Accelerated G1 Phase Progression Induced by the Human T Cell Leukemia Virus Type I (HTLV-I) Tax Oncoprotein*

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Tax, the human T cell leukemia virus type I oncoprotein, plays a crucial role in viral transformation and the development of the virally associated disease adult T cell leukemia. Because oncogenesis involves alterations in cell growth, it is important to examine the effects of Tax on cell cycle progression. Using a synchronized cell system, we have found that Tax expression accelerates G1 phase progression and S phase entry with concomitant DNA replication. This accelerated progression is accompanied by an earlier onset of cdk2 kinase activity. In contrast to the shortening of G1 phase, the length of S phase is unaffected by Tax expression. As a result of a more rapid cell cycle progression, cells expressing Tax exhibit faster growth kinetics and display an altered cell cycle distribution. Additionally, the decreased time allowed for growth in the presence of Tax results in a decreased cell size. Tax-associated acceleration of cell cycle progression may play a role in the ability of this viral oncoprotein to mediate cellular transformation and promote the development of human T cell leukemia virus type I-associated diseases.

Because of the important regulatory role these cdk complexes play in normal cell growth, they often serve as targets of oncogenic viruses. Cancer-causing viruses encode one or more viral oncoproteins that, through various mechanisms, disrupt the regulation of cdk kinase complexes. For example, large T antigen of SV40, E1A of adeno viruses, and E7 of papillomaviruses all bind to and inactivate the tumor suppressor protein pRb (6–8). This inactivation relieves the pRb-mediated repression of the transcription factor E2F, which is then able to activate genes essential for S phase progression, including cyclin E and cyclin A. Therefore, these viral oncoproteins allow for the unregulated expression of the cdk2 kinase regulatory subunits, which ultimately results in the dysregulation of cdk2 kinase activity, thereby altering cell cycle progression.

Human T cell leukemia virus type I (HTLV-I), a human retrovirus known to be the etiologic agent of adult T cell leukemia (ATL) (9), encodes a viral regulatory protein Tax which has been suggested to play a role in HTLV-I-mediated transformation. The Tax protein is a transcriptional transactivator that enhances expression of viral as well as select cellular genes. Tax shares many characteristics with classic viral oncoproteins including the ability to immortalize primary cells in culture (10, 11), induce tumors in transgenic mice (12, 13), functionally inactivate tumor suppressor proteins such as p53 (14–17) and p16INK4A (18–20), and inhibit cellular DNA repair (21, 22). However, the effects of the Tax oncoprotein on cell cycle progression remain unclear and, therefore, serve as the focus of this report.

Infection with HTLV-I has been associated with changes in cellular proliferation including growth factor independence (23) and resistance to growth inhibitory signals (20). Although these findings demonstrate that HTLV-I is capable of modulating cell growth, the viral protein mediating these effects has not been identified. The viral regulatory protein Tax has been shown to inhibit negative cell cycle regulators such as p53 (14–17), p16INK4A (18–20), and p27Kip1 (24) and stimulate positive cell cycle regulators such as cdk4/6 (25, 26), d-type cyclins (26–28), and E2F (29) (reviewed in Ref. 30). Given the ability of Tax to alter the activities of such key regulatory molecules, it is important to examine the effects of Tax on cell cycle progression.

Despite the fact that Tax affects positive and negative cell growth regulators, little work has been reported on the effects of these activities on cell cycle progression. This study was aimed at examining the effects of Tax on cell cycle progression. Using a synchronized cell system, we found that Tax expression was associated with an accelerated G1 phase progression with an earlier onset of cdk2 kinase activity and with earlier S phase entry. In contrast, progression through S phase was unaffected by Tax expression. Also, Tax expression resulted in an accelerated growth rate causing an alteration in the cell cycle distribution pattern. Consistent with this reduced time allowed for...
growth during the cell cycle, cells expressing Tax exhibited a decrease in cell size. These results suggest that Tax expression accelerates cell cycle progression, which may play a role in the ability of Tax to mediate HTLV-I induced cellular transformation and disease.

EXPERIMENTAL PROCEDURES

Cell Lines—CREF-neo and CREF-Tax cells were previously described (31). Cells were maintained in Dulbecco's modified Eagle's serum supplemented with 10% fetal bovine serum.

