The Transcriptional Co-activator ADA5 Is Required for HAC1 mRNA Processing in Vivo*

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Accumulation of unfolded proteins in the endoplasmic reticulum (ER) activates signaling pathways to induce transcription of a number of genes encoding ER protein chaperones and-folding catalysts. In Saccharomyces cerevisiae this transcriptional induction is mediated by an increase in the synthesis of the transcription factor Hac1p. The transmembrane receptor Ire1p/Ern1p containing a Ser/Thr protein kinase and endoribonuclease activity transmits the unfolded protein response (UPR) from the ER to the nucleus. Activation of Ire1p kinase induces its endoribonuclease activity to cleave unspliced HAC1 mRNA and generate exon fragments that are subsequently ligated by tRNA ligase (RLG1). Whereas unspliced HAC1 mRNA is poorly translated, spliced HAC1 mRNA is efficiently translated. Subunits of the yeast transcriptional co-activator complex SAGA also play a role in the UPR. Deletion of GCN5, ADA2, or ADA3 reduces, and deletion of ADA5 completely abolishes, the UPR. Although HAC1 mRNA requires only Ire1p and Rlg1p in vitro, we demonstrate that ADA5 is required for the Ire1p/RLG1-dependent splicing reaction of HAC1 mRNA in vivo. In addition, Ada5p interacts with Ire1p. These results suggest that subcomponents of transcriptional co-activator complexes may be involved in RNA processing events.

The lumen of the endoplasmic reticulum (ER) is a highly specialized compartment in eukaryotic cells. It is the primary site for folding of secretory and transmembrane proteins that constitute about one-third of all cellular proteins. The ER lumen provides an oxidizing environment and contains a number of resident chaperones, such as BiP (GRP78), that facilitate protein folding. These chaperones are proposed to catalyze protein folding and/or prevent aggregation of folding intermediates. Perturbation of the protein folding machinery in the ER leads to an accumulation of unfolded proteins. Cells respond to unfolded protein in the ER by up-regulating the synthesis of resident chaperones, thereby increasing the folding capacity in the ER compartment. This cellular response is termed the unfolded protein response (UPR) and is conserved in all eukaryotic organisms (1).

In the budding yeast Saccharomyces cerevisiae, genes that are transcriptionally activated in response to unfolded proteins in the ER contain a 22-base pair cis-acting promoter element, termed the UPR element (UPRE), that is necessary and sufficient to mediate the transcriptional induction (2). The UPREs in these genes contain a partially palindromic sequence (CAGCGTG) with a spacer of one nucleotide that is required for the transcriptional induction (3). The trans-acting factor that binds the UPRE is a basic leucine zipper protein (bZIP) called Hac1p (4, 5). Recent studies demonstrated that activation of the UPR is dependent upon the cellular levels of Hac1p. HAC1 is constitutively transcribed independently of the protein folding status in the ER. In the absence of unfolded proteins in the ER, HAC1 mRNA is exported to the cytoplasm and engaged with ribosomes, but translation is stalled. A 252-nucleotide fragment near the 3’ end of HAC1 mRNA acts as a translational attenuator to limit Hac1p synthesis (6, 7). However, in the presence of unfolded proteins in the ER, the translational attenuator in HAC1 mRNA is removed by an unconventional splicing reaction that does not utilize the cellular splicing machinery. HAC1 mRNA splicing allows efficient translation of Hac1p and subsequent transcriptional activation of genes regulated by the UPR.

Perhaps the most important component of the UPR pathway is Ire1p/Ern1p (8, 9). Ire1p is a type 1 transmembrane protein of the ER that is a bifunctional enzyme. The cytosolic domain contains both a serine/threonine kinase (10, 11) and a site-specific endoribonuclease activity (12). In response to unfolded proteins in the ER, Ire1p forms oligomers that mediate trans-autophosphorylation to activate the site-specific endoribonuclease activity that cleaves at the splice site junctions within the 3’ end of HAC1 mRNA. The cleaved 5’ and 3’ exons of HAC1 mRNA are ligated together by the tRNA ligase RLG1, generating a new mRNA species that is efficiently translated (13). Because permanent activation of the UPR pathway is detrimental to cell growth (11, 14), the UPR needs to be tightly regulated. Upon phosphorylation, Ire1p recruits a serine/threonine phosphatase, PTC2, that dephosphorylates Ire1p and down-regulates the UPR (15).

