The endoplasmic reticulum (ER) transmembrane proteins, ATF6α and ATF6β, are cleaved in response to ER stress, which can be induced by tunicamycin. The resulting N-terminal fragments of both ATF6 isoforms, which have conserved basic leucine-zipper and DNA binding domains but divergent transcriptional activation domains, translocate to the nucleus where they bind to ER stress-response elements (ERSE) in ER stress-response genes (ERSRG), such as GRP78. Although it is known that ATF6α is a potent activator of ERSRGs, the transcriptional potency and functions of ATF6β remain to be explored. Accordingly, N-terminal fragments of each ATF6 isoform (N-ATF6α and N-ATF6β) were overexpressed in HeLa cells and the effects on GRP78 induction were assessed. When expressed at similar levels, N-ATF6α conferred ~200-fold greater GRP78 promoter activation than N-ATF6β. Because ER stress activates nuclear translocation of both ATF6α and β and because both bind to ERSRs, the effect of co-expressing them on GRP78 induction was assessed. Surprisingly, N-ATF6β inhibited N-ATF6α-mediated GRP78 promoter activation in a dominant-negative manner. Moreover, N-ATF6β inhibited TN-mediated GRP78 promoter activation, which requires endogenous ATF6α. ATF6 isoform-specific small inhibitory RNAs were used to show that, as expected, endogenous ATF6α was required for maximal ERSRG induction; however, endogenous ATF6β moderated ERSRG induction. These results indicate that compared with ATF6α, ATF6β is a very poor activator of ERSRG induction and it represses ATF6α-mediated ERSRG induction. Thus, ATF6β may serve as a transcriptional repressor functioning in part to regulate the strength and duration of ATF6α-mediated ERSRG activation during the ER stress response.

Stresses that alter the ER1 environment can cause the incorrect folding of nascent ER proteins (1–4). The proteins encoded by a number of genes induced under such conditions are targeted to the ER where they act as chaperones to aid in folding and thus counteract the stress. A regulatory element located in many of these ER stress-response genes (ERSRG) is the ER stress-response element (ERSE), which is required for transcriptional induction.

ATF6α, a member of the ATF/CREB family of transcription factors, is required for the maximal induction of numerous ERSGs (5, 6). ATF6α is comprised of 670 amino acids and resides in the ER membrane (6). Upon ER stress, the cytosolic N-terminal portion of ATF6α (N-ATF6α) comprising ~400 amino acids is released as a result of regulated intramembrane proteolysis (RIP) (7, 8). N-ATF6α possesses a transcriptional activation domain (TAD), basic leucine-zipper (b-Zip) domain, DNA binding domain, and nuclear localization signals. N-ATF6α translocates to the nucleus where it combines with several other proteins to form an ERSE-binding complex that is responsible for the induction of ERSGs such as the ER chaperone, glucose-regulated protein 78 kDa (GRP78) (7–9). N-ATF6α is rapidly degraded in a proteasome-mediated process, and mutated inactive forms of N-ATF6α are slowly degraded (10). Thus, similar to several other potent transcription factors that exert rapid transient effects (11), the degradation of ATF6α upon transcriptional engagement apparently serves as a mechanism to rapidly turn off ERSG induction.

Another member of the ATF/CREB family of transcription factors (G13), which is also an ER membrane protein, was recently shown to be structurally homologous to ATF6α and to be cleaved during ER stress to generate a N-terminal fragment of approximately 400 amino acids (12). Because of its high degree of homology to ATF6α, G13 has been named ATF6β (12). N-ATF6α and N-ATF6β possess highly conserved b-Zip domains and DNA binding domains. This conservation apparently allows N-ATF6α and β to bind to ERSEs as homodimers or heterodimers (13); however, the functional significance of the binding of N-ATF6β to ERSEs, either alone or as a heterodimer with N-ATF6α, is currently unknown.

