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Shear stress-initiated signaling and its regulation of endothelial function

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Abstract

Atherosclerosis develops preferentially at branches and curvatures of the arterial tree, where blood flow pattern is disturbed rather than being laminar, and wall shear stress has an irregular distribution without defined directions. The endothelium in the atherosusceptible regions, in comparison to that in atheroresistant regions, shows activation of pro-proliferative and pro-inflammatory gene expressions, reduced production of nitric oxide (NO), increased leukocyte adhesion and permeability, as well as other atheroprone phenotypes. Differences in gene expressions and cell phenotypes have been detected in endothelia residing in native atherosusceptible and atheroresistant regions of the arteries, or in arteries from animal models with artificial creation of disturbed flow. Similar results have also been shown in *in vitro* systems that apply controlled shear stresses with or without clear directions to cultured endothelial cells (ECs) in fluid-dynamically designed flow-loading devices. The available evidence indicates that the coordination of multiple signaling networks, rather than individual separate pathways, link the mechanical signals to specific genetic circuitries in orchestrating the mechanoresponsive networks to evoke comprehensive genetic and functional responses.

Keywords

Shear stress; Mechanotransduction; Endothelial phenotype; Atherogenesis

1. Introduction

The interactions of blood flow with complex vessel geometry generate hemodynamic characteristics, including the heterogeneous spatial and temporal mechanical forces acting on the vessel wall. Vascular endothelial cells (ECs) covering the inner surface of blood vessels are constantly exposed to shear stress due to the frictional force created by the blood flow. ECs respond to the changes of local shear stress to modulate intracellular signaling,

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which leads to alterations of gene expression, cell morphology, and structural remodeling[1, 2].

The correlation of atheroma location and 'site-specific' endothelial dysfunctional phenotype with the non-laminar characteristics of blood flow and shear stress at curved regions, branch points, and bifurcations indicates that such disturbed flow patterns are atheroprone. At these atheroprone regions, the flow departs from pulsatile, unidirectional shear stress to create flow-separation zones that include flow reversal, oscillating shear stress and occasional turbulence[3]. In contrast, the shear stress in the straight atheroresistant part of the arteries is pulsatile and has well-defined directions. The shear stresses resulting from different flow patterns initiate differential steps of signaling events in the endothelium, including mechanosensing, intracellular transmission of stress, conversion of mechanical force to biochemical signals, and feedback mechanisms[3]. As a result, the endothelium develops different adaptive phenotypes to differentially react with other coexistent risk factors, such as high cholesterol, hypertension, obesity, diabetes, and smoking, to contribute to the site-specific susceptibility for the initiation and progression of atherosclerosis. The aim of this review is to provide a brief summary of the current knowledge with a focus on the shear stress-initiated signaling and its regulation of endothelial function and dysfunction, as well as the communication between ECs and other vascular cells. The pathologic implications in atherosclerosis and future perspectives are also discussed. The effects of fluid shear stress on endothelial gene expression and the functional consequences have been previously reviewed in depth (e.g., by Chiu and Chien[4] and Davies *et al*[2]).

2. Endothelial phenotypes in atherosusceptible regions *in vivo*

2.1 Endothelial phenotypes in native atherosusceptible regions

The earliest atherosclerotic lesions characteristically develop with focal patterns (i.e., preferentially at branches and curves of the arterial tree) where the local blood flow is disturbed[4]. The endothelium lining these atherosuscepetible regions have *1)* increased permeability to plasma macromolecules, *2)* increased turnover (proliferation and apoptosis), and *3)* increased adhesiveness for monocytes that attach and migrate into the arterial wall, with subsequent alterations in EC morphology and structure[4]. Changes in expression or activation of signaling and functional molecules have been observed in the endothelium of atherosclerotic plaques or atherosusceptible regions (e.g., inner curvatures of aortic arch or carotid bifurcations) as compared with non-lesion regions or the straight segments (e.g., the descending thoracic aorta). Examples of molecules involved include the vascular factors related to homeostasis: endothelial nitric oxide synthase (eNOS)[5], NF-E2-related factor 2 (Nrf2)[6], Kruppel-like factor 2 (KLF2)[7], pregnane X receptor (PXR)[8], AMP-activated protein kinases (AMPKs)[9], microRNA(miR)-10a[10], angiopoietin-2[11], as well as other factors related to stress-responses: platelet-derived growth factors (PDGFs) and their receptors[12], early growth response protein 1 (Egr-1)[13], nuclear factor-κB (NF-κB)[14-16], toll-like receptors (TLRs)[17], p21-activated kinases (PAK)[18], SHC (Src homology 2 domain containing) transforming protein 1 (Shc)[19], c-Jun N-terminal kinase (JNK)[20], x-box binding protein 1 (XBP-1)[21], histone deacetylase 3 (HDAC3)[22], bone morphogenetic protein-2/-4 (BMP2/4)[23, 24], Smad1/5[25], monocyte chemoattractant protein-1 (MCP-1)[26], intercellular

