Available online at www.sciencedirect.com
SCIENCE DIRECT®
Biochemical and Biophysical Research Communications 320 (2004) 279–285
BBRC
www.elsevier.com/locate/ybbrc

Herpesvirus saimiri STP A11 protein interacts with STAT3 and stimulates its transcriptional activity

Junsoo Park, Taegun Seo, Jun Jung, and Joonho Choe*

Department of Biological Sciences, Korea Advanced Institute of Science and Technology, Daejon 305-701, Republic of Korea

Received 14 May 2004
Available online 10 June 2004

Abstract

Herpesvirus saimiri (HVS) is an oncogenic γ-2 herpesvirus that causes lymphoma in New World primates. HVS can be further divided into subgroups A, B, and C, based on sequence divergence. Saimiri transforming protein (STP) is coded for by the first open reading frame at the left end of the HVS genome and is responsible for its oncogenic potential. Here we show that STP A11 binds to signal transducers and activators of transcription 3 (STAT3), stimulates STAT3 phosphorylation, and activates STAT3-dependent transcription. STP A11 recruited c-Src kinase to phosphorylate STAT3 protein, and co-expression of STP A11 with c-Src dramatically increased STAT3 phosphorylation. We found that the amino terminal domain of STP A11 is required for both STAT3 interaction and activation, and that physical interaction is required for STAT3 activation.

Keywords: Herpesvirus saimiri; STAT3; STP A11

Although signal transducers and activators of transcription (STATs) were initially discovered as effectors for normal cytokine signaling, further study revealed STAT signaling (especially STAT3) is also involved in oncogenesis [1]. Expression of a diverse range of oncogenes can activate STAT3, and constitutive activation of STAT3 contributes to cell transformation [2]. STAT3 is activated in various human cancer cells, indicating STAT3 activation is a useful marker for oncogenic transformation [1,3]. Activated STAT3 can induce transcription of several genes, including Bcl-X_L, cyclin D1, $p21^{WAF1/CIP1}$, and c-Myc [4–6]. Genes regulated by STAT3 are associated with oncogenesis through regulation of cell cycle progression and/or apoptosis, implying that STAT3 is involved in these processes.

Herpesvirus saimiri (HVS) belongs to the γ-2 herpesvirus subfamily, which includes Epstein–Barr virus (EBV) and Kaposi's sarcoma-associated herpesvirus (KSHV). HVS naturally infects squirrel monkeys (*Saimiri sciureus*) without any apparent disease, but infection of other New World primate species results in fulminant lymphomas, lymphosarcomas, and leukemia of T cell origin [7]. HVS can be further divided into subgroups A, B, and C, based on the extent of DNA sequence divergence at the left end of L-DNA [8–10]. Subgroups A and C are highly oncogenic and able to immortalize common marmoset T lymphocytes in vitro such that they become interleukin 2-independent, while none of the B subgroups tested have this ability [11,12].

Saimiri transforming protein (STP) is located at the left end of the HVS genome, and both STP A and C families have transforming and tumor-inducing activities independent of the rest of the herpesvirus genome [13]. The detailed mechanism of STP C488 has been well studied, and cellular ras is known to be an important partner for transformation [14]. STP A11 of HSV subgroup A is not required for viral replication but is required for immortalization of common marmoset T lymphocytes in vitro and for lymphoma induction in vivo [9,10,15]. Although the location of STP A11 is equivalent to STP C488, STP A11 has only limited sequence similarity with STP C488, suggesting that its molecular mechanism for cell transformation is different from that of STP C488 [8,13]. c-Src and TRAF family

* Corresponding author. Fax: +82-42-869-5630.
E-mail address: jchoe@kaist.ac.kr (J. Choe).

0006-291X/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbrc.2004.05.162

members bind STP A11 [6,16], but the detailed mechanism of oncogenic transformation is not known. In the present study, we report that STP A11 interacts with STAT3 protein and activates STAT3 transcription activity.

Materials and methods

Cell culture and transfection. 293T cells were grown in Dulbecco's Modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum and antibiotics. Transfections were carried out in 293T using the standard calcium phosphate method. For luciferase assays, 293T cells were seeded in 6-well plates in DMEM 18 h prior to transfection. Total DNA for transfections was typically 2 μg per plate, comprising 1 μg luciferase reporter construct (pTK/SIE or pTK), 0.5 μg β-galactosidase (β-Gal) internal control vector, and the amounts of expression vector indicated.

Plasmids. Plasmids encoding AU1-tagged STP A11 (AU1-STP A11) and STP B (AU1-STP B) were provided by Jung and co-workers [16,17]. Amino terminal truncated mutants of STP A11 were generated using PCR amplification and subcloned into pGEX4T-1 and pcDNA3 vectors. STP A11 point mutants were generated using the Quick Change Site-Directed Mutagenesis kit (Stratagene, La Jolla, CA), and each mutant was completely sequenced to verify the presence of the mutation and the absence of any other changes.