Although N-ATF6α and β have conserved b-Zip domains and DNA binding domains located near the center of each protein, the structure of the N-terminal region of N-ATF6α, which possesses the TAD, differs markedly from that of N-ATF6β. Notably, an 8 amino acid sequence located in the TAD of ATF6α, which is required for maximal transcriptional activity (10), is absent from ATF6β. This structural difference led us to hypothesize that compared with N-ATF6α, N-ATF6β should exhibit much lower transcriptional activity (10). Moreover, if ATF6β is a poor transcriptional activator yet can bind to ERSEs with or in place of ATF6α, it seems probable that ATF6β might serve as an endogenous repressor of the transcriptional induction effects of ATF6α. This study was undertaken to test these hypotheses.
FLAG-ATF6 or β, μg plasmid

Fig. 1. Effect of N-ATF6α or N-ATF6β expression constructs on GRP78 ERSE-Luc or GRP78 Prom-Luc activation. Panel A, GRP78 ERSE-Luc. HeLa cells were co-transfected with increasing amounts of expression constructs encoding FLAG-N-ATF6α or FLAG-N-ATF6β and GRP78 ERSE-Luc. After 48 h, cultures were extracted and analyzed for reporter enzyme activities as described under “Materials and Methods.” Values shown are mean fold of control (i.e. no expression construct) ± S.E. (n = 3). Panel B, GRP78 Prom-Luc. HeLa cells were transfected as described above with the exception that GRP78 Prom-Luc was the reporter. * and † = p < 0.05, different from all of the other values as determined using ANOVA followed by Newman-Keuls post hoc analysis. Con, control.

MATERIALS AND METHODS
Cell Culture
HeLa Cells were maintained in DMEM containing 10% fetal calf serum. HeLa cells were resuspended at 5 × 10⁶ cells/400 μl of cold Dulbecco’s PBS and electroporated in a 0.4-cm gap electroporation cuvette at 250 V and 950 microfarads using a GenePulser II Electroporator (Bio-Rad). The cells were then plated at a density of 0.5 × 10⁶/24-mm well plate for luciferase and 1.5 × 10⁶/35-mm well plate for Western blots, or 3 × 10⁶/60-mm dish for metabolic labeling experiments.

Plasmids
Cytomegalovirus-Galactosidase—Cytomegalovirus-β-galactosidase, which codes for a galactosidase reporter driven by the cytomegalovirus promoter, was used to normalize for transfection efficiency.

N-ATF6α and N-ATF6α-DN—Construction of vectors encoding FLAG-tagged versions of N-ATF6α (3× FLAG-ATF6α(1–373)) and N-ATF6α-DN (3× FLAG-ATF6α(94–373)) has been described previously (11). All of the references to FLAG in this paper refer to 3× FLAG epitope.

N-ATF6β and N-ATF6β-DN—N-ATF6β (3× FLAG-ATF6β(1–392)) was prepared by PCR using HeLa cDNA as a template and PCR primers that introduced an XhoI site at amino acid 1 and a termination codon and EcoR1 site at amino acid 392. The resulting PCR product was cloned into 3× FLAG-pcDNA3.1, which was described previously (10). N-ATF6β-DN (3× FLAG-ATF6β(116–392)) was prepared by PCR using the FLAG-ATF6β(1–392) as a template and a PCR primer that introduced an XhoI site at amino acid 116 and the reverse sequencing primer. The resulting PCR product was excised with XhoI and EcoR1 and cloned into 3× FLAG-pcDNA3.1.

GRP78-ERSE-Luc—This construct encodes an active ERSE from the human GRP78 gene driving SV40/luciferase in the vector pGL2-p (Promega) and has been described previously (11).

N-ATF6β-Mediator—-galactosidase values. All of the values shown are the mean densities ± S.E. were determined from three cultures and normalized to maximum GRP78 expression level. * and † = p < 0.05, different from the empty vector control (None) as determined using ANOVA followed by Newman-Keuls post hoc analysis.

