In response to changes in vascular homeostasis, endothelial cells secrete endothelin-1 (ET-1), which in turn regulates gene expression and phenotype in underlying vascular cells. We characterized a nuclear signaling cascade in which Src protein-tyrosine kinases link the ET-1 receptor to induction of c-fos transcription. A dominant negative Src-K—kinase mutant blocked ET-1-stimulated c-fos transcription. Expression of the COOH-terminal Src kinase (Csk), which represses Src kinases, also blocked induction of c-fos transcription by ET-1. Activation of the c-fos promoter by ET-1 required both the CArG DNA sequence of the c-fos serum response element and the Ca\(^2+\)/cAMP response element. In contrast, Src-induced c-fos transcription required only the CArG cis-element, demonstrating a divergence in signals regulating c-fos transcription. Thus, Src kinases contribute to a nuclear signaling cascade linking an ET-1 receptor to the c-fos serum response element; a Src-based pathway might play a more general role to propagate ET-1 nuclear signals that regulate cell growth and development. In addition, these results point to a widening role for nonreceptor protein-tyrosine kinases in propagating signals from G protein-coupled receptors.

The function and phenotype of vascular cells is controlled in part by diffusible, endothelial-derived mediators such as endothelin-1 (ET-1)\(^1\) (1–3). ET-1 is a 21-amino acid vasoconstrictor peptide that also regulates gene expression and growth of vascular and nonvascular cells in culture (4–8). Accumulating evidence suggests that ET-1 contributes to growth and compensatory remodeling of the vasculature in vivo (9–12), and gene targeting studies demonstrate a critical role for ET-1 nuclear signaling in cell differentiation and development (13–15). ET-1 binds to heterotrimeric G protein-coupled receptors and evokes a nuclear signaling cascade that activates immediate early gene transcription (16). Transcription of immediate early genes is thought to convert ET-1-dependent nuclear signals into phenotypic changes in target cells. However, the molecular mechanisms linking ET-1 receptors to immediate early gene transcription remain unclear.

An ET-1 nuclear signaling cascade might involve nonreceptor protein-tyrosine kinases. ET-1 rapidly stimulates pp60 c-Src and pp125 focal adhesion kinase activity, resulting in tyrosine phosphorylation of specific cellular proteins (17–21). A role for c-Src in ET-1 signaling is also supported by the observation that ET-1-stimulated phosphoinositide turnover is greatly amplified in v-src-transformed fibroblasts (22). Protein tyrosine phosphorylation is required for induction by ET-1 of the c-fos immediate early gene (19), which is one of the earliest genomic responses to ET-1 (19, 23, 24). These observations, and the finding that v-Src elevates c-fos transcription (i.e. see Ref. 25), suggest that the pathways that propagate ET-1 signals to the nucleus might involve c-Src.

In this study, we investigated whether c-Src or other Src family kinases participate in a nuclear signaling cascade linking G protein-coupled ET-1 receptors to the c-fos promoter in mesangial cells. We report here that ET-1-stimulated c-fos transcription is blocked by expression of a dominant negative c-Src mutant and by the COOH-terminal Src kinase (Csk), which both repress c-Src kinase activity. Moreover, full activation of the c-fos promoter by ET-1 requires c-Src-dependent pathways regulating the CArG box of the c-fos SRE and c-Src-independent pathways regulating the Ca\(^2+\)/cAMP response element.

**EXPERIMENTAL PROCEDURES**

Reagents—Fetal bovine serum (FBS) was from Hyclone (Logan, UT). Endothelin-1 was from American Peptide Company (Sunnyvale, CA). All other reagents are as described previously (20, 22).

Mesangial Cell Culture—Glomerular mesangial cell strains from male Sprague-Dawley rats were isolated and characterized as reported previously (26).

Plasmids—The following plasmids were as described: pSR1K— (27, 28); pCMV-Csk (29); pCMV-Src and pMv-Src (30); pRaf1L (31); pAhn17-c-Ha-Ras (32); and p356wt/fos CAT and point mutant (pm) fos CATs (33–36) (see also Table I). To construct the p356wt/fosLUC reporter (Fig. 1A), the HindII/XbaI fragment of p356wt/fosCAT (33), containing genomic DNA sequences −356 to +109 of the murine c-fos promoter, was subcloned into the HindII/Xbal sites of the pBK-RSV (Promega, Madison, WI) multiple cloning site. The c-fos promoter fragment was then excised as a Sad/XbaI fragment and directionally subcloned into the Sad/Ihcl sites of pUC3LUC (Promega). The resulting construct, which was verified by restriction mapping, expressed the luciferase gene under transcriptional control of the −356 to +109 sequence of the c-fos promoter.

