NO Inhibits Stretch-induced MAPK Activity by Cytoskeletal Disruption*

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Mesangial cells (MC) grown on extracellular matrix protein-coated plates and exposed to cyclic strain/relaxation proliferate and produce extracellular matrix protein, providing an in vitro model of signaling in stretched MC. Intra-cellular transduction of mechanical strain involves mitogen-activated protein kinases, and we have shown that p42/44 mitogen-activated protein kinase (extracellular signal-regulated kinase (ERK)) is activated by cyclic strain in MC. In vivo studies show the increased production of nitric oxide (NO) in the remnant kidney limits glomerular injury without reducing glomerular capillary pressure, and we have observed that NO attenuates stretch-induced ERK activity in MC via generation of cyclic guanosine monophosphate (cGMP). Accordingly, we sought to determine whether NO affects strain-induced ERK activity after strain and how this is mediated. Strain-induced ERK activity was dependent on time and magnitude of strain and maximal after 10 min at -27 kilopascals. Actin cytoskeletal disruption with cytochalasin D abrogated this. The non-metabolizable cGMP analogue 8-bromo cyclic GMP (8-Br-cGMP) dose-dependently attenuated strain-induced ERK activity. Cytoskeletal stabilization with jasplakinolide prevented this inhibitory effect of 8-Br-cGMP. Cyclic strain increased nuclear translocation of phospho-ERK by immunofluorescent microscopy, again attenuated by 8-Br-cGMP. Jasplakinolide prevented the inhibitory effect of 8-Br-cGMP on activated ERK nuclear translocation after strain. Strain increased ERK-dependent AP-1 nuclear protein binding, which was attenuated by cytochalasin D and 8-Br-cGMP. These data indicate that cGMP can inhibit cyclic strain-induced ERK activity, nuclear translocation, and AP-1 nuclear protein binding. Cytoskeletal disruption leads to the same effect, whereas cytoskeleton stabilization reverses the effect of 8-Br-cGMP. Thus, NO inhibits strain-induced ERK activity by cytoskeletal destabilization.

Glarmerulon mesangial cells (MC) are positioned as architectural supports for capillary loops and are therefore exposed to pulsatile stretch/relaxation (1). Whereas little resident glomerular cell proliferation or sclerosis is demonstrable in normal animals (2), MC proliferation and matrix production, eventually resulting in sclerosis, can be induced by maneuvers that increase intraglomerular pressure by 10 mmHg (3–5). Moreover, in these models, preventing the intraglomerular pressure rise attenuates sclerosis (5–7). We and others have shown reduction of sclerosis and MC proliferation in remnant glomeruli by oral L-arginine supplementation to increase NO production (8, 9). L-Arginine increases nitric oxide production by the remnant kidney and reduces glomerular endothelin-1 expression but does not lower glomerular capillary pressure (8).

The effects of mechanical forces on MC in vitro can be modelled by culturing cells in wells with deformable bottoms and then applying a vacuum to the wells to generate alternating cycles of strain and relaxation. Initial experiments using this methodology showed induction of mRNA for the proto-oncogene and AP-1 transcription factor component c-fos at 30 min (1). Subsequently, increases in both MC proliferation (2) and collagenous and non-collagenous extracellular matrix protein synthesis were observed by 48 h, the sine qua non of sclerotic injury (10, 11).

We and others have studied the link between mechanical stress and c-fos induction in stressed MC (12–14). We demonstrated increases in all three canonical mitogen-activated protein kinase (MAPK) pathways in response to strain (14). The most well described mammalian MAPK cascade, p42/44 or ERK, is well recognized to lie upstream of AP-1 (15, 16). ERK-dependent AP-1 induction has been demonstrated in endothelial cells in response to shear (17). In vivo, cyclic strain in the aortic wall activates ERK and AP-1 (18), and glomerular ERK activation and AP-1 nuclear protein binding have been shown in response to angiotensin II infusion (19). AP-1 activation may be important in the pathogenesis of glomerular sclerosis, because AP-1 activation has been shown to mediate transforming growth factor beta-1 induction (20, 21).

