Vascular Mechanobiology
— Endothelial Cell Responses to Fluid Shear Stress —

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Endothelial cells (ECs) lining blood vessel walls respond to shear stress, a fluid mechanical force generated by flowing blood, and the EC responses play an important role in the homeostasis of the circulatory system. Abnormal EC responses to shear stress impair various vascular functions and lead to vascular diseases, including hypertension, thrombosis, and atherosclerosis. Bioengineering approaches in which cultured ECs are subjected to shear stress in fluid-dynamically designed flow-loading devices have been widely used to analyze EC responses at the cellular and molecular levels. Remarkable progress has been made, and the results have shown that ECs alter their morphology, function, and gene expression in response to shear stress. Shear stress affects immature cells, as well as mature ECs, and promotes differentiation of bone-marrow-derived endothelial progenitor cells and embryonic stem cells into ECs. Much research has been done on shear stress sensing and signal transduction, and their molecular mechanisms are gradually coming to be understood. However, much remains uncertain, and many candidates have been proposed for shear stress sensors. More extensive studies of vascular mechanobiology should increase our understanding of the molecular basis of the blood-flow-mediated control of vascular functions. (Circ J 2009; 73: 1983–1992)

Key Words: Blood flow; Endothelial cells; Hemodynamic force; Mechanotransduction; Shear stress

Blood vessels are not just tubes through which the blood passes, but are active organs with a variety of functions that maintain the homeostasis of the circulatory system. It is a well-established fact that vascular functions are controlled by biochemical mediators, including hormones, cytokines, and neurotransmitters. However, it has recently become apparent that the biomechanical forces generated by blood flow and blood pressure regulate vascular functions. Flowing blood constantly exerts a frictional force, shear stress, on the endothelial cells (ECs) lining blood vessel walls, and the ECs respond to shear stress by changing their morphology, function, and gene expression. EC responses to shear stress are thought to play a critical role in blood-flow-dependent phenomena, including angiogenesis,1 vascular remodeling,2 and atherosclerosis.3 The fact that ECs respond to shear stress indicates that they have the ability to sense shear stress as a signal and transmit it into the interior of the cell. Numerous studies have been devoted to clarifying the mechanisms of shear stress mechanotransduction, and they have demonstrated that multiple signal transduction pathways are activated by shear stress through a variety of membrane molecules and cellular microdomains, including ion channels, G protein, tyrosine kinase receptors, adhesive proteins, caveolae, the cytoskeleton, the glycocalyx, and primary cilia. The mechanisms of shear stress mechanotransduction, however, are not yet fully understood. We review the literature on EC responses to shear stress and the role of their responses in the regulation of the circulatory system, and address the issues of shear stress sensing and signaling mechanisms.

EC Responses to Shear Stress

A considerable amount of information on EC responses to shear stress has accumulated as a result of various in vivo, ex vivo, and in vitro experiments. In vitro experiments in which cultured ECs have been subjected to controlled levels of shear stress in fluid-dynamically designed flow-loading devices, in particular, have enabled analysis of EC responses to shear stress at cellular and molecular levels.4–7 In this section, we describe the effects of shear stress on EC morphology, function, and gene expression, and on the differentiation of immature cells, such as endothelial progenitor cells (EPCs) and embryonic stem (ES) cells, into ECs.

Morphology

When examined in vivo, ECs lining segments of blood vessels in which blood flow is rapid and unidirectional are spindle-shaped and aligned with their long axis parallel to the direction of blood flow, whereas ECs lining segments in which blood flow is turbulent or stagnant are much rounder in shape and do not have a uniform orientation.8,9 Because of these findings, shear stress is thought to determine the shape and orientation of ECs. When cultured ECs have been

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subjected to shear stress in a flow-loading device in vitro, they become elongated and undergo a net cellular movement that orients them in the direction of the shear stress (Figure 1A). This morphological change is accompanied by cytoskeletal reorganization, with actin filaments becoming rearranged into bundles of stress fibers and aligned in the direction of the shear stress.11–13