adhesion molecule 1 (ICAM-1)[27-29, 30], vascular cell adhesion protein 1 (VCAM-1)[28-30], and endothelial leukocyte adhesion molecule 1 (E-selectin)[27].

2.2 Endothelial phenotypes in experimental models of disturbed flow *in vivo*

Several animal models have been created to study the effects of disturbed flow with oscillatory and low shear stress on endothelial phenotypic responses. The strategies commonly employed to create disturbed flow are the following:

1. The introduction of a local stenosis by constricting a segment of a large vessel, such as the carotid artery or abdominal aorta of mice, rats or rabbits[31-33]. While ECs are well aligned and elongated in the direction of flow at the stenosis throat, where the flow is laminar with a relatively high shear stress, the cells immediately downstream to the stenosis throat are rounded and their proliferation is significantly increased[25] in this post-stenotic region with flow separation and low-velocity recirculation[31, 32]. The vascular endothelial (VE)-cadherin in endothelial adherens junctions[34] and the endothelial-protective KLF2[7] are highly expressed in ECs in regions with laminar flow, but not in the downstream regions with disturbed flow. In addition, bone morphogenetic protein receptor (BMPR)-specific Smad1/5 are found to be highly phosphorylated in ECs at poststenotic sites to cause cell cycle progression and cell proliferation[25].

2. The partial ligation of a carotid artery of rats or mice. In this model, the three branches (external carotid, internal carotid, and occipital) of one carotid artery are ligated and the superior thyroid artery is left intact, resulting in low and oscillating shear stress in the common carotid artery of the operated side[35]. The partial ligation down-regulates KLF2 and eNOS while up-regulating ICAM-1, VCAM-1, and BMP4, and it impairs endothelium-dependent vasorelaxation and induces atherosclerosis in ApoE$^{-/-}$ mice fed a high-fat diet [35].

3. The creation of an arteriovenous fistula (AVF). This is often created between the carotid artery and the jugular vein or between the femoral artery and the femoral vein of rats or larger animals such as rabbit or swine, with juxta-anastomotic AVF. The AVF causes low and oscillating wall shear stress in zones where flow stagnation occurs on the outer wall of the artery and on the inner wall of the juxta-anastomotic site[36, 37]. In the venous segment of the rat AVF model, MCP-1 mRNA and protein increase in both the ECs and smooth muscle cells (SMCs), accompanied by increased activities of the transcription factors NF-κB and AP-1[38]. In the swine AVF model, significant luminal stenosis and intima-media thickening are present as early as 28 days and 42 days post-surgery, respectively, in the juxta-anastomotic regions of the femoral artery and vein[37].

All the *in vivo* results indicate that flow patterns play significant roles in vascular homeostasis. The mechanotransduction mechanisms involved have been analyzed by using *in vitro* flow systems; where the mechanical stimuli applied can be controlled and the molecular and functional responses can be studied in detail.

