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The Rabies Virus Interferon Antagonist P Protein Interacts with Activated STAT3 and Inhibits Gp130 Receptor Signaling

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Immune evasion by rabies virus depends on targeting of the signal transducers and activator of transcription 1 (STAT1) and STAT2 proteins by the viral interferon antagonist P protein, but targeting of other STAT proteins has not been investigated. Here, we find that P protein associates with activated STAT3 and inhibits STAT3 nuclear accumulation and Gp130-dependent signaling. This is the first report of STAT3 targeting by the interferon antagonist of a virus other than a paramyxovirus, indicating that STAT3 antagonism is important to a range of human-pathogenic viruses.

The principal response of mammalian cells to viral infection is the activation of the type I interferon (IFN)-mediated innate immune response through the production of type I IFNs (IFN- α and - β). IFN- α/β bind to receptors on infected and neighboring cells to activate intracellular signal transducers and activator of transcription 1 (STAT1) and STAT2 proteins by tyrosine phosphorylation. Activated STAT1 and -2 translocate to the nucleus to activate antiviral gene expression essential to the establishment of an antiviral state (reviewed in reference 1).

Subversion of the host IFN system is a key component of pathogenic viral infection and is mediated by virus-encoded IFN antagonist proteins (2). Because of their pivotal roles in antiviral innate immunity, STAT1 and -2 are among the principal targets of IFN antagonists (2, 3), including the lyssavirus phosphoproteins (P proteins) (see below), paramyxovirus V proteins, and dengue virus NS5 protein, which interact physically with STAT1 and/or -2 to inhibit their activity (4–8). However, it is well known that IFN- α/β signaling also activates other members of the STAT family, including STAT3 (which is activated by phosphorylation at residue Y705), resulting in the generation of alternative STAT complexes that modify the IFN-activated transcriptional signature (1). STAT3 is also a principal mediator of Gp130 receptor-dependent

signaling and thus plays roles in cellular activation by a number of alternative immune stimuli, in particular, by members of the interleukin-6 (IL-6) cytokine family, including IL-6, oncostatin M (OSM), and leukemia inhibitory factor (9, 10).

STAT3 is a highly pleiotropic member of the STAT family with roles in diverse processes, including proliferation, cell survival, and embryogenesis, in addition to immune signaling (reviewed in reference 11). The potential importance of STAT3 signaling in responses to certain viruses has been indicated by reports that the V proteins of the paramyxoviruses measles virus and mumps virus and the mumps virus-related bat virus Tioman virus specifically target STAT3 and inhibit STAT3-dependent signaling (12–14). However, there are no reports of STAT3 binding and inhibition by

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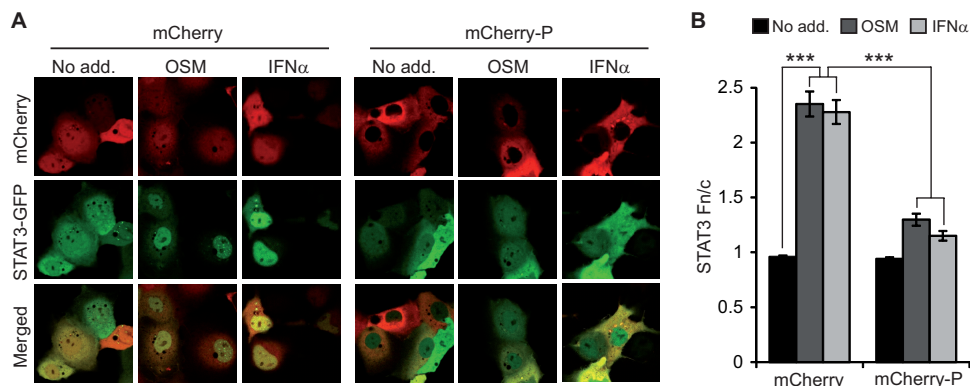


FIG 1 RABV P protein inhibits nuclear translocation of cytokine-activated STAT3 in living cells. COS-7 cells cotransfected to express the indicated proteins were treated at 20 h posttransfection without or with 10 ng/ml OSM (Biovision Inc., San Francisco, CA; catalog no. 4466-10) or 1,000 U/ml IFN- α (PBL interferon source; catalog no. 11200-2; Pestka Biomedical Laboratories, Piscataway, NJ) for 15 min before live-cell imaging with an Olympus Fluoview 1000 confocal laser scanning microscope with a heated chamber; CLSM images in the red and green channels were sampled sequentially (25, 26). Digitized CLSM images were analyzed using ImageJ software (National Institutes of Health, Bethesda, MD) to calculate the Fn/c ratio corrected for background fluorescence (6, 21, 25, 26) (mean Fn/c ratio \pm the standard error of the mean; $n > 44$). Results are from a single assay representative of two or more independent assays. Statistical analysis (Student's *t* test) was performed using Microsoft Excel software. ***, $P < 0.0001$. No add., no addition.