Mesangial Cell Transfection and Reporter Gene Assays—Transient transfection of mesangial cells was carried out by the calcium phosphate method as reported previously (37) with modifications for cells in six-well plates. Briefly, cells in six-well plates (5 mm, 2 × 10\(^5\) cells/well) were transfected with 1 μg of p356wt/fosLUC, 1 μg of pRSV)Gal internal control, and the indicated expression vectors (usually 2 μg, except where indicated) and carrier DNA (pUC19) to a total of 6 μg of DNA.
Fig. 1. Expression of the dominant negative SrcK– mutant blocks ET-1-stimulated c-fos transcription. A, schematic representation of the −356/w fos luciferase (LUC) reporter and expression plasmids transfected into mesangial cells. Transcription of v-src and c-src inserts is driven by the M-murine leukemia virus long terminal repeat (LTR), whereas expression of the SrcK− insert is driven by the SV40 enhancer/promoter. B, left, mesangial cells transfected with the −356w/fosLUC reporter (1 μg) with or without the −SrcK– expression plasmid (2 μg) were rendered quiescent in DMEM, 0.5% FBS. In all experiments promoter strength was held constant by inclusion of the appropriate amount of expression plasmid lacking a cDNA insert. As a negative control, cells were also transfected with 1 μg of the pGL3LUC parent vector lacking the c-fos promoter fragment. Cells were then left untreated (−−−−) or were treated with ET-1 (100 nM) or FBS (10%) for 16 h before cell lysis and measurement of luciferase activity. Data are normalized for β-galactosidase activity and are expressed relative to untreated cells transfected with −356w/fosLUC (−−−−). Mesangial cells were also transfected with a vector expressing ARaf-1 (31) plus and minus the SrcK− plasmid. Right, mesangial cells transfected with −356w/fosLUC (1 μg) and vectors expressing SrcK− (2 μg) or v-Src (2 μg) were treated as above with ET-1 (100 nM, 16 h). Typical relative light unit values ranged from 500 to 2000 in 20 μl of lysates from untreated cells transfected with −356w/fosLUC.

RESULTS

We used cultured rat mesangial cells in this study to investigate the potential role of c-Src in activation of the c-fos promoter by ET-1. Mesangial cells derive from the glomerular microvasculature of the kidney, and ET-1 apparently contributes to the compensatory growth of mesangial cells and remodeling of glomerular capillaries following renal injury (8, 9). Previous experiments using cultured mesangial cells showed that receptors of the ET_A subtype stimulate c-Src activity and tyrosine phosphorylation of cellular proteins (19, 38). Moreover, induction of c-fos mRNA by ET-1 is blocked by protein-tyrosine kinase inhibitors (19). These results suggest that the signaling mechanisms that transduce the ET-1 signal from receptor to the nucleus are intact in mesangial cells and might involve c-Src protein-tyrosine kinases (17, 19, 20).

To determine whether c-Src contributes to c-fos promoter activation by ET-1, we subcloned a genomic DNA fragment containing nucleotides −356 to +109 of the murine c-fos gene into a plasmid to drive transcription of a luciferase gene (Fig. 1A). When this reporter construct (−356w/fosLUC) was transiently transfected into mesangial cells, ET-1 stimulated a 3.6-fold increase in luciferase activity (Fig. 1B). These results demonstrate that the −356w/fosLUC reporter contains the necessary cis-elements to confer responsiveness to ET-1. Moreover, transfection with a luciferase vector without the c-fos promoter sequence (Fig. 1B, pGL3LUC) confirmed that the increase in transcription observed with ET-1 was not due to activation of spurious regulatory elements in the luciferase vector.

We next employed a dominant negative mutant strategy (39).
to determine whether c-Src contributes to activation of c-fos transcription by ET-1. A kinase-inactivating mutation in c-Src (Lys395 → Met, SrcK–) forms a dominant negative c-Src protein that blocks signaling by platelet-derived growth factor and epidermal growth factor in NIH 3T3 fibroblasts (27, 28). Mesangial cells were co-transfected with the –356wt/fos LUC reporter and a vector expressing SrcK– under control of the SV40 promoter/enhancer (Fig. 1A) followed by stimulation with ET-1. The dominant negative SrcK– construct prevented the increase in c-fos transcription in cells stimulated by ET-1 (Fig. 1B, 3.6-fold versus 1.2-fold with SrcK–). The wild-type SrcK+ construct (2 μg) (27) did not inhibit ET-1-stimulated c-fos transcription (data not shown). SrcK– failed to decrease transcription in cells transfected with the pGL3LUC control reporter (Fig. 1B), and SrcK– only partially inhibited c-fos transcription in cells stimulated by fetal bovine serum (Fig. 1B, 6.2-fold versus 4.4-fold with SrcK–). The ability of SrcK– to inhibit ET-1-stimulated c-fos transcription suggests a role for c-Src in ET-1 nuclear signaling.