Immunoprecipitation and immunoblotting. For immunoprecipitation, cells were harvested and resuspended in lysis buffer [150 mM NaCl, 50 mM Hepes (pH 8.0), and 0.5% NP40] containing phosphatase inhibitor (0.1 mM Na_2VO_3) and a protease inhibitor cocktail (Roche, Germany). Immunoprecipitated proteins from precleared cell lysates were used for immunoblotting. Immunoblot detection was performed with a 1:1000 or 1:2000 dilution of primary antibody, and an enhanced chemiluminescence system (ECL; Amersham, Chicago, IL). Antibodies for STAT3 and phosphoSTAT3 were purchased from Cell Signaling (Beverly, MA).

Results

STP A11 activates a Stat3-dependent promoter

Expression of viral oncogenes often results in the activation of STAT3, and constitutive STAT3 activation contributes to cell transformation. STP A11 is responsible for the transforming activity of HVS [10,12]. We examined whether STP A11 activated STAT3. Plasmids encoding STP A11 protein were transiently transfected into 293T cells along with a STAT3-dependent pTK/SIE-Luc reporter to measure STAT3 transcription activity. Twenty-four hours after transfection, luciferase activity was measured and normalized according to β-galactosidase activity. We found that STP A11 expression increased STAT3 transcription activity up to fourfold (Fig. 1A). In contrast, STP A11 transfection did not significantly affect pTK reporter activity, showing that STP A11 specifically activated STAT3-dependent transcription.

Phosphorylation of STAT3 is the critical event for dimerization, nuclear localization, and DNA binding, and phosphorylation of tyrosine 705 in particular is required for STAT3 activation [18,19]. We examined whether STP A11 protein could induce phosphorylation of STAT3. FLAG-tagged STAT3 (FLAG-STAT3) and AU1-STP A11 were transiently expressed in 293T cells, and 48 h after transfection cells were lysed, FLAG-STAT3 was immunoprecipitated with anti-FLAG antibody and subjected to immunoblotting with an anti-phosphotyrosine antibody (4G10). STAT3 phosphorylation was detected when STP A11 and STAT3 were co-expressed (Fig. 1B, lane 4). These data indicate that STP A11 specifically activates STAT3 signaling.

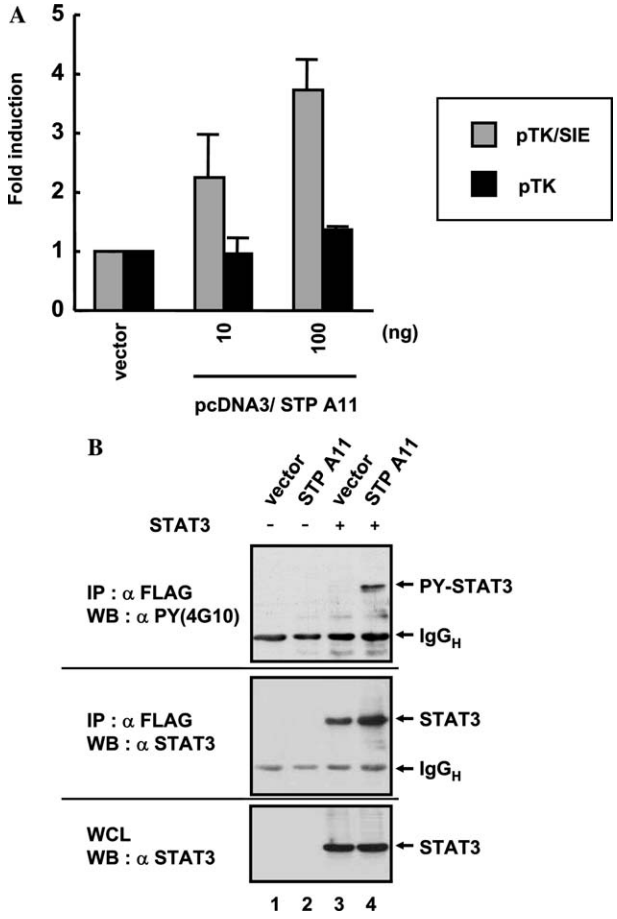

Fig. 1. Activation of STAT3 by STP A11 protein. (A) STP A11 induces transcriptional activation of a STAT3-dependent promoter. 293T cells were transfected with 0, 10 or 100 ng pcDNA3/STP A11, together with either 1 μg pTK/SIE-Luc or pTK-Luc to measure transcriptional activation of the STAT3-dependent promoter. β-Gal (0.5 μg) was included as an internal control. Twenty-four hours after transfection, luciferase activity was measured and normalized according to β-galactosidase activity in each sample. Transfections were performed in triplicate and the standard deviation is shown. (B) STP A11 induces phosphorylation of STAT3. 293T cells were transfected with pCMV/FLAG-STAT3 (lanes 3 and 4) in combination with pcDNA3/STP A11 (lanes 2 and 4). STAT3 proteins were immunoprecipitated with anti-FLAG antibody, and the immunoprecipitates were immunoblotted with anti-phosphotyrosine antibody (4G10). The membrane was re-probed with anti-STAT3 antibody, and whole cell lysates (WCL) were immunoblotted with anti-STAT3 antibody.