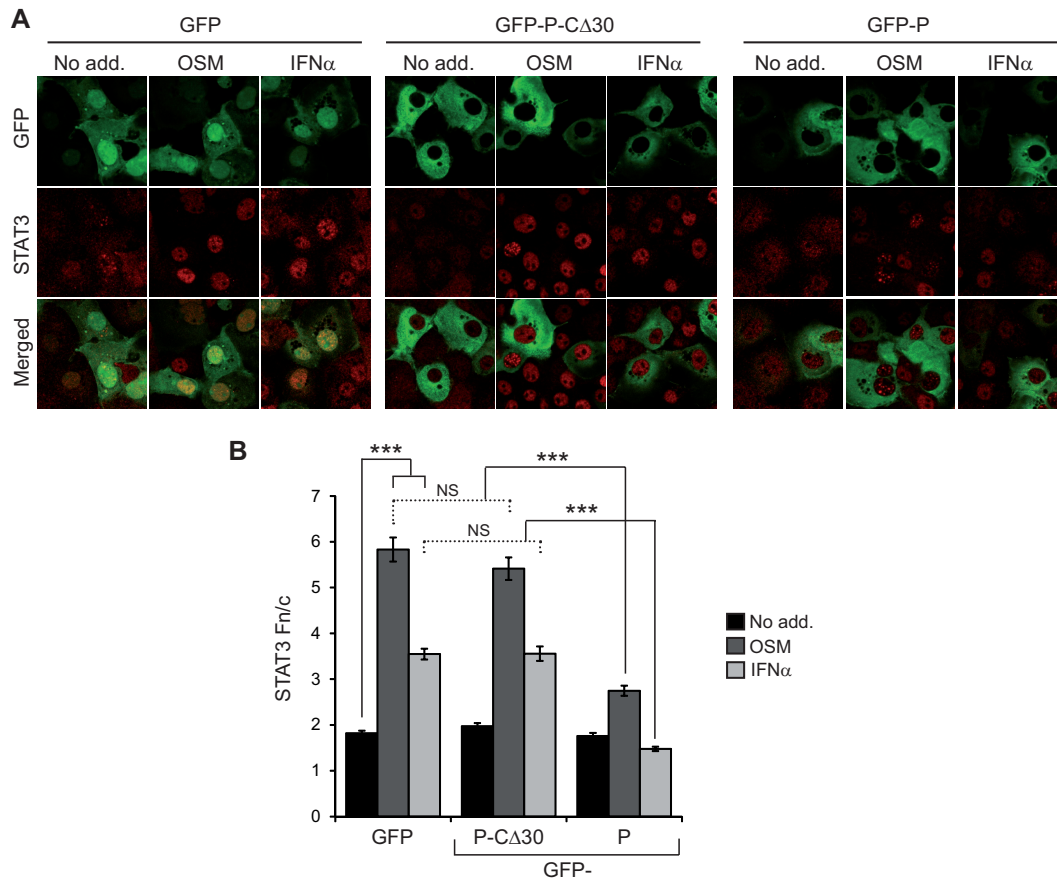


FIG 2 RABV P protein inhibits nuclear translocation of endogenous cytokine-activated STAT3. (A) COS-7 cells transfected to express the indicated proteins and treated at 20 h posttransfection without or with 10 ng/ml OSM or 1,000 U/ml IFN- α for 15 min were fixed and immunostained with anti-STAT3 (Santa Cruz Biotechnology, Santa Cruz, CA; catalog no. sc-482) and Alexa Fluor 568-labeled secondary (Invitrogen, Carlsbad, CA; catalog no. A11034) antibodies before analysis using a Nikon C1 confocal laser scanning microscope; CLSM images in the red and green channels were sampled sequentially. (B) Calculation of the Fn/c ratio (mean Fn/c ratio \pm the standard error of the mean; $n > 60$) for Alexa Fluor 568-labeled STAT3 and statistical analysis (Student's t test) were performed as described in the legend to Fig. 1. Results are from a single assay representative of six independent assays (GFP and GFP-P) or two independent assays (GFP-P-C Δ 30). ***, $P < 0.0001$; NS, not significant; No add., no addition.