Cell Synchroization—CREF cells were plated at a density of 1.0 × 10⁶ cells/100-mm dish and allowed to reach 100% confluence. Cells were maintained at 100% confluence for 48 h. To release cells from the cell cycle arrest, they were split 1:12 into fresh 100-mm dishes.

Antibodies—Anti-cdk2 (M2), anti-cyclin E (M20), anti-cyclin A (H432), anti-p107 (SD9), anti-p130 (C20), anti-pRb (IF8), and anti-E2F4 (C15) antibodies were purchased from Santa Cruz Biotechnology.

FITC-conjugated anti-BrdUrd antibody was purchased from Becton Dickinson.

Propidiod Iodide (PI) Staining—One million cells were resuspended in 0.9% NaCl, fixed in 95% ethanol, and incubated at room temperature for 30 min followed by storage at 4 °C. To release the cells from the cell cycle arrest, they were split 1:12 into fresh 100-mm dishes.

Antibodies—Anti-cdk2 (M2), anti-cyclin E (M20), anti-cyclin A (H432), anti-p107 (SD9), anti-p130 (C20), anti-pRb (IP8), and anti-E2F4 (C15) antibodies were purchased from Santa Cruz Biotechnology. FITC-conjugated anti-BrdUrd antibody was purchased from Becton Dickinson.

Cell Extracts—For kinase assays, cells were lysed directly on ice. Thirty milligrams of nuclear extract, 10 mg of histone H1, 5 μg of histone H1, 5 μg of histone H1, and 15 μg of bovine serum albumin, 1 μg of sonicated herring sperm DNA, and 5 ng of 32P-labeled DNA probe. The binding reaction was incubated at room temperature for 30 min then resolved on a 4% polyacrylamide gel with 5% glycerol) in TBE (50 mM Tris borate, 1 mM EDTA) at 4 °C for 4 h at 150 V. For competition reactions, 500 ng of double-stranded unlabeled oligonucleotide of either the specific competitor, E2F/wt (sequence shown above), or the nonspecific competitor, E2Fmut, with the following sequence (5'-CTAGACTCTAGTTTCGTTCTGCGCTTAAATTTGA-3') was used. For super-shift analyses, 0.5 μg of the specific antibody was used in each binding reaction.

RESULTS

Tax Expression Accelerates Entry into S Phase—The ability of classic oncoproteins to stimulate cell growth is believed to be important for the transformation processes mediated by these proteins. To examine the effects of a viral oncoprotein, HTLV-I Tax, on cell cycle progression, a synchronized cell system was used to monitor progression through a single cell division cycle. In this system, an established rat embryo fibroblast cell line (CREF) stably expressing Tax (CREF-Tax) or a control gene (CREF-neo) were arrested by contact inhibition for 48 h then released into the cell cycle by replating at a lower density. Synchronization by cell contact inhibition typically results in cell cycle arrest and accumulation of cells in a quiescent, or G0, state. When CREF-neo and CREF-Tax cells were synchronized by contact inhibition for 48 h followed by flow cytometric analysis, almost 90% of the cells contained a 2N DNA content indicative of a cell in G0/G1 phase (Fig. 1A).

To determine the effects of Tax on G1 phase progression, CREF-neo or CREF-Tax cells were released from the cell cycle block and monitored for cell cycle progression. At various times postrelease, cells were fixed and stained with the DNA binding dye PI, and the cell cycle distribution was analyzed by flow cytometry. Analysis of S phase entry demonstrated that upon release from a G0 block, CREF-Tax cells enter S phase ~4 h
Tax Accelerates Cell Cycle Progression

Fig. 2. Tax expression accelerates the onset of cdk2 kinase activity. CREF-neo and CREF-Tax cells were synchronized by contact inhibition and released. At the indicated times postrelease, whole cell extracts were prepared. Cdk2 was immunoprecipitated from these extracts, and kinase activity was analyzed in an in vitro kinase assay using histone H1 as a substrate. PhosphorImager quantitation of relative cdk2 kinase activity over time was determined. Data from one of three representative experiments are shown.

