Human T-cell Leukemia Virus Type I Tax Repression of p73β Is Mediated through Competition for the C/H1 Domain of CBP*

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The Tax protein, encoded by the human T-cell leukemia virus type I (HTLV-I), is required for high level viral transcription and HTLV-I-associated malignant transformation. Although the precise mechanism of malignant transformation by Tax is unclear, it is well established that Tax represses the transcription function of the tumor suppressor p53, possibly accelerating the accumulation of genetic mutations that are critical in HTLV-I-mediated malignant transformation. Tax repression of p53 transcription function appears to occur, at least in part, through competition for the cellular coactivator CBP/p300. In this study, we characterize the effect of Tax on the p53 family member, p73. We demonstrate that Tax also represses the transcription function of p73β and that the repression is reciprocal in vivo, consistent with the idea that both transcription factors may compete for CBP/p300 in vivo. We provide evidence showing that both Tax and p73 interact strongly with the C/H1 domain of CBP and that their binding to this region is mutually exclusive in vitro. This finding provides evidence supporting the idea that reciprocal transcriptional repression between Tax and p73 is mediated through coactivator competition.

Human T-cell leukemia virus type I (HTLV-I)1 is the etiological agent of adult T-cell leukemia (ATL) which is an aggressive and fatal hematological malignancy (1, 2). Only a small percentage of people infected with HTLV-I develop ATL, generally 20–40 years following infection (3). The infrequency of ATL, coupled with the long latency period, suggests that ATL occurs as a consequence of multiple genetic mutations that accumulate during the prolonged period of asymptomatic HTLV-I infection. Although the molecular basis of HTLV-I pathogenesis is not well understood, there is strong emerging evidence that expression of the viral trans-activator protein Tax plays an essential role in the oncogenic process. Indeed, the expression of Tax is able to immortalize primary T-cells (4), transform rat fibroblasts in vitro (5), and promote tumorgenesis and leukemogenesis in a mouse model (6).

With the goal of understanding the role of Tax in leukemogenesis, several studies have examined how Tax affects proteins involved in regulation of the cell cycle (for review see Ref. 7). These proteins include the cyclin-dependent kinase inhibitors p16\(^{INK4a}\), p18\(^{INK4a}\), p21\(^{WAF1/CIP1}\), and p27\(^{Kip1}\) (8–13), cyclin D (8, 14, 15), the transcription factors E2F-1 and E2F-2 (16–19), and the tumor suppressor protein p53 (12, 20–30). p53 is a transcription factor that is activated in response to genotoxic stress. Once activated, p53 induces expression of genes critical for cell cycle arrest or apoptosis, thus preventing the transmission of genetic mutations to progeny cells (31). Loss of p53 activity has been found in 60% of human malignancies examined (32, 33), consistent with a role for p53 in genome surveillance and suppression of malignant transformation.

Most interesting, in HTLV-I-infected and Tax-expressing cells, p53 is present at elevated levels, with a relatively low frequency of mutation (<25%) (12, 20, 21, 30, 34, 35). paradoxically, several studies have demonstrated that although generally wild type, p53 is functionally inactive. For example, HTLV-I-infected cells do not respond appropriately to a variety of p53 stimuli, including gamma and ionizing irradiation (12, 22, 36, 37). Furthermore, Tax expression alone abrogates p53-induced G1 arrest and apoptosis following DNA damage (24) and inhibits the activation of a panel of known p53-responsive genes (22). Several recent studies provide evidence showing that Tax inhibition of the tumor suppressor activities of p53 is directly due to Tax inhibition of p53 transcription function (21, 22, 24).

It is well established that Tax does not directly bind p53 (12, 22, 27, 36, 38); thus, Tax appears to compromise p53 function via an indirect mechanism. Several reports have indicated that Tax repression of p53 may occur through alterations in the phosphorylation state of p53 (23, 39). Alternatively, other studies indicate that the repression occurs as a consequence of competition between Tax and p53 for the cellular coactivators CBP/p300 (25–27). Both Tax and p53 utilize the cellular coactivators CBP/p300 as mediators of transcriptional activation (40–44). The site of competition on CBP/p300 appears to be the KIX domain (amino acids 588–683), as both Tax and p53 have high affinity for the KIX domain (8, 14, 15, 51). The KIX domain (amino acids 588–683), as both Tax and p53 have high affinity for the KIX domain (8, 14, 15, 51).

