Direct Binding and Activation of STAT Transcription Factors by the Herpesvirus saimiri Protein Tip*

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Herpesvirus saimiri is an oncogenic herpesvirus that induces leukemias and lymphomas in susceptible hosts. Susceptible hosts include most species of new world monkeys, New Zealand White rabbits, and human peripheral blood lymphocytes. Cells transformed by this virus are primarily CD8+CD25- and manifest CTL activity (1). Two proteins expressed by this virus have been shown to be required for viral transformation, but not for viral replication (2, 3). Both proteins are expressed from a single bi-cistronic message. One protein, termed STP for non-terminal tail region. One site of phosphorylation lies within a consensus YXXQ binding site for the SH2 domains of STATs 1 and 3. We demonstrate that tyrosine phosphorylation of Tip at this site is required for the binding of STATs, and the induction of STAT dependent transcription. Furthermore, we demonstrate that, similar to STAT activation by v-Src, the optimum induction of STAT-dependent transcription by Tip requires Ras/Rac mediated signaling events.

The Tip protein from Herpesvirus saimiri specifically binds to and activates the protein tyrosine kinase, p56lck. It has been demonstrated that the expression of Tip in T cells is capable of inducing the DNA binding of members of the signal transducers and activators of transcription (STAT) family of transcription factors. We have examined the mechanism behind which STATs 1 and 3 are activated by Tip expression. Tip becomes tyrosine phosphorylated by p56lck at two sites in the amino-terminal tail region. One site of phosphorylation lies within a consensus YXXQ binding motif for the SH2 domains of STATs 1 and 3. We demonstrate that tyrosine phosphorylation of Tip at this site is required for the binding of STATs, and the induction of STAT dependent transcription. Furthermore, we demonstrate that, similar to STAT activation by v-Src, the optimum induction of STAT-dependent transcription by Tip requires Ras/Rac mediated signaling events.

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MATERIALS AND METHODS

Cell Culture and Antibodies—A derivative of the human Jurkat T cell leukemia that stably expresses the SV-40 large T antigen, was

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† The abbreviations used are: STAT, signal transducers and activators of transcription; SH2, Src homology domain 2; SIE, Sis-inducible element; Tricine, N-[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]glycine; PIPES, 1,4-piperazinediethanesulfonic acid; PAGE, polyacrylamide gel electrophoresis.
grown in RPMI supplemented with l-glutamine and 10% fetal calf serum. A similar derivative of the 293 human kidney cell line, 293T, was grown in Dulbecco-Vogt modified Eagle’s media also supplemented with 10% fetal calf serum. Rabbit antisera specific for Tip and p56lck have been described elsewhere (7, 15). Monoclonal antibodies (Transduction Laboratories) and rabbit antisera to STATs 1 and 3 were generous gifts from Dr. Michael David.

Expression Plasmids—Wild type Tip was expressed from the pRc/RSV plasmid (Invitrogen) which uses the Rous sarcoma virus long terminal repeat as a promoter. Tyrosine to phenylalanine mutations of Tip were generated using a polymerase chain reaction-based site-directed mutagenesis, and confirmed by sequencing. Wild type murine p56lck was expressed using the pCEP4 plasmid (Invitrogen). F505lck was placed in the SREa vector, which uses human immunodeficiency virus long terminal repeat sequences to drive expression. All c-Fos luciferase constructs were a generous gift from Dr. Brent Cochran, and have been described elsewhere (16). N17 Rac1 was expressed from the pEXV vector and was a gift from Dr. Alan Hall. The N17 Ha-Ras has been described previously (17).