**Vascular Tone**

When blood flow increases in vessels, they acutely dilate, and the dilation is mainly mediated by nitric oxide (NO) released by ECs.14 A stimulatory effect of shear stress on NO production has been demonstrated in cultured ECs (Figure 1B).15–17 and shear stress has been found to increase NO production via activation of endothelial NO synthase (eNOS) and upregulation of its gene expression.18 Shear stress induces an increase in the intracellular concentrations of Ca$^{2+}$ and tetrahydrobiopterin, an essential cofactor of eNOS, and activation of protein kinases leads to eNOS activation.19–22 eNOS expression increases in response to shear stress as a result of an increase in transcription that involves transcription factor NF-κB and a shear stress response element (GAGACC) located in the eNOS gene promoter, and as a result of eNOS mRNA stabilization through its 3’ polyadenylation.23–25 Production of other potential vasodilators, including prostacyclin, C-type natriuretic peptide, and adrenomedulin, also increases in ECs exposed to shear stress.26–28 Production of the vasoconstrictor, endothelin, and cell surface expression of angiotensin-converting enzyme, which generates the potent vasoconstrictor angiotensin II, on the other hand, decreases in response to shear stress.29,30

**Antithrombotic Activity**

Shear stress enhances the antithrombotic activity of ECs. ECs express the antithrombotic membrane glycoprotein, thrombomodulin, which inactivates the procoagulant factor.
thrombin and activates the anticoagulant protein C, which retards the coagulation process by degrading activated coagulation factors. We have demonstrated that shear stress increases the expression of thrombomodulin by cultured human umbilical vein ECs (HUVECs) time- and dose-dependently (Figure 1C).

Shear stress also contributes to maintaining ECs as nonthrombogenic by increasing the production of heparan sulfate proteoglycans and tissue-type plasminogen activator.

Growth Factors and Cytokines
ECs produce a variety of growth factors and cytokines, and shear stress has been shown to increase their production of platelet-derived growth factor (PDGF), heparin binding-epidermal growth factor-like growth factor (HB-EGF), basic fibroblast growth factor (bFGF), transforming growth factor-β (TGF-β), interleukin-1 and -6 (IL-1 and IL-6), and granulocyte/macrophage colony stimulating factor (GM-CSF).

Adhesive Interactions With Leukocytes
It is well known that local blood flow conditions affect the adhesive interactions between ECs and leukocytes. Shear stress modulates the adhesion of leukocytes to ECs by altering EC expression of adhesion molecules. When murine lymph node venule ECs, which express abundant vascular cell adhesion molecule-1 (VCAM-1), are exposed to shear stress in a flow-loading device, VCAM-1 expression decreases markedly (Figure 1D), and the decrease results in a significant reduction in the number of lymphocytes that adhere to the cells.

Gene Expression
When EC functions change in response to shear stress, usually the expression of related genes also changes. Our DNA microarray analysis revealed that approximately 3% of all genes examined responded in some way to shear stress.

Reactive Oxygen Species (ROS)
ROS, including the superoxide anion (O$_2^-$) and hydrogen peroxide (H$_2$O$_2$), are produced in ECs and act as intracellular second messengers or mediators of human diseases such as atherosclerosis and reperfusion injury. Shear stress affects the production and elimination of ROS in ECs. Exposure of ECs to oscillatory shear stress has been demonstrated to markedly increase ROS production through activation of the O$_2^-$-producing NAD(P)H oxidase, whereas laminar shear stress has been shown to increase superoxide dismutase (SOD), which inactivates ROS. In addition, increased mRNA and protein levels of Cu/Zn SOD, as well as increased Cu/Zn SOD activity, have been observed in cultured human aortic ECs exposed to laminar shear stress. A recent study showed that laminar shear stress, but not oscillatory shear stress, increased expression of antioxidant enzyme peroxiredoxins by ECs.