The transcriptional co-activator Gcn5p was isolated as a specific interactor with Ire1p in a yeast two-hybrid screen (16). In eukaryotes, transcriptional activation requires functional interaction between the activators that bind upstream activating sequences and the basal factors that occupy the TATA box. It is proposed that functional interaction between these two classes of transcription factors is mediated by transcriptional co-activators. Gcn5p along with other transcriptional co-activators, including Ada1, Ada2p, Ada3p, Spt3p, Spt7p, and Spt8p,
and Ada5p/Spt20p, constitute a 1.8-mDa SAGA complex that is responsible for histone acetylation during transcriptional activation (17–24). Mutations in the ADA genes were isolated as suppressors of the lethality induced by over-expression of the herpes simplex virus potent acid transcriptional activator VP-16 (19). The SPT genes were isolated as suppressors of Ty transposon insertions (23). Both sets of genes are required for maximal transcriptional activation from TATA-containing promoters. Yeast strains lacking Gen5p, Ada2p, and Ada3p are partially defective in transcriptional activation of genes encoding ER protein chaperones in response to unfolded proteins in the ER. In contrast, cells lacking Ada5p are completely defective for the UPR but contain an intact heat shock response, demonstrating a specific requirement for Ada5p in the UPR (16). In the present study, we investigated the role of ADA5 in the UPR pathway. We found that apart from its function as a transcriptional co-activator in the UPR pathway, ADA5 is also required for HAC1 mRNA processing, a hitherto novel function for a transcriptional co-activator. Moreover, our data reveal the molecular basis for the defective UPR in ada5Δ cells.

**EXPERIMENTAL PROCEDURES**

**Yeast Strains, General Methods, and Plasmid Constructions—**The *Escherichia coli* strain DH5α was used for the propagation of plasmids. The genotype of the *S. cerevisiae* strain used in this study was BWG1-7a, *Mata leu2·3,112 his4·519 ade1·100 ura3·52* (19). The genetic methods and standard media were previously described (25).

The construction of pAW65 (16), pGEM4Z-ACT1 (15), and the fusion protein containing the Ire1p cytoplasmic (10) domain with glutathione S-transferase (GST) were previously described. To construct GST-HAC1 fusion constructs, PCR amplified fragments from the wild-type *HAC1* were subcloned into the BamHI and EcoRI sites of the bacterial expression vector, pGEX1T (Amersham Pharmacia Biotech). The expression GST-Hac1p fusion product was confirmed by Western blotting with anti-GST antibodies. To construct pGEM4Z-HAC1, a 240-base pair fragment from *HAC1* was amplified by PCR using primers 5′-ccctctaggacctgtcggaaatcactcttatg-3′ and 5′-tcaaagcttgcaacaaaagcgtcgtggc-3′ and subcloned into the XbaI and HindIII sites of pGEM-4Z. Similarly, a 206-base pair fragment from *IRE1* was amplified by PCR using primers 5′-gaccttgaattcactcttatg-3′ and 5′-aattacagggaggaggttggcaaacgcacg-3′ and subcloned into the EcoRI and HindIII sites of pGEM-4Z to derive pGEM4Z-IRE1. Construction of plasmid pJC835 containing HAC1′ was described previously (4).

The yeast strain carrying the null allele of HAC1′ was created by the method of one step gene disruption (26). BGW1-7a cells were transformed with *Bam*HI digested pHAK01 (4). Transformants containing the desired *hac1* were selected for uracil prototrophy and the gene disruption was confirmed by PCR and Southern/Northern blot analyses. The construction of *sire1* and *ada5Δ* strains was described previously (16).

**Analysis of Protein Expression—**Yeast cell lysates were prepared according to Williams et al. (27). Western blotting was performed by standard procedures (28) using anti-Hac1p primary antibodies (generously provided by Dr. Peter Walter, University of California, San Francisco) and horseradish peroxidase-conjugated goat anti-mouse secondary antibodies (Life Technologies, Inc.). Band intensities were determined by autoradiography and PhosphorImager scanning (Molecular Dynamics, Sunnyvale, CA).