Luciferase Assays—Jurkat cells were transfected using the DMRIE-C reagent (Life Technologies) under serum-free conditions for 4–5 h. The cells were then overlaid with serum containing media to give a final serum concentration of 1%. Cells were then sample 24 h post-transfection. For cell stimulation, cells were incubated with a mixture of 60 nM phorbol 12-myristate 13-acetate and 1.5 mM ionomycin (Sigma) for 3 h prior to cell lysis. Inhibitors PD98059 (Sigma) and SB202190 (BioMol) were also added 3 h prior to lysis. Cells were harvested and washed once in cold phosphate-buffered saline. The cells were then lysed in 100 μl of lysis buffer (0.1 M potassium phosphate buffer at pH 7.8, 1% Triton X-100, 1 mM dithiothreitol, and 2 mM EDTA). Cells were incubated in lysis buffer for 15–20 min on ice before pelleting in a microcentrifuge for 2 min at high speed to remove cellular debris. 30 μl of cell lysate was mixed with 100 μl of assay buffer (30 mM Tricine, 3 mM ATP, 15 mM MgSO4, 10 mM dithiothreitol, pH 7.8) in a 96-well microtiter plate just prior to measurement. Plates were assayed using the MLX microtiter luminescence detection system (Dynex Technologies) which injects 100 μl of the substrate (1 mM d-luciferin in assay buffer) prior to measuring luminescence.

Human 293T cells were transfected by a standard calcium phosphate precipitation method. In general, 293T cell luciferase assays were per-

**Fig. 1. Activation of STAT-dependent transcription by Tip.** 2 × 10⁶ T-antigen expressing Jurkat T cells were transfected using the DMRIE-C reagent (Life Technologies, Inc.). All transfections were with 4 μg of total DNA. In all cases, 1 μg of the SIE/luciferase construct was transfected along with 3 μg of Tip expression plasmid, p56lck expression plasmid, or empty plasmid. After 24 h, some cells were stimulated for 3 h with 60 nM phorbol 12-myristate 13-acetate and 1.5 μM ionomycin. Lysates were prepared and then assayed as described under "Materials and Methods." Data plotted are arbitrary relative luciferase units derived from four separate transfections.

**Fig. 2. Determination of the sites of tyrosine phosphorylation in Tip.** Human 293T cells were transfected with the indicated Tip and p56lck constructs by a standard CaPO₄ method. 48 h after transfection, the cells were lysed and immune complexes prepared with antisera to Tip. A, immune complexes were resolved using a large gel to better demonstrate the differences in migration of Tip mutants. These samples were transferred to nitrocellulose and immunoblotted with antisera to Tip. B, immune complexes were prepared from separate transfections and resuspended in kinase buffer with 5 μCi of [γ-32P]ATP for 10 min at 30°C. Precipitates were then washed and resolved on a 12.5% SDS-PAGE mini-gel.
form as described for Jurkat cells, although the cells were first scraped into the tissue culture medium (4 ml) before 500 μl of resuspended cells was transferred to a microcentrifuge tube and washed with phosphate-buffered saline. Assays for the expression of p56lck Activity—In general, immunoprecipitates were resuspended in kinase buffer (40 mM Na2HPO4, 40 mM NaH2PO4, 10 mM KCl, 1 mM MgSO4, and 40 mM 2-mercaptoethanol) and incubated 5 min at room temperature. The samples were then mixed with 100 μl of Z Buffer containing 4 mg/ml β-galactopyranoside and incubated at 37 °C until the color changed to yellow (3–10 min). The reaction was stopped with 500 μl of 1 M sodium carbonate. Data were obtained by measuring the absorbance at 420 nm.

Cell Lysis and Immunoprecipitation—Techniques used for cell lysis and immunoprecipitation have been described previously (18). In general, a lysis buffer containing 1% Nonidet P-40 was used to lyse cells, while immunoprecipitates were washed with the addition of 0.1% SDS. Antibody-antigen complexes were collected using Pansorbin (Calbiochem).

