Shear stress plays a significant role in endothelial cell biology and atherosclerosis development. Previous work by our group has shown that fluid flow stimulates important functional changes in cells through protein expression regulation. Peroxiredoxins (PRX) are a family of antioxidant enzymes but have yet to be investigated in response to shear stress. Studies have shown that oscillatory shear stress (OS) increases reactive oxygen species (ROS) levels in endothelial cells, whereas laminar shear stress (LS) blocks this response. We hypothesized that PRX are responsible for the anti-oxidative effect of LS. To test this hypothesis, bovine aortic endothelial cells (BAEC) were subjected to LS (15 dyn/cm²), OS (±5 dyn/cm², 1 Hz), or static conditions for 24 h. Using Western blot and immunofluorescence staining, all six isoforms of PRX were identified in BAEC. When compared with OS and static, exposure to chronic LS up-regulated PRX 1 levels intracellularly. LS also increased expression of PRX 5 relative to static controls, but not OS. PRX exhibited broad subcellular localization, with distribution in the cytoplasm, Golgi, mitochondria, and intermediate filaments. In addition, PRX 1 knock down, using specific small interference RNA, attenuated LS-dependent reactive oxygen species reduction in BAEC. However, PRX 5 depletion did not. Together, these results suggest that PRX 1 is a novel mechanosensitive antioxidant, playing an important role in shear-dependent regulation of endothelial biology and atherosclerosis.

Shear stress acting on the blood vessel wall plays an important role in the development of atherosclerosis. Straight regions of the arterial tree are considered “protected” from atherogenesis by high levels of unidirectional laminar shear stress (LS)³ (1, 2). In contrast, plaque-prone areas in curves and bifurcations of the vasculature correspond to locales exposed to low or unstable shear stress, including oscillatory shear stress (OS) (2–4). These local mechanical forces have been correlated to the behavior of the exposed endothelium.

Endothelial cells exposed to disturbed flow experience oxidative stress, inflammatory molecule expression, and monocyte recruitment as early signatures of atherosclerosis (5–9). In vitro studies have established that OS is a potent stimulator of reactive oxygen species (ROS) production in endothelial cells, and quantitative measurements by our group showed a significant increase in both OS-dependent superoxide (O₂⁻) and hydrogen peroxide (H₂O₂) production (9–12). We found that OS-stimulated ROS occurs in an NADPH oxidase-dependent manner and leads to inflammatory responses (ICAM-1) (intercellular adhesion molecule 1) expression and monocyte adhesion (10, 11). Conversely, LS acts to reduce ROS production and subsequent inflammatory response (10). Nevertheless, the mechanism by which LS restricts oxidative stress remains unclear.

Antioxidant defense systems are critical to the protection of cellular macromolecules. They work to maintain a reductive cytosolic environment using both catalytic and non-enzymatic processes (13). In particular, it has been hypothesized that antioxidants are likely to regulate intracellular hydrogen peroxide in a localized manner. Production of H₂O₂ occurs where needed for intracellular signaling, while hydrogen peroxide molecules diffusing away from the site of action are destroyed (14). Recently, a new group of ubiquitous antioxidant proteins has been acknowledged in yeast, plant, and animal cells. The peroxiredoxins (PRX) are thiol specific-, non-selenium-containing enzymes that use redox-active cysteines to reduce peroxides and eliminate ONOO⁻. They are produced at high levels in the cell, having been reported to comprise 0.1–1% of soluble protein in mammalian cells (15). Based on conserved cysteine residues, six isoforms of peroxiredoxins (PRX 1–6) have been identified in mammalian systems, and a variety of investigations have described their functional roles in vascular remodeling, cancer, and pulmonary and neurodegenerative diseases.
In this study, we tested the hypothesis that shear stress alters PRX function by regulating protein expression and localization, which in turn affect the redox status of endothelial cells. Our studies show that all six forms of PRX are abundantly expressed in bovine aortic endothelial cells (BAEC) and that atherosprotective LS increased intracellular PRX 1 levels compared with atherogenic OS. In addition, PRX 1 knockdown experiments implicated PRX 1, but not PRX 5, as an important regulator of shear-dependent cellular redox state.

**EXPERIMENTAL PROCEDURES**

**Endothelial Cell Culture**—Bovine aortic endothelial cells were obtained from Cell Applications Inc. Cells were maintained in a standard humidified incubator (37 °C, 5% CO₂) in Dulbecco’s minimum Eagle’s medium (Invitrogen) supplemented with 10% fetal bovine serum (Atlanta Biologicals), heparin sodium (American Pharmaceutical Partners), endothelial cell growth supplement (isolated by us), and minimum non-essential amino acids (Invitrogen). BAEC from passage 8–15 were used in the following experimental protocols.