Fig. 3. Tax expression accelerates the onset of both cyclin E- and cyclin A-associated cdk2 kinase activities. CREF-neo and CREF-Tax cells were synchronized by contact inhibition and released. At the indicated times postrelease, whole cell extracts were prepared. Cyclin E (A) or cyclin A (B) was immunoprecipitated from the extracts and used in an in vitro kinase assay with histone H1 as a substrate. Relative kinase activity was determined by PhosphorImager analysis. Data from one of three representative experiments are shown.

Tax Expression Accelerates Onset of cdk2 Kinase Activity—The accelerated entry of Tax-expressing cells into S phase may result from stimulation of the G1/S phase transition, an event dependent upon kinase activity of the cyclin E-cdk2 protein complex. Aberrant activation of this kinase activity stimulates the G1/S transition (35). To determine whether Tax expression dysregulates cdk2 kinase activity during cell cycle progression, this activity was examined in synchronized CREF-neo and CREF-Tax cells. At various times postrelease from the contact-inhibited arrest, whole cell extracts were prepared. Cdk2 was immunoprecipitated from these extracts and used in an in vitro kinase assay with histone H1 as a substrate. As shown in Fig. 2, induction of cdk2 kinase activity is first detectable at 12 h postrelease in CREF-Tax cells, whereas the first detectable induction of this activity in the absence of Tax does not occur until 16 h postrelease. Both the time of induction and the 4-h difference in the onset of this kinase activity between Tax-expressing and non-expressing cells correlates with the difference in S phase entry demonstrated in Fig. 1, B and C.

Because cdk2 is found sequentially in complex with cyclin E, regulating the G1/S transition, and with cyclin A, regulating S phase progression, it was important to determine whether the cdk2 activity observed in Fig. 2 could be attributed to one or both of these cyclin complexes. When cyclin E- and cyclin A-associated cdk2 kinase activities were analyzed separately using an in vitro kinase assay following cyclin-specific immunoprecipitation, results similar to those using total cdk2 activity were observed (Fig. 3). Cyclin E-cdk2 kinase activity (Fig. 3A), the activity required for the G1/S phase transition, was induced earlier than cyclin A-cdk2 kinase activity (Fig. 3B), the activity required for S phase progression in both CREF-Tax and CREF-neo cell lines. Additionally, cyclin E-cdk2 and cyclin A-cdk2 kinase activities were apparent ~4 h earlier in cells expressing Tax. These results are similar to those observed for the induction of total cdk2 kinase activity (Fig. 2) as well as for entry into S phase (Fig. 1, B and C). The protein levels of cdk2, cyclin E, and cyclin A were determined by Western blotting and were induced at expected times during the cell cycle (data not shown). These data suggest that Tax expression results in an earlier onset of both cyclin E- and cyclin A-associated cdk2 kinase activity. This dysregulated activation of cdk2 may be responsible for the earlier entry into S phase of cells expressing Tax.

Tax Expression Does Not Affect the Length of S Phase—The data described above suggest that Tax expression causes a shortening of G1 phase resulting in an accelerated entry into S phase. To determine whether these effects are specific to this phase of the cell cycle or whether other phases may be affected in the presence of Tax, progression through S phase was measured by completion of the phase and entry into G2/M phase. At various time points postrelease from the cell cycle arrest, cells were fixed and stained with PI, and their cell cycle distribution was analyzed by flow cytometry (Fig. 4). Cells expressing Tax complete S phase and enter G2/M phase ~4 h earlier than control cells (19 and 23 h postrelease, respectively). This difference in phase transition is the same as that seen with entry into S phase, suggesting that the time required for a cell to proceed through and complete S phase is unaffected by Tax expression.

Tax Does Not Affect Entry into or Exit from G0—The above
results suggest that Tax expression stimulates G1 phase progression. However, it is possible that Tax affects some aspect of cell synchronization, thereby contributing to the earlier onset of cdk2 activity and S phase entry. For example, if Tax-expressing cells arrested at the beginning of G1 phase in response to contact inhibition, they would still appear to be synchronized in a G0/G1 peak as we observed by flow cytometry (as shown in Fig. 1A), but they would gain a time advantage over non-Tax-expressing cells for progression through G1 phase upon release from the cell cycle arrest. Alternatively, Tax-expressing cells may arrest in G0 but may enter the cell cycle more rapidly, such that the differences in cell cycle progression map to the G0/G1 phase transition rather than to G1 phase progression. To address these questions, a quiescence, or G0 phase-specific, marker was analyzed.