Recent data indicates that the actin cytoskeleton is important for ERK signaling. Cytochalasin-D prevented strain-induced ERK activity in vascular smooth muscle cells (22). Interestingly, LIM kinase-1 is intimately involved in induction of serum response factor by serum, suggesting a central role for the actin cytoskeleton in intracellular signaling (23). ERK does interact with the actin cytoskeleton (24), and ERK signaling in response to lysophosphatidic acid (25) or epidermal growth.

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The abbreviations used are: MC, mesangial cell(s); MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; Pa, pascal(s); 8-bromo-cGMP, 8-bromo cyclic guanosine monophosphate; PBS, phosphate-buffered saline; TBS, Tris-buffered saline; SNAP, S-nitroso-N-acetylpenicillamine.
Mechanical Stress and Cytoskeleton in Mesangial Cells

factor (26) is dependent on the presence of an intact actin cytoskeleton.

Recent studies indicate a role for NO in inhibition of cytoskeletal organization. Several NO donors and a constitutively active form of cyclic guanosine monophosphate (cGMP) inhibited NC adhesion to extracellular matrix protein via inhibition of focal adhesion kinase phosphorylation and actin cytoskeletal disruption (27). In vascular smooth muscle cells, cGMP-dependent kinase phosphorylated and inactivated RhoA, thereby disrupting the actin cytoskeleton (28). Consequently, we hypothesized that nitric oxide, via cyclic GMP, would limit NC signaling in response to mechanical strain through cytoskeletal disruption.

EXPERIMENTAL PROCEDURES

Cell Culture

Mesangial cells (5 × 10^4/well) were plated on 6-well plates with flexible bottoms coated with bovine type I collagen (Flexcell International Corp., McKeeseport, PA). Cells were grown to confluence for 72 h and then rendered quiescent by incubation for 24 h in Dulbecco’s modified Eagle’s medium supplemented with 20% fetal calf serum (Life Technologies, Inc.). Streptomycin (100 μg/ml), penicillin (100 units/ml), and 2 mM glutamine at 37 °C in 95% air, 5% CO2. Experiments were carried out in cells between passage 15–20.

Application of Strain/ Relaxation

Mesangial cells (5 × 10^4) were cultured in Dulbecco’s modified Eagle’s medium supplemented with 20% fetal calf serum (Life Technologies, Inc.), streptomycin (100 μg/ml), penicillin (100 units/ml), and 2 mM glutamine at 37 °C in 95% air, 5% CO2. Experiments were carried out in cells between passage 15–20.

RESULTS

ERK Nuclear Translocation—After each strain protocol with or without inhibitors, cells were washed three times with PBS and fixed with 3.7% formaldehyde (300 μl/well) for 10 min at room temperature. Cells were subjected to one wash with ice-cold PBS, and immunofluorescent staining was performed as described above and then permeabilized by dipping in acetone for 5 min at 20 °C. Subsequently, Texas Red phalloidin solution (Molecular Probes) was applied for 20 min at room temperature. Cells were washed, mounted, and analyzed exactly as described above.

Nuclear Protein Binding to AP-1 Consensus Sequences

After each strain protocol, 3C were washed in cold PBS, and nuclear extracts were prepared by lysis in hypotonic buffer (20 mM Hepes, pH 7.9, 1 mM EDTA, 1 mM EGTA, 200 μM NaF, 1 mM Na3VO4, 1 mM Na4P2O7, 1 mM DTT, 0.5 mM phenylmethylsulfonyl fluoride, 1 μg/ml aprotinin, 1 μg/ml leupeptin, 1 μg/ml pepstatin A, 0.6% Nonidet P-40), homogenized, and then centrifuged at 16,000 × g for 20 min at 37 °C. Pelleted nuclei were resuspended in hypotonic buffer containing 0.42 M NaCl2, 20% glycerol and rotated for 30 min at 4 °C. After centrifugation for 20 min at 16,000 × g, supernatant containing nuclear proteins was collected, and the protein concentration was measured with the Bio-Rad assay kit.