Recent studies have identified that p53 family members p73a, p73b, and p73c (45, 46). Interestingly, one form of p73, which lacks the transactivation domain, has been shown to be pro-apoptotic in neurons (50, 51). Specific p53 mutant proteins have been shown to associate with p73a (52) and p73b (53), resulting in interference with p73 transcriptional activity and the ability...
to induce apoptosis (52–54). As predicted from local regions of strong homology in the DNA binding domains of both proteins, p73 binds the canonical p53-binding sites (55). Furthermore, when ectopically expressed, p73 can trans-activate a variety of p53 promoters (p21, bax, mdm2, and GADD45) and induce apoptosis in p53-deficient cell lines (45, 48, 52, 56–59). Similar to p53, the activation domain of p73 interacts with the cellular coactivators CBP/p300 (60); however, the site of interaction appears to differ. Whereas p53 interacts with a carboxyl-terminal region and the KIX domain (25, 43), p73 has recently been shown to bind the C/H1 domain of CBP, located near the amino terminus of the coactivator (60).

p73 has been classified as a possible tumor suppressor based on substantial sequence homology and functional similarity with p53. This classification was strengthened by the observation that the p73 gene maps to chromosome 1p36, a region frequently deleted in several malignancies including neuroblastomas, colorectal cancers, and breast cancers (45). p73 activity is induced by exposure of cells to DNA-damaging agents such as cisplatin, taxol, and γ-irradiation (61–64). Furthermore, in lymphoid malignancies there is evidence that hypermethylation, and thus silencing, of the p73 gene may play a role in the development and/or progression of the neoplasm (65, 66). Loss of a single p73 allele has been linked to increased risk of developing some cancers actually shown increased levels of p73. In contrast to p53-deficient mice, p732/−/− mice show no increased susceptibility to spontaneous malignancies. These conflicting results suggest that altered expression of the p73 gene, rather than a loss of p73 function, may play a role in malignant transformation.

In this report, we investigate the function of p73 in HTLV-I-transformed, Tax-expressing T-cell lines. We demonstrate that in the presence of Tax the stability of p73β is increased, yet paradoxically, the transcription function of p73β is decreased. We also show that in the presence of p73 the transcription function of Tax is reduced, indicating that the transcriptional repression is reciprocal. The reciprocal transcriptional repression appears to arise from intracellular competition for CBP/p300, an observation very similar to that reported for Tax repression of p53 (25–27). Although these effects of Tax on p73 function are very analogous to the effects of Tax on p53 function, we provide evidence indicating that the site of competition on the surface of CBP/p300 differs. We demonstrate biochemically that both Tax and p73β bind strongly to the C/H1 domain of CBP and that the binding of the two transcription factors is mutually exclusive in vitro. These data suggest that Tax may inactivate p73β transcription function by specifically competing for the p73-C/H1 interaction in vivo. Disruption of both the p53 and p73β interactions with CBP/p300 in HTLV-I-infected cells may alter the transcription function of these key regulatory proteins.

MATERIALS AND METHODS

Cell Culture, Transient Cotransfection Assays, and Mammmalian Expression Plasmids—HTLV-I-negative T-cells (CEM, HUT-78, Jurkat, and Molt-4) and HTLV-I-transformed T-cells (C8166/45, C91/PL, MT2, SLB-1, and HUT-102) were cultured in Iscove’s modified Dulbecco’s medium supplemented with 10% fetal bovine serum, 2 mM l-glutamine, and penicillin/streptomycin. The HCT-116 cells and 293 cells were cultured in Dulbecco’s modified Eagle’s medium supplemented with