STP A11 interacts with STAT3 in vitro and in vivo

Using an in vitro binding assay, we examined whether STP A11 directly interacted with STAT3. A GST-STP A11 fusion protein was produced in bacteria, and to facilitate expression of this molecule its hydrophobic region for membrane anchoring (aa 137–164) was truncated. This protein was termed GST-STP A11 ΔTM. When GST-STP A11 ΔTM was mixed with FLAG-STAT3 protein in vitro, we found that the two molecules bound to each other (Fig. 2A). To determine whether these two molecules interacted in cells, plasmids encoding AU1-STP A11 protein and FLAG-STAT3 protein were transiently transfected into 293T cells. Forty-eight hours after transfection, STP A11 protein was immunoprecipitated with anti-AU1 antibody and bead-bound STAT3 proteins were detected by immunoblotting using anti-FLAG antibody. The results of these co-immunoprecipitation assays indicated that STAT3 specifically interacts with STP A11 in vivo (Fig. 2B).

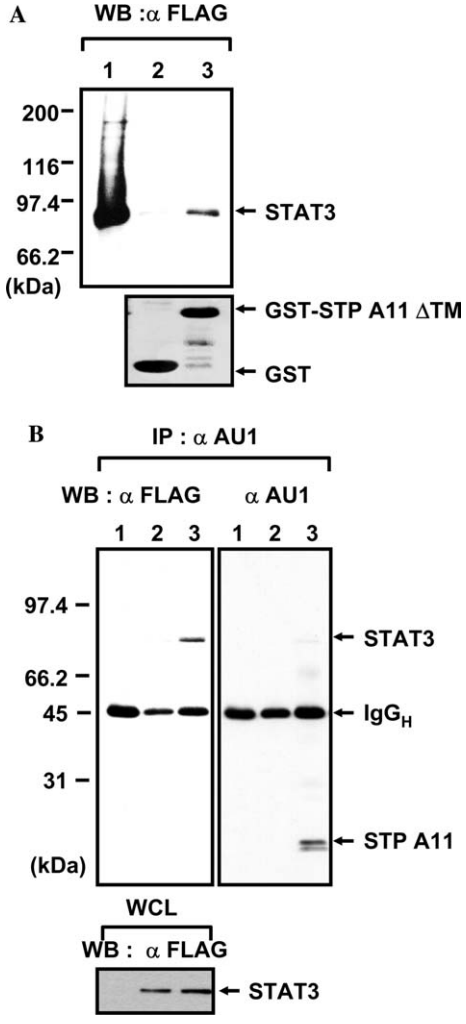

Fig. 2. Interaction between STP A11 and STAT3. (A) STP A11 interacts with STAT3 in vitro. FLAG-STAT3 proteins were transiently expressed in 293T cells and incubated with equal amounts of GST and GST-STP A11 ΔTM proteins. The bead-bound proteins were eluted and blotted with anti-FLAG antibody (upper panel). The membrane was stained with Ponceau S solution to visualize GST and GST-STP A11 ΔTM (lower panel). (B) STP A11 interacts with STAT3 in vivo. 293T cells were transiently transfected with 1 μg pCMV/STAT3 in combination with either 5 μg pFJ/STP A11 or a control vector (pFJ). STP A11 proteins were precipitated with anti-AU1 antibody and immunoprecipitates were immunoblotted with anti-FLAG antibody to detect STAT3. The membrane was re-probed with anti-AU1 antibody and WCL were probed with anti-FLAG antibody.

STP A11 recruits c-Src tyrosine kinase to phosphorylate STAT3

Although STP A11 co-transfection caused STAT3 phosphorylation (Fig. 1B), STP A11 does not have kinase activity, suggesting a kinase is recruited to the complex. STP A11 is known to interact with c-Src tyrosine kinase [16]. We examined whether c-Src is involved in the STP A11/STAT3 interaction. 293T cells were transiently transfected with FLAG-STAT3 together with c-Src in the presence or absence of AU1-STP A11. c-Src was immunoprecipitated with anti-c-Src antibody and bead-bound STAT3 and STP A11 were detected by immunoblotting using anti-FLAG and anti-AU1 antibodies. We found that STAT3 was associated with a complex containing c-Src and STP A11 (Fig. 3A). These data indicate the presence of a c-Src/STP A11/STAT3 ternary complex.