Two additional experiments confirmed that SrcK– did not simply produce its blockade by a general inhibition of transcription. First, mesangial cells were co-transfected with the –356wt/fos LUC reporter and a vector expressing a constitutively activated c-Raf-1 mutant (ΔRaf-1) that lacks the 303 NH2-terminal amino acids (31). c-Raf-1 acts downstream of c-Src in a signaling pathway that increases c-fos transcription (see Refs. 40–42 for review), and therefore SrcK– would not be predicted to inhibit c-Raf-1-induced transcription. Consistent with this prediction, ΔRaf-1 stimulated a 3.0-fold increase in c-fos transcription that was not inhibited by SrcK– (Fig. 1B). Second, the actions of dominant negative mutants should be reversible (39), and we demonstrated that expression of v-Src (Ref. 30 and Fig. 1A) reversed inhibition of ET-1-stimulated c-fos transcription by SrcK– (Fig. 1B). Taken together, these results strongly suggest that the dominant negative actions of SrcK– are specific and that c-Src contributes to activation of c-fos transcription by ET-1.

To obtain independent evidence that c-Src propagates an ET-1 signal to the nucleus, we transfected cells with a vector expressing COOH-terminal Src kinase (Csk) (29)). Csk is a protein-tyrosine kinase containing SH2 and SH3 domains that phosphorylates the COOH-terminal tyrosine (i.e. Tyr527) of c-Src and other Src family tyrosine kinases (43). Phosphorylation of the COOH-terminal tyrosine suppresses Src kinase activity, and gene targeting and other studies demonstrate that Csk negatively regulates Src family tyrosine kinase activity in vivo (29, 44–46). Csk expression blocked the increase in c-fos transcription in cells treated with ET-1 (Fig. 2, 4.1-fold versus 1.2-fold with Csk). Csk only partially inhibited FBS-stimulated c-fos transcription and had no effect on Δ-Raf-1-stimulated transcription. These results support the hypothesis that Csk or other Src family kinases contribute to an ET-1 signaling cascade that increases c-fos transcription.

We next asked which cis-elements of the c-fos promoter are activated by the ET-1/Src signaling pathway. Plasmids expressing either c-Src or v-Src (Fig. 1A) were co-transfected with a plasmid in which a genomic c-fos promoter sequence (bp −356 to +109) was subcloned upstream of a chloramphenicol acetyltransferase reporter gene (−356wt/fos CAT) (33). Both c-Src and v-Src increased c-fos transcription (Fig. 3A, 2.4-fold versus 5.2-fold, respectively), demonstrating that this −356 to +109 c-fos promoter fragment contains Src-responsive cis-elements. We therefore transfected mesangial cells with a series of point mutants −356wt/fos CAT reporters (33–36). These extensively characterized point mutations prevent binding of cognate trans-acting factors to their respective cis-elements, thereby enabling analysis of the function of specific cis-elements in activation of the c-fos promoter by ET-1 and Src (see Table I).

Mutation of the CArG sequence of the c-fos SRE, which binds dimers of serum response factor, prevented transcriptional activation by ET-1 and v-Src (Fig. 3B, pm12). That FBS-stimulated transcription of the pm12fos CAT reporter plasmid demonstrated that the mutant construct was transcriptionally active. A promoter containing point mutations in the sis-inducible element, AP-1/CRE-like element, and Ca2+/CRE (CaCRE), but not in the SRE, were not responsive to ET-1 but were responsive to v-Src (Fig. 3B, pm3.69). Although promoters containing five tandem repeats of the SRE responded to v-Src, ET-1 failed to stimulate transcription of these constructs (Fig. 3B, S/SRE). Point mutation of the Ets DNA sequence of the c-fos SRE, which recognizes p62 ternary complex factors (i.e. Elk-1 or Sap-1), did not inhibit c-fos transcription stimulated by ET-1 or v-Src (Fig. 3B, pm18). In mesangial cells, the ability of v-Src to stimulate c-fos transcription in the absence of Ets-binding proteins is consistent with our previous observation that ET-1-stimulated c-fos transcription did not require Ets DNA-protein interactions (37) and substantiate the apparently cell-type-specific requirement for p62 ternary complex factors in c-fos promoter regulation (25, 47–49). Taken together, these results argue that c-fos transcription stimulated by ET-1 and v-Src requires the CArG DNA sequence of the SRE. Unlike v-Src, however, DNA sequences in addition to the CArG box are necessary for ET-1-stimulated c-fos transcription.