**Shear Stress Studies**—BAEC were grown to confluency monolayers in 100-mm tissue culture dishes (Falcon) and were subsequently exposed to static (ST) culture conditions or arterial levels of shear stress via cone-and-plate shear apparatus. Atheroprotective LS at 15 dynes/cm² was simulated by rotating a Teflon cone (0.5° cone angle) unidirectionally in medium as previously described by us (20). To mimic unstable atherogenic OS, the cone was rotated bidirectionally in medium using a stepping motor (Servo Motor) and computer program (DC Motor Company). Endothelial cells were exposed to OS at ±5 dynes/cm² with directional changes of flow at 1 Hz frequency (7). All shear stress studies were performed in low serum (0.5% fetal bovine serum) growth medium for 24 h.

**Preparation of Whole Cell Lysate**—Following experimental treatment, cells were washed three times with ice-cold phosphate-buffered saline and lysed with 600 μl of lysis buffer (50 mM Tris-Cl, pH 7.4, at 4 °C, 1% Nonidet P40, 0.25% sodium deoxycholate, 150 mM NaCl, 1 mM EDTA, 30 mM NaF, 40 mM β-glycerophosphate, 10 mM Na₃PO₄, 2 mM Na₃VO₄, 1 mM phenylmethylsulfonyl fluoride, 0.1% SDS). The lysate was further homogenized by sonication. The protein content of each sample was determined by Bio-Rad DC assay.

**Immunoblotting**—Aliquots of cell lysate (20–40 μg of protein each) were resolved by size on 12.5% or 15% SDS-polyacrylamide gels and subsequently transferred to a polyvinylidene difluoride membrane (Millipore). The membrane was incubated with primary antibody overnight at 4 °C, followed by incubation with an alkaline phosphatase-conjugated secondary antibody for 1 h at room temperature. Protein expression was detected by a chemiluminescence method, and the intensities of immunoreactive bands were determined via densitometry using the NIH Image program (21). Primary antibodies specific for PRX 1, 2, 3, 4, 5, and 6 (Lab Frontier), phospho-endothelial nitric-oxide synthase (Ser1177) (Cell Signaling Technology), total endothelial nitric-oxide synthase (BD Biosciences), and β-actin (Santa Cruz Biotechnology) were used.

**RESULTS**

**LS Up-regulates PRX 1 Expression in Cell Lysates**—Our previous work established that fluid shear stress critically affects...
endothelial cell function by regulating protein expression patterns. The PRX family is undeniably significant to cellular physiology and pathology but remains understudied in the fluid flow field. This led us to investigate whether shear stress regulates the intracellular expression of mammalian PRX in BAEC. To this end, total BAEC lysates were collected after 24 h of static culture, LS (15 dynes/cm²), or OS (±5 dynes/cm²) and analyzed by Western blot using PRX-specific antibodies. In these studies, ST, cells cultured under no shear stress, were used as a control for the shear system. As previously described, physiologically “normal” arterial endothelial cells are not exposed to chronic static conditions but, rather, experience continuous fluid flow. Therefore, LS is a more relevant control, representing a healthy state, which we will compare with OS, the disease state. With this in mind, all six PRX were detected in BAEC, and densitometric analysis indicated the level of PRX 1 was significantly increased by LS compared with OS and static controls. In addition, PRX 5 expression was significantly increased by LS with respect to static conditions but was not statistically different from OS (Fig. 1). Endothelial cell alignment and phosphorylated endothelial nitric-oxide synthase and total endothelial nitric-oxide synthase were included as internal controls. These findings suggest that PRX 1 is mechanosensitive and likely to play an important role in shear-dependent cell biology.

**PRX Exist in Various Subcellular Locations throughout BAEC**—Via Western blots, we have thus far found that shear stress regulates PRX 1 and 5 expression in BAEC. Based on the large number of PRX family members, we hypothesized that individual PRX likely play important roles in specific subcellular compartments. To investigate the intracellular distribution of PRX, confocal immunofluorescence staining studies were performed. This study revealed data consistent with Western blot analysis of shear-induced protein expression in BAEC. Image analysis of staining intensities indicated that PRX 1 increased after 24 h of LS compared with OS and static conditions (Fig. 2A).