STP A11 contains three conserved tyrosine residues at 37, 54, and 115 [16]. Tyrosine 115 is a component of the Src Homology 2 Binding (SH2B) motif and is required for interaction with c-Src. To further investigate the role of c-Src in STAT3 and STP A11 interactions, each STP A11 conserved tyrosine residue was replaced with alanine, and the effect on STAT3 binding was tested. Co-immunoprecipitation assays revealed that all three STP A11 mutants associated with STAT3 (Fig. 3B). However, while STAT3 was phosphorylated in complexes containing STP A11 mutants Y37A or Y54A, it was not phosphorylated in complexes containing STP A11 Y115A. These data suggest that STAT3 is phosphorylated by c-Src kinase.

To further characterize the connection between c-Src and STAT3 activation, a plasmid encoding c-Src was transfected into 293T cells in combination with either STP A11 or STP A11 Y115A together with FLAG-STAT3, and FLAG-STAT3 proteins were immunoprecipitated with anti-FLAG antibody and then immunoblotted with an anti-phosphoSTAT3 antibody. Typical data from these experiments are presented in Fig. 3C. We found that STAT3 was phosphorylated in cells co-expressing STP A11 (lane 3), and that low level c-Src expression (10 ng) increased phosphorylation up to 7- to 8-fold (lane 6). These data suggest that STP A11 and c-Src kinase act in concert to phosphorylate STAT3. Long exposures of the immunoblots revealed