**RNAse Protection Analysis—**Total RNA was isolated according to Schmitt et al. (30) from cells treated with or without Tm for 90 min for analysis using an RNase protection kit (Roche Molecular Biochemicals). pGEM-4ZHAC1, pGEM-4ZIRE1, and pGEM-4ZACT1 were linearized with XbaI, and antisense RNA probes were synthesized using T7 RNA polymerase (Roche Molecular Biochemicals) and [α-32P]CTP (Amersham Pharmacia Biotech). A DNA sequencing ladder from a known template was used as size markers.

**RESULTS**

**Transcription of HAC1 and/or IRE1 Is Not Attenuated in ada5Δ Cells—**GCN5, ADA2, ADA3, and ADA5 are required for the maximal transcriptional induction of genes encoding ER resident chaperones including *KAR2/BiP* in response to protein misfolding in the ER (16). In contrast, the SAGA complex is not required for the heat-mediated transcriptional activation of *KAR2* (16), suggesting that these co-activators play a specific role in the UPR as opposed to global transcriptional induction. Among these co-activators, Ada5p is the most interesting because cells lacking Ada5p are completely defective in responding to unfolded proteins in the ER and are insusceptible auxotrophs, the two phenotypes associated with *sire1* and *hac1* cells. To elucidate the mechanistic role of the SAGA complex in the UPR pathway, we asked whether the defective UPR in cells lacking these co-activators results from inefficient HAC1 transcription. HAC1 encodes the bZIP transcription factor Hac1p, which is essential for transcriptional induction of genes responding to the UPR. The levels of HAC1 mRNA were measured in ada5Δ cells by an RNase protection assay. In this assay, the presence of HAC1 mRNA (both processed and unprocessed) should protect a 240-base pair nucleotide fragment from the internal labeled probe. ACT1 mRNA served as an internal control for the amount of RNA in the reaction. The results show that HAC1 was transcribed in ada5Δ as well as in *sire1* cells. The level of HAC1 transcription in these cells was comparable with that in the wild-type cells with or without tunicamycin (Tm) treatment, a drug that inhibits N-linked glycosylation and therefore disrupts protein folding in the ER (Fig. 1A, lanes 1–4).
and 6–7). These results demonstrate that Δada5 cells efficiently transcribe HAC1. Therefore, the Δada5 cells are similar to Δire1 cells where the abrogated UPR does not arise from defective HAC1 transcription.

The cellular level of Hac1p regulates the UPR. Although HAC1 is constitutively transcribed, only the processed transcripts are translated. HAC1 mRNA processing requires the activity of the site-specific endoribonuclease, Ire1p. We therefore asked whether IRE1 transcription is reduced in Δada5 cells. An RNase protection assay demonstrated that both wild-type and Δada5 cells had comparable levels of IRE1 mRNA, indicating that IRE1 is efficiently transcribed in Δada5 cells (Fig. 1B, lanes 1–4). Therefore, the defective UPR in these cells is not due to reduced IRE1 transcription.

Components of the SAGA Complex Directly Interact with Ire1p and Hac1p—These results demonstrate that Δada5 cells efficiently transcribe HAC1. Therefore, the Δada5 cells are similar to Δire1 cells where the abrogated UPR does not arise from defective HAC1 transcription.

