Promoter-bound steroid receptors activate gene expression by recruiting members of the p160 family of coactivators. Many steroid receptors, most notably the progesterone and estrogen receptors, are regulated both by cognate hormone and independently by growth factors. Here we show that epidermal growth factor regulates the activities of the p160 GRIP1 through the extracellular signal-regulated kinase (ERK) family of mitogen-activated protein kinase kinases. ERKs phosphorylate GRIP1 at a specific site, Ser-736, the integrity of which is required for full growth factor induction of GRIP1 transcriptional activation and coactivator function. We propose that growth factors signal to nuclear receptors in part by targeting the p160 coactivators.

Nuclear receptors such as the estrogen receptor (ER) and progesterone receptor (PR) tether via their DNA binding domain to response elements in the promoter region of target genes and stimulate transcription. To do so the receptors must bind to coactivators that they recruit through transcriptional activation functions, the constitutive AF-1, found in the amino-terminal receptor domain, and the hormone-activated AF-2 in the carboxyl ligand binding domain (LBDM) (for review, see Ref. 1). Perhaps the most important of these coactivators is the p160 family, SRC-1 (N-CoA1), GRIP1 (TIF2/N-CoA2), and ACTR (pCIP/AIB1/RAC3). These bind to the LBDM only in the presence of cognate hormone, and their binding is blocked by antagonist ligands. The mechanism of binding is now understood in atomic detail and involves the docking of coactivator nuclear receptor boxes, which have the motif LXXLL with a hydrophobic cleft that forms on the surface of the hormone-bound LBD (2–6).

The AF-1 domain of the estrogen, androgen, and perhaps other receptors also contacts the p160s but does so through surfaces outside of the nuclear receptor boxes (7, 8).

The p160s are complex proteins with multiple domains (Fig. 1). In addition to the nuclear receptor boxes they have two intrinsic transcriptional activation domains AD1 and AD2, whose activities may be monitored when the coactivators are directly tethered on DNA via fusion to a heterologous DNA binding domain (8, 9). AD1, which is essential for transcriptional mediation by p160s, is coextensive with the binding domain for the CBP/p300 family of coactivators. CBP/p300 complexes with the p160s and synergizes in coactivator function (10, 11). In particular, CBP/p300s contain a potent acetyltransferase activity that can transfer acetate from acetyl-CoA to histones and also to other proteins in the complex on DNA (12–18). AD2 contributes to coactivation by p160s in some circumstances and does so in part by binding CARM1 and other proteins that have histone methylation transferase activity (19). The coactivators are believed to mediate transcriptional activation by remodeling chromatin through their histone modification activities and also by direct effects on the transcriptional complex.

In addition to regulating AF-2, hormones regulate steroid receptors (but not other nuclear receptors) in part by releasing the receptors from inhibitory complexes with heat shock proteins. The activity of steroid receptors is not regulated solely by hormones, however. Growth factors, such as EGF and insulin-like growth factor 1, can have profound and surprising effects on steroid receptors, even in the absence of cognate hormone (for review, see Ref. 20). In the most dramatic examples, EGF activates progesterone receptors almost as well as does hormone (21) and will partly activate ER in the absence of hormone and enhance activity in the presence of hormone (22). This later activity has been traced in part to EGF initiation of a cascade through the ERK family of MAP kinases that ultimately phosphorylates the ER at Ser-118 in the AF-1 region (23–26). Phosphorylation of Ser-118 leads to increased AF-1 activity by increasing binding of a p68 RNA helicase that is or becomes bound to CBP. This Ser-118-dependent link of AF-1 to CBP is in addition to the Ser-118-independent link with GRIP1 and thereby CBP (27).

Although EGF-mediated phosphorylation of steroid receptors underlies part of EGF enhancement, it cannot underlie all of it. In particular, mutation of Ser-118 to glutamate in the ER AF-1 domain, while blocking phosphorylation, nonetheless preserves EGF enhancement of ER action (25). Furthermore, careful mutation of sites of phosphorylation in the progesterone receptor again reveals a potent action of EGF in the absence of direct receptor phosphorylation (21). These studies suggest the existence of a pathway of EGF action that targets a nonrecep-
tor protein. We have explored the possibility that this unknown target is one of the p160 coactivators, particularly GRIP1. We present evidence that at least part of the signal from EGF to steroid receptor is conducted through the p160 coactivators.

**Experimental Procedures**

*Cell Culture, Transient Transfection, and Luciferase Assay*

HeLa cells were transfected by electroporation as previously described (28). Generally transfections included 5 μg of luciferase reporter plasmid, 1.0 μg of Gal-GRIP expression vectors, and 1.0 μg of β-actin-β-galactosidase expression vector for internal control. After electroporation, cells were treated with vehicle EGF (25 ng/ml) or TGF-C (15 ng/ml). Luciferase and chloramphenicol acetyltransferase values are the means and standard deviations of triplicate treatments from a single experiment, representative of at least three independent experiments.