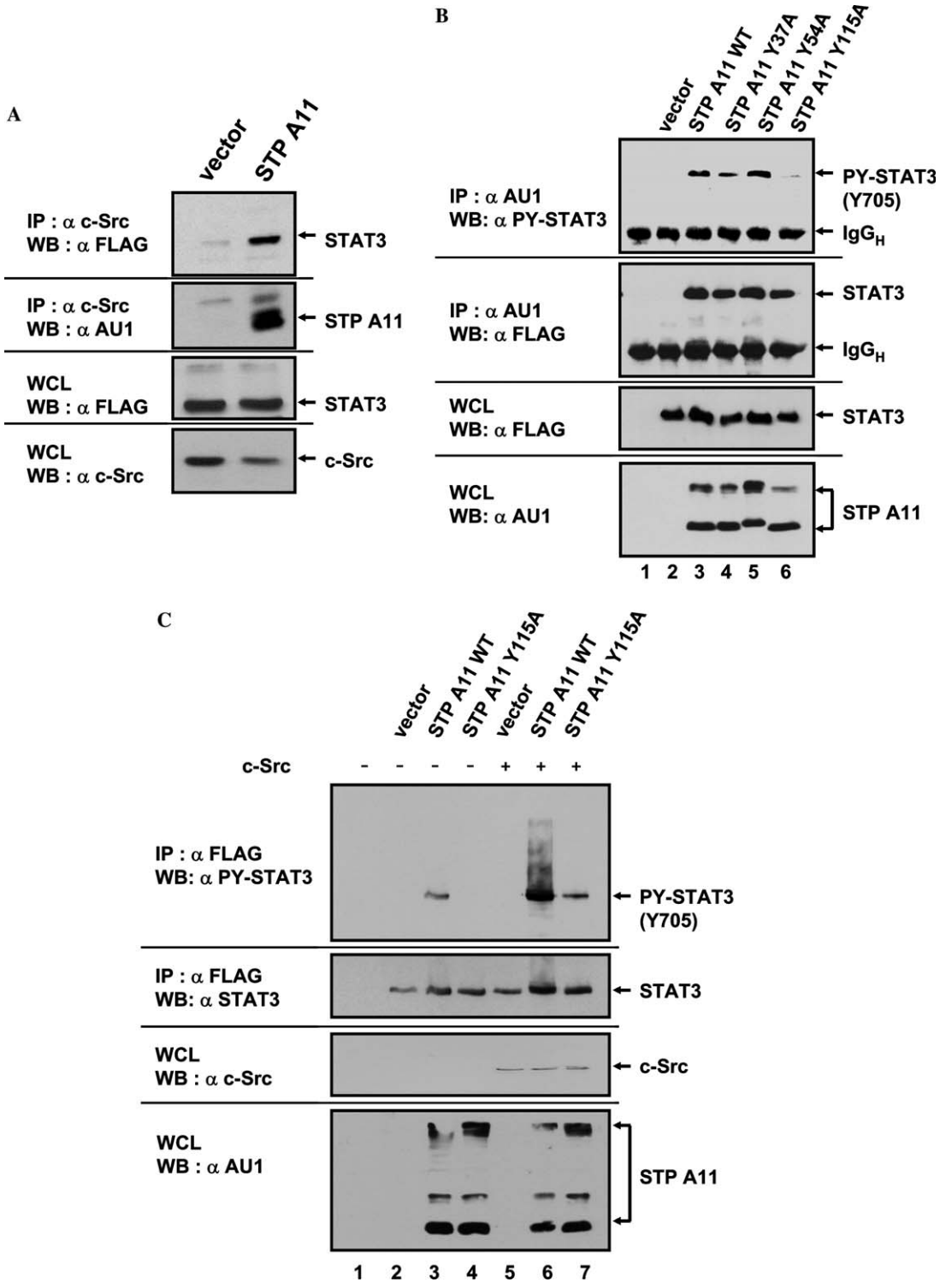

Fig. 3. STP A11 recruits c-Src tyrosine kinase to phosphorylate STAT3. (A) STP A11 induces interaction between STAT3 and c-Src. 293T cells were transiently transfected with 1 μg pCMV/STAT3 and 3 μg pcDNA3/c-Src in combination with either 3 μg pFJ/STP A11 or a control vector (pFJ). c-Src was immunoprecipitated with anti-c-Src antibody, bead-bound proteins were eluted and immunoblotted with anti-FLAG (STAT3) and anti-AU1 (STP A11) antibodies. (B) c-Src binding is required for STAT3 phosphorylation. 293T cells were transfected with pCMV/STAT3 in combination with a vector control (lane 2), pFJ/STP A11 WT (lane 3), pFJ/STP A11 Y37A (lane 4), pFJ/STP A11 Y54A (lane 5), or pFJ/STP A11 Y115A (lane 6). STP A11 was immunoprecipitated with anti-AU1 antibody and immunoprecipitates were immunoblotted with anti-phosphoSTAT3 (PY-STAT3, Y705) and anti-FLAG antibodies. (C) c-Src and STP A11 act in concert to phosphorylate STAT3. 293T cells were transiently transfected with 1 μg pCMV/STAT3 in the presence (+) or absence (−) of 10 ng pcDNA3/c-Src, together with 1 μg control vector (pFJ, lanes 2 and 5), pFJ/STP A11 WT (lanes 3 and 6), or pFJ/STP A11 Y115A (lanes 4 and 7). STAT3 was immunoprecipitated with anti-FLAG antibody and the immunoprecipitates were immunoblotted with anti-PY-STAT3 and anti-FLAG antibodies.

trace amounts of STAT3 were phosphorylated in cells expressing c-Src alone (data not shown). Compared to STP A11 WT (lanes 3 and 6), STAT3 phosphorylation was dramatically decreased in cells expressing STP A11 Y115A either in the absence (lane 4) or presence (lane 7) of c-Src kinase. Our data suggest that since STP A11 Y115A has very little binding affinity for c-Src [16], its co-expression with c-Src induces low level of STAT3 phosphorylation (lane 7).

Direct interaction between STAT3 and STP A11 is required for STAT3 activation

To determine whether direct interaction with STP A11 is required for STAT3 activation, we constructed a series of amino terminal mutants of STP A11 and termed them N1 (aa 31–164), N2 (aa 50–164), N3 (aa 80–164), and N4 (aa 99–164). In addition to the amino terminal truncation, the carboxyl terminal hydrophobic domain of each mutant was also removed for better expression in bacteria (STP A11 ΔTM). Each mutant protein was produced in bacteria and in vitro binding assays were performed to determine their interactions with STAT3 (Figs. 4A and B). We found that STP A11 N1 (31–136) bound strongly to STAT3, while STP A11 N2 (50–136) bound poorly (Fig. 4B). These data suggest that the 31–50 region of STP A11 is important for interaction with STAT3 proteins. c-Src was used as a positive control, and it bound to all mutants since all contained SH2B domains [16]. We determined the effect of STP A11 amino terminal truncation on STAT3 activation. We found that STP A11 WT and STP A11 N1 activated STAT3-dependent transcription, but STP A11 N2 and N3 mutants, which had low binding affinity with STAT3, poorly activated STAT3 (Fig. 4D). These data indicate that STP A11 interaction with STAT3 is required for STAT3 activation. STP A11 N1 was only able to activate STAT3 to half the level of that achieved by STP A11 WT. These data suggest that amino terminal residues 1–30 are required for full STAT3 activation. Since STP A11 and its mutants were efficiently expressed (Fig. 4C), the lack of STAT3 activation was not due to different expression levels of mutants.