Assays for p56lck Activity—In general, immunoprecipitates were resuspended in kinase buffer (40 mM sodium PIPES, pH 7.2, 10 mM MnCl2) at 4 °C (19). For quantitation of Lck, a fraction of the precipitate was used for Western blot analysis. The remainder of the sample was subjected to a protein kinase assay using [γ-32P]ATP and 5 mM [Val5]angiotensin. These precipitates were then incubated at room temperature. Samples were removed at 1, 3, and 5 min and assayed for the incorporation of phosphate into the exogenous peptide substrate, angiotensin. A small sample from the original precipitate was resolved on a 15% SDS-PAGE and transferred to nitrocellulose and immunoprecipitates were washed with the addition of exogenous substrate.

**RESULTS**

**Tip Activation of STAT-dependent Transcription**—The H. saimiri protein Tip has been demonstrated to induce the DNA binding of STATs 1 and 3 (14, 20). This Tip-induced DNA binding is dependent on the presence of p56lck. Given that the DNA binding of different transcription factors does not always correlate with transcriptional activity (21), we commenced our studies by testing the ability of Tip to induce STAT-dependent transcription.

T antigen expressing Jurkat T cells were transfected with a construct that uses three copies of the c-Fos SIE to drive transcription of the luciferase gene. Some cells were co-transfected with a construct to express the Tip protein from strain 484 of H. saimiri, or an activated mutant of p56lck, F505lck. Treatment with phorbol 12-myristate 13-acetate and ionomycin was used as a positive control and is commonly used to mimic T cell activation. We find that Tip-mediated signals generate a dramatic induction of STAT-dependent transcription (Fig. 1). In contrast, the constitutively activated F505lck is unable to induce any transcription above the background level. The same construct is able to induce NFAT-dependent transcription and transcription from the interleukin-2 promoter (data not shown and Ref. 22). These results confirm that Tip is able to induce STAT-dependent transcription in T cells. The inability of the activated and transforming p56lck mutant to induce STAT-dependent transcription suggests that the Tip-induced signal involves more than an increase in p56lck tyrosine kinase activity.

**Tip Tyrosine Phosphorylation Provides a Docking Site for STAT Activation by Tip**—STAT transcription factors are recruited to tyrosine-phosphorylated cell surface receptors by their SH2 domains. Once bound to these activated receptors, the STATs are themselves tyrosine phosphorylated, at which point they dissociate from the receptor and hetero- or homodimerize before moving to the nucleus to induce transcription. It has long been known that Tip is tyrosine phosphorylated by p56lck, although the sites of phosphorylation have yet to be demonstrated. There are 5 tyrosines in Tip-484, including one within a consensus, YXPQ, binding motif for the SH2 domains of STATs 1 and 3. We proceeded to generate a panel of tyrosine to phenylalanine point mutants of Tip to determine which tyrosine(s) is phosphorylated in Tip, and if these sites affected STAT activation.

**Fig. 3. Activation of p56lck by tyrosine mutants of Tip.** Human 293T cells were transfected with p56lck with and without Tip constructs as shown. 48 h after transfection by CaPO4, immune complexes were generated using antisera to p56lck (when p56lck was expressed alone), or antisera to Tip (all samples). Precipitates were resuspended in kinase buffer with 15 μCi of [γ-32P]ATP and 5 mM [Val5]angiotensin. These precipitates were then incubated at room temperature. Samples were removed at 1, 3, and 5 min and assayed for the incorporation of phosphate into the exogenous peptide substrate, angiotensin. A small sample from the original precipitate was resolved on a 15% SDS-PAGE and transferred to nitrocellulose for Western immunoblot detection of p56lck using 125I-Protein A. The levels of p56lck in each precipitate were quantified by a PhosphorImager and used to normalize values for phosphate incorporation. Data are from a single experiment, but representative of two others.
Tip expressed alone in 293T epithelial kidney cells migrates as a single band of around 30 kDa on SDS-PAGE (Fig. 2). In the presence of p56\textsuperscript{lck}, Tip resolves as three separate bands ranging in size from 30 to 37 kDa. Only the two slower migrating forms of Tip are labeled with phosphate following an \textit{in vitro} kinase reaction (Fig. 2, and Ref. 6). Single mutations of either Tyr-72 or Tyr-85 alters the mobility shift of Tip when expressed with p56\textsuperscript{lck}. Mutation of both Tyr-72 and Tyr-85 to phenylalanine prevents the ability of p56\textsuperscript{lck} to incorporate phosphate into Tip and reduces the mobility of Tip to that when expressed alone. Phosphoamino acid analysis was performed using \textit{in vivo} labeled Tip and confirms that tyrosines 72 and 85 account for all the phosphate incorporated into tyrosine residues, although there is significant serine phosphorylation even in the absence of p56\textsuperscript{lck} co-expression (data not shown). Mutation of other tyrosines in Tip has no effect on the \textit{in vitro} phosphorylation of Tip by p56\textsuperscript{lck} (data not shown).