RESULTS

p73β Is Overexpressed in HTLV-I-Transformed T-Cell Lines—It is well established that the HTLV-I Tax protein pro-
motes stabilization of endogenous p53. To determine whether Tax might similarly stabilize p73, we examined the steady-state levels of p73 in whole cell extracts from the following Tax-expressing, HTLV-I-transformed cell lines: C8166/45, C91PL, MT2, SLB-1, and HUT-102 (Fig. 1, lanes 1–5). For comparison, we examined p73 expression levels in the following uninfected human T-cell lines: CEM, HUT-78, Jurkat, and MOLT-4 (Fig. 1, lanes 7–10). Kidney 293 cells, which express high levels of the p73β isoform (55), were used as a positive control (Fig. 1, lane 6). Each of the HTLV-I-transformed cell lines, with the exception of HUT-102, had detectable levels of p73β (Fig. 1, lanes 1–5). Interestingly, we were able to detect p73β in HUT-102 nuclear extracts (data not shown). In contrast, we did not detect p73β expression in any of the uninfected T-cell lines (Fig. 1, lanes 7–10). For comparison, we also measured p53 expression levels and found that, as previously reported, p53 was detectable in all of the HTLV-I-transformed cell lines (12, 20, 22, 24, 30, 35, 37) as well as uninfected CEM and MOLT-4 (77) (Fig. 1, lanes 11–20). We also examined Tax expression levels in the HTLV-I-infected cell lines (Fig. 1, lanes 21–25). Most interesting, we observed a direct correlation between expression of this Tax fusion protein and the nuclear localization of p73β in HUT-102 nuclear extracts (data not shown). In control HCT-116 cells, as they have previously been used in p73β half-life studies (62). Representative Western blots of p73β levels following cycloheximide treatment in SLB-1 and C8166/45 are shown in Fig. 2A. Graphical representation of the data is presented in Fig. 2B. In the control HCT-116 cells, we found that, like p73α (62), the p73β half-life in these cells was 45 min (Fig. 2B, left panel). Most interesting, the p73β half-life in SLB-1 and C8166/45 was measured at 210 and 165 min, respectively (Fig. 2B, center and right panels). These data correspond to a p73β half-life increase of 4-fold in these HTLV-I-infected T-cells.

The viral protein Tax has previously been shown to increase directly p53 protein stabilization (21, 22), although the mechanism for this stabilization is unknown. To determine if Tax is directly involved in p73β stabilization, we cotransfected expression plasmids for p73β and Tax into human Jurkat T-lymphocytes, and we measured Tax and p73 protein levels by Western blot analysis. We selected the HTLV-I-negative Jurkat cells, as they are negative for both p73β and p53 (see Fig. 1, lane 9 and 19, respectively) (79, 80). Fig. 3A shows that expression of Tax produced a significant increase in p73β protein levels (lanes 2 and 3). In the absence of Tax, a small amount of p73β was detected by Western blot, consistent with the short half-life of the protein (Fig. 3A, lane 1). Both 1 and 2 μg of the transfected Tax expression plasmid produced a comparable increase in p73 levels, suggesting that the lower amount of Tax is saturating for p73β stabilization. As a control, Tax stabilization of p53 is also shown (Fig. 3B).
Tax Inhibits the Transcription Function of p73β—Several groups have previously shown that the viral oncoprotein Tax, in addition to stabilizing p53, represses p53 transcription function (21, 22, 24, 25). Based on these observations, we were interested in determining whether Tax similarly repressed the transcription function of p73β. To examine this possibility, we utilized the p53-responsive reporter plasmid, pG13-Luc for these studies, as overexpression of p73β has been shown to activate many p53-responsive genes (45, 48, 52, 56–59). (Genes that are specifically responsive to p73 have not yet been identified.) We transfected the pG13-Luc reporter plasmid, which carries 13 copies of the consensus p53-response element driving expression of the luciferase gene, into HTLV-I-negative Jurkat T-cells (Fig. 4A). Consistent with the observation that Jurkat T-cells do not express p73 or p53 (Fig. 1, lanes 9 and 19), we did not detect significant luciferase activity produced from the pG13-Luc reporter plasmid in these cells (Fig. 4A, lane 1). As expected, cotransfection of the p73β expression plasmid strongly activated transcription from the p53-responsive reporter plasmid (Fig. 4A, compare lanes 1 and 2). Interestingly, cotransfection of the Tax expression plasmid produced a dose-dependent repression of p73β-mediated transcriptional activation, strongly supporting a direct role for Tax in repression of p73β transcription function (Fig. 4A, lanes 3–5).