3. Shear stress-induced signal transduction, gene expression, and phenotypic changes in ECs

3.1 Mechanosensing and signaling in ECs

In vitro investigations have shown that application of shear stress to ECs can activate multiple mechanosensors located at the cell membrane (the biomolecules that are the initial responders to the changes in mechanical environment to trigger mechanotransduction). These include integrins[39, 40], tyrosine kinase receptors (particularly vascular endothelial growth factor receptor-2, VEGFR-2)[41], G proteins and G protein-coupled receptors[42], ion channels[43], and intercellular junction proteins[44]. Other possible mechanosensors are local membrane structures such as caveolae, gap junctions, membrane lipids, and glycocalyx[45]. The mechanosensing, transmitted via adaptor molecules, triggers a cascade of signaling pathways and modulates the expression of functional genes (e.g., genes concerned with proliferation or growth arrest, inflammation or anti-inflammation, and many others). For example, integrins ($\alpha_v\beta_3$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, and $\alpha_6\beta_1$), which mediate the effects of shear stress on cytoskeletal proteins (e.g., actin filaments), typically trigger both outside-in and inside-out signals to transmit and modulate the tensions among focal adhesion sites, membrane receptors, and the extracellular matrix[1, 39, 40]. Integrin activation results in phosphorylation of focal adhesion kinase (FAK), Paxillin and p130CAS (Crk-Associated Substrate), and leads to the activation of mitogen-activated protein kinases (MAPKs) via Ras GTPase[46]. The activation of VEGFR-2 by shear stress results in its association with casitas B-lineage lymphoma (Cbl), VE-cadherin, β-cadherin associated protein (catenin), and phosphatidylinositol-3-kinase (PI3K) to phosphorylate the downstream Akt (protein kinase B, PKB) [41]. Shear stress regulates EC alignment and remodeling through the activation of Rho family GTPases (Cdc42, Rho, and Rac) that enhance the formation of stress fibers and focal adhesions, and regulates cytoskeletal reorganization[42, 47]. In addition, shear stress preferentially increases membrane fluidity at the upstream side of the ECs; this may induce the polarization of the cell and facilitate the lateral mobility of membrane proteins and enhance their interactions[45, 48]. Increasing evidence suggests that those mechanosensing and signaling mechanisms in ECs are not mutually exclusive, but are most likely interconnected. Recently, transmembrane proteins Piezo1 and Piezo2 have been identified as essential components of mechanically activated ion channels[49, 50] in many cell types and may also serve as novel mechanotransduction molecules in ECs. Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) have also been identified recently as nuclear relays of mechanical signals exerted by extracellular matrix (ECM) rigidity and cell shape[51]. Therefore, YAP/TAZ are suggested to serve as novel sensors and mediators of mechanical cues[51]. Investigations on the involvement and functions of Piezo and YAP/TAZ in shear stress-induced signaling in ECs may be an attractive direction for mechano-biochemical transduction research.

3.2 Shear stress-induced gene expression and functional consequences in ECs

eNOS is the essential molecule for the synthesis and release of the potent vasodilator, anti-oxidant and anti-inflammatory mediator: nitric oxide. Impaired expression of eNOS is a crucial element for fluid shear stress regulation of site-specific endothelial functional

phenotype. In both cultured ECs and intact vessels, atheroprotective laminar shear stress (LSS, mean stress ≥12 dyn/cm^2 without oscillation) upregulates the protein expression level and/or activity of eNOS[52, 53]. The mechanism responsible for shear stress-regulation of eNOS remains unclear despite some suggestions of regulatory pathways based on *in vitro* investigation. The well-characterized residues for flow-regulated eNOS phosphorylation are active sites Ser 1177, Ser 633, Ser 635, and inhibitory sites Tyr 657[54-57]. LSS stimulates Akt phosphorylation, which in turn phosphorylates eNOS at Ser 1177, leading to eNOS activation and NO production[54]. LSS also increases the expression of proline-rich tyrosine kinase 2 (PYK2) and its association with eNOS, which phosphorylates eNOS at the repressive Tyr 657 and hence decreases eNOS activity[56]. The PYK2-dependent inhibition of NO production may serve to balance the eNOS activity and to limit the detrimental over-production of NO, i.e., the generation of cytotoxic peroxynitrite. Another key molecule for vascular endothelial homeostasis is the Krüppel-like factor (KLF) family zinc finger-containing transcription factor. KLF2 is abundantly expressed in ECs and positively regulates eNOS expression. Atheroprotective LSS or pulsatile shear stress (PSS, mean stress ≥12 dyn/cm^2 with oscillation), but not atheroprone oscillatory shear stress (OSS, mean stress = 0∼0.5 dyn/cm^2 with oscillation), causes a sustained increase of the mRNA level of KLF2 via the mediation of the signaling cascade comprising of extracellular-signal-regulated kinase (ERK) 5, myocyte enhancer factor-2 (MEF2), AMPK, and/or miR-92a to result in increased eNOS expression[58, 59]. Other mechanisms contributing to shear stress-mediated eNOS expression and activation include protein kinase A (PKA)[55], NF-E2-related factor 2 (Nrf2)[60], SIRT1[57], and other HDACs (e.g., HDAC5)[61]. The interactions among these signaling pathways remain to be elucidated.