Fluorescence Microscopy

ERK activity was measured by suspending the pellet in 50 μl of 1× kinase buffer containing 200 μM ATP and 2 μg of Elk1 fusion protein as substrate. After incubation for 30 min at 30 °C, the reaction was terminated with 25 μl 3× SDS sample buffer (187.5 mM Tris-HCl (pH 6.8), 6% w/v SDS, 30% glycerol, 150 mM dithiothreitol, 0.5% w/v bromphenol blue), boiled for 5 min, vortexed, and then microcentrifuged for 20 s. Twenty μl of sample was loaded onto 4–20% polyacrylamide gel electrophoresis gel. After blotting to nitrocellulose, membranes were incubated for 3 h at room temperature with 25 ml of blocking buffer (1× TBS, 0.1% Tween 20 with 5% w/v nonfat dry milk) and then overnight at 4 °C with phosho-specific anti-Elk1 (Ser383) antibody 1:1000 in 10 ml of antibody dilution buffer. Membranes were washed, incubated with horseradish peroxidase-conjugated anti-rabbit secondary antibody (1:2000) for 1 h at room temperature. After three further washes in TBS, the membrane was processed as above.

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Fluorescence Microscopy
cytochalasin D (1 mg/ml, 60 min) disrupted actin stress fiber organization (Fig. 3, compare A and D). Pre-incubation with 1 mg/ml cytochalasin D for 60 min prevented the stretch-induced ERK activity (Fig. 2), indicating actin cytoskeleton-dependent transmission of the stretch signal.

8-bromo-cGMP Inhibits Strain-induced Actin Cytoskeletal Organization and ERK Activity—To determine whether nitric oxide, via induction of cyclic GMP, could prevent actin cytoskeleton organization and ERK activity in response to strain, MC cultures were incubated with the stable active cGMP analogue 8-bromo-cGMP for 10 min prior to strain. Initially, we sought to determine the effects of NO donors on the cytoskeleton in unstretched MC. Incubation for 10 min with either 70 μM S-nitroso-N-acetylpenicillamine (SNAP) or 1 mM 8-bromo-cGMP resulted in marked disruption of actin fibers in unstretched MC (Fig. 3, compare A, B, and C). Again, application of a −27-kPa stretch for 10 min to MC resulted in marked organization of actin stress fibers by phalloidin staining (Fig. 3, compare A and D), effectively prevented by 10 min of pre-incubation with either 70 μM SNAP or 1 mM 8-bromo-cGMP (Fig. 3, compare D, E, and F). In addition, pre-incubation with 8-bromo-cGMP for 10 min prior to strain dose-dependently inhibited the stretch-induced ERK activity (data not shown), with complete inhibition at 1 mM (Fig. 4, lane 3).

Cytoskeletal Stabilization Restores ERK Activity in Response to Stretch—The preceding experiments show an association between disruption of the actin cytoskeleton and prevention of stretch-induced ERK activity. To cement this link, we sought to prevent 8-bromo-cGMP-induced actin cytoskeleton disruption with jasplakinolide. Jasplakinolide stabilizes actin stress fibers primarily by decreasing the dissociation rate of actin subunits (29), although at higher concentrations (200 nM) and longer times (24 h), stress fibers disappear and are replaced by F-actin masses (29). Jasplakinolide competes with phalloidin for its actin binding site (30), making actin visualization difficult. Accordingly, we sought to determine whether low concentrations of jasplakinolide could restore stretch-induced ERK signaling in the presence of 8-bromo-cGMP. Fig. 4 shows prevention of stretch-induced ERK activity by 8-bromo-cGMP. Pre-incubation for 60 min with jasplakinolide at the indicated doses restored ERK1/2 activity, with complete restoration at 50 nM jasplakinolide.

Strain-induced Nuclear Translocation of Phospho-ERK Is Prevented by 8-Bromo-cGMP and Restored by Jasplakinolide—We sought to confirm the above observations by determining nuclear translocation of active (phospho) ERK after stretch using immunofluorescent microscopy. Application of a −27-kPa cyclic stretch for 10 min led to both induction of phospho-ERK and nuclear translocation (Fig. 5, compare B and C). This was largely prevented by pre-incubation for 10 min with 1 mM 8-bromo-cGMP (Fig. 5D). Addition of 50 nM jasplakinolide with 1 mM 8-bromo-cGMP restored both induction of ERK and nuclear translocation (Fig. 5E). Jasplakinolide alone (Fig. 5F) did not affect induction of phospho-ERK in response to stretch, although more fluorescent label appeared to be retained in the cytoplasm.