**In Vitro Kinase Assay**

GST-GRIP fragments were expressed in bacteria (HB101) and partially purified by glutathione-Sepharose affinity column. Beads bearing the fusion proteins (1–3 μg of total protein) were subjected to *in vitro* phosphorylation by activated ERK2 according to the instructions of the supplier (Stratagene, La Jolla, CA). The phosphorylated products were extracted from the beads, resolved by 10% polyacrylamide gel electrophoresis, transferred with Coomassie Blue to monitor expression, and subjected to autoradiography.

**Phosphorylation Site Mapping**

Approximately 8.5 μg of total protein on beads were labeled in a 50-μl final reaction volume, extracted from the beads, and purified by 10% SDS-polyacrylamide gel electrophoresis. The gel was fixed, dried, and exposed to x-ray film to visualize the radiolabeled proteins. In-gel digestion of the protein with trypsin or endoproteinase Glu-C (Roche Diagnostics, Indianapolis, IN) was carried out as described previously (29). The resultant peptides were separated using reversed phase HPLC on a microbore C8 column (Vydac, Hesperia, CA), and the collected fractions were subjected to scintillation counting. Individual peptides were subjected to covalent Edman degradation on a Sequelon AA membrane (PerSeptive Biosystems, Cambridge, MA) with a protein sequencer (model 492; Applied Biosystems, Foster City, CA). The anilinothiazolone amino acids were extracted from the filter with neat trifluoroacetic acid and scintillation counted. Radioactive profiles for *Xenopus* amino acids were extracted from the filter with neat trifluoroacetic acid and scintillation counted. Radioactive profiles for amino acids were extracted from the filter with neat trifluoroacetic acid and scintillation counted.

**Plasmids**

*Expression Vectors—*To construct GalDBD-GRIP1, the GalDBD coding fragment from pGBT9-GRIPFL (32) was removed with HindIII-EcoRI and ligated to Smal-EcoRI-cut pBS (Stratagene) giving rise to pBS-Gal4DBD. An EcoRI fragment of GRIP1 (amino acids 5–1462) from pGBT9 vector was then inserted into pBS-Gal4DBD. The entire Gal4 DBD-GRIP1 coding segment was then removed with XbaI-EcoRV and subcloned into the Nhel-EcoRV site of commercially available pCMV vector (Stratagene). GalDBD-CBP has been described by Swope et al. (30). GST-GRIP1–479, GST-GRIP1–766, GST-GRIP184–766 vectors for bacterial expression have been described by Webb et al. (7). The mutants GST-GRIP736S and GST-GRIPSS55A for mammalian expression were generated by polymerase chain reaction from parental vector GST-GRIP184–766 incorporating a mutagenic primer with Phul polymerase (QuickChange site-directed mutagenesis kit, Stratagene). MPK-1 (CL100) expression vector was a gift of D. Stokoe (Cancer Center, University of California, San Francisco). MEK947R expression vector has been described by Mansour et al. (31). pSG5-GRIP736A was constructed from pSG5-GRIPFL (32) using mutagenic primer incorporation by polymerase chain reaction as described above. Gal-GRIP736S and Gal-GRIP55S are derivatives of Gal-GRIPFL vector and were mutated as indicated above. All the mutants were confirmed by sequencing, and generally, functional assays of two clones were carried out. pGFP-GRIP has green fluorescent protein fused to the Memorial Sloan-Kettering Cancer Center GRIP expression vector and was a gift from Yihong Wan (University of Colorado, Health Sciences Center), and pGFP-GRIP736A was constructed by removing a 1612-nucleotide BstXI-BspEI fragment from pSG5-GRIP736A and inserting it into the BstXI-BspEI sites of pGFP-GRIP. The point mutation was confirmed by sequencing. The pSG5ER S118A mutant is a derivative of HEO (33) and is described by Webb et al. (7).

**Results**

A recent report suggests that growth factor stimulation of the transcriptional activation functions of CBP (38, 39) requires the domain of CBP that mediates p160 binding (10). We thus examined in transfected cells whether the p160 GRIP1 tethered to a reporter gene promoter by fusion to the heterologous Gal4 DNA binding domain (Gal-GRIP1, Fig. 1) could activate transcription in response to growth factors. EGF and TGF-α had no effect on reporter gene expression in the absence of GRIP1 (Fig. 1A), but these ligands of the EGF receptor each activated transcription 5–10-fold when GRIP1 was bound to the promoter. The GRIP1 response to EGF and TGF-α required the action of the ERK family of MAP kinases because it was abolished by overexpression of the MAP kinase phosphatase CL100, by a dominant negative MEK that specifically prevents activation of ERKs, and by PD98059, a specific inhibitor of MEK activation (Fig. 1, B and C). In control experiments EGF failed to stimulate reporter gene transcription mediated by a Gal4 fusion to the herpesvirus VP16 protein, and as expected, neither PD98059 nor CL100 nor dominant negative MEK was inhibitory (data not shown). Thus GRIP1 contains an EGF-regulated transcriptional activation function, and ERKs are a component of the pathway of activation.