Figure 2. Signal transduction factors that are capable of being activated by shear stress. Multiple pathways are involved in the shear stress signal transduction that leads to alterations in endothelial cell morphology and function, and to activation of various transcription factors. R, receptor; G, G protein; AC, adenylate cyclase; cAMP, cyclic adenosine 3',5'-monophosphate; ATP, adenosine 5'-triphosphate; TK, tyrosine kinase; PL, phospholipids; PLA$_2$, phospholipase A$_2$; AA, arachidonic acid; PG, prostaglandin; PLC, phospholipase C; IP$_3$, inositol 1,4,5-triphosphate; DG, 1,2-diacylglycerol; PKA, protein kinase A; CaM-K, calmodulin kinase; PKC, protein kinase C; PI3-K, phosphatidylinositol 3-phosphate; Ras and Raf, small G proteins; MEK, MAP kinase-ERK kinase; MEKK, MAP kinase-ERK kinase kinase; ERK, extracellular signal-regulated kinase; JNK, c-jun N-terminal kinase; p38 MAPK, mitogen activated kinase; Sos and Grb2, adaptor proteins; FAK, focal adhesion kinase; O$_2^-$ and H$_2$O$_2$, reactive oxygen species; CREB/ATF, cAMP-responsive element-binding protein/activating transcription factor; NF-κB, nuclear factor κ B; Jun & Fos family (AP-1), transcription factors.
showed variable, not uniform, patterns. Thus, EC responses to shear stress seem to consist of complex cascades of gene responses with different temporal profiles. Shear stress regulates endothelial gene expression transcriptionally and/or posttranscriptionally.\(^5\)\(^2\)\(^3\)\(^4\) The transcriptional regulation is mediated by transcription factors, including AP-1, NF-κB, Egr-1, SP-1, GATA 6, and Kruppel-like factor 2 (KLF2), each of which binds to its consensus motif in the gene promoter.\(^5\)\(^3\)–\(^5\)\(^8\) The posttranscriptional regulation is mediated by RNA-binding proteins that bind to mRNA and control its degradation rate. We have shown that the expression of genes encoding GM-CSF and urokinase-type plasminogen activator (uPA) is upregulated by shear stress through mRNA stabilization.

**Cell Differentiation**

Bone-marrow-derived EPCs circulating in peripheral blood migrate toward their target tissue where they differentiate and contribute to the formation of new vessels.\(^5\)\(^9\) During this process, they are exposed to shear stress generated by interstitial fluid flow and blood flow, and when cultured EPCs are subjected to shear stress in a flow-loading device, their differentiation into mature ECs accelerates significantly.\(^6\)\(^0\) ES cells are exposed to fluid-mechanical forces, including shear stress, and the cyclic strain generated by the beating heart during the process of embryonic development.\(^6\)\(^1\) However, we have demonstrated that shear stress and cyclic strain have very different effects on ES cell differentiation: shear stress induces differentiation of ES-cell-derived VEGF receptor 2 (VEGFR2)-positive cells\(^6\)\(^2\) into the EC lineage, whereas cyclic strain induces differentiation of VEGFR2-positive cells into the smooth muscle cell (SMC) lineage.\(^6\)\(^3\)–\(^6\)\(^4\) Interestingly, differentiation into the EC lineage or into the SMC is mediated by ligand-independent phosphorylation of VEGFR2 and PDGF receptors, respectively, by shear stress. Moreover, our recent study has shown that shear stress increases expression of an arterial EC marker, ephrinB2, in EPCs, suggesting that shear stress can affect the arterial–venous differentiation of ECs.\(^6\)\(^5\) It seems likely that fluid-mechanical forces act as regulators of EPC-mediated neovascularization and of ES-cell-mediated early embryonic vascular development.

**Shear Stress Mechanotransduction**

A vast number of studies have been undertaken to clarify the mechanisms underlying shear stress mechanotransduction, but much about the subject remains obscure.\(^6\)\(^6\) Based on the image, it seems that there is a diagram of various mechanisms involved in shear stress mechanotransduction.
on the results of numerous studies, multiple pathways appear to be involved in the shear stress signal transduction (Figure 2). At present, however, it remains unclear which pathways are primary and which are secondary, because the initial sensing mechanism or sensors that recognize shear stress have not been identified. Thus far, various membrane molecules and cellular microdomains, including ion channels, growth factor receptors, G proteins, caveolae, adhesion proteins, the cytoskeleton, the glycocalyx, and primary cilia, have been shown to play important roles in the shear stress sensing mechanism (Figure 3). The next section will address candidates for shear stress sensors.