Reporter Assays
β-Galactosidase—After the indicated times, cells were lysed in 500 μl of ice-cold lysis buffer (25 mM Gly-Gly, pH 7.8, 15 mM MgSO₄, 4 mM EDTA, 0.25% Triton X-100, and 1 mM diethiothreitol). Cell lysate was centrifuged, and 100 μl of supernatant was combined with 400 μl of galactosidase buffer (60 mM Na₂HPO₄, 40 mM NaH₂PO₄, 10 mM KCl, 1 mM MgSO₄, 1 mM chlorophenol red-n-galactopyranoside, and 50 mM 2-mercaptoethanol). After incubation for 1 h, the absorbance was measured at 570 nm.

Luciferase—After cell lysis and centrifugation as described above, 100-μl samples of cell lysate were combined with 100 μl of luciferase buffer (the above described lysis buffer containing 45 mM MgSO₄, 0.3 mM n-luciferin, and 3 mM ATP). An Optocompt II luminometer (MGM Instruments, Inc) was used to measure light emission of each sample for 10 s. Relative luciferase activities were determined by dividing luciferase values by β-galactosidase values. All of the values shown are the means of three cultures ± S.E.

Immunoblotting—Cultures were extracted in a lysis buffer composed of 20 mM Tris-HCl, pH 7.5, 150 mM NaCl, 1% Triton X-100, 0.1% SDS, 1 mM phenylmethylsulfonyl fluoride, 10 μg/ml leupeptin, and 10 μg/ml aprotinin. After clearing by centrifugation, the protein concentration of the lysate was determined, and after dilution with the appropriate amount of 2× Laemmlli buffer, equal amounts of protein from each sample were fractionated by 10% SDS-PAGE and then transferred to a polyvinylidene difluoride membrane. Membranes were then probed...
with a GRP78 antiserum (sc-1050, Santa Cruz Biotechnology) or with a FLAG antiserum, M2 antibody (F-3165, Sigma), or with antisera raised against human ATF6α or human ATF6β (a gift from Dr. K. Mori).

**Pulse-Chase Labeling**—HeLa cells were transfected with 30 μg of the test expression vector as described above, and 3 × 10⁶ cells were plated on 60-mm dishes. Following a 48-h incubation in serum-containing medium, the cells were rinsed three times with warm Hanks’ buffer (Invitrogen) and incubated for 2 h with 250 μCi of [³⁵S]methionine/cysteine (Easytag Express protein-labeling mixture (PerkinElmer Life Sciences)) diluted in 2 ml of methionine/cysteine-free DMEM (Invitrogen) supplemented with 5% dialyzed fetal calf serum (Invitrogen). Following a 2-h incubation, this medium was removed and the cultures were washed twice with DMEM and then incubated with 3 ml of chase medium (DMEM containing 10% fetal calf serum, 2 mM unlabeled methionine, and 2 mM unlabeled cysteine). At the indicated times, the cells were rinsed three times with PBS and then scraped into 100 μl of lysis buffer (50 mM Tris, pH 7.5, 1 mM EDTA, 1 mM EGTA, 1% Triton X-100, 5 mM sodium pyrophosphate, 10 mM sodium glycerophosphate, 50 mM NaF, and 150 mM NaCl) containing 0.1% SDS. The lysate was then diluted with 400 μl of lysis buffer without SDS to a final concentration of 0.02% SDS and then cleared by centrifugation. The supernatant was incubated 12–18 h at 4°C with 2 μg of FLAG antiserum (F-3165, Sigma) followed by incubation with protein G-Sepharose beads. Immunoprecipitated material was then resolved by SDS-PAGE (10% SDS gel) and dried down and exposed on a phosphorimaging screen.