IFN antagonists of viruses other than these paramyxoviruses, and this function varies even among the V proteins of different members of the *Paramyxoviridae* family; for example, those of the Nipah and Hendra viruses target STAT1 and -2 but not STAT3 (15, 16). Thus, viral targeting of STAT3 is highly selective, indicative of specific requirements of different viruses to modulate STAT signaling to regulate immunity and/or other aspects of cell biology.

Rabies virus (RABV) and other members of the genus *Lyssavirus* target STAT1 and -2 by a highly conserved, unique mechanism, whereby the IFN antagonist P protein binds to STAT1/2 only in IFN-activated cells (6, 17–20) and inhibits their localization to the nucleus (21, 22). Because P protein is both the IFN antagonist and the essential polymerase cofactor of RABV, this mechanism is thought to ensure that P protein is occupied with roles as a STAT1/2 antagonist only as required (22). However, as the period between RABV exposure and the onset of symptoms can vary from weeks to years (23), this strategy might also ensure that the biology of infected cells is not perturbed by targeting of STAT proteins in the absence of IFN stimulation (i.e., nonphosphorylated STAT proteins), which have key roles in cellular processes other than IFN-activated antiviral responses (1).

It is unknown whether RABV P protein targets STAT proteins other than STAT1 and -2 (6, 17, 19–21) and if this targeting shows similar selectivity for activated proteins. To examine the potential interaction of RABV P protein with STAT3, we cotransfected COS-7 cells to express STAT3 fused to green fluorescent protein (GFP) (24) with either the red fluorescent protein mCherry alone or mCherry fused to the P protein (mCherry-P) from challenge virus standard (CVS) strain RABV, which is known to interact with IFN- α -activated STAT1/2 and inhibit their nuclear localization and signaling (6, 17). Cells were treated without or with 1,000 U/ml IFN- α before analysis by live-cell confocal laser scanning microscopy (CLSM) (25, 26) to monitor the nucleocytoplasmic localization of STAT3-GFP (Fig. 1). To examine the potential effects of P protein on STAT3 nuclear accumulation activated by Gp130-dependent signaling, we also treated equivalently transfected cells with 10 ng/ml OSM, which signals through Gp130-associated receptor complexes (10).

As expected, fusion of mCherry to P protein caused mCherry to become excluded from the nucleus because of the activity of the P-protein N-terminal nuclear export signal (Fig. 1A) (27). In untreated cells, STAT3-GFP localized diffusely between the nucleus and the cytoplasm but was localized strongly in the nucleus in

IFN- α - or OSM-treated cells, as expected. However, in IFN- α - or OSM-treated cells expressing mCherry-P, STAT3-GFP remained diffusely distributed between the cytoplasm and the nucleus, indicating that P protein can inhibit STAT3 nuclear translocation activated by these cytokines.

Quantification of the ratio of nuclear to cytoplasmic GFP fluorescence (Fn/c) was performed as previously described (6, 21, 25, 26), using ImageJ software to analyze CLSM images of randomly sampled fields of view; all of the cells in the field (ca. 12 to 15/field) coexpressing mCherry or mCherry-P protein with STAT3-GFP were analyzed ($n > 44$ per condition) (Fig. 1). The results confirmed that cytokine-activated nuclear localization of STAT3 was significantly ($P < 0.0001$) inhibited in mCherry-P-protein-expressing cells compared with that in control cells expressing mCherry alone.

To confirm the function of P protein in the inhibition of endogenous cellular STAT3 protein, we transfected cells with CVS strain P protein fused to GFP (GFP-P) or a GFP-only control and treated cells without or with IFN- α or OSM as described above before fixation and immunostaining with anti-STAT3 antibody and an Alexa Fluor 568-labeled secondary antibody and analysis by CLSM (6, 21, 25, 26) (Fig. 2). We also included samples expressing GFP fused to P protein from which the C-terminal 30 residues have been deleted (GFP-P-C Δ 30), which is sufficient to prevent P-protein-STAT1/2 binding (19). As for mCherry (see above), fusion of P protein or P-C Δ 30 to GFP caused its exclusion from the nucleus (Fig. 2A).

Both cytokines strongly induced STAT3 nuclear localization in control cells expressing GFP alone. Consistent with greater activation of STAT3 by OSM than by IFN- α (1, 9), the Fn/c ratio of STAT3 in OSM-treated cells was higher than that in cells treated with IFN; that this effect was not evident in the live-cell analysis in Fig. 1 is attributable to the higher levels of ectopically expressed STAT3-GFP. Despite this, in a fashion identical to that of the live-cell assays, the nuclear accumulation of endogenous cytokine-activated STAT3 was significantly ($P < 0.0001$) reduced by the expression of GFP-P. Importantly, GFP-P-C Δ 30 was unable to inhibit STAT3 nuclear translocation, indicating that this function is dependent on the presence of the C-terminal 30 residues of the P protein. Thus, the requirements for P-protein-STAT3 interaction appear to be comparable to those for P-protein-STAT1/2 interaction (6, 17, 19). We also found that expression of RABV N protein, which we have shown does not interact with or inhibit STAT1 or -2 trafficking/signaling (6, 21), had no effect on the nuclear localization of IFN- α - or OSM-activated STAT3 compared with control cells expressing GFP only (data not shown), confirming that this effect is specific to RABV P protein.