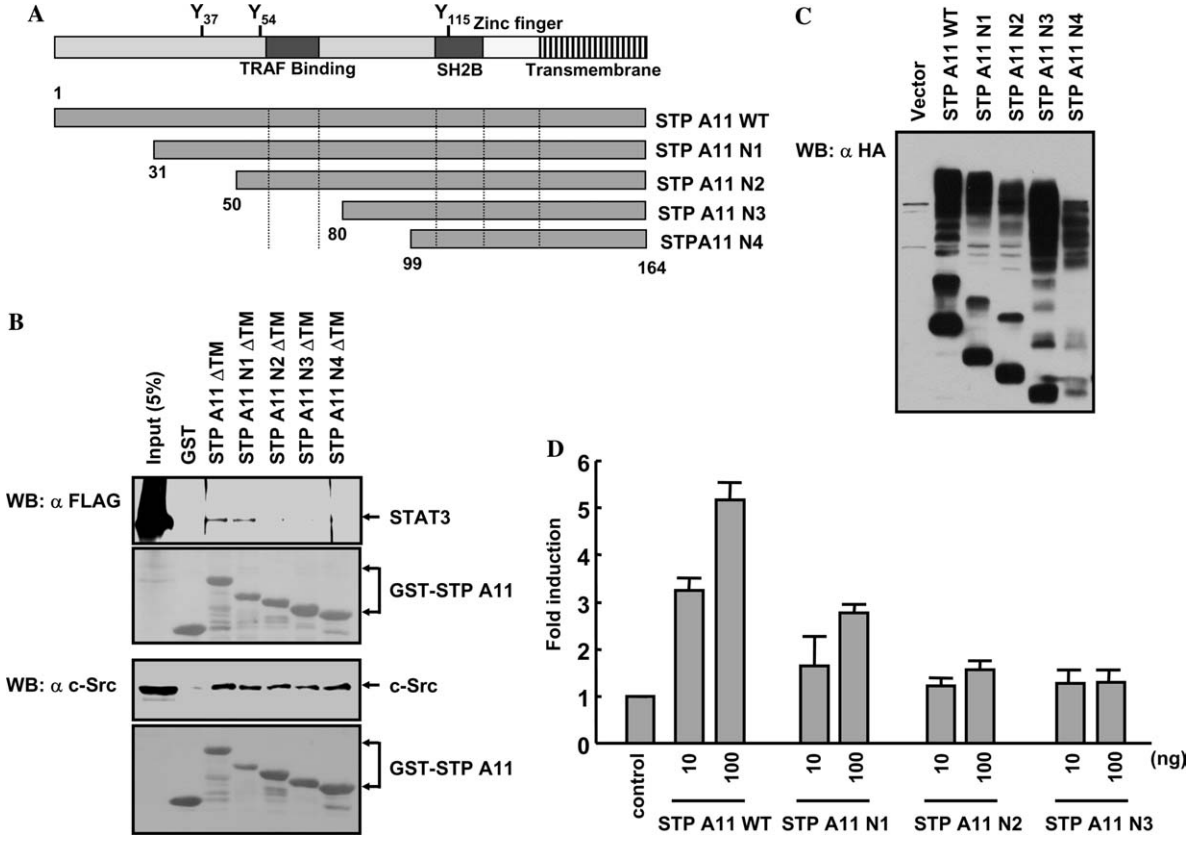

Fig. 4. Identification of STAT3 binding regions in STP A11. (A) Schematic diagrams of STP A11 deletion constructs. WT (amino acids 1–164), N1 (31–164), N2 (50–164), N3 (80–164), and N4 (99–164). (B) FLAG-STAT3 and c-Src were transiently expressed in 293T cells and the cleared cell lysates were incubated with GST, GST-STP A11 ΔTM (amino acids 1–136), N1 ΔTM (30–136), N2 ΔTM (50–136), N3 ΔTM (80–136) or N4 ΔTM (99–136). The bead-bound proteins were eluted and immunoblotted with anti-FLAG and anti-c-Src antibodies. GST and GST fusion proteins were visualized by Ponceau S staining. (C) Expression of STP A11 and its mutants in 293T cells. HA-STP A11 and its mutants were detected by immunoblotting using anti-HA antibody. (D) Luciferase activity in 293T cells transfected with STP A11 and its mutants.

STAT3 interaction is conserved between STP A and B

Among HVS subgroups, A and C, but not B, are regarded as oncogenic (13, 14). Similarly, STP A and C, but not B, are oncogenic [11,12,17]. Since STP A and B have a significant level of sequence homology, and share a binding partner (c-Src), STP B may potentially associate with STAT3 [17]. Co-immunoprecipitation assays were performed to test for this possibility. We found that STAT3 bound to both STP A11 and STP B, with the level of STP B interaction with STAT3 being comparable to that of STP A11 (Fig. 5A). These data indicate STAT3 interaction is conserved between STP A and B. We examined whether STP B could induce STAT3 activation using a luciferase assay to measure STAT3-dependent transcription. We found that STP A11 dose-dependently activated STAT3-dependent transcription, as did STP B but in a weaker manner (Fig. 5B). These data indicate that while STAT3 activation is conserved between STP A11 and STP B, the level of STAT3 activation correlated with the oncogenic potential of the STP protein.