To examine whether GRIP1 might serve as a direct substrate for ERKs, we prepared recombinant GRIP1 in *Escherichia coli* and incubated it with activated ERK2 in vitro. Among fragments that represent the entire protein, two fragments from amino acids 1–766 and 184–766 were strongly phosphorylated by MAP kinase (Fig. 2A). Fragment 1–479 was unreactive, and fragment 766–1462 was barely reactive. Thus GRIP1 serves as a MAP kinase substrate in *vitro*, and the major site(s) of phosphorylation lies within amino acids 184–766, most likely between 480 and 766.

The precise site of action of ERK MAP kinase was determined by using enzymatic protein digests and Edman analysis.
of the phosphate-labeled GRIP1-(184–766). Each of these digests yielded a single major labeled peptide on HPLC, and the phosphate label was on the fifth amino acid of the tryptic peptide and the ninth of the V8 peptide (Fig. 2B). Each of these assays predicts that the major site of phosphorylation of GRIP1 is serine 736 (Fig. 2B), which is an ERK consensus site. To confirm the identity of the site, the phosphorylation reactions were repeated with wild type GRIP1-(184–766) and mutants in which Ser-736 or Ser-554, chosen because it resembles a MAP kinase site, was mutated to alanine. Phosphorylation was diminished on GRIP1 mutated on Ser-736 (Fig. 2C). The S554A mutant was phosphorylated as efficiently as wild type. In control experiments, JNK1, a MAP kinase with different specificity, phosphorylated all three substrates equally. We concluded that Ser-736 is a major target for phosphorylation of GRIP1 by ERK but not JNK in vitro.

To examine the role of Ser-736 in vivo, we repeated our studies of EGF activation of tethered GRIP1 using both wild type and mutants. EGF potentiated transcriptional activation mediated by wild type GRIP1 or the S554A mutant but was consistently weaker on the S736A mutant (Fig. 3A, upper panel). Despite this diminution of response, the Gal-GRIP554A mutant was well expressed as detected by Western blots (not shown) and by its ability to serve as “bait” in a mammalian two-hybrid assay (Fig. 3A, lower panel). These results indicate that GRIP1 bound directly to the promoter requires Ser-736 for full activation by EGF.

We then tested the requirement for Ser-736 when GRIP1 functions as a coactivator for the PR activated by EGF signaling. We used a reporter gene with three response elements from the tyrosine aminotransferase promoter (TAT3-luc), which the PR activates 3-fold in the presence of EGF (Fig. 3B).
Wild type GRIP1 as well as the S554A mutant potentiated PR-mediated transcription of the reporter gene approximately 4-fold after activation with EGF. Both the hormone-liganded and constitutive activity of the PR were potentiated, as is frequently observed for nuclear receptors with overexpressed coactivators (data not shown). The S736A mutant was only half as effective as wild type in potentiating PR action. In control experiments with hormone-activated glucocorticoid receptor, which does not respond to EGF, both wild type and S736A GRIP1 potentiated receptor action to similar extents (data not shown), indicating that the Ser-736 mutant of GRIP1 retains full function in some contexts. S736A GRIP1 was, however, less able than wild type GRIP1 to potentiate progestin-activated PR. Some of this deficit may reflect a role for low level activation of ERK or some other kinase on the inducible functions of GRIP1 on progestin-PR, even in the absence of deliberate EGF stimulation (data not shown). For other potential explanations see Lange et al. (40). Thus S736A GRIP1 retains full ability to serve as a coactivator in some circumstances but is deficient in EGF-regulated coactivator function on the PR.

Estrogen receptor activation of transcription from a reporter gene regulated by a consensus ERE is potentiated by EGF to varying extents depending on cells and culture conditions. We tested the ability of an ER S118A, mutated in the major site of EGF-dependent phosphorylation, for response to EGF with GRIP1. Without elevated GRIP1, EGF had little or no effect on transcriptional activation by ER S118A either in the absence or presence of estrogen (Fig. 4A, E2). With elevated GRIP1, EGF potentiated both unliganded and estrogen-liganded ER S118A action 2-fold. Interestingly, the S736A mutant was unable to support an EGF response. The isolated ER AF-2 function, which can be tested as a fusion of the ER LBD to the yeast Gal4 DNA binding domain tethered on a Gal4 response element, does not respond to EGF (Fig. 4B). The S736A mutant was unimpaired in its ability to function as a coactivator for isolated ER AF-2. Thus, S736A retains full coactivator function with the isolated ER LBD but is deficient in coactivator function for full-length ER S118A.