The Tax protein utilizes the coactivator CBP to mediate transcriptional activation of the HTLV-I promoter (40, 41). Recently, two groups have reported that p73β also utilizes CBP to mediate transcriptional activation (59, 60). Since there is significant emerging evidence for coactivator competition as a mechanism of transcriptional repression (25–27), we were interested in testing whether CBP competition may account for the observed Tax repression of p73β transcription function. To test this hypothesis, we utilized a point mutant of Tax (K88A) that has previously been shown to be defective for interaction with the KIX domain of CBP (73) andTax transactivation in vivo (25, 73). If Tax repression of p73β is occurring through competition specifically for the KIX domain of CBP, then Tax K88A should be unable to repress p73β function. Unexpectedly, cotransfection of mutant Tax K88A strongly repressed the transactivation function of p73β to a level greater than that observed with wild type Tax (Fig. 4A, compare lanes 2–8). We then tested whether K88A was defective for Tax transactivation, as previously described (73), by examining K88A function on a reporter plasmid carrying three copies of the Tax-responsive viral CREs (viral CRE-Luc) driving expression of the luciferase gene (40). Transfection of the wild type Tax expression plasmid strongly activated transcription from the Tax-responsive promoter, whereas Tax K88A was defective for activation (Fig. 4B, lanes 2 and 3). Western blot analysis of nuclear extracts showed that both the wild type and mutant Tax proteins were expressed in the transfection assay (Fig. 4C, lanes 1–3). These data suggest that, if Tax repression of p73β is mediated through coactivator competition, the site of competition resides outside of the KIX domain of CBP.

As an alternate means to examine whether competition for a common coactivator may participate in Tax repression of p73, we next examined whether overexpression of p73β similarly repressed Tax function. We reasoned that if repression of p73β
by Tax occurs as a consequence of competition for CBP, then overexpression of p73β should similarly repress Tax function. To test this possibility, we performed the reciprocal experiment using the Tax-responsive viral CRE-Luc reporter plasmid. As expected, cotransfection of the Tax expression plasmid strongly activated transcription from the Tax-responsive reporter plasmid (Fig. 4D, lanes 1 and 2). Consistent with the theory of coactivator competition, cotransfection of increasing amounts of the expression plasmid for p73β repressed Tax transactivation in a dose-dependent fashion (Fig. 4D, lanes 3–5). Together, these data support a mechanism of reciprocal repression where Tax and p73β bind to a common coactivator, ultimately recruiting the coactivator to their respective target genes.

p73β and Tax Both Bind to the C/H1 Domain of CBP—The transient transfection data suggesting that Tax and p73β were competing for CBP binding led us to determine whether there might be a common site on CBP where both transcription factors interact. We considered the amino-terminal C/H1 domain of CBP, as Zeng et al. (60) reported, that p73β binds to this domain of CBP. To confirm this observation, we analyzed the binding of p73β to several regions of CBP using the GST pull-down assay. Purified GST fusion proteins carrying various regions of CBP (see Fig. 5A) were bound to glutathione-agarose beads and then incubated with labeled and in vitro translated p73β protein. Fig. 5B shows that, as expected, p73β bound well to the two GST constructs that carried the C/H1 domain of CBP (lanes 3 and 4). We did not detect significant binding of p73β to GST alone, KIX (aa 588–683), or to three carboxyl-terminal regions of CBP, comprising amino acids 1514–1894, 1894–2212, and 2212–2441 (Fig. 5B, lanes 2 and 5–8). These results are consistent with the report by Zeng et al. (60) who showed that the interaction of the amino-terminal activation domain of p73β with C/H1 modulates p73β transcription function.

To determine whether Tax might also bind to C/H1, we tested purified recombinant Tax protein in a GST pull-down assay with the C/H1 domain. As shown in Fig. 5C, both wild type Tax and KIX binding defective K88A Tax bound well to the C/H1 domain (lanes 5 and 6). Together, these observations indicate that both Tax and p73β bind to the C/H1 domain of CBP, possibly to recruit CBP to their target promoters. This common interaction site on CBP provides support for the hypothesis that Tax and p73β may compete for CBP in vivo, accounting for the observed reciprocal transcriptional repression.

p73β and Tax Binding to C/H1 Is Mutually Exclusive—To test directly whether the binding of Tax and p73β to C/H1 is mutually exclusive, we performed a GST pull-down competition assay. Glutathione-agarose beads bound with GST-C/H1

![Fig. 3. Stabilization of p73β by Tax.](http://www.jbc.org/content/15724/1/)