Shear Stress Sensors

Ion Channels
Various types of ion channels have been listed as candidates for shear stress sensors. Potassium ion channels open in response to shear stress, and their opening results in hyperpolarization of the plasma membrane, whereas activation of chloride ion channels by shear stress induces membrane depolarization. Some types of Ca^{2+}-permeable cation channels have been shown to be shear-stress-responsive; for example, P2X purinoceptors and transient receptor potential (trp) channels, both of which are Ca^{2+}-permeable.
channels expressed by ECs, open in response to shear stress and mediate the influx of extracellular Ca\(^{2+}\) across the plasma membrane.\(^{71-74}\) The Ca\(^{2+}\) influx triggers subsequent Ca\(^{2+}\)-dependent signaling pathways that lead to EC responses to shear stress. The next section will review what has been discovered about P2X purinoreceptor-mediated Ca\(^{2+}\) signaling of shear stress.

**Ca\(^{2+}\) Signaling of Shear Stress**

When cultured ECs were subjected to shear stress, the intracellular Ca\(^{2+}\) concentration increases in a dose-dependent manner (Figure 4A).\(^{75-77}\) The Ca\(^{2+}\) response is related to an influx of extracellular Ca\(^{2+}\) via P2X4, a subtype of ATP-operated cation channel P2X purinoreceptor. Treatment of ECs with an antisense oligonucleotide that targeted to their P2X4 channels blocked the shear-stress-induced Ca\(^{2+}\) influx (Figure 4B). Activation of P2X4 required ATP, which was supplied in the form of endogenous ATP released by the ECs.\(^{78}\) The ECs released ATP dose-dependently in response to shear stress (Figure 4C), and suppression of ATP release with the ATP synthase inhibitor, angiotatin, abolished the shear-stress-induced Ca\(^{2+}\) responses (Figure 4D).

These findings suggest that ECs are capable of accurately converting information regarding shear stress intensity into changes in intracellular Ca\(^{2+}\) concentrations through ATP release and P2X4 activation. Although the mechanism responsible for the ATP release in response to shear stress remains unclear, several possibilities have been suggested: shear stress may increase ATP release through vesicular exocytosis or ATP binding of cassette transporters, or it may activate cell surface ATP synthase to catalyze the synthesis of ATP.\(^{79-81}\)

**Physiological Roles of Shear Stress Ca\(^{2+}\) Signaling in the Circulatory System**

Our study of P2X4 gene knockout (KO) mice revealed physiological roles of P2X4-mediated shear stress signal transduction in the circulatory system.\(^{82}\) The P2X4 KO mice did not exhibit normal EC responses to shear stress, such as a Ca\(^{2+}\) influx and subsequent production of NO. The vasodilation induced by acute increases in blood flow in situ was much weaker in the P2X4 KO mice, and the P2X4 KO mice had higher blood pressure than wild-type mice. No adaptive vascular remodeling (ie, decrease in vessel size in response to a chronic decrease in blood flow) was observed in the P2X4 KO mice. The impaired vascular remodeling resembled that observed in eNOS KO mice. These findings suggest that Ca\(^{2+}\) signaling of shear stress via P2X4 plays a crucial role in the control of vascular tone, and in blood flow-dependent vasodilation and vascular remodeling, through endothelial NO production.

**Tyrosine Kinase Receptors**

Activation of tyrosine kinase receptors, including VEGFR2 and the angiopeptin receptor, Tie-2, occurs in ECs exposed to shear stress, and the activation is assumed to be ligand-independent, because it occurs in the absence of VEGF or angiopeptin.\(^{83-86}\) We showed that shear stress induces ligand-independent phosphorylation of VEGFR2 in ES-cell-derived VEGFR2-positive cells. Although the mechanisms by which mechanical forces activate tyrosine kinase receptors are not well understood, mechanical forces may trigger dimerization of VEGFR2 monomers by affecting their spatial distribution in the cell membrane, or they may activate the receptors by changing their conformation and promoting the binding of tyrosine kinases, such as Src, that are capable of phosphorylating the receptors. Phosphorylation of these tyrosine kinase receptors leads to activation of various protein kinases, including ERK, JNK, PI3-kinase, and Akt, which results in eNOS activation and inhibition of apoptosis.

