences exist in measles virus V protein for specific targeting of STAT2. Both amino acid sequence and zinc finger integrity were found to contribute to STAT2 association. The high conservation in the paramyxovirus V protein CTD enabled computer modeling of the measles virus CTD on the SV5 structure (Fig. 4E). This model illustrates that the Box1 and the Box2 regions lie on the same surface of the zinc fingers. Plotting the positions of incapacitating mutations revealed the close proximity of D248 and F246 within a three-dimensional pocket formed by both fingers that apparently serves to coordinate STAT2 associations along a single V protein interface. As this fold requires intact zinc coordination, such a model accounts for the observation that both structural integrity and amino acid sequence are required for STAT2 interaction. The reverse side of the CTD is free of STAT2-binding residues. It is tempting to speculate that this more conserved face of the CTD is responsible for multimeric interactions (46) or for association with other viral or cellular proteins such as MDA5, the RNA signaling helicase (1).

Results indicate that STAT1 can be targeted by V protein under optimal experimental conditions. This STAT1 interaction is mediated by an amino terminal peptide requiring residues 110 through 130, a region noted for high sequence conservation among members of the *Morbillivirus* family (8), that is present in both the P and V proteins. It is interesting that Nipah virus and Hendra virus, distantly related paramyxoviruses of the *Henipavirus* genus, also bind to STAT1 with residues in the P/V common region, via amino acids 100 to 160 for the Nipah virus P, V, and W proteins (26, 39, 42). For measles virus, this region originates with tyrosine 110, a residue that has been implicated in control of IFN responses. The original measles virus infectious clone, Ed-TAG, was shown to be de-

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**FIG. 5.** D248F mutation prevents V-mediated STAT2 cytoplasmic sequestration. 2TGH cells were transiently transfected with empty vector or expression plasmids for the WT or mutant measles virus V (MeV) proteins indicated. Cells were left unstimulated (UNT) or were treated with 1,000 U of IFN-α/ml for 30 min prior to fixation, permeabilization, and sequential staining for a FLAG epitope tag to detect V protein and antiserum to detect endogenous STAT2. Arrows point to V-expressing cells.

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**FIG. 6.** D248F mutation is required for antiviral evasion. (A) Reporter virus assay for antiviral effects. 2TGH stable cell lines expressing the empty vector or the V proteins indicated were left untreated (-IFN) or treated with IFN-α (+IFN) for 8 h and then infected with 9 × 10^5 PFU of VSV-GFP/well for 22 h prior to fluorescence microscopy. (B) Demonstration of V protein expression in stable cell lines with FLAG antibody and anti-α-tubulin control. (C) Quantification of VSV-GFP. The cells described for panel A were harvested, and 10,000 cells were analyzed by flow cytometry for GFP fluorescence.
fective in IFN evasion (7, 31, 37), and sequence comparisons revealed the presence of two amino acid substitutions. One of these changed cysteine 272 to arginine, destroying the CTD zinc finger, and a second was a substitution of histidine for tyrosine 110 (Y110H) (31). Subsequent reports of studies using the Moraten, Schwartz, or CAM70 strains confirmed the importance of Y110 in STAT1 interference (3, 8, 10). Our data presented here give insight into the development of small molecules that can be used for the improvement of existing measles virus vaccines and as adjuvants for the use of measles virus as an oncolytic vector for human therapeutics (43), especially for patients with intact IFN systems.

ACKNOWLEDGMENTS

We are grateful to Patricia Devaux and Roberto Cattaneo for insightful discussions, members of the Horvath Laboratory for critical evaluation and comments on the manuscript, and Louise E. Ludlow for generating the Y110H mutant. This work was supported by NIH grant R01AI050707.

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