**Small Interfering RNAs**—Small interfering (si)RNA was generated using a kit (Dicer siRNA generation kit, catalog number 7S10001) from Gene Therapy Systems, Inc. (San Diego, CA) according to the manufacturer’s protocol. Forward and reverse PCR primers were designed such that they would generate PCR products between 500 and 1,000 bp in length. For human ATF6α, the forward primer was 5’-GCGCTTTATT-GCTTCAGCAG-3’ and the reverse primer was 5’-TCTTGGCTTTG-GACTAGGAC-3’. For human ATF6β, the forward primer was 5’-CCCAGTTCCGAGATCC-3’ and the reverse primer was 5’-CACCCCTGGAAGACCACTG-3’. The ATF6 sequences in each primer were flanked on the 5’ end with 20 nucleotides from the T7 RNA polymerase promoter. Human ATF6α or β cDNAs were used as the templates for PCR. After PCR, the products (586 bp for ATF6α; 622 bp for ATF6β) were used as templates for in vitro transcription using T7.
RNA polymerase, which resulted in the formation of dsRNA ATF6-related fragments. The resulting material was treated with DNase to remove the DNA template and RNase to remove any ssRNA. The resulting ATF6 dsRNA was then cleaved into small segments of RNA with the RNA Dicer enzyme and then transfected into HeLa cells using LipofectAMINE according to the manufacturer’s protocol.

Immunocytofluorescence—Following transfection with the appropriate siRNA, HeLa cells were incubated in 10% fetal calf serum for 48 h. After washing twice with PBS, the cells were fixed with 4% paraformaldehyde, washed with PBS, permeabilized with 0.1% bovine serum albumin and 0.2% Triton X-100 in 1× TBST, and blocked with 5% bovine serum albumin/TBST for 45 min. For detection of endogenous ATF6 or β, cells were incubated with primary antibody for 1 h at 37°C. Anti-ATF6 and anti-ATF6β antisera were gifts from Dr. Kazutoshi Mori. ATF6 antisera binding was visualized with fluorescein isothiocyanate-conjugated secondary antiserum (1:500, Jackson Immunoresearch, Baltimore, MD).

RESULTS

To compare ATF6α and β-mediated ERSR induction, we assessed the abilities of constructs encoding FLAG epitope-tagged versions of the putatively active N-terminal fragments of each isoform (N-ATF6α and N-ATF6β) to induce a luciferase reporter under the control of an isolated ERSE derived from the GRP78 promoter (6, 14). Increasing the levels of the N-ATF6α construct in transfection experiments resulted in progressive increases in reporter expression as expected; however, the N-ATF6β construct appeared to have no effect on reporter activity, even at the highest concentration tested (Fig. 1A). Because reporter constructs regulated by isolated ERSE usually exhibit lower activity than native ERSE-containing promoters, we decided to examine the abilities of each construct to activate transcription from the native GRP78 promoter (6).

Again, as expected, increasing levels of the N-ATF6α construct conferred a progressive increase in reporter expression amounting to a maximum of 48-fold over control (Fig. 1B). However, only at the highest concentration tested did the N-ATF6β construct exhibit apparent reporter induction, which did not reach statistical significance (Fig. 1B). A similar trend was observed when the relative abilities of N-ATF6α and β to activate endogenous ERSR expression were assessed. Although N-ATF6α conferred an approximate 4-fold increase in endogenous GRP78 protein levels, N-ATF6β conferred at most a 1.5-fold increase (Fig. 2, A and B).

To determine whether the differences between N-ATF6α- and β-mediated reporter induction might be attributed to different transgene expression levels, FLAG immunoblot analyses were carried out. Surprisingly, at any given plasmid concentration, N-ATF6α, which was transcriptionally more active, was always expressed at very low levels, whereas N-ATF6β, which had essentially no transcriptional activity, was expressed at very high levels (Fig. 3A). Densitometric analyses demonstrated that at a given plasmid concentration, N-ATF6β was expressed at 10–15-fold higher levels than N-ATF6α (Fig. 3B). Based on the activity and expression results shown in Figs. 1 and 2, it was estimated that the specific transcriptional activity of N-ATF6α was approximately 200-fold greater than that of N-ATF6β.