Increased expression of biomarkers such as MCP-1, ICAM-1, VCAM-1, and E-selectin are a hallmark of the endothelial inflammatory phenotype in atherosusceptible regions. The initial application of LSS to static ECs causes a brief Ras GTPase and MAPK activation, which leads to the transient MCP-1 gene expression; prolonged LSS, however, decreases Ras activity and MCP-1 expression[1]. Such repression of MCP-1 by sustained LSS may be due to the eNOS expression and NO production that inhibit protein kinase C (PKC)-ε and ERK 1/2 [62]. Furthermore, prolonged PSS induces the AMPK / poly [ADP ribose] polymerase 1(PARP-1) / B-cell lymphoma-6 (Bcl-6) pathway to inhibit expressions of VCAM-1, MCP-1, and MCP-3[63]. The Tie family of receptor tyrosine kinases (RTK) has been shown to contribute to the pro-inflammatory endothelial phenotype, as indicated by the findings that depletion of Tie1 augments the LSS-induced simulation of eNOS and -inhibitions of kappa B (I-κB) activity and ICAM-1 expression [64]. In contrast, OSS induces MCP-1 and VCAM-1 activities; these are mediated by the miR-21/peroxisome proliferator-activated receptor alpha (PPARα) /activator protein 1 (AP-1) cascade[65]. OSS induces a sustained miR-21 expression to inhibit PPARα translation, leading to the activation of AP-1 and its association with the promoter regions of MCP-1 and VCAM-1 to increase their expressions[65]. Flow-sensitive miR-10a has been demonstrated to provoke endothelial inflammation via NF-κB-mediated activation of MCP-1, VCAM-1, E-selectin, and Interleukins IL-6, and IL-8[10]. BMP-4 has been shown to exert proinflammatory effects on endothelium. OSS induces endothelial BMP-4 expression, which in turn activates ICAM-1 expression and monocyte adhesion through the production of reactive oxygen species (ROS)[66]. HDAC-3/5/7 have

been found to mediate the inductive effect of OSS on VCAM-1 expression[67]. A recent investigation shows that the application of OSS to ECs activates sterol regulatory element binding protein 2 (SREBP2) to induce NLRP3 inflammation, and hence the increased innate immunity to cause topographical distribution of atherosclerotic lesions[68].

Evidence from *in vivo* animal models, with the introduction of disturbed flow, suggests that increased EC proliferation is an early event of site-specific atherogenesis. *In vitro* studies verify that prolonged LSS or PSS reduces the number of ECs with bromodeoxyuridine (BrdU) incorporation and prevents ECs from entering S phase, with the majority of cells arrested in the G_0 or G_1 phase[69, 70]. In contrast, cells exposed to OSS, or at the disturbed flow reattachment area, have accelerated turnover rate with enhanced G_0/G_1-S transition[25, 26]. Among the important mediators involved in flow-regulated cell cycle progression are Smad1/5. Application of OSS to ECs causes the sustained phosphorylation of Smad1/5 through integrin/BMP receptor association and FAK/ERK cascade, resulting in activation of the mammalian target of rapamycin (mTOR)/p70S6 kinase, and leading to the up-regulation of cyclin A, down-regulation of p21 and p27, and consequential cell cycle progression[25, 71]. LSS stabilizes the tumor suppressor protein p53 and increases its phosphorylation by JNK, thus leading to the inhibition of EC growth[69]. LSS also increases the expression of the growth arrest proteins GADD45 (growth arrest and DNA damage inducible protein 45) and p21, and decreases the phosphorylation of the retinoblastoma (Rb), thus leading to cell cycle arrest[69]. MicroRNAs have been identified recently as important players in the regulation of endothelial proliferation under shear stress. We have shown with our collaborators that miR-19a[72] and miR-23b[70] mediate the LSS/PSS-induced cell cycle arrest via a decrease in E2F1 and hypophosphorylation of Rb, or directly targeting cyclin D1. All these findings demonstrate that shear flows with and without a clear direction differentially activate multiple signaling events to modulate EC growth (Fig. 1); these findings have helped to elucidate the molecular mechanisms underlying the focal nature of vascular diseases.