To examine directly whether the inhibition of STAT3 nuclear import relates to physical interaction of P protein with STAT3, we expressed GFP, GFP-P, and GFP-P-C Δ 30 and treated cells with OSM or IFN- α before lysis, immunoprecipitation of GFP or GFP-fused P proteins with the GFP-Trap system (6), and Western analyses with anti-STAT3 and anti-GFP antibodies (Fig. 3). Specific bands for GFP, GFP-P and GFP-P Δ 30, were detected in the corresponding immunoprecipitate samples and, consistent with the data from the CLSM assays (Fig. 1 and 2), STAT3 did not coprecipitate with GFP or GFP-P-C Δ 30 from untreated cells or cells treated with OSM or IFN- α . STAT3 also did not coprecipitate with GFP-P from untreated cells but was clearly present in GFP-P precipitates from cells treated with OSM or IFN- α and was de-

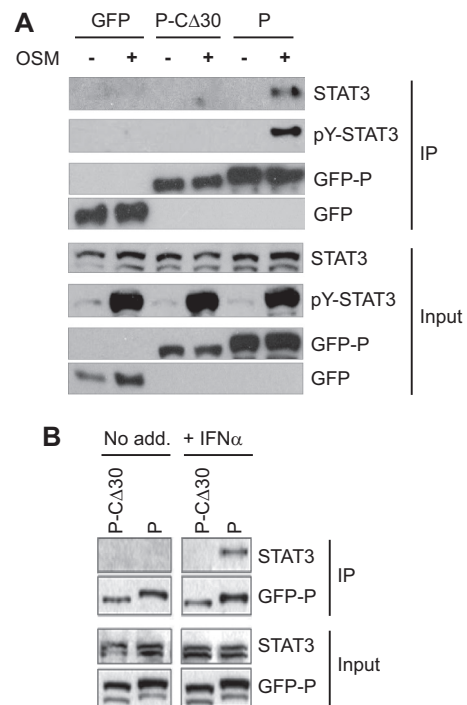


FIG 3 RABV P protein interacts selectively with cytokine-activated STAT3. COS-7 cells transfected to express GFP only, GFP-P-C Δ 30, or GFP-P were treated with or without 10 ng/ml of OSM for 15 min (A) or 500 U/ml IFN- α for 30 min (B) before lysis. Immunoprecipitation was performed using GFP-Trap (ChromoTek GmbH) (6). Cell lysates (input) and immunoprecipitates (IP) were analyzed by Western blotting with antibodies against STAT3, pY-STAT3 (Cell Signaling, Danvers, MA; catalog no. 9145), and GFP (Roche Applied Science, Indianapolis, IN; catalog no. 11814460001). The upper band in the input lanes (B) correspond to GFP-P or GFP-P-C Δ 30. Results are from a single assay representative of two or more separate assays. No add., no addition.

tected at similar levels in these samples. Importantly, OSM treatment upregulated cellular levels of Y705-phosphorylated/activated STAT3 (pY-STAT3) without affecting levels of total STAT3, and P protein efficiently coimmunoprecipitated with pY-STAT3 (Fig. 3A). Thus, P-protein interaction with STAT3 is dependent on STAT3 activation and on the C-terminal 30 residues of P protein, consistent with analogous requirements for P-protein interactions with STAT3 and STAT1/2, and suggesting that these interactions potentially involve the same or closely associated sites within the C-terminal domain (see above). Consistent with this, we found that a virus-encoded isoform of P protein, P3, that differs from the full-length P protein by deletion of the N-terminal 52 residues but contains the same C-terminal domain and targets STAT1/2 also coimmunoprecipitated with STAT3 in an activation-dependent manner (data not shown). In contrast, the interactions of the mumps and measles virus V proteins with STAT1, -2 and -3 are independent of activation (12, 13), indicating that RABV is unique in using an activation-dependent mechanism of STAT3 binding.