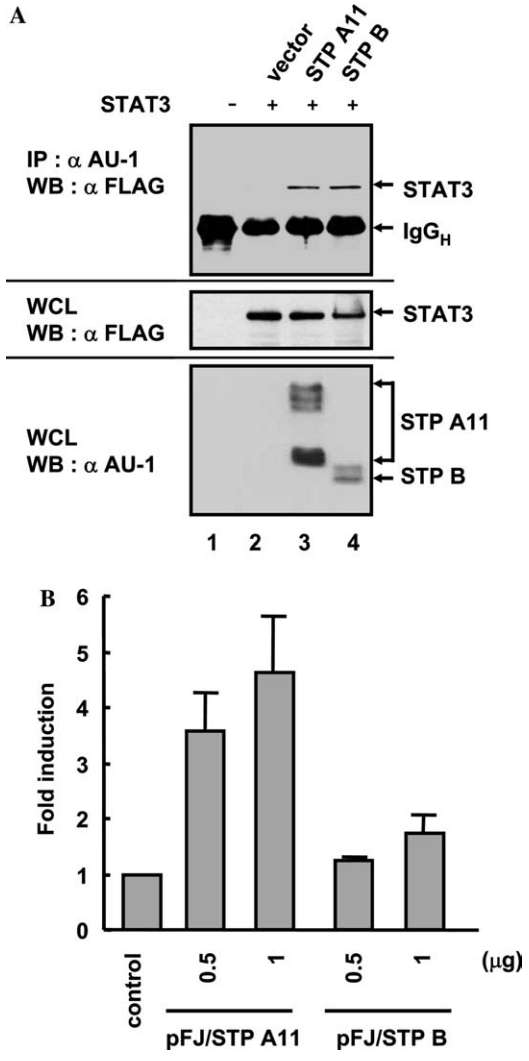

Fig. 5. STAT3 interaction is conserved between STP A and B. (A) Both STP A11 and STP B can interact with STAT3. AU1-STP A11 and B were immunoprecipitated and the bead-bound proteins were immunoblotted with anti-FLAG antibody. (B) STP B induces STAT3 activation but it is weaker than STP A11. 293T cells were transfected with pTK/SIE-Luc in combination with either pFJ/STP A11 or pFJ/STP B (24–76) and luciferase activity was measured.

Discussion

In this report we demonstrate that STP A11 can associate with STAT3 and induce its transcriptional activity. STAT3 tyrosine phosphorylation is critical for its activation [18,19], and our data indicate STP A11 recruits c-Src to phosphorylate STAT3. It appears STAT3 is activated by the interaction with STP A11 since the STP A11 amino terminal deletion mutant lacking amino acids 1–49 was unable to bind or activate STAT3. Because STP A and B share the sequence homology, STAT3 interaction and STAT3-dependent transcriptional activation are conserved between STP A and B.

Our data suggest the ability to activate STAT may be conserved in most γ herpesvirus families. Latent membrane protein 1 (LMP1) of EBV is absolutely required for B cell transformation, and it is the counterpart of HVS STP [20,21]. LMP1 interacts with janus kinase 3 (JAK3) and activates STAT proteins [22]. In HVS subgroup C, the tyrosine kinase interacting protein (TIP) associates with STAT1 and STAT3 and activates STAT-dependent transcription, and this is dependent on Lck interaction [23,24]. Thus, it appears that although LMP1, TIP, and STP A11 do not have tyrosine kinase activity, they recruit cellular kinases such as JAK3, Lck, and c-Src to phosphorylate and activate STAT.

In conclusion, we have demonstrated that the STP A11 herpesvirus protein can bind and activate mammalian STAT3. STAT3 tyrosine phosphorylation is critical for its activation [18,19], and our data indicate STP A11 recruits c-Src to phosphorylate STAT3.

Acknowledgments

This work was supported in part by grants from the National Research Laboratory Program of the Korea Institute of Science and Technology Evaluation and Planning and the BK21 Program of the Ministry of Education, Korea.

References

[1] T. Bowman, R. Garcia, J. Turkson, R. Jove, STATs in oncogenesis, Oncogene 19 (2000) 2474–2488.

[2] J. Turkson, T. Bowman, R. Garcia, E. Caldenhoven, R.P. De Groot, R. Jove, Stat3 activation by Src induces specific gene regulation and is required for cell transformation, Mol. Cell. Biol. 18 (1998) 2545–2552.