Strain-induced AP-1 Nuclear Protein Binding Is Prevented by 8-Bromo-cGMP and Restored by Jasplakinolide—ERK signaling is known to increase AP-1 transactivational activity in several cell lines (15, 16) including MC (18). Accordingly, we sought to determine whether strain led to ERK-dependent increases in nuclear protein binding to AP-1 consensus sequences and to determine the effects of 8-bromo-cGMP and jasplakinolide. Strain resulted in a marked increase in binding of nuclear proteins to AP-1 consensus sequences (Fig. 6, compare lanes 1 and 2), which was ERK-dependent, because it was abrogated by pre-treatment with PD98059 (Fig. 6, lane 5). Pre-incubation with 8-bromo-cGMP markedly attenuated the nuclear protein binding induced by stretch (Fig. 6, lane 3). This was again restored by pre-incubation with 50 nM jasplakinolide.
for 60 min (Fig. 6, lane 4), indicating that the effect of 8-bromo-cGMP was on the actin cytoskeleton.

**DISCUSSION**

In the best-characterized animal model of chronic renal failure, the subtotally nephrectomized rat, increased glomerular capillary pressure (as little as 20%) triggers MC responses that ultimately result in glomerulosclerosis (10, 11, 31). In vitro studies of the application of cyclic mechanical strain to MC have demonstrated that this stimulus results in MC proliferation (2, 32, 33) and production of collagenous protein (2) and fibronectin (12).

We and others have studied how the mechanical signal is transduced in mesangial cells. The first site of transduction is at the cell membrane (34). Initial studies of mechanical strain in MC noted increased proliferation in concert with induction of expression of the proto-oncogene and AP-1 component c-fos (1). Both down-regulation of protein kinase C (32) and calcium chelation (32) were shown to attenuate c-fos expression induced by strain. Studies of the proliferative effects of mechanical strain showed matrix dependence. Cells adherent to fibronectin showed the greatest strain-induced proliferative response, and this was inhibited by coincubation with RGD peptides (35). Integrin-focal adhesion complex interactions have been studied, and tyrosine phosphorylation of the focal adhesion-associated kinase pp125Fak was seen in stretched MC (36). Integrin binding to extracellular matrix protein leads to clustering and the formation of a signaling complex termed a focal adhesion that associates with actin filaments, leading to their reorganization into filamemtous stress fibers (37). Stretched MC elongate and align in the direction of stress, and actin filaments coalesce and orient themselves along this long axis (2). Various tyrosine kinases associate with focal adhesions after their formation, in particular focal adhesion kinase and the Src family kinases (38). In mesangial cells, cyclic strain-induced increases of vascular permeability factor mRNA are Src-dependent (39), providing evidence that the assembly of the focal adhesion complex and its association with kinases are important in the transduction of mechanical signals in MC. Further downstream, Src and focal adhesion kinase activate Ras via the Shc-Grb2-Sos complex (40). Ras is activated in response to cyclic strain in vascular smooth muscle cells (41, 42).

Signaling of mechanical stimuli to the cell nucleus after membrane events involves the ubiquitous MAPK cascades. ERK interacts with the actin cytoskeleton (24), which is indispensable for signaling in response to lysophosphatidic acid (25) or epidermal growth factor (26). Each of the MAPK cascades consists of three protein kinases acting sequentially, a mitogen-activated protein kinase kinase activator (MKK), a mitogen-activated protein kinase activator (MEK), and a mitogen-activated protein kinase (15). We have shown activation of all three cascades in MC in response to cyclic strain (14). More recently, we have demonstrated inhibition of strain-induced ERK and stress-activated protein kinase/c-Jun NH2-terminal kinase by NO donors (43). In the nucleus, both ERK and stress-activated protein kinase/c-Jun NH2-terminal kinase by NO donors (43) activate protein kinase/c-Jun NH2-terminal kinase by NO donors (43). In the nucleus, both ERK and stress-activated protein kinase/c-Jun NH2-terminal kinase by NO donors (43) and AP-1 (15, 16). As noted, cyclic strain in the aortic wall activates ERK and AP-1 (18), and glomerular ERK activation and AP-1 nuclear protein binding occur with angiotensin II infusion (19), a maneuver that would be expected to increase glomerular pressure.