Shear stresses with different flow patterns induce differential gene expression and functional consequences via complex mechanisms, which also include redox regulation[73], endoplasmic reticulum-stress and protein unfolding[74], and lipid metabolism[75]. Systems biology approaches such as high-throughput transcriptomics, proteomics, and miR-omics have been employed to investigate the shear stress-induced gene expressions and the consequential phenotypes in ECs *in vitro* or *in vivo*[70, 76-79]. In an *in vitro* flow model, miR profiling in ECs showed that 21 miRs were differentially expressed (8 up- and 13 down-regulated) in response to 24 hours of PSS as compared to static condition[70]. In an *in vivo* disturbed flow model, 62 and 523 genes were found to change significantly in the endothelium of mouse carotid arteries by 12 hours and 48 hours after partial ligation, respectively[76]. This study led to the discovery of novel mechanosentitive genes, including LMO4 (LIM domain only 4), KLK10 (Kallikrein-related peptidase 10) and DHH (desert hedgehog) [76]. In native atherosusceptible and atheroresistant regions in porcine aorta, cDNA microarray was employed to study gene expressions in the endothelium, and ≈2,000 putatively differentially expressed genes were identified. Analyses of these differentially expressed gene indicated that atheroprone flow primes ECs toward inflammatory responses pending on other risk

factors [80].However, proteomics and other comprehensive system-wide analyses such as metabolomics in atherosusceptible endothelium are restricted by the limited size of the specimen within the hemodynamic regions of interest and potential inclusion of multiple cell types. It would be of interest to overcome these technical hurdles to gain comprehensive insights for vascular disease progression.

4. Shear stress-modulation of communication between ECs and smooth muscle cells

In vivo investigations with animal models have shown an accelerated neointimal hyperplasia of the vessels after disturbance or cessation of blood flow in comparison with shame-operated controls with normal blood flow[35, 81]. *In vitro* experiments corroborate and greatly extend the *in vivo* findings by showing that application of atheroprotective shear stress to ECs co-cultured with vascular smooth muscle cells (SMCs) causes phenotypic switch of SMCs from de-differentiation to differentiation, induces contractile marker expression, and inhibits SMC migration and proliferation[82-84]. In contrast, application of atheroprone shear stress to ECs decreases SMC contractile marker genes (e.g., smooth muscle α-actin and myocardin), and induces SMC proinflammatory phenotype (e.g., expressions of VCAM-1, IL-8, and MCP-1)[85]. Several secretory molecules that mediate the flow-regulated effects via ECs on SMC gene expression and phenotype have been documented, including NO[83, 86], prostacyclin (PGI2)[87], PDGF-BB and TGF-β1[88], and miRs[81, 89] (Fig. 2). MiR-143/-145 secreted by LSS-stimulated ECs have been shown to target gene expression and control phenotypes in co-cultured SMCs[89]. MiR-143/-145-containing extracellular vesicles derived from KLF2-expressing ECs can reduce atherosclerotic lesion formation in the aorta of $ApoE^{-/-}$ mice[89]. More recently, we also reported the findings of miRs in EC-SMC communication by showing that the endothelial miR-126/Argonaut 2 (Ago2) complex targets gene expression in the co-cultured SMCs to increase SMC turnover and that such effects are reduced by the application of atheroprotective LSS to ECs[81]. Systemic depletion of miR-126 in mice inhibited neointimal lesion formation of carotid arteries induced by cessation of blood flow[81]. These results suggest that the manipulation or interference of EC-secreted miRs provides a promising strategy to combat atherosclerosis.

Concluding remarks and perspectives

Hemodynamic forces can modulate the gene expression and phenotype of vascular ECs *in vitro* and *in vivo*. LSS and PSS that have well-defined directions are of utmost importance in maintaining vascular homeostasis. They activate signal transduction pathways and gene expression in ECs to suppress aberrant EC proliferation, inflammation, and atherosclerosis. In contrast, oscillating shear stress with a very low mean value and a reciprocating flow promotes atheroprone phenotype of ECs, with increases in EC proliferation, inflammation, leukocyte adhesion, lipoprotein uptake, and SMC migration and proliferation, thus contributing to atherogenesis. The diversity of endothelial functions is reflected in the variety of mechanisms of shear stress-induced signaling, and suggests that multiple mechanisms are coordinated in response to a given type of stimulus. A major challenge in this field is the integration of a large body of data on EC responses to shear stress with different flow patterns at the molecular level and the global scale to identify the shear stress-