**G Proteins**

G-protein-coupled receptors (GPCRs) have been postulated to play a role in shear stress signal transduction.\(^{87,88}\) GPCR conformational dynamics in a single EC were detected by real-time molecular imaging using fluorescence resonance energy transfer, and shear stress was found to cause a conformational transition of bradykinin B2 GPCRs that led to activation of the receptors.\(^{89}\) Shear stress was also demonstrated to activate purified G proteins reconstituted in liposomes in the absence of receptor proteins, suggesting that G proteins themselves act as a primary mechanotransducer.\(^{90}\)

**Caveolae**

Caveolae are membrane microdomains measuring approximately 50–100 nm in length that are visible as flask-shaped invaginations below the surface of cells, and they contain many signaling molecules, including receptors, ion channels, and protein kinases.\(^{91}\) It has been well documented that caveolae play an important role in shear stress signal transduction.\(^{92-94}\) We have observed that flow-induced Ca\(^{2+}\) responses in ECs start at the caveolae and propagate through the entire cell in the form of a Ca\(^{2+}\) wave.\(^{95}\) The Ca\(^{2+}\) increase occurring in the vicinity of caveolae causes caveolae to rapidly liberate eNOS into the cytoplasm, where the activated eNOS catalyzes the production of NO. The role of caveolae and of caveolin-1 in shear-stress-mediated regulation of vascular functions has been assessed in caveolin-1 KO mice, which exhibit complete absence of caveolae in the vessel walls.\(^{96}\) The caveolin-1 KO mice are characterized by impaired blood-flow-dependent vascular remodeling and vasodilator responses in comparison with wild-type mice. These impairments are rescued by reconstituting caveolin-1 into the endothelium of the KO mice, suggesting that caveolae and caveolin-1 are involved in shear stress-mediated control of vascular functions.

**Adhesive Proteins**

It has been proposed that shear stress is transmitted from the apical surface of ECs through the cytoskeleton to points of attachment at cell–cell and cell–matrix adhesions, and if that is true, adhesive proteins may serve as mechanotransducers.

Integrins are transmembrane glycoproteins composed of \(\alpha\) and \(\beta\) subunits. Their extracellular domain binds directly to extracellular matrix proteins, and their cytoplasmic domains interact with many proteins aggregated at focal contacts, including both signaling molecules, such as focal adhesion kinase (FAK), Src family protein kinases, Fyn, and p130CAS, and cytoskeletal proteins, such as \(\alpha\)-actinin, vinculin, talin, tensin, and paxillin.\(^{97,98}\) Evidence has been found that shear stress activates integrins. When integrins are activated by shear stress, FAK, paxillin, c-Src, Fyn, and p130CAS are rapidly activated, thereby leading to the activation of Ras-ERK pathways.\(^{99,100}\) The results of experiments in which a magnetic twisting device was used to apply shear stress directly to cell surface integrins suggested that integrins are capable of functioning as mechanosensors and transmitting shear stress signals to the cytoskeleton.\(^{101,102}\)
Indeed, when integrins are twisted by magnetic microbeads coated with antibodies against integrins, cytoskeletal filaments become reoriented and a force-dependent cell stiffening response occurs.

Platelet adhesion molecule-1 (PECAM-1), a member of the immunoglobulin superfamily, is localized to the cell–cell borders of ECs, where it mediates leukocyte extravasation during the inflammatory response. A novel mechano-signaling pathway via PECAM-1 has been proposed. PECAM-1 is tyrosine that is phosphorylated within 30 s of the start of exposure to shear stress, and as a result the Ras signaling pathway is activated, leading to ERK activation. Similar signaling events occur when magnetic beads coated with antibodies against PECAM-1 are used to directly apply tugging force to PECAM-1 molecules on the EC surface. These results seem to indicate that PECAM-1 is a mechanosensitive molecule.