When normal cells are cycling, or non-quiescent, several E2F protein complexes, such as those containing p107, pRb, or “free” E2F (i.e. E2F not complexed with a pocket protein), are present, but the p130-E2F complex is absent. Upon induction of quiescence, the p130-E2F complex forms, and the p107- and pRb-containing complexes as well as free E2F complexes dissociate (36–38). Therefore, the presence of p130-E2F complexes serves as a marker of quiescent cells, whereas the appearance of free E2F or p107-E2F complexes is indicative of cells proceeding through the cell cycle.

To verify that the contact-inhibited cells were arrested in a G0 state EMSAs were performed to analyze the E2F complexes present in the synchronized cells (Fig. 5). Nuclear extracts from asynchronously growing CREF-neo and CREF-Tax cells contained p107-associated E2F complexes as well as free E2F complexes but lacked detectable p130-containing E2F complexes. However, synchronization of both cell lines by contact inhibition resulted in reduction of the p107-E2F and free E2F complexes with the concomitant appearance of a p130-E2F complex. The specificity of these complexes was demonstrated by competition with wild type and mutant E2F competitors (lanes 4 and 9) were used to establish specificity of the complexes. Antibodies to p107 (lanes 5 and 10) or p130 (lanes 6 and 11) were used in supershift reactions to verify complex composition. The position of E2F complexes is shown.

analyzed by PI staining every 12 h until the cells had been maintained at 100% confluence for 48 h. CREF-neo and CREF-Tax cells reach their respective maximum cell number at the same time (72 h postplating) and at the same rate as indicated by the slope of the curve (Fig. 6A). The slightly higher number of Tax-expressing cells at confluence is likely due to their reduced size (discussed later) and ability to grow to a higher density than cells without Tax. Examination of the cell cycle distribution during synchronization demonstrated that the rate at which CREF-neo and CREF-Tax cells accumulate with a G0/G1 content of DNA was similar and correlated with the maintenance of constant cell number following confluence at 72 h postplating (Fig. 6B).

To further investigate the rate at which CREF-neo and CREF-Tax cells synchronize in response to contact inhibition, nuclear extracts were prepared at intervals following confluence, and the various E2F complexes were analyzed by EMSA (Fig. 6C). The p107-E2F complex as well as free E2F was present in cells with and without Tax until 12 h after the cells had reached 100% confluence. At 24 h postconfluence, both CREF-neo and CREF-Tax cells appear to have lost p107-E2F complexes and free E2F. In their place, p130-E2F complexes were observed in both cell types at 24 h postconfluence and persisted for the remainder of the experiment. Specificity of these complexes was demonstrated by competition analysis and the positions of p107, p130, and free E2F complexes were confirmed by supershift (data not shown). Using this analysis, there was no detectable difference in the rate at which CREF-neo and CREF-Tax cells become synchronized in a G0 state.

Several lines of evidence suggest that Tax facilitates the release of cells from a cell cycle arrest (20, 25). Thus, it was possible that Tax expression would promote exit from the quiescent state and entry into the cell cycle at an accelerated pace. To examine this possibility, CREF-neo and CREF-Tax cells

F. J. Lemoine and S. J. Marriott, unpublished observation.
were synchronized in G0 by contact inhibition and released as described above. At 2-h intervals following release, nuclear extracts were prepared, and the E2F complexes present were analyzed by EMSA (Fig. 6D). At the time of release (0 h), both cell lines contained p130-E2F complexes as shown in Fig. 4. At 4 h postrelease, free E2F complexes indicative of G1 phase began to accumulate. The composition of these complexes was verified by supershift analysis using specific antibodies (data not shown). An equivalent rate of free E2F accumulation was observed between CREF-neo and CREF-Tax cells. The slightly higher levels of E2F seen here in CREF-Tax cells at 4 h was not observed reproducibly. These results suggest Tax expression does not alter the ability of CREF cells to exit a quiescent state nor does it affect the rate at which cells enter G1 phase of the cell cycle.