specific endothelial gene expression and phenotype. System-targeted high-throughput sequencing with increasingly sophisticated statistical and bioinformatics analyses are of particular importance in determining the intercellular and intracellular flow-responsive networks. Comparisons of genomic, epigenomic, translational, and post-translational profiles in the atherosusceptible and atheroresistant regions of arteries *in vivo* will enable the identification of genes and regulatory networks that may have direct pathophysiological relevance to endothelial function in health and disease. Current analyses have suggested that endothelial phenotypes are highly heterogeneous over different regions of the arterial trees. Analyses on homogenates of endothelium may mask and neutralize the changes in cells of interests due to the presence of cells with different behaviors in neighboring locations. Therefore, spatial and temporal studies on genomic and/or epigenomic profiling at single cell level would be a fruitful future direction. In addition, other biochemical risk factors (e.g., cholesterol, glucose, as well as blood cells) may also play important roles in regulating EC function, in conjunction with hemodynamic regulators. The interplays between mechanical and biochemical factors in atherogenesis remain to be elucidated. Therapeutic application of the currently identified target biomarkers for atherogenesis should not focus only on signal molecules, but rather to consider also the possible involvement of multiple targets in a variety of fundamental cellular processes. An attractive therapeutical option is the combined targeting of multiple molecules in the same or opposite pathways to achieve synergistic effects.

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Significance

Atherosclerosis is associated with the patterns of blood fluid shear stress and the 'site-specific' endothelial phenotypes. The aim of this review is to provide a brief summary of the current knowledge with a focus on the shear stress-initiated signaling and its regulation of endothelial function, as well as the communication between ECs and other vascular cells. The pathologic implications in atherosclerosis and future perspectives are also discussed. This review highlights some of the recent progress that has been made in our laboratory and others in the field of mechano-signal transduction in endothelial biology and their potential impacts as well as challenges.

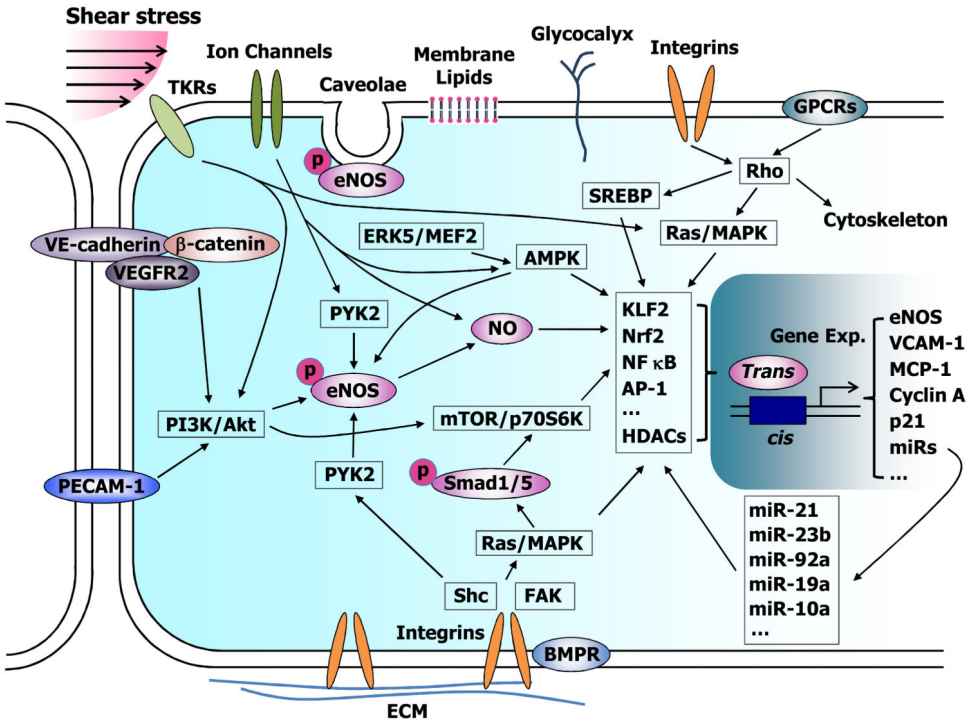

Figure 1.