To examine whether P-protein binding to and inhibition of nuclear accumulation of Gp130-activated STAT3 correlate with inhibition of Gp130-dependent signaling, we examined the effect of RABV infection on the OSM-dependent transactivation of a target reporter gene in a dual-luciferase assay. For the reporter plasmid, we used the m67-luc construct, in which luciferase ex-

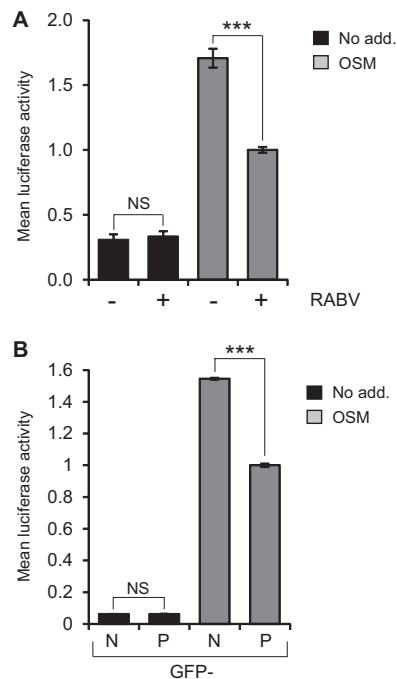


FIG 4 RABV infection and P-protein expression inhibit Gp130 receptor-dependent signaling. (A) U373-MG cells transfected with plasmids m67-luc and pRL-TK (which expresses *Renilla* luciferase under the control of a constitutively active promoter) were infected with RABV (+) or mock infected (-) and treated 24 h later without or with 10 ng/ml OSM (8 h) before analysis in a dual-luciferase assay as previously (6, 18, 19). Firefly luciferase activity was normalized to that of *Renilla* luciferase, and values were calculated relative to those obtained for OSM-treated, RABV-infected cells (mean luciferase activity \pm the standard error of the mean, $n = 3$). Results are from a single assay representative of two independent assays. (B) Cells transfected with plasmids m67-luc and pRL-TK and plasmids that express GFP-N- or -P protein were treated without or with 10 ng/ml OSM (8 h) before analysis by the dual-luciferase assay. Data show normalized values for luciferase activity calculated relative to the values obtained with OSM-treated cells expressing P protein (mean \pm the standard error of the mean; $n = 3$). Results are from a single assay representative of four independent assays. Statistical analysis was performed as described in the legend to Fig. 1. ***, $P < 0.0001$; NS, not significant. No add., no addition.

pression is under the control of a promoter containing high-affinity STAT3 binding sites and which was previously used to characterize the STAT3-antagonistic activity of the mumps virus V protein (28). U373-MG cells were transfected with m67-luc before mock infection or infection with CVS strain RABV (24 h), treatment with OSM (10 ng/ml, 8 h), and analysis in a dual-luciferase assay (6, 18, 19) (Fig. 4A). OSM induced significant transactivation of m67-luc in mock-infected cells, as expected, and this was significantly ($P < 0.0001$) reduced in RABV-infected cells, indicating that RABV encodes Gp130 antagonist activity. To directly examine the capacity of RABV P protein to inhibit Gp130-dependent signaling, we transfected HEK293T cells to express GFP-P or a GFP-N-protein control before treatment without or with OSM and analysis of luciferase activity as described above (Fig. 4B). OSM induced clear transactivation of m67-luc in cells expressing N protein, but luciferase activity was significantly ($P < 0.0001$) reduced in cells expressing P protein, indicating that P protein mediates the inhibition of Gp130-dependent signaling via its interaction with STAT3. The fact that some transactivation over that observed for control nontreated samples could be detected in both

RABV-infected cells and cells transfected to express P protein can be attributed to the selectivity of P-protein binding to activated/phosphorylated STAT3, so that STAT3 is able to mediate some transactivation in response to OSM stimulation before P protein effects the sequestration of pY-STAT3 to the cytoplasm.

In conclusion, we show here that RABV P protein interacts with STAT3 and inhibits STAT3 responses to cytokine activation. This represents the first demonstration of STAT3 targeting by an IFN antagonist of a virus which is not within the *Paramyxoviridae* family, indicating that STAT3 antagonism is important to infection by diverse viruses. Notably, however, STAT3 targeting by RABV P protein is unique in that it is activation dependent, indicating that RABV specifically targets STAT3 to inhibit responses to cytokines, whereas the measles, mumps, and Tioman viruses also target nonactivated STAT3 (12–14), which is known to have distinct roles in constitutive gene expression to affect cellular processes other than cytokine signaling (11). Thus, our results for viral targeting of STAT3 by RABV P protein indicate precise, virus-specific requirements for the modulation of signaling pathways mediated by STAT family members to generate optimal cellular conditions for viral replication and spread.

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