Tax Expression Affects Cell Growth Kinetics—All of the results described above are consistent with an effect of Tax on cell cycle progression during G1 phase progression or at the G1/S phase transition. The ability of Tax to stimulate cell cycle progression would also likely stimulate cell proliferation resulting in accelerated cell growth. To examine whether Tax expression affected the length of the complete cell division cycle, cell proliferation and growth kinetics of CREF-neo and CREF-Tax cells were analyzed. Equivalent numbers of cells were plated in 150-mm dishes, and the total cell number was determined every 24 h for 6 days, during which time cells were maintained at subconfluence. Over the course of the experiment, CREF-Tax cells outgrew CREF-neo cells by ~1.6-fold (Fig. 7). This correlates with an approximate cell division time of 16 h for CREF-Tax and 19 h for CREF-neo cells and suggests that Tax, like other oncogenes, is able to stimulate cell growth. These effects have been reproduced in p53 null mouse embryo fibroblasts and SaOS2 cells, both of which stably express Tax (data not shown).

For a cell to divide more rapidly some alteration(s) of the cell cycle must occur, resulting in the shortening of one or more of the phases of the cell cycle such that the time required for completion of the entire cell division process is decreased. If such a change has taken place, it may be detectable as a difference in the proportion of cells in each phase of the cell cycle. With the observation that CREF-Tax cells divide more rapidly than control cells, the ability of Tax expression to affect changes in the cell cycle distribution pattern of asynchronous cells was examined. Asynchronously growing CREF-neo and CREF-Tax cells were fixed and stained with PI, and their cell cycle distribution was analyzed by flow cytometry. The percentage of cells in each phase of the cell cycle as determined by relative DNA content demonstrated that Tax expression is associated with changes in the cell cycle profile of CREF cells (Fig. 8). Although these differences are small, there is a reproducible decrease in the percentage of cells with a G0/G1 (2N) content of DNA in the presence of Tax. These results are consistent with Tax affecting cell proliferation by facilitating a shortening of G1 phase and confirm that the accelerated cell cycle progression stimulated by Tax is not simply an effect of cell synchronization.

Tax Expression Affects Cell Size—As a consequence of Tax stimulating cell cycle progression, cells have less time to pro-
that may be responsible for the accelerated G1/S phase transition displayed an earlier onset of cdk2 kinase activity, an aberration with concurrent DNA replication. These synchronized cells also exhibited an approximate 12% reduction in cell size. This effect was also observed in SaOS2 cells stably expressing Tax (data not shown). Reduced cell size in the presence of Tax expression is consistent with the acceleration of G1 phase progression described above. Indeed, additional flow cytometry studies demonstrated a 10% reduction in cell size in the G1 population and a recovery of cell size in subsequent cell cycle phases (data not shown).

**DISCUSSION**

This study examined the effect of a viral transforming protein on cell cycle progression. The results are summarized in a schematic diagram (Fig. 10). Upon analysis of cell cycle progression and phase transitions using a synchronized cell system, we found that Tax expression accelerated progression through G1 phase resulting in an earlier entry into S phase with concurrent DNA replication. These synchronized cells also displayed an earlier onset of cdk2 kinase activity, an aberration that may be responsible for the accelerated G1/S phase transition. We demonstrated that Tax expression resulted in an accelerated growth rate in rat embryo fibroblasts as well as a reduction in cell size. These results support the idea that the viral oncoprotein, Tax, accelerates cell cycle progression. This ability to promote cellular proliferation may play an important role in the virally associated transformation mediated by Tax.

Previous reports have suggested a role for Tax in the stimulation of cell cycle progression (20, 25). These studies have examined the ability of Tax to promote entry into the cell cycle from a quiescent or arrested state such that in the absence of Tax expression proliferation was inhibited. However, when Tax was expressed, cells were stimulated to enter the cell cycle. The results suggest that Tax can stimulate an early event resulting in cell cycle entry, but they do not address directly the effects of Tax expression on the progression of cells that are actively proceeding through the cell cycle.