[3] M. Masuda, M. Suzui, R. Yasumatu, T. Nakashima, Y. Kuratomi, K. Azuma, K. Tomita, S. Komiyama, I.B. Weinstein, Constitutive activation of signal transducers and activators of transcription 3 correlates with cyclin D1 overexpression and may provide a novel prognostic marker in head and neck squamous cell carcinoma, Cancer Res. 62 (2002) 3351–3355.
[4] D. Sinibaldi, W. Wharton, J. Turkson, T. Bowman, W.J. Pledger, R. Jove, Induction of p21WAF1/CIP1 and cyclin D1 expression by the Src oncoprotein in mouse fibroblasts: role of activated STAT3 signaling, Oncogene 19 (2000) 5419–5427.
[5] T. Bowman, M.A. Broome, D. Sinibaldi, W. Wharton, W.J. Pledger, J.M. Sedivy, R. Irby, T. Yeatman, S.A. Courtneidge, R. Jove, Stat3-mediated Myc expression is required for Src transformation and PDGF-induced mitogenesis, Proc. Natl. Acad. Sci. USA 98 (2001) 7319–7324.
[6] R. Catlett-Falcone, T.H. Landowski, M.M. Oshiro, J. Turkson, A. Levitzki, R. Savino, G. Ciliberto, L. Moscinski, J.L. Fernandez-Luna, G. Nunez, W.S. Dalton, R. Jove, Constitutive activation of Stat3 signaling confers resistance to apoptosis in human U266 myeloma cells, Immunity 10 (1999) 105–115.
[7] J.U. Jung, J.K. Choi, A. Ensser, B. Biesinger, Herpesvirus saimiri as a model for gamma herpesvirus oncogenesis, Semin. Cancer Biol. 9 (1999) 231–239.
[8] B. Biesinger, J.J. Trimble, R.C. Desrosiers, B. Fleckenstein, The divergence between two oncogenic Herpesvirus saimiri strains in a genomic region related to the transforming phenotype, Virology 176 (1990) 505–514.
[9] P. Medveczky, E. Szomolanyi, R.C. Desrosiers, C. Mulder, Classification of herpesvirus saimiri into three groups based on extreme variation in a DNA region required for oncogenicity, J. Virol. 52 (1984) 938–944.
[10] R.C. Desrosiers, A. Bakker, J. Kamine, L.A. Falk, R.D. Hunt, N.W. King, A region of the Herpesvirus saimiri genome required for oncogenicity, Science 228 (1985) 184–187.
[11] E. Szomolanyi, P. Medveczky, C. Mulder, In vitro immortalization of marmoset cells with three subgroups of herpesvirus saimiri, J. Virol. 61 (1987) 3485–3490.
[12] R.C. Desrosiers, D.P. Silva, L.M. Waldron, N.L. Letvin, Nononcogenic deletion mutants of herpesvirus saimiri are defective for in vitro immortalization, J. Virol. 57 (1986) 701–705.
[13] J.U. Jung, J.J. Trimble, N.W. King, B. Biesinger, B.W. Fleckenstein, R.C. Desrosiers, Identification of transforming genes of subgroup A and C strains of Herpesvirus saimiri, Proc. Natl. Acad. Sci. USA 88 (1991) 7051–7055.
[14] J.U. Jung, R.C. Desrosiers, Association of the viral oncoprotein STP-C488 with cellular ras, Mol. Cell. Biol. 15 (1995) 6506–6512.
[15] J.M. Koomey, C. Mulder, R.L. Burghoff, B. Fleckenstein, R.C. Desrosiers, Deletion of DNA sequence in a nononcogenic variant of Herpesvirus saimiri, J. Virol. 50 (1984) 662–665.
[16] H. Lee, J.J. Trimble, D.W. Yoon, D. Regier, R.C. Desrosiers, J.U. Jung, Genetic variation of herpesvirus saimiri subgroup A transforming protein and its association with cellular src, J. Virol. 71 (1997) 3817–3825.
[17] J.K. Choi, S. Ishido, J.U. Jung, The collagen repeat sequence is a determinant of the degree of herpesvirus saimiri STP transforming activity, J. Virol. 74 (2000) 8102–8110.
[18] J.E. Darnell Jr., I.M. Kerr, G.R. Stark, Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins, Science 264 (1994) 1415–1421.
[19] J.N. Ihle, Cytokine receptor signalling, Nature 377 (1995) 591–594.
[20] K.M. Kaye, K.M. Izumi, G. Mosialos, E. Kieff, The Epstein-Barr virus LMP1 cytoplasmic carboxy terminus is essential for B-lymphocyte transformation; fibroblast cocultivation complements a critical function within the terminal 155 residues, J. Virol. 69 (1995) 675–683.
[21] K.M. Kaye, K.M. Izumi, E. Kieff, Epstein–Barr virus latent membrane protein 1 is essential for B-lymphocyte growth transformation, Proc. Natl. Acad. Sci. USA 90 (1993) 9150–9154.
[22] O. Gires, F. Kohlhuber, E. Kilger, M. Baumann, A. Kieser, C. Kaiser, R. Zeidler, B. Scheffer, M. Ueffing, W. Hammerschmidt, Latent membrane protein 1 of Epstein–Barr virus interacts with JAK3 and activates STAT proteins, EMBO J. 18 (1999) 3064–3073.
[23] D.A. Hartley, K. Amdjadi, T.R. Hurley, T.C. Lund, P.G. Medveczky, B.M. Sefton, Activation of the Lck tyrosine protein kinase by the Herpesvirus saimiri tip protein involves two binding interactions, Virology 276 (2000) 339–348.
[24] T. Lund, M.M. Medveczky, P.G. Medveczky, Herpesvirus saimiri Tip-484 membrane protein markedly increases p56lck activity in T cells, J. Virol. 71 (1997) 378–382.