Schematic diagram showing endothelial mechanotransduction and signaling induced by shear stress. Shear stress stimulates endothelial cells (ECs) through the activation of mechanosensors, including integrins, tyrosine kinase receptors (TKRs), G proteins and G protein-coupled receptors (GPCRs), ion channels, intercellular junction proteins (e.g., VE-cadherin and PECAM-1), caveolae, membrane lipids, and glycocalyx. These mechanosensors act through adaptor molecules (e.g., Shc) to trigger the activation of signaling molecules such as Ras, Rho, phosphatidylinositol-3-kinase (PI3K), and mitogen-activated protein kinases (MAPKs), which then activate eNOS, Smad1/5, and the transcription factors and cofactors (e.g., KLF2, NF kB, and AP-1) to regulate the expression of a number of functional genes such as eNOS, VCAM-1, and MCP-1, as well as microRNAs (miRs). This diagram illustrates that multiple signaling pathways coordinate to form mechanoresponsive networks to modulate EC phenotype and function.

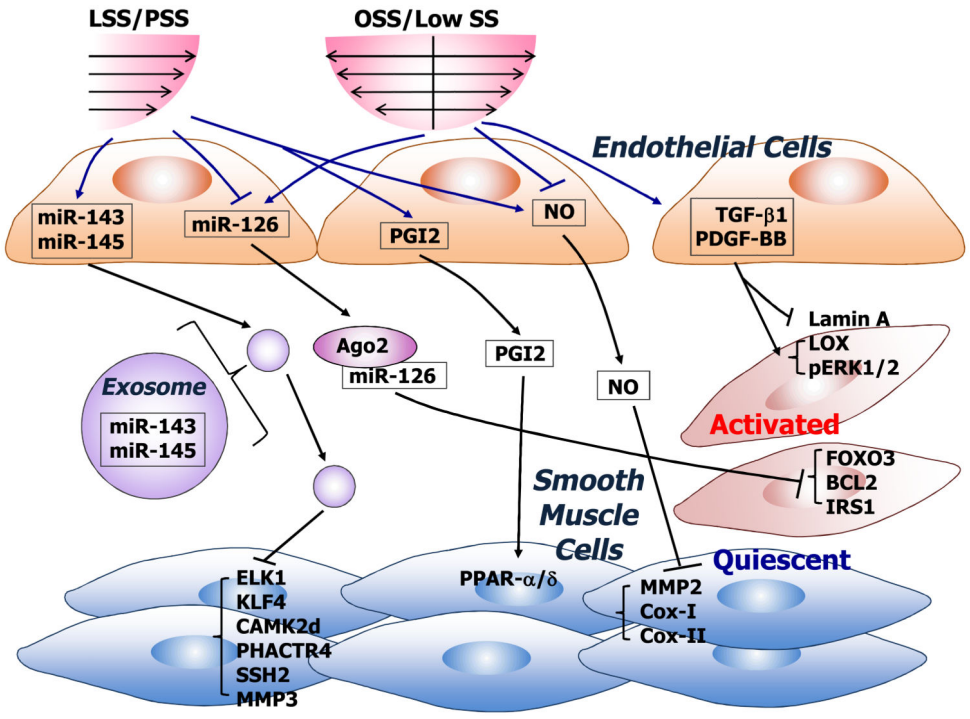

Figure 2.

Schematic diagram showing the modulation of gene expression and phenotype of smooth muscle cells (SMCs) by shear stress via ECs. Shear stress with sufficient magnitude and clear directions, i.e., laminar shear stress (LSS) and pulsatile shear stress (PSS), differ from that with a low magnitude and no clear direction, i.e., low shear stress and oscillatory shear stress (OSS) in their regulation of the release of secretory molecules such as NO, prostacyclin (PGI2), PDGF-BB and TGF-b1, and miRs. The uptake of NO, PGI2, and exosome-embedded miR-143/-145 by SMCs leads to functional targeting in SMCs with the promotion of a quiescent phenotype. In contrast, the PDGF-BB, TGF-b1, and Argonaute 2 (Ago2)-carried miR-126 released by ECs subjected to low shear stress or OSS induce an activated phenotype of SMCs.