As noted above, GRIP1 is also bound to and synergizes with CBP/p300 (10, 11, 41). It is possible that EGF regulates GRIP1 coactivator activities by affecting the efficiency of this interaction. Indeed, it was recently reported that activated MEK in-
increased the association of CBP and the p160 AIB1 (42). Although expression of activated MEK led to phosphorylation of AIB1 the site(s) was not analyzed. We therefore examined the ability of wild type and S736A GRIP1 to potentiate transcription mediated by CBP. We tethered CBP directly to a promoter by fusion to a heterologous Gal4 DNA binding domain. In the absence of overexpressed GRIP1 the CBP domain weakly activates transcription (Fig. 5). Coexpression of wild type GRIP1 or the S554A mutant markedly potentiates transcription, which becomes sensitive to further induction by EGF. The S736A mutant of GRIP1 is, however, compromised in its ability to activate tethered CBP, and the EGF response is decreased.

To confirm that the defects of the S736A mutant are not due to loss of stability or nuclear localization ability, we fused both wild type and Ser-736 were well expressed and both localized to the nucleus (Fig. 6, top panel). Western blots indicated equal expression of wild type and mutant (Fig. 6, middle panel). When fused to GFP wild type GRIP1 had full coactivator action with tethered CBP and EGF, but the S736A mutant was diminished (Fig. 6, bottom panel). Thus the S736A mutation does not affect GRIP1 expression or localization yet has a specific effect on EGF-responsive coactivator function.

**DISCUSSION**

The observations above indicate that EGF-activated ERK MAP kinase potentiates the transcriptional activation functions of GRIP1. Furthermore, activated ERKs phosphorylate GRIP1 on serine 736 in vitro. Mutation of Ser-736 to alanine substantially reduces the ability of GRIP1 to enhance transcription of the EGF-activated PR and of the estrogen- and EGF-potentiated ER. Because the mutant GRIP1 is fully able to function as a coactivator for the GR and for the isolated ER LBD AF-2, receptors that do not respond to EGF, it appears that the defect of S736A is limited and may indeed be specific for GRIP1 coactivator function with EGF-responsive steroid receptors or other transcription factors. In sum these observations suggest that EGF-activated ERKs increase selected coactivator functions of GRIP1 through a pathway requiring the integrity and most likely the phosphorylation of Ser-736.

While this study was in preparation, it was reported that AIB1, another member of the p160 family, contained a transcriptional function that was activated by transfection with constitutive MEK, a potent activator of ERKs (42). Activation by MEK was independent of the D2 domain of AIB1, suggesting that AD1 was responsible. Indeed fragments of AIB1 that contain AD1 and the nuclear receptor boxes are phosphorylated in MEK-transfected cells, suggesting that the target of MEK activation is in this region and may require AD1 for an output. Interestingly, a deletion of AD1 of GRIP1 compromises the EGF response with ER and PR (data not shown). Activation by MEK was also reported to increase the binding of CBP with AIB1 fragments that contain the AD1 domain. Our studies complement this observation in that we observed an EGF-induced increase in the functional interaction between the p160 binding domain of CBP and tethered AIB1.

**FIG. 5.** Mutation of Ser-736 to Ala impairs the ability of GRIP1 to serve as an EGF-inducible coactivator for Gal-CBP. Expression of the GalRE-luc reporter gene when activated by a fusion of the p160 binding domain of CBP to yeast Gal4 DNA binding domain (Gal-CBP), wild type or mutant versions of GRIP1, and EGF is as indicated.

**FIG. 6.** Expression and localization of GRIP1 is unaffected by the S736A mutation. Top panels, fluorescence from fusions of GFP to GRIP1 wild type or S736A expressed in HeLa cells either untreated or EGF-treated as indicated. Middle panel, Western blot of the transfected cell extracts probed with anti-GFP. Lower panel, effect of GFP-GRIP1 wild type or S736A on expression of a GalRE-luc reporter gene activated with Gal-CBP and EGF as indicated.
hints that in the absence of direct phosphorylation, such as when the ER Ser-118 is mutated to glutamate, an EGF response persists. Thus, we suggest that for an EGF-induced signal cascade to be fully effective the cascade may need to target both the transcription factor and the recruited coactivator. This double requirement may prevent random biological noise from activation of the EGF response.

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