Point mutations in the c-fos CaCRE, which binds homo- or heterodimers of CREB and ATF, block c-fos transcription stimulated by cAMP and [Ca2+]i (36, 50, 51). ET-1 does not increase intracellular cAMP in mesangial cells (52), but elevation of [Ca2+]i is an important effector in ET-1 signaling (16). We therefore tested whether the Ca/CRE was required for ET-1 and Src nuclear signaling to the c-fos promoter. A c-fos promoter with Ca/CRE point mutations was not responsive to ET-1 but was stimulated by v-Src (Fig. 3B, pm3). Thus, ET-1 signaling to the c-fos promoter requires the Ca/CRE. Moreover, Src or effectors upstream of Src represent a point of divergence for nuclear signals stimulating c-fos transcription in cells treated with ET-1.
We previously demonstrated that a dominant negative Ras mutant (Asn-17-c-Ha-Ras) blocks activation of the c-fos SRE by ET-1 (37). Because Ras has been reported to be downstream of c-Src in NIH 3T3 cells (53, 54), we asked whether Asn-17-c-Ha-Ras would block Src-stimulated transcription from the c-fos promoter fragment in mesangial cells. As expected (37), Asn-17-c-Ha-Ras inhibited c-fos transcription in cells treated with ET-1 (Fig. 4). Asn-17-c-Ha-Ras also inhibited c-fos transcription stimulated by c-Src (Fig. 4), thereby confirming that Ras lies downstream of Src in this pathway.

DISCUSSION

ET-1 evokes nuclear signaling cascades leading to differential expression of genes that control cell growth and/or differentiation. Previous studies have shown that ET-1 receptors activate nonreceptor protein-tyrosine kinases such as c-Src and focal adhesion kinase, but it is not clear whether nonreceptor protein-tyrosine kinases contribute to nuclear signaling by ET-1. The goal of these studies was to determine whether c-Src or Src family kinases contribute to transcriptional activation of the c-fos immediate early gene by ET-1. Our results, based on inhibition with dominant negative SrcK2 mutants and Csk,
strongly suggest that c-Src contributes to a nuclear signaling pathway linking ET-1 receptors to c-fos transcription. c-Src appears to participate in a pathway specifically linking ET-1 receptors to the CArG cis-element of the c-fos SRE. Although stimulation of c-fos transcription by ET-1 signaling also requires the Ca/CRE, c-Src does not appear to participate in this limb of the pathway (Fig. 5).

c-Src or Src Family Protein-tyrosine Kinases Contribute to a Nuclear Signaling Cascade Linking ET-1 Receptors to the c-fos Promoter—We and others (17–21) have previously demonstrated that ET-1 receptors increase c-Src and focal adhesion kinase protein-tyrosine kinase activity. Our strategy was to test the role of c-Src in propagating ET-1 signals to the c-fos promoter by co-transfecting cells with a c-fos promoter-luciferase plasmid and with plasmids expressing either a dominant negative mutant of c-Src (Srk<sup>-</sup>) or Csk, which antagonize c-Src-dependent signaling by independent mechanisms (27–29, 43–46). Co-transfection with either dominant negative c-Src or Csk effectively inhibited activation of c-fos transcription by ET-1. Several lines of evidence demonstrated that dominant negative c-Src and Csk did not antagonize ET-1 activation of the c-fos promoter by nonspecific inhibition of transcription. Wild-type c-Src (Srk<sup>+</sup>) did not inhibit activation of the c-fos promoter by ET-1, and the inhibitory effects of dominant negative c-Src were reversed by v-Src. Dominant negative c-Src and Csk only partially inhibited FBS-stimulated c-fos transcription. Raf-1 acts downstream of c-Src, and neither dominant negative c-Src nor Csk inhibited c-fos transcription in cells transfected with a constitutively activated ΔRaf-1. Thus, these experiments support the hypothesis that c-Src contributes to a nuclear signaling cascade linking ET-1 receptors to activation of the c-fos promoter.

As it is possible that both SrcK<sup>-</sup> and Csk inhibit other closely related members of the Src family of protein-tyrosine kinases such as Fyn and Lyn (27, 28, 44, 46), we cannot formally rule out possible involvement of other Src-related kinases in ET-1 nuclear signaling. However, we have been unable to demonstrate stimulation of other Src-related kinases by ET-1 in mesangial cells. For example, mesangial cells contain abundant levels of p62 c-Yes, but ET-1 does not stimulate c-Yes protein-tyrosine kinase activity. We therefore think that it is likely that c-Src contributes to transduction of the ET-1 signal to the c-fos promoter in these cells.