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Components of the SAGA Complex Directly Interact with Ire1p and Hac1p—Gen5p was identified as a component in the UPR by its interaction with Ire1p, detected by the yeast two-hybrid system and by co-immunoprecipitation from cells co-expressing Gen5p and Ire1p (16). To identify the component(s) of this complex that interact directly with Ire1p, in vitro affinity adsorption experiments were performed with [35S]methionine-labeled in vitro transcription-translation products of GCN5, ADA2, ADA3, and ADA5. Hac1p and Ire1p were produced as soluble GST fusion proteins (GST-Hac1p, GST-Ire1p) in E. coli and purified by adsorption to glutathione-Sepharose beads. Beads containing either GST-Hac1p or GST-Ire1p fusion proteins were used to capture the Gen5p, Ada2p, Ada3p, or Ada5p translation products from reticulocyte lysates. As a control, Sepharose beads bound to equimolar amounts of GST were used. In these in vitro pull-down assays, the amounts of Ada2p, Ada3p, and Ada5p bound to GST-Hac1p were not significantly different from that obtained with control GST beads (Fig. 2, lanes 5–8 and 10–12). In contrast, GST-Hac1p brought down a 4.5-fold greater amount of Gen5p than the GST control (Fig. 2, lane 5 versus lane 9), indicating a direct interaction between the two proteins. GST-Ire1p, on the other hand, interacted with Ada2p and Ada5p (4.1- and 3.1-fold more than the GST control, respectively) (Fig. 2, lanes 14 and 16) but not with Gen5p or Ada3p (Fig. 2, lanes 13 and 15). The specificity for the interaction with Ada5p was further demonstrated by the enrichment of the full-length Ada5p translation products by GST-Ire1p. These results indicate that Ire1p directly interacts with Ada2p and Ada5p and suggest that the original yeast two-hybrid interaction detected between Ire1p and the SAGA complex was mediated through Ada2p and Ada5p but not through Gen5p. Therefore, the original interaction between Gen5p and Ire1p detected in yeast was likely indirect and due to endogenous levels of Ada2p and Ada5p that could bridge Gen5p with Ire1p.

HAC1 mRNA Processing Is Defective in Δada5 Cells—The site-specific endoribonuclease activity of Ire1p is required for the HAC1 mRNA processing event that leads to the generation of a translatable form of HAC1 mRNA and subsequent activation of the UPR. The direct interaction between Ire1p and some components of the SAGA complex suggested that the SAGA complex might play a role in HAC1 mRNA processing. To test this hypothesis, we used a HAC1 probe to perform Northern blot analysis on RNA isolated from different yeast strains. In wild-type cells, upon Tm treatment, the majority of the HAC1 mRNA was processed to a smaller RNA species (HAC1, Fig. 3A, lanes 1 and 2). In contrast, upon Tm treatment of Δire1 cells, processed HAC1 mRNA was not generated, indicating a complete absence of UPR-activated Ire1p-dependent HAC1 mRNA processing in these cells (Fig. 3A, lanes 3 and 4). Deletion of GCN5, ADA2, and ADA3 had no effect on the Ire1p-dependent HAC1 mRNA processing, as similar amounts of HAC1 mRNA were detected after ER stress compared with the wild-type strain (Fig. 3A, lane 2 versus lanes 6, 8, and 10). Like the Δire1 cells, Δada5 cells were completely defective in HAC1 mRNA processing upon activation of the UPR (Fig. 3A, lanes 11 and 12), demonstrating that Ada5p plays a critical role in this mRNA processing reaction.
tive in HAC1 mRNA processing and are therefore incapable of generating a translatable form of HAC1 mRNA.

Expression of Processed HAC1 (HAC1i) Partially Restores the UPR Pathway in Δada5 Cells—The data presented thus far suggest that the abrogated UPR in Δada5 cells result from defective HAC1 mRNA processing. We therefore asked whether the UPR could be restored upon expression of HAC1i in Δada5 cells. To evaluate the UPR, cells were transformed with a centromere-containing reporter plasmid harboring a lacZ reporter gene under the control of a single 22-base pair UPRE. The resultant transformed wild-type cells turned blue on plates containing X-gal and Tm, indicating an intact UPR pathway. In contrast, Δada5 strains harboring the UPRE-lacZ vector remained white, demonstrating a defective UPR pathway. However, after the introduction of HAC1i, both the wild-type and Δada5 strains turned blue and light blue, respectively, on media containing X-gal plus Tm (data not shown). The amount of HAC1 mRNA detected in Δada5 cells harboring the HAC1i plasmid was greater than in the wild-type cells (Fig. 1A, lanes 1 and 2 and 9 and 10). This observation further strengthens the notion that the defective UPR in Δada5 cells is not the result of abrogated HAC1 transcription. Quantification of the UPR by liquid assay, revealed that the basal level of β-galactosidase expression from the 22-base pair UPRE was reduced 3.5-fold in the Δada5 strain compared with the wild-type strain (Fig. 4, lanes 1 and 5). Upon Tm treatment, induction of β-galactosidase was reduced 20-fold compared with wild-type cells (Fig. 4, lanes 2 and 6). Expression of HAC1i increased the basal level of β-galactosidase activity by 10- and 6-fold in the wild-type and Δada5 strains, respectively (Fig. 4, lanes 1, 3, 5, and 7). However, β-galactosidase expression in HAC1i-expressing Δada5 cells was reduced 6-fold compared with HAC1i-expressing wild-type cells (Fig. 4, lanes 3 and 7). On the other hand, Tm induction of β-galactosidase activity was comparable in both wild-type and Δada5 strains expressing HAC1i, at 6- and 8-fold respectively (Fig. 4, lanes 3, 4, 7, and 8). Therefore, expression of Hac1p restored induction, although the basal expression level was reduced. Taken together, these results suggest that both transcriptional co-activator and RNA processing functions of ADA5 are essential for maximal transcriptional activation from the UPRE.