Cytoskeleton

Living cells stabilize their structure and shape by means of an interconnected network of cytoskeletal components that include microfilaments, microtubules, and intermediate filaments. The tensegrity cell model has been proposed to explain how mechanical forces are transduced into a biochemical response. The cell model is constructed with a series of isolated compression-resistant sticks that resist the pull of surrounding tensile strings and thereby create an internal pre-stress that stabilizes the entire network. When mechanical forces are applied to the tensegrity model, the structural elements rearrange without undergoing any topographical disruption or loss of tensional continuity, which may directly activate signaling molecules associated with the cytoskeleton. The cytoskeleton has been shown to play an important role in shear-stress-induced NO production and ICAM-1 gene expression by ECs.

Glycocalyx

The surface of ECs is covered with a layer of membrane-bound macromolecules that constitute the glycocalyx. The glycocalyx has been considered a possible shear stress sensor because it is located between the flowing blood and the cell membrane. Involvement of the glycocalyx in EC responses to shear stress has been demonstrated by the finding that degradation of hyaluronic acid glycosaminoglycans with hyaluronidase significantly decreases flow-induced NO production in isolated canine femoral arteries and by the finding that enzymatic removal of heparan sulfate with heparinase completely inhibits NO production in response to shear stress. Two possible mechanisms have been proposed to explain how the EC glycocalyx mediates shear stress mechanotransduction. One is that heparan sulfate proteoglycan is present as a random coil under no-flow conditions, but with increasing flow becomes unfolded into a filament structure. This conformational change is accompanied by an increase in binding sites for Na⁺ ions, and Na⁺ binding may trigger the signal transduction. In addition to glycocalyx-mediated regulation of the local concentration gradient and transport of ions, amino acids, and growth factors, it is also possible that shear stress is transmitted to the cell interior through the actin cytoskeleton or intracellular signaling molecules that directly associate with the core protein of the glycocalyx.

Primary Cilia

The presence of primary cilia with a rod-like, non-motile structure and protruding from the apical cell membranes has been reported in embryonic ECs, HUVECs, and human aortic ECs. Recent studies provide evidence that the primary cilia mediate the mechanism by which ECs sense and respond to shear stress. Because primary cilia are physically connected to cytoskeletal microtubules, their bending by flow is assumed to transmit shear stress signals into the cells through the cytoskeleton. The bending of the primary cilia may also activate Ca²⁺-permeable ion channels and trigger Ca²⁺ signaling. It has recently been shown that polycystin-1, an 11-transmembrane protein with a long extracellular domain, and polycystin-2, a member of the superfamily of trp channels, are localized on the cilia of ECs and together are involved in shear stress sensing. ECs in which polycystin-1 and polycystin-2 have been knocked out are unable to transduce shear stress into changes in intracellular Ca²⁺ concentration or to produce NO in response to shear stress.

Conclusion

A striking feature of shear stress mechanotransduction is that the shear stress activates a variety of membrane molecules and microdomains almost simultaneously, leading to signal transduction through multiple pathways. It should be noted in regard to shear-stress sensing by ECs that they are simultaneously exposed to both shear stress and cyclic strain in vivo. As a physical force, cyclic strain is roughly 10,000-fold greater than shear stress, and causes a large deformation of ECs that ranges from 5% to 10% at a frequency of approximately 1 Hz. Because this means that ECs would have to recognize shear stress while being greatly deformed by cyclic strain, it seems unlikely that ECs sense shear stress through integrins, the cytoskeleton, or unfolding of molecules directly caused by mechanical force. Unknown principles may be at work in the shear-stress sensing mechanisms. Recent studies have provided data suggesting that changes in the properties of the plasma membrane are involved in shear stress mechanotransduction. Plasma membrane fluidity has been shown to increase in response to shear stress. The response occurred within 10 s of the application of shear stress and is assumed to lead to activation of G-protein-coupled receptors. It has also been demonstrated that depleting cholesterol from the plasma membrane abolishes EC responses to shear stress, including ERK activation and eNOS activation. Shear stress may first modify the properties of the plasma membrane and then affect ion channels, receptors, adhesion proteins, and the phosphorylation status of signaling molecules.
Elucidation of the shear-stress-sensing mechanisms should lead to a better understanding of how blood flow regulates the circulatory system, how physical exercise exerts a beneficial effect on the human body, and how hemodynamic factors are involved in the pathophysiology of vascular diseases, including hypertension, thrombosis, aneurysms, and atherosclerosis.

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