In addition to the shear dependence, Fig. 2 also shows that PRX members exhibited assorted staining patterns. This result raised two interesting questions: 1) Are PRX located in specific subcellular locations and 2) does shear stress alter this subcellular localization? To clearly characterize the location of each PRX within specific subcellular compartments, colocalization staining was performed in static BAEC using PRX-specific antibodies and organelle-specific markers for Golgi (GM 130), endoplasmic reticulum (KDEL receptor, data not shown), lysosome (cathepsin S, data not shown), intermediate filament (vimentin), and mitochondria (Mitotracker). PRX 1 staining (green) overlapped with the Golgi marker staining (red), shown as yellow in the merged image (Fig. 3A), suggesting that PRX 1 exists in the Golgi apparatus. In addition, PRX 2, 4, 5, and 6 also appeared to be found in the Golgi (Fig. 3, B and E–G). The PRX 3 staining pattern was distinctly different from other PRX, showing clear colocalization with the mitochondria marker (Fig. 3D). Interestingly, PRX 2 staining revealed colocalization with the intermediate filament marker (Fig. 3C). In addition to these subcellular localizations, PRX 1, 2, 4, 5 and 6 were also expressed in the cytosol (Fig. 3, A–C and E–G). Next, we examined whether shear stress stimulated expression of PRX members in other subcellular locations. Subcellular location did not appear to change in response to shear stress, although Golgi were located upstream of the direction of flow after chronic LS, consistent with previous reports (Fig. 2, A, B, and
Taken together, these results clearly indicate that PRX are abundantly expressed throughout the subcellular organelles of endothelial cells.

PRX 1 Prevents Oxidative Stress in Endothelial Cells Exposed to LS—PRX 1 is a prominent antioxidant, and our data indicate its expression is highly up-regulated by LS (22). Consequently, we investigated whether PRX 1 was responsible for the decreased ROS levels in endothelial cells exposed to LS. The depletion of individual PRX from cellular systems provides a useful tool to study the functional role of each PRX isoform. Here, specific siRNAs were used to knock down either PRX 1 or PRX 5 protein levels in order to investigate PRX-dependent ROS accumulation. Western blots with isoform-specific PRX antibodies were used to determine the efficacy and specificity of these siRNAs. Compared with non-silencing siRNA and Alexa Fluor 546-labeled non-silencing siRNA (50 nM each), 48 h of treatment of BAEC with PRX 1 siRNA dramatically reduced (by 75% of non-silencing control) expression of PRX 1 at a concentration as low as 10 nM (Fig. 4A). As shown in Fig. 4B, 10 nM PRX 5 siRNA also effectively reduced PRX 5 expression (by 90% of non-silencing control). Using Western blots, the specificity of PRX 1 and 5 siRNAs was assessed by examining the expression of all other PRX family members (Fig. 4, A and B). Using isoform-specific PRX antibodies, we found that these siRNAs had no significant effect on other PRX, indicating that they exclusively targeted PRX 1 or 5, respectively, among all PRX family members (Fig. 4, A and B). Therefore, PRX 1 and 5 siRNAs were confidently used at 10 nM concentration in subsequent functional studies.

It has been well established that chronic exposure of endothelial cells to OS stimulates, while LS inhibits, ROS production (10, 11, 23, 24). Utilizing an Amplex Red assay in the presence or absence of catalase, we verified that hydrogen peroxide levels were 87% less in BAEC exposed to LS compared with those treated with OS (Fig. 5A). Using a standard hydrogen peroxide dose curve, we also found that the relative hydrogen peroxide levels following static culture, LS, and OS were consistent with expected cellular concentrations (Fig. 5B). To determine whether PRX 1 was responsible for the LS-dependent decrease in ROS levels in BAEC, we knocked down PRX 1 using PRX 1 siRNA as indicated above (Fig. 4A). PRX 1 depletion significantly increased catalase-inhibitable hydrogen peroxide by 2-fold above non-silencing controls in static-, LS-, and OS-treated BAEC (Fig. 5C). To investigate whether this was a global effect of mechanosensitive PRX family members, we also knocked down PRX 5 using PRX 5-specific siRNA. However, when compared with non-silencing controls, PRX 5 depletion had no significant effect on hydrogen peroxide levels in any group. Taken together, these data suggest that PRX 1 is a critically important regulator of ROS levels in both a basal and shear-dependent manner.

DISCUSSION

Through protein expression analysis and subsequent functional studies, we have discovered PRX 1 as a mechanosensitive antioxidant.
Peroxiredoxins as Mechanosensitive Antioxidants

FIGURE 5. PRX 1 knock down increases H$_2$O$_2$ production in BAEC, whereas PRX 5 knock down does not. Catalase-inhibitable hydrogen peroxide levels, measured via Amplex Red assay, and average values (mean ± S.E., n = 6–12) are shown in bar graphs as % of non-silencing (NS) siRNA-treated static controls. A, confluent BAEC were exposed to ST, LS, or OS for 24 h prior to assay. B, a hydrogen peroxide dose curve was used to estimate relative hydrogen peroxide concentrations in cells conditioned with shear stress. C, BAEC were transfected with either non-silencing or PRX 1 siRNA (10 nM) for 48 h and then exposed to ST, LS, or OS for 24 h prior to assay. D, BAEC were transfected with either non-silencing or PRX 5 siRNA (10 nM) for 48 h and then exposed to ST, LS, or OS for 24 h prior to assay. *, p < 0.05 designates significance between indicated groups.

antioxidant. Data to support this concept include: 1) PRX 1 is up-regulated intracellularly by chronic LS compared with OS, 2) PRX exhibit broad staining patterns in BAEC and localize in important cellular structures, 3) ROS production is significantly reduced in cells exposed to chronic LS, and 4) this effect can be attenuated by PRX 1 depletion, but not PRX 5 depletion.