DISCUSSION

Upon accumulation of unfolded proteins in the lumen of the ER, Ire1p initiates a novel mRNA splicing reaction. The endoribonuclease activity of Ire1p cleaves the 5′ and 3′ splice site junctions within HAC1 mRNA. Each splice site junction is composed of a simple structure, a stem with a seven-member loop. Only 4 bases within the loop are apparently required for specificity of the cleavage reaction (31). The 5′ and 3′ exons of HAC1 mRNA are tethered together by base pairing and joined by tRNA ligase (RLG1). Whereas precursor HAC1 mRNA is not translated well, the product HAC1i mRNA is efficiently translated. This splicing reaction was reconstituted in vitro.
with only two components, Ire1p and Rlg1p (12). However, data suggest that the HAC1 mRNA processing reaction is more complex in vivo. First, the low degree of specificity for the stem-loop structure in HAC1 mRNA would indicate that other cellular mRNAs may be non-specifically cleaved by the Ire1p endoribonuclease. This notion is consistent with the observation that oligonucleotides consisting of the stem-loop structures are less efficient substrates than a 600-base-pair substrate that contains both 5′ and 3′ splice site junctions (12). Second, when the intron within the 3′ end of HAC1 mRNA was placed into the 3′ untranslated region of a green fluorescent protein (GFP) marker gene, GFP was not translated (7). This result is consistent with the proposed role of the intron as a translational attenuator (6). However, upon induction of the UPR, the HAC1 intron within the GFP mRNA was not removed, indicating that Ire1p does not simply recognize the stem-loop and intron sequence within HAC1 mRNA. Fourth, although human Ire1p can cleave the 5′ splice site of yeast HAC1 mRNA in vitro, yeast HAC1 mRNA was not cleaved when expressed in mammalian cells (32). Finally, using a temperature-sensitive mutant of RNA polymerase, it was shown that only newly transcribed cellular mRNAs may be nonspecifically cleaved by the Ire1p processing role for Ada5p, a subunit of the transcriptional activator (6). However, upon induction of the UPR, the marker gene, GFP was not translated (7). This result is consistent with detection of Rlg1p-mediated exon-exon ligation. Third, Ire1p does not simply recognize the stem-loop and possibly the nuclear pore complex (33), suggesting a subpopulation preferentially associated with the nuclear envelope, adjacent to the nuclear pore. Both Ada2p and Ada5p interact with Ire1p, although only Ada5p function is required to promote Ire1p-mediated cleavage of HAC1 mRNA. Although we have not demonstrated that Ada5p acts directly in this reaction, the finding that Ada5p interacts with Ire1p would suggest that Ada5p may function to increase the efficiency of HAC1 mRNA processing by Ire1p. 