Previous reports have suggested Tyr-114 in Tip from strain 488 plays a role in the binding of Tip to p56\textsuperscript{lck} and the resultant regulation of p56\textsuperscript{lck} activity by Tip (23). This tyrosine is analogous to Tyr-72 in Tip-484, as determined by sequence alignment. We can find no interaction of the p56\textsuperscript{lck} SH2 domain with any Tip construct (data not shown). In addition, we compared the ability of these tyrosine mutants to increase p56\textsuperscript{lck} activity. Human 293T cells were transfected with p56\textsuperscript{lck} alone, or co-transfected with different Tip constructs. Following cell lysis, immune complexes were isolated and tested \textit{in vitro} for p56\textsuperscript{lck} tyrosine kinase activity against an exogenous substrate. These experiments show no significant difference in the ability of any Tip construct to interact with (Fig. 2), or increase the activity of p56\textsuperscript{lck} (Fig. 3).

The data in Fig. 2 shows that Tyr-72 in Tip is a site of tyrosine phosphorylation by p56\textsuperscript{lck}. We next looked at whether Tip tyrosine phosphorylation is required for the binding of STATs, and the induction of STAT tyrosine phosphorylation. Human 293T cells were again transfected with p56\textsuperscript{lck} and Tip constructs alone and together. STAT3 was precipitated from these cells and Western blot analysis was performed to test for the tyrosine phosphorylation status of STAT3. Expression of Tip or p56\textsuperscript{lck} alone fails to induce the tyrosine phosphorylation of STAT3 (Fig. 4A). However, when WT Tip or F85 Tip are co-expressed with p56\textsuperscript{lck} there is an increase in the tyrosine phosphorylation of STAT3. Immunoprecipitates of STAT3 from these cells are also able to co-precipitate Tip and p56\textsuperscript{lck}. In contrast, co-expression of F72 Tip and p56\textsuperscript{lck} fails to induce the tyrosine phosphorylation of STAT3, or the inclusion of STAT3 into a Tip-p56\textsuperscript{lck} complex. Tyrosine 72 in Tip is also required for STAT1 tyrosine phosphorylation by Tip and p56\textsuperscript{lck} (Fig. 4B).

The tyrosine phosphorylation of STATs is required for their ability to induce transcription. Given the observed importance of Tip tyrosine phosphorylation in the binding to and tyrosine phosphorylation of STATs 1 and 3, we next investigated if this
correlated with the ability to induce STAT-dependent transcription. As mentioned previously, p56$^{lk}$ is normally expressed only in lymphoid tissues and therefore 293T cells provides a system to study the effect of Tip in the absence of p56$^{lk}$. Human 293T cells were transfected with combinations of Tip and p56$^{lk}$ constructs. All cells were also co-transfected with the SIE-dependent luciferase reporter and a $\beta$-galactosidase expression plasmid. Expression from the $\beta$-galactosidase plasmid was used to normalize for differences in transfection efficiency, although no normalization greater than 1.5 was necessary. As with the Tip induced binding and tyrosine phosphorylation of STATs, we find that Tip requires both p56$^{lk}$ and Tyr-72 to induce STAT-dependent transcription (Fig. 5A). A similar dependence for Tyr-72 can be observed in T cells (Fig. 5B).