Our previous results showed that the expression levels and half-lives of various mutated forms of N-ATF6α were inversely related to their transcriptional activities, such that the higher the transcriptional activity, the lower the expression level and the shorter the half-life (10). Because N-ATF6β exhibited low activity yet was expressed at high levels, we compared its half-life to that of N-ATF6α. The results of pulse-chase labeling experiments were consistent with this hypothesis showing that, after 3 h of chase incubation, >50% of the labeled N-ATF6α had disappeared (Fig. 4, A, lanes 7 and 8), whereas very little of the labeled N-ATF6β had disappeared (Fig. 4A, lanes 15 and 16). Additional experiments showed that the half-lives
of N-ATF6α and β were ~2 and 5 h, respectively (Fig. 4B). Thus, the expression level and half-life of N-ATF6β mimic those of low activity N-ATF6α mutants.

Because the ER forms of ATF6α and β are both cleaved in response to ER stress and because the N-terminal cleavage products both translocate to the nucleus and bind to ERSEs (13), we assessed the effects of co-expressing N-ATF6α and β on GRP78 promoter activation. As expected, N-ATF6β alone exhibited very low levels of GRP78 promoter activation (Fig. 5A, bar 4) compared with N-ATF6α alone (Fig. 5A, bar 5). However, N-ATF6β inhibited N-ATF6α-mediated GRP78 promoter activation in a dose-dependent manner (Fig. 5A, bars 6–8). Thus, N-ATF6β exhibited a dominant-negative-like effect over N-ATF6α. Truncated forms of N-ATF6α and N-ATF6β that are missing the putative N-terminal TADs have been shown to have DN effects on ERSRG induction (8, 12). Because N-ATF6β appeared to behave similar to a DN, we compared its effects to N-ATF6α-DN and N-ATF6β-DN. In contrast to N-ATF6β, neither N-ATF6α-DN nor N-ATF6β-DN was able to elicit any measurable transcriptional activation of the GRP78 promoter on its own (Fig. 5B, bar 4, and C, bar 4). However, in comparison to N-ATF6β, both N-ATF6α-DN and N-ATF6β-DN effectively blocked N-ATF6α-mediated GRP78 promoter stimulation (Fig. 5B, bars 6–8, C, bars 6–8). Thus, compared with N-ATF6α, N-ATF6β exhibited a very low level of transcriptional activity and it acted in a dominant-interfering manner to repress N-ATF6α-mediated gene induction.

The effects of ATF6α and β on ER stress induced by TN were also assessed. Cultures transfected with empty vector exhibited low basal GRP78 promoter activity that was stimulated by >20-fold by TN as expected (Fig. 6, Con). Cultures that were transfected with N-ATF6α exhibited robust GRP78 promoter activation that was increased further upon TN treatment, also as expected (Fig. 6, ATF6α). In the absence of TN, N-ATF6β conferred a very small induction of ERSRG. However, cultures transfected with N-ATF6β were unable to mount a full ER stress response following TN treatment, exhibiting 3–4-fold less GRP78 promoter activation than cultures transfected with empty vector (Fig. 6, ATF6β). Although neither N-ATF6α-DN nor N-ATF6β-DN alone exhibited activity, it effectively blocked TN-mediated GRP78 promoter induction (Fig. 6, ATF6α-DN and ATF6β-DN), as expected from their previous characterization as dominant-interfering proteins. Thus, N-ATF6β was an effective blocker of the endogenous ER stress-response machinery responsible for GRP78 promoter activation.

To examine the roles of endogenous ATF6α and β, siRNAs directed against each ATF6 isoform were developed. Immunocytofluorescence showed that cultures transfected with a control siRNA directed against GFP exhibited robust ATF6α and β expression pattern consistent with localization to the rough ER and Golgi (Fig. 7, A and D). In contrast, cultures transfected with ATF6α siRNA exhibited considerably reduced ATF6α expression (Fig. 7, B versus A) but no effect on ATF6β expression (Fig. 7, E versus D). Moreover, cultures transfected with ATF6β siRNA showed no apparent effect on ATF6α expression (Fig. 7, C versus A) but reduced ATF6β expression (Fig. 7, F versus D).