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REFERENCES

1. Kaufman, R. J. (1999) Genes Dev. 13, 1211–1223
2. Mori, K., Sant, A., Kohno, K., Normington, K., Gething, M. J., and Sambrook, J. (1992) EMBO J. 11, 2227–2235
3. Mori, K., Ogawa, N., Kawahara, T., Yanagi, H., and Yura, T. (1998) J. Biol. Chem. 273, 9912–9920
4. Cox, J. S., and Walter, P. (1996) Cell 87, 391–404
5. Mori, K., Kawahara, T., Yoshiida, H., Yanagi, H., and Yura, T. (1996) Genes Cells 1, 803–817
6. Kawahara, T., Yanagi, H., Yura, T., and Mori, K. (1997) Mol. Biol. Cell 8, 1485–1482
7. Chapman, R. E., and Walter, P. (1997) Curr. Biol. 7, 850–859
8. Cox, J. S., Shamu, C. E., and Walter, P. (1993) Cell 73, 1197–1206
9. Mori, K., Ma, W., Gething, M. J., and Sambrook, J. (1993) Cell 74, 743–756
10. Welihinda, A. A., and Kaufman, R. J. (1996) J. Biol. Chem. 271, 18181–18187
11. Shamu, C. E., and Walter, P. (1996) EMBO J. 15, 3028–3039
12. Sidrauski, C., and Walter, P. (1997) Cell 90, 1031–1039
13. Sidrauski, C., Cox, J. S., and Walter, P. (1996) Cell 87, 405–413
14. Wang, X. Z., Harding, H. P., Zhang, Y., Jolicoeur, E. M., Kuroda, M., and Ron, D. (1998) EMBO J. 17, 5708–5717
15. Welihinda, A. A., Tirasophon, W., Green, S. R., and Kaufman, R. J. (1998) Mol. Cell. Biol. 18, 1967–1972
16. Welihinda, A. A., Tirasophon, W., Green, S. R., and Kaufman, R. J. (1997) Proc. Natl. Acad. Sci. U. S. A. 94, 4289–4294
17. Georgakopoulos, T., and Threiss, G. (1999) EMBO J. 18, 4145–4152
18. Grant, P. A., Duggan, L., Cote, J., Roberts, S. M., Brownell, J. E., Candau, R., Ohba, R., Owen-Hughes, T., Allis, C. D., Winston, F., Berger, S. L., and Workman, J. L. (1997) Genes Dev. 11, 1640–1650
19. Horiiuchi, J., Silverman, N., Marcus, G. A., and Guerente, L. (1995) Mol. Cell. Biol. 15, 1203–1209
20. Horiiuchi, J., Silverman, N., Pina, B., Marcus, G. A., and Guerente, L. (1997) Mol. Cell. Biol. 17, 3220–3228
21. Marcus, G. A., Horiiuchi, J., Silverman, N., Berger, S. L., Horiiuchi, J., and Guerente, L. (1994) EMBO J. 13, 4807–4815
22. Marcus, G. A., Horiiuchi, J., Silverman, N., and Guerente, L. (1996) Mol. Cell. Biol. 16, 3197–3205
23. Roberts, S. M., and Winston, F. (1996) Mol. Cell. Biol. 16, 3206–3213
24. Sterner, D. E., Grant, P. A., Roberts, S. M., Duggan, L. J., Belotserkovskaya, R., Pacella, L. A., Winston, F., Workman, J. L., and Berger, S. L. (1998) Mol. Cell. Biol. 18, 89–98
25. Sherman, F., Fink, G. R., and Hicks, J. (1996) Methods in Yeast Genetics, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY
26. Rothstein, R. (1991) Methods Enzymol. 194, 281–301
27. Williams, F. E., Varanasi, U., and Trumbly, R. J. (1991) Mol. Cell. Biol. 11, 3507–3516
28. Harlow, E., and Lane, D. (1988) Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Plainview, NY
29. Lasemmi, U. K. (1970) Nature 227, 680–685
30. Schmitt, M. E., Brown, T. A., and Trumpower, B. L. (1990) Nucleic Acids Res. 18, 3091–3096
31. Gonzalez, T. N., Sidrauski, C., Dorfler, and Walter, P. (1999) EMBO J. 18, 3119–3124
32. Foti, D. M., Welihinda, A. J., Kaufman R. J., and Lee, A. S. (1999) J. Biol. Chem. 274, 30402–30409
33. Tirasophon, W., Welihinda, A. A., and Kaufman, R. J. (1998) Genes Dev. 12, 1812–1824
34. Clark, M. W., and Abelson, J. (1987) J. Cell Biol. 105, 1515–1526
35. Kawahara, T., Yanagi, H., Yura, T., and Mori, K. (1998) J. Biol. Chem. 273, 1802–1807
36. Cox, J. S., Chapman, R. E., and Walter, P. (1997) Mol. Cell. Biol. 8, 1805–1814
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