**Fig. 5.** Activation of STAT-dependent transcription requires Tyr-72 in Tip. A, human 293T cells were transfected with 1 $\mu$g of the SIE/luciferase construct, and 1 $\mu$g of a $\beta$-galactosidase expression plasmid. Cells were also transfected with 2 $\mu$g of Tip expression plasmid with or without 1 $\mu$g of p56$^{lk}$ expression plasmid. Where both Tip and p56$^{lk}$ were not expressed, an empty plasmid was used to make a total of 5 $\mu$g of DNA transfected. Cells were lysed after 24 h and assayed for both luciferase and $\beta$-galactosidase expression. Data are plotted as relative luciferase units divided by the absorbance at 420 nm. These are from a single experiment, but are representative of three others. B, T antigen expressing Jurkat T cells were transfected using the DM-RIE-C reagent as described in the legend to Fig. 1.

**Tip Is Able to Induce Transcription from the c-Fos Promoter**—The preceding experiments used the SIE from the c-Fos promoter to assay for STAT-dependent transcription. Others have shown that the SIE can play an important role in driving transcription of the c-Fos promoter (16). Given the robust ac-
activation of STATs by Tip, we wished to test the ability of Tip to induce c-Fos transcription. T antigen expressing Jurkat T cells were transfected with a construct using the full-length c-Fos promoter to drive transcription of a luciferase gene. Some cells were co-transfected with Tip or p56\textsuperscript{lyk} constructs. Expression of Tip is able to induce a 2-fold activation of transcription from the c-Fos promoter (Fig. 6). In contrast, expression of the activated F505\textsuperscript{lyk} construct in T cells is not able to induce any significant transcription from the c-Fos promoter. These results correlate with the abilities of Tip and F505\textsuperscript{lyk} to activate STAT-dependent transcription from the SIE within the c-Fos promoter. Consistent with the activation of STATs, we find that the F72 Tip is unable to induce transcription from the full-length c-Fos promoter. In addition, Tip is unable to induce c-Fos transcription when the SIE has been removed.

Requirement for Ras/Rac-mediated Serine Phosphorylation—Considerable evidence has demonstrated that for maximum transcriptional activity, STATs need to be serine phosphorylated as well as tyrosine phosphorylated (26–28). A known substrate of p56\textsuperscript{lyk} is the hematopoietic specific Rac/Cdc42 exchange factor, p95\textsuperscript{Vav} (24). An effector of Rac and Cdc42 is the ubiquitously expressed Ser/Thr kinase Pak1. In T cells, the activation of Pak has been shown to lie upstream of Ras activation following cross-linking of the T cell receptor (25). The Src-mediated serine phosphorylation of STAT3 has been reported to involve both Ras/ERK phosphorylation and Rac induced JNK/p38 phosphorylation (29). We proceeded to test whether the Tip induced activation of STATs 1 and 3 in T cells required a similar activation of Ras- and Rac-mediated signaling pathways. The inhibitor, PD98059, selectively blocks the activity of MAP kinases, MEK1/2. Treatment of Tip-transfected cells with 50 \mu M PD98059 resulted in nearly a 50% reduction in the Tip-induced STAT-dependent transcription (Fig. 7). The specific inhibitor of p38, SB202190, has a similar inhibitory effect on the Tip activation of STATs. Consistent with these results we find that co-expression of Tip with dominant negative mutants of Ras or Rac1 has a strong inhibitory effect on the activation of STATs by Tip. These results for Tip induced transcription from the c-Fos SIE are similar to those demonstrated for v-Src-induced STAT3 transcription (29). We can also observe an inhibition of the Tip-induced c-Fos transcription by co-expression of dominant negative Ras or Rac1 mutants (data not shown).