Accordingly, we sought to determine how NO interfered with transmission of the stretch signal to ERK. Given recent data showing that 8-bromo-cGMP inhibited actin cytoskeletal organization via cyclic GMP kinase-mediated phosphorylation of RhoA (28), we elected to study whether the effect of NO donors...
on stretch-induced ERK activity was through cytoskeletal disruption.

We first observed that stretch led to the formation of actin stress fibers within 10 min in MC. Prevention of stretch-induced actin stress fiber formation in MC completely eliminated the usual stretch-induced ERK activity. This is consistent with a recent report in vascular smooth muscle cells using the same stretch system (22). Having established cytoskeletal dependence of stretch-induced ERK activity in MC, we sought to characterize the effects of NO on the actin cytoskeleton after stretch. Phalloidin staining of F-actin revealed that either SNAP or 8-bromo-cGMP led to cytoskeletal disassembly after 10 min of incubation. This has been observed in resting aortic smooth muscle cells with 40 min of 100 μM 8-bromo-cGMP (28). Pre-incubation with 8-bromo-cGMP also inhibited stretch-induced ERK activation in MC in this study, consistent with its effects on the cytoskeleton. In accord with this, phospho-ERK induction and nuclear translocation, which was easily visualized after 10 min of stretch, was essentially prevented by pre-incubation with 8-bromo-cGMP.

Whereas these data demonstrate an association between cytoskeletal disruption and prevention of strain-induced ERK activity by 8-bromo-cGMP, we sought to strengthen this link by studying cytoskeletal stabilization. A major finding of this study is that incubation with jasplakinolide in addition to 8-bromo-cGMP prior to and during stretch prevented 8-bromo-cGMP-mediated inhibition of strain-induced ERK1/2 activity. Furthermore, induction and nuclear translocation of phospho-ERK by immunofluorescent microscopy was also preserved by co-incubation with jasplakinolide. The effects of jasplakinolide on the actin cytoskeleton are complex, but jasplakinolide appears to stabilize actin stress fibers by decreasing the dissociation rate of actin subunits (29). It binds to actin at or near the same site as phalloidin, at the interface of three actin subunit dissociation from filaments (29). We did not image the cytoskeleton when jasplakinolide was applied to MC because of competition between jasplakinolide and phalloidin.

Finally, we sought to relate these findings to an intranuclear event and chose to study nuclear protein binding to AP-1 consensus sequences by gel-shift assay, because induction of the AP-1 component c-fos is one of the paradigmatic MC responses to stretch (1). Another major finding of this study was that stretch led to a prompt (10 min) increase in nuclear protein binding to AP-1 consensus sequences, which was prevented by the ERK inhibitor PD98059. Pre-incubation with 8-bromo-cGMP also prevented the stretch-induced increase in binding but not when co-incubated with jasplakinolide. These data indicate that 8-bromo-cGMP-mediated inhibition of ERK signaling to AP-1 is dependent on its ability to induce actin cytoskeletal disassembly.

How might NO affect the cytoskeleton? In cervical epithelia, NO donors were found to disrupt the actin cytoskeleton through action on cyclic GMP kinase (45). Subsequently, it was demonstrated that cyclic GMP kinase phosphorylates RhoA in vitro and that transfection of a non-phosphorylatable RhoA mutant abrogated the ability of 8-bromo-cGMP to induce cytoskeletal disassembly (28). Rho-dependent inhibition of myosin light chain phosphatase activity is important in stimulation of actin cytoskeletal stress fibers in response to carbachol (46) and endothelin-1 (47). Consequently, it is possible that 8-bro-
mo-cGMP inhibits stretch-induced actin cytoskeleton organization in MC through this mechanism.

In conclusion, the data presented here clearly demonstrate that stretch-induced ERK activity and AP-1 nuclear protein binding is dependent on an intact actin cytoskeleton. 8-Bromo-cGMP inhibits stretch-induced actin cytoskeleton organization in MC through this mechanism.

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