![Fig. 4. Reciprocal repression of transcription function between Tax and p73β.](http://www.jbc.org/content/15724/1/)
(CBP aa 302–451) were incubated with a constant amount of in vitro transcribed/translated p73β and increasing amounts of purified Tax (Fig. 6). If the two proteins bind to C/H1 in a mutually exclusive manner, we reasoned that increasing amounts of Tax, relative to p73β, would displace p73β from C/H1. Fig. 6 shows that the coinubation of increasing amounts of purified Tax protein in the binding reaction reduced p73β binding to C/H1 (compare lanes 3–6, upper panel). The competition was dose-dependent and corresponded directly with a concomitant increase in Tax binding (Fig. 6A, lanes 3–6, lower panel). We next tested whether the Tax point mutant K88A, which bound C/H1 similar to wild type Tax, could also compete for CH/1 binding. As expected, increasing amounts of the Tax point mutant also dramatically reduced p73β binding to C/H1 (Fig. 6A, lanes 7 and 8). In the reciprocal competition experiment, GST-C/H1 was incubated with a constant amount of purified Tax protein and increasing amounts of in vitro transcribed/translated p73β. Similar to the results obtained above, increasing amounts of p73β reduced the binding of Tax, with a concomitant increase in p73β binding to the C/H1 domain (Fig. 6B, lanes 3–6). Together, these data indicate that the binding of p73β and Tax to C/H1 is mutually exclusive in vitro, providing a possible mechanism for the observed repression of p73 by Tax.

**FIG. 5. Tax and p73β bind to the C/H1 domain of CBP.** A, schematic illustration of the CBP protein and positions of the C/H1 and KIX domains. B, p73β binds to the C/H1 domain of CBP in vitro. The p73β 35S-labeled in vitro translation product (0.5 μl) was incubated with GST alone or the indicated GST fusion proteins (10 pmol). Bound p73β and protein standards are indicated. p73β output (40%) is shown (lane 1). C, wild type and K88A mutant Tax protein bind to the C/H1 domain of CBP. Purified wild type and mutant recombinant Tax proteins (10 pmol) were incubated with 10 pmol of GST alone (lanes 3 and 4) and GST-C/H1-(aa 302–451) (lanes 5 and 6). Bound Tax and proteins standards are indicated. Wild type and mutant Tax output (20% each) is shown (lanes 1 and 2).

**FIG. 6. Tax and p73β binding to C/H1 is mutually exclusive.** A, Tax inhibits p73β binding to C/H1. The p73β 35S-labeled in vitro translation product (0.5 μl) was incubated with GST alone or GST-C/H1-(aa 302–451) (10 pmol) in the presence of increasing amounts of purified recombinant wild type (10, 20, and 40 pmol) or K88A mutant Tax protein (20 and 40 pmol) (lanes 4–6 and 7 and 8, respectively). p73β and Tax were detected as described under "Materials and Methods." Protein standards are indicated. p73β output (40%) is shown (lane 1). B, p73β inhibits Tax binding to C/H1. Purified recombinant Tax protein (10 pmol) was incubated with GST alone or GST-C/H1-(aa 302–451) (10 pmol) in the presence of increasing amount of p73β 35S-labeled in vitro translation product (0.5, 2.5, and 10 μl) (lanes 4–6). Tax and p73β were detected as described under "Materials and Methods." Protein standards are indicated. Tax output (20%) is shown (lane 1).

**DISCUSSION**

In this report, we characterize the effect of the HTLV-I-encoded oncoprotein Tax on the functionality of the p53 family member p73. These studies were undertaken as several previous reports have shown that Tax has dramatic effects on both the stability and transcription function of p53. We show that, like p53, Tax represses the transcription function of p73 while paradoxically enhancing the stability of the protein. We demonstrate that the transcriptional repression is reciprocal, as p73 represses the transcription function of Tax. The molecular basis of the reciprocal repression appears to be competition for the cellular coactivators CBP/p300, as both p73 and Tax bind to the amino-terminal C/H1 domain of CBP, and their binding is mutually exclusive in vitro.