DISCUSSION

Our data demonstrate that tyrosine 72 acts as a docking site for the recruitment of STATs 1 and 3 to Tip (Fig. 4). The Jak family of tyrosine kinases typically mediates the activation of STATs following cytokine stimulation (10). For the activation of STATs by Jak kinases to proceed, both the kinase and STATs need to be recruited to activated cytokine receptors. Our data suggest a similar model whereby Tip acts as an activated receptor with sites of tyrosine phosphorylation used to recruit STATs, and other domains used to recruit tyrosine kinases (p56\textsuperscript{lyk}). The lack of p56\textsuperscript{lyk} induced activation of STATs in the absence of Tip suggests that there may be no endogenous adaptor in T cells to allow for p56\textsuperscript{lyk} to activate STATs during normal T cell activation events (30).

It is clear from many different reports that Src is able to phosphorylate and activate members of the STAT family of transcription factors (11, 12). It has been suggested that v-Src will bind STAT3 by co-precipitation experiments (11). However, these experiments do not define whether the SH2 or SH3 domains of v-Src are involved, or whether the interaction is direct. Specifically, the authors do not address the potential role of other tyrosine-phosphorylated proteins found in the precipitates to act as docking or linker proteins between v-Src and STAT3. To our knowledge, no experiments performed with v-Src can rule out that a receptor/adaptor mediates the association between Src and STATs. Since there is a high degree of homology between Src family members, we suggest that the interaction between v-Src and STAT3 may involve a docking protein that remains to be defined. Given that STAT3 activation is required for cellular transformation by v-Src, it is possible that the activation of STATs by Tip also plays an important role in the transformation of T cells by H. saimiri.

It has been shown that tyrosine phosphorylation of STATs is sufficient to induce DNA binding, but that serine phosphorylation is required for the induction of transcription (26). Our test for the activation of STATs by Tip was to measure the induction of STAT-dependent transcription by using a luciferase reporter assay. Previous work on the Tip activation of
STATs has utilized electrophoretic mobility shift assays to measure the ability of STATs to bind DNA (20). The dramatic activation of p56\(^{lck}\) by Tip or mutation of the regulatory tyrosine (Tyr-505) leads to the tyrosine phosphorylation of numerous cellular proteins (7), possibly including STATs 1 and 3 (31). While the results in Fig. 4 suggest that p56\(^{lck}\) is unable to phosphorylate STATs in the absence of Tyr-72 in Tip, we have found a weak induction of STAT tyrosine phosphorylation in the presence of F72 Tip with p56\(^{lck}\) in some experiments. Therefore, it appears that Tip tyrosine phosphorylation both increases the efficiency and specificity of substrate phosphorylation, including STATs 1 and 3. The recruitment of STATs to Tip will also bring the STATs into an efficient signaling complex to provide serine phosphorylation to induce their transcriptional activation.

Other research has suggested roles for Tyr-72 other than the recruitment of STATs. In particular, data with the Tip protein from strain 488 of H. saimiri has suggested an involvement of tyrosine 114 in the binding and regulation of p56\(^{lck}\) activity by Tip-488 (23). Tyr-72 in Tip-484 is analogous to Tyr-114 in Tip-488 (Tyr to Ser, or Tyr to Gly) were non-conservative in nature and may explain the differences with our results as to the role of Tyr-72 in Tip.

The data presented here suggest a model whereby Tip binds to and activates the tyrosine kinase p56\(^{lck}\) in transformed T cells. Following this, Tip becomes tyrosine phosphorylated at two sites by p56\(^{lck}\), one of which promotes the binding of STATs 1 and 3. The recruitment of STATs to a phosphorylated tyrosine in Tip allows their subsequent tyrosine phosphorylation by the activated p56\(^{lck}\). Once tyrosine phosphorylated, the STATs can then dimerize and proceed to the nucleus to induce transcription of target genes. We suggest a similar model would occur during transformation of cells by v-Src. In this model, v-Src binds to and phosphorylates an adaptor protein which creates a binding site for the recruitment of STATs. Upon recruitment of STATs to the adaptor protein, v-Src will then phosphorylate and activate the STATs directly, leading to gene transcription.

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