Through this work, we reveal for the first time that PRX are regulated by shear stress in endothelial cells. Previous studies have shown that other antioxidants are also controlled by shear stress. LS has been shown to up-regulate antioxidant genes, including endothelial nitric-oxide synthase, CuZn superoxide dismutase, manganese superoxide dismutase, glutathione peroxidase, glutathione, and thioredoxin (25–29). In addition, Chen et al. (30) observed that many genes protective against oxidative stress are induced by exposure to prolonged LS. They have also noted that such genes are regulated through a conserved, shear-sensitive antioxidant response element. In support of our finding that PRX 1 expression is LS-dependent, recent work has shown that PRX 1 is a target gene of nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2), a key transcription factor that binds to antioxidant response element (31). Collectively, these studies indicate that cells possess an elaborate system of shear-responsive antioxidants and that each may play an independent role to mediate oxidative stress and modulate redox-sensitive signaling pathways.

The ubiquitous nature of the PRX family itself exemplifies this concept. Immunofluorescence microscopy revealed PRX throughout the cellular milieu of BAEC, colocalizing with the cytoplasm, Golgi apparatus, mitochondria, and intermediate filaments. These observations were consistent with previously reported localization studies in other cell types, but we are the first to report an apparent PRX 2 colocalization with vimentin (32, 33). This costaining of PRX 2 with vimentin suggests that it may be located in the intermediate filament, but further studies will be necessary to confirm this finding. Although detection of PRX in the Golgi body likely reflects protein processing or packaging, localization within other organelles indicates that PRX may act both globally and in a site-specific manner to regulate ROS in endothelial cells. In the endothelium, ROS, such as O$_2^-$ and H$_2$O$_2$, arise from several sources, including NADPH oxidase, xanthine oxidase, mitochondrial oxidase, cytochrome P450, and uncoupled nitric-oxide synthase (34, 35). At relatively low concentrations, ROS play critical roles in redox signaling and normal cell function. However, higher concentrations of ROS induce oxidative damage of DNA, proteins, carbohydrates, and lipids (36–38). This damage has been shown to critically affect cellular function and apoptosis when it occurs in mitochondria, lysosomes, and nuclei (39–41). In addition, cytosolic proteins modified by ROS have been shown to affect local cell signaling and, collectively, the redox status of the cell (11, 42, 43). Ubiquitous distribution of PRX in BAEC may reflect diverse sources of ROS throughout the cells and provide protection for important macromolecules and structures against local ROS production. In addition, widespread allocation of PRX may be important for comprehensive management of the overall oxidative state of cells.

Several studies have shown that oxidative stress is regulated by shear stress in endothelial cells (10–12, 24, 26). We have previously published that both LS and OS stimulate ROS production acutely but the ROS transiently elevated by LS returns to basal levels within a few hours (10). However, unlike LS, OS continues to increase ROS production, maintaining elevated levels as long as cells are exposed to OS (10, 24, 26). The mechanism by which ROS levels are lowered in cells exposed to chronic LS is undefined. This study demonstrates that endothelial cells exposed to chronic LS express much more PRX 1 compared with OS and static conditions. These findings suggest that PRX 1 is up-regulated by LS and that this may be responsible for LS-mediated decrease in ROS levels.

As previously determined by electron spin resonance spectrometry and dichlorofluorescein-diacetate methods, endothel-
H2O2 is the primary ROS component. In contrast, endothelial cells treated with chronic, unidirectional high shear generate considerably less O2•−. Here, we used Amplex Red assay as an independent method to measure ROS levels in BAEC. Consistent with our previous reports, OS increased and LS decreased ROS production (Fig. 5A). The ROS measured by this assay was inhibitable by catalase, indicating that H2O2 is the primary ROS component.

PRX 1 is the most abundant and ubiquitously distributed member of mammalian PRX (22). Our current study demonstrated that PRX 1 is dramatically up-regulated by chronic LS compared with OS and is located in the cytoplasm and Golgi. Knock down of PRX 1 using siRNA resulted in significantly increased and LS decreased ROS production (Fig. 5). In summary, we have shown that shear stress regulates expression of the PRX family and that PRX 1 plays a critical role in regulating ROS levels in endothelial cells. Furthermore, this discovery of PRX 1 as a mechanosensitive antioxidant may contribute important insights into endothelial cell biology and vascular diseases.

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