We also show that p73 is overexpressed in HTLV-1-transformed T-cell lines, due to an apparent increase in the half-life of the p73 protein. This stability is directly due to the viral oncoprotein Tax. This observation is supported by a prolonged p73 half-life in the HTLV-1-transformed cell line C8166/45, which expresses the viral protein Tax but not Rex (81). Furthermore, transient transfection studies show that cotransfection of Tax promotes elevated p73 protein levels, relative to that observed in the absence of Tax. The mechanism of Tax stabilization of p73 remains unknown. In previous studies examining the p53 degradation pathway, it has been suggested that the interaction of p53 with the C/H1 domain CBP/p300 promotes degradation (82). It is plausible that p53 and p73 competition with Tax for CBP binding could potentially repress the degradation pathway, resulting in an increase in the half-life of both proteins. The fact that CBP is limiting in cells provides further support for a mechanism that involves competition (83). Alternatively, Tax may contribute to higher levels of p73 protein levels through transcriptional activation of the p73 gene. Although this would not account for the observed increase in the p73 half-life, precedence for this idea comes from the observation that the transcription factor E2F-1 has
been shown to stimulate p73 gene expression (68, 84, 85). Since Tax increases the level and activity of E2F-1 in HTLV-I-transformed T-cells (16, 18), enhanced E2F levels may directly increase transcription of the p73 gene.

Although p73 is present at elevated levels in Tax-expressing HTLV-I-infected T-cells, it is functionally compromised for transcription activation. Several possibilities might account for this loss of p73 transcription function in the presence of Tax. For example, some viruses, such as adenovirus or hepatitis B, encode proteins that bind and sequester p53 in the cytoplasm (86, 87). This is not the case for Tax repression of p73, as we observe generally high levels of p73 in nuclear extracts (data not shown). This is consistent with a recent study indicating that Tax and p73β do not directly interact (28). We have also determined that Tax does not compete with p73 binding to the DNA (data not shown). The observation that Tax and p73 reciprocally repress transcription function, in the absence of a direct interaction, strongly suggests competition for limiting CBP/p300. There is precedence for this scenario with Tax and p53, as we and others (25–27, 38) have previously shown that the reciprocal transcriptional repression between these two factors occurs, at least in part, through competition for CBP. In support of this hypothesis, we show in this report that both Tax and p73 bind the C/H1 domain of CBP in vitro, and that this binding is mutually exclusive. Furthermore, we show that a Tax mutant, K88A, which is defective for KIX binding (73) but not C/H1 binding, can also repress p73 activation. This observation strongly supports the idea that Tax and p73β compete for CBP utilization in vitro, specifically through the C/H1 domain of the coactivator. Our observation that Tax K88A represses p73β transcription function is in contrast to a recent report by Kaida et al. (28) who showed that this Tax mutant failed to repress the p73β activity. The nature of this discrepancy is not known, however Kaida et al. (28) used Saos-2 cells, whereas we used mature CD4+ Jurkat T-cells. This difference in cell type may account for the observed discrepancy.

Currently, Tax is known to bind the KIX domain and the carboxyl-terminal SRC-interacting domain of CBP, with both interactions apparently contributing to Tax transactivation of HTLV-I transcription (40, 41).2 Interestingly, the data presented herein indicate that Tax additionally interacts with the C/H1 domain of CBP, perhaps further contributing to Tax transcription function. The C/H1 domain, named for its cysteine/histidine-rich domain, is composed of two zinc finger modules (88) that have recently been shown to be involved in interactions with several proteins, including two viral proteins (89, 90). C/H1 is located immediately amino-terminal to the KIX domain, and this contiguous C/H1-KIX region (aa 302–683) may form a strong binding platform for Tax. This idea is supported by our observation that C/H1-KIX bound with high affinity (relative to either domain alone) to the ternary complex containing Tax, CREB, and the viral CRE DNA.3 These data suggest that multiple, distinct Tax-CBP interactions occur simultaneously and perhaps cooperate to enhance coactivator-mediated transcriptional activation.

Several recent studies (45, 48, 52, 56–59) have shown that p73 promotes apoptosis in p53-deficient cells. Our observation that Tax inhibits p73 transcription functions would suggest that Tax also represses p73-mediated apoptosis. Thus, the inactivation of both p73 and p53 by Tax may together contribute to HTLV-I-dependent leukemogenesis. Although Tax levels are generally low in HTLV-I-infected cells (91), intermittent high levels of Tax may saturate multiple sites on CBP/p300, derail-
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