Immunoblot analyses were carried out to further assess the effects of the siRNA reagents on endogenous ATF6α and β. As expected, cultures that were transfected with GFP siRNA expressed the highest levels of endogenous ATF6α and β (Fig. 8A, lane 1, and B, lane 1). Cultures transfected with ATF6α siRNA exhibited an approximate 82% reduction in ATF6α expression2 (Fig. 8A, lane 2 versus 1) but no change in the levels of endogenous ATF6β (Fig. 8B, lane 2 versus 1). In contrast, cultures transfected with ATF6β siRNA exhibited a small 37% reduc-

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2 The transfection efficiency in these experiments averaged 70–80%. Thus, because there was an 82% reduction in the level of ATF6α in the culture extract, the reduction of ATF6α in those cells that were transfected was essentially complete.
To examine the effects of knocking down endogenous ATF6α and/or β on the ER stress response, cultures were co-transfected with the various siRNAs and the GRP78 promoter-driven luciferase construct. When cultures were transfected with siRNA directed against GFP, they retained a robust ER stress response as measured by TN-activated GRP78 promoter-driven luciferase induction (data not shown).

**DISCUSSION**

The results of this study show that, compared with ATF6α, ATF6β possesses very low specific transcriptional activity and, most likely by virtue of this characteristic, ATF6β can serve as a repressor of ATF6α-mediated ERSRG induction. In support of our findings that ATF6β exhibits low specific transcriptional activity is a recent gene array study that failed to identify a single gene induced by ATF6β (20). Consistent with the repression roles for ATF6β was our finding that knocking down ATF6β expression using siRNA actually increased TN-mediated ERSRG induction (Fig. 9).

It is of interest to consider the consequences of these apparently opposing actions of ATF6α and β on the ER stress response. At least in part, the ratio of N-ATF6α/N-ATF6β must play a role in determining the magnitude and duration of the ATF6-dependent component of ERSRG induction. To a first approximation, the N-ATF6α/N-ATF6β ratio would be determined by the relative expression levels of the membrane forms of ATF6α and β and the relative rates of cleavage of these forms following the onset of ER stress. Although these parameters remain to be determined in detail, several published studies may provide some insight. Immunoblot analyses suggest that in HeLa cells the levels of the membrane forms of ATF6α and β are similar (12, 13); however, the rates of cleavage appear to differ. In response to TN, the cleavage of ATF6α was shown to be maximal after approximately 3–4 h, whereas the cleavage of ATF6β did not reach a maximum until 8 h after TN treatment.
Thus, the relative expression levels and times of generation are consistent with the hypothesis that N-ATF6β is generated after N-ATF6α and that it serves as an endogenous modulator of ATF6α-mediated gene induction. Moreover, the half-lives of ATF6α and β are also consistent with the view that ATF6β, which is relatively long-lived, serves as an inhibitor of ATF6α, which is extremely short-lived (Fig. 4).

Although the ATF6α/β ratio and the rates of cleavage of each isoform are consistent with the hypothesis that N-ATF6β is a transcriptional repressor, it remains unclear why a specific inhibitor of N-ATF6α-mediated gene induction is necessary. There are several other cases of transcription factor homologues that serve as repressors that ensure transient gene induction. For example, CREB and ICER are CREB/ATF family members that exert opposing effects on cAMP-dependent signaling. Thus, similar to CREB and ICER, perhaps ATF6

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β work in concert to finely tune the extent and magnitude of ATF6-mediated gene induction analogous to CREB and ICER? Are the rates of ATF6α and β generation and degradation regulated so they can be varied to suit the severity and nature of the ER stress? How do ATF6α and β collaborate with XBP1 to regulate the temporal induction of ER stress-response genes? Future studies on the rates of ATF6α and β cleavage in response to different stresses, as well as the mechanisms by which β exerts its inhibitory effects on α, will be necessary to provide answers to these provocative questions.
Opposing Roles for ATF6α and ATF6β in Endoplasmic Reticulum Stress Response Gene Induction
Donna J. Thuerauf, Lisa Morrison and Christopher C. Glembotski

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