The results presented here demonstrate that Tax expression causes an accelerated entry into S phase following the similar entry into G1 of cells with and without Tax expression. Because there is no difference in cell cycle entry upon release from the synchronization block (as shown in Fig. 6D), it appears that Tax exerts its effect at a later point during G1 phase. There are two possible explanations for such an effect. First, Tax may accelerate the progression through a complete G1 phase such that the cell reaches the G1/S phase transition earlier. Alternatively, Tax may stimulate the G1/S phase transition such that the cell is induced to enter S phase before the completion of G1 phase. Further studies will distinguish between these two potential explanations. Our results definitively demonstrate the ability of Tax to accelerate cell cycle progression in actively dividing cells and show that this effect is mediated at a point between entry into the cell cycle at G1 phase and the G1/S phase transition. The accelerated cell cycle progression reported here is not a consequence of the synchronization process because asynchronously synchronized cells showed a shorter cell division time, an altered cell cycle distribution, and a smaller size corresponding well with accelerated progression following synchronization.

Previous reports have shown that Tax can stimulate cdk4/6 kinase activity (25, 26), which is necessary for proper G1 phase progression. This increased cdk4/6 activity may play a role in the accelerated progression through G1 phase observed here. However, we cannot overlook the possibility that Tax may independently stimulate cyclin E-cdk2 kinase activity with concomitant induction of the G1/S phase transition regardless of G1 phase completion. Determining which kinase activity affected by Tax facilitates the observed acceleration of cell cycle progression will be an important next step in understanding this activity.

Infection with the transforming retrovirus HTLV-I has been associated with changes in cellular growth (20, 23). The results presented in this study demonstrate that the HTLV-I regula-

![Fig. 8. Tax expression affects cell cycle distribution.](Image 86x363 to 260x729)

**Fig. 8. Tax expression affects cell cycle distribution.** The cell cycle distribution of asynchronously growing CREF-neo and CREF-Tax cells was analyzed by flow cytometry following PI staining. The proportion of cells in each phase of the cell cycle for asynchronously growing CREF-neo and CREF-Tax cells was determined by ModFit analysis of PI staining results. The results are the average of at least three independent experiments.

![Fig. 9. Tax expression affects cell size.](Image 332x530 to 531x729)

**Fig. 9. Tax expression affects cell size.** One million asynchronously growing CREF-neo and CREF-Tax cells were fixed, stained with PI, and analyzed by flow cytometry. Results shown are one of three representative experiments.

![Fig. 10. Schematic diagram of the effects of Tax on cell cycle progression.](Image 337x437 to 526x481)

**Fig. 10. Schematic diagram of the effects of Tax on cell cycle progression.** Upon release from a G0 cell cycle arrest induced by contact inhibition, CREF-neo and CREF-Tax cells enter G1 phase at the same rate. CREF-Tax cells display a shortened G1 phase with an earlier onset of cdk2 kinase activity. Tax-expressing cells also display an earlier entry into G2/M suggesting that the length of S phase is similar in Tax (+) and (-) cells. The complete cell division time for Tax-expressing cells is shorter than non-Tax-expressing cells suggesting that the length of G1/M is similar in both cell types. The ability of Tax to cause an accelerated cell cycle progression may play a role in HTLV-I-mediated transformation induced by Tax.
tory protein Tax can induce alterations in cellular proliferation and, therefore, may be the viral protein responsible for the effects observed with HTLV-I infection. The ability of HTLV-I Tax to alter cellular proliferation likely plays an important role in viral-mediated transformation. This effect of Tax is similar to that described for other viral oncoproteins such as large T antigen of SV40 and E1A of adenovirus. The finding that the retroviral oncoprotein Tax shares a common mechanism of stimulating cellular growth with DNA tumor virus-transforming proteins suggests the importance of dysregulating the cell division cycle in viral-mediated transformation. A greater understanding of the mechanism(s) underlying the ability of these viral oncoproteins to induce cell growth will provide insight into the regulation of cell cycle progression and cellular transformation and facilitate our understanding of mechanisms underlying the development of both virally and non-virally associated cancers.

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