Activation of the c-fos Promoter by ET-1 Requires Both the CArG Box of the SRE and the Ca/CRE—To further characterize the ET-1-Src-based signaling cascade, we needed to identify which cis-elements of the c-fos promoter were required for activation of c-fos transcription by ET-1. We first showed that a −356 to +109 genomic DNA fragment of the c-fos promoter contains DNA sequences that confer responsiveness to ET-1. Activation of the c-fos promoter by many growth factors and oncogenes requires the SRE, which is comprised of a CArG box that binds dimers of serum response factor (SRF) and the Ets DNA sequence that binds ternary complex factors (TCF, i.e. Elk-1, Sap-1) in an SRF-dependent manner (34, 55, 56). We demonstrated that point mutations in the CArG box that prevent SRF binding (35) completely blocked c-fos promoter activation by ET-1. However, point mutations in the Ets DNA sequence that inhibit p62TCF binding to the SRE (34) did not block ET-1-induced c-fos transcription. These experiments support our previous finding that ET-1-induced c-fos transcription does not require p62TCF binding (37) and are consistent with the recent results of Hill et al. (57) that activation of the c-fos SRE by lysophosphatidic acid, which also binds to a G protein-coupled receptor, does not require p62TCF. Our present results also showed that although the SRE was required for c-fos promoter activation by ET-1, the SRE alone was not sufficient to confer this response.

We demonstrated that full activation of the c-fos promoter by ET-1 also required the Ca/CRE, which binds homo- or heterodimers of CREB and ATF. Point mutations in the Ca/CRE that prevent binding of CREB/ATF (36) blocked ET-1-stimulated c-fos transcription. The dual requirement of the c-fos SRE and Ca/CRE for c-fos promoter activation by ET-1 is similar to nerve growth factor-induced c-fos transcription, which also requires the c-fos SRE and Ca/CRE (58). Our data are also consistent with recent results by Robertson et al. (59) in transgenic mice, where regulation of c-fos transcription by external stimuli required multiple, interdependent cis-elements in the c-fos promoter.

Src Participates in the ET-1-Ras-c-fos CArG Box Signaling Cascade—We then asked whether c-Src contributes to ET-1-induced activation of the CArG box of the SRE, the Ca/CRE, or both. Point mutations in the CArG box but not the Ets/TCF motif of the SRE completely prevented v-Src-induced transcription of c-fos. Point mutations in the Ca/CRE did not affect c-fos promoter activation by v-Src, and point mutations in the sis-inducible element and FAP were similarly ineffective. Taken together, these results demonstrate that Src-based signals regulate the c-fos CArG box and suggest that c-Src contributes to signaling cascades whereby ET-1 regulates the c-fos CArG box but not the c-fos Ca/CRE. Src or effectors upstream of Src apparently represent a point of divergence whereby ET-1-derived signals regulate c-fos transcription (Fig. 5). We previously showed that Ras proteins participate in a signaling cascade linking ET-1 receptors to the CArG box of the SRE (37). Our present results with a dominant negative Ras mutant, Asn-17-Ha-c-Ras, demonstrate that c-Src lies upstream of Ras in this pathway. Although c-Src does not apparently contribute to the ET-1-Ca/CRE signaling pathway, we are currently investigating the possible role of Ras and other effectors in this cascade.

Our experiments also provide additional support for the importance of ET-1-evoked signals in initiating immediate early gene transcription in vascular and nonvascular cells. The re-

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2 W. H. Herman and M. S. Simonson, unpublished data.
sults do not exclude, however, the importance of other second messenger systems to regulate immediate early gene transcription and cell growth following exposure to ET-1. Indeed, we and others (19, 60) have found that protein kinase C is required for mitogenic signaling by ET-1 and for enhancement by ET-1 of EGF-induced transformation. Nonetheless, c-Src activation is an early step following ET-1 receptor activation and is temporally situated to transduce signals leading to long term changes in gene expression and vascular cell phenotype. Src kinases might also contribute to ET-1 nuclear signals that regulate determination of cell fate and development (13-15). Finally, these results also point to a widening role for nonreceptor protein-tyrosine kinases in propagating signals from G protein-coupled receptors.

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Nuclear Signaling by Endothelin-1 Requires Src Protein-tyrosine Kinases
Michael S. Simonson, Yuan Wang and William H. Herman

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