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Mechanical forces and metabolic changes cooperate to drive cellular memory and endothelial phenotypes

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Abstract

Endothelial cells line the innermost layer of arterial, venous, and lymphatic vascular tree and accordingly are subject to hemodynamic, stretch, and stiffness mechanical forces. Normally quiescent, endothelial cells have a hemodynamic set point and become “activated” in response to disturbed hemodynamics, which may signal impending nutrient or gas depletion. Endothelial cells in the majority of tissue beds are normally inactivated and maintain vessel barrier functions, are anti-inflammatory, anti-coagulant, and anti-thrombotic. However, under aberrant mechanical forces, endothelial signaling transforms in response, resulting cellular changes that herald pathological diseases. Endothelial cell metabolism is now recognized as the primary intermediate pathway that undergirds cellular transformation. In this review, we discuss the various mechanical forces endothelial cells sense in the large vessels, microvasculature, and lymphatics, and how changes in environmental mechanical forces result in changes in metabolism, which ultimately influence cell physiology, cellular memory, and ultimately disease initiation and progression.

Keywords

endothelial cell metabolism; glycolysis; shear stress; oxidative phosphorylation; stiffness; barrier; inflammation; contraction

Introduction

The plasticity of cell types is a fundamental concern in biology, from differentiation of stem cells to tissue and organ specialization. Each of these processes relies on a combination of pre-programmed differentiation timing, paracrine chemical gradients, or membrane receptor clustering due to differential tension. This review is focused on the mechanical forces involved in metabolic signaling in endothelial cells especially as they relate to vascular disease and endothelial plasticity. Mechanical forces are involved in development but also in disease progression. In general, mechanical forces can be divided based on the tissue bed or the type of force, such as hemodynamic, stretch, and stiffness forces. As endothelial cells contract, migrate, signal inflammation, and possibly transdifferentiate into other cell types, they usually do so as a response to changes in mechanical forces, and coordinate

their metabolism to meet this plasticity need (Table 1). This underscores the significance of cellular metabolism to coordinate genetic changes with phenotypic changes.

Mechanotransduction in large vessels: blood flow and stiffness in the aorta

Macrovascular flow (vessels > 10 μm in diameter) is complex, varying in both space and time as vessel boundary conditions continuously change and heart pump strength is modulated dynamically by both neural and volumetric fluid inputs in a beat to beat fashion. Endothelial cells are subjected to shear stress from 10 to 50 dyne/cm^2 in large arteries (Paszkowiak & Dardik, 2003). Arterial flow can be classified into two classes: “atheroprotective” and “atheroprone” (Davies, 1995). Atheroprotective flow is unidirectional (“unidirectional flow”, UF) whereas atheroprone has no time-averaged direction but is instead chaotic and reminiscent of eddy currents or vortexes (“disturbed flow”, DF).

Aortic hemodynamics have been the most studied in the context of development (Combs & Yutzey, 2009; O’Donnell & Yutzey, 2020; Vermot et al., 2009) and atherosclerosis, as arterial branch points and vessel curvature result in disturbed flow, leading to coronary artery disease, aortic atherosclerosis, and carotid artery disease (Chiu et al., 2009; Davies et al., 2013) (Figure 1). Aortic and carotid hemodynamics have been modeled based on magnetic resonance imaging studies of flow, which are used in clinical practice (Ferdian et al., 2020), making *in vitro* study of flow-related changes in endothelial cell biology possible (Dai et al., 2004; Krause et al., 2018; Maurya et al., 2021; Parmar, 2005; C. Wu et al., 2015). In general, unidirectional flow results in elaboration of nitric oxide, barrier protection, and is protective against inflammation and thrombosis, whereas disturbed flow results in vessel constriction, permeable barriers, thrombotic pathways, and inflammatory signaling – hallmarks in the development of atherosclerosis. Although not discussed in detail here, vascular endothelial cells are also subjected to significant circumferential cyclic stretch (Fang et al., 2019). For instance, heart propulsions result in cyclic stretch in arterial endothelium and spontaneous respiration (or mechanical ventilation in critically ill patients) causes mechanical stretch of lung microvascular endothelium. Mechanotransduction through hemodynamics is mediated by transcriptional, posttranscriptional and epigenetic mechanisms and flow-sensitive transcription factors are instrumental to the endothelial responses to blood flow (Andueza et al., 2020; Krause et al., 2018; Ku et al., 2019; Nagel et al., 1999; Partridge et al., 2007; Peghaire et al., 2019; Zhou et al., 2014).

Microenviroemntal stiffness also plays a fundamental role in cell differentiation. Matrix stiffness properties *per se* can cause mesenchymal stem cell differentiation (Engler et al., 2006)- neuronal differentiation programs are activated on soft surfaces (0.1–1 kPa), whereas muscle or bone differentiation programs are activated by hard surfaces (10–100 kPa). Tissue culture plastic is in the ~10^6 kPa range. Thus, if not properly considered stiffness may cause experimental artifacts. Endothelial cells produce fold-changes in actin with increasing substrate stiffness (Byfield et al., 2009) and affects, for instance, leukocyte transmigration in *in vitro* studies (Stroka & Aranda-Espinoza, 2011). Like flow, mechanotransduction by stiffness sensors causes nuclear translocation of transcription factors.

Matrix stiffness and disturbed flow work in tandem, amplifying disease processes. Stiffer vessels could lead to increased flow and/or reduced pulsatility, which is particularly harmful

to endothelial cells in the brain vascular bed. Vascular stiffening is by itself sufficient to explain primary hypertension (Pettersen et al., 2014). In the systemic arterial circulation, increased vascular stiffness is associated with and precedes systemic hypertension (Beltran, 2001; Pettersen et al., 2014), and is a predictor of cardiovascular morbidity (Benetos et al., 2012; Smulyan et al., 2016) and mortality (Laurent et al., 2001).

Vascular stiffening is also pathological in the pulmonary circulation and microvasculature. Increased macrovascular stiffness promotes microvascular damage (Cardoso & Salles, 2016; Cooper et al., 2018; Mitchell, 2008) and therefore end-organ damage through dysregulated transmission of hemodynamics from large vessels and stiffness-dependent control of RhoA GTPase activity, permeability, and inflammation (Birukova et al., 2013; Mambetsariev et al., 2014; Meng et al., 2015). Besides arterial hypertension, microvascular stiffness in the pulmonary circulation has been identified as an independent cause of mortality in pulmonary hypertension (Campo et al., 2010; Gan et al., 2007; Hunter et al., 2008; Mahapatra et al., 2006; Thenappan et al., 2016). Current standard of care antihypertensive treatment is thought to have an anti-stiffness component (Y. Chen et al., 2017) and improves mortality (Brunström & Carlberg, 2018).

Mechanotransduction in microvasculature and lymphatics.

The microvasculature is composed of capillaries. The lung has the most microvasculature (vessel diameter 10 μm or less) in the body, as its estimated capillary surface area is roughly 50–70 m^2, which is 20-times that of all other vessels (Albertine, 2016; Weibel, 1973). Lung microvascular ECs are subjected to shear stress, which has profound consequences to microvascular barrier function (Adamson et al., 2013; R.-T. Huang et al., 2017; Ostrowski et al., 2014) and production of reactive oxygen species (Milovanova et al., 2006). Shear stress in the microvasculature can theoretically be higher than in large vessels since shear stress is inversely proportional to the 3rd power of vessel radius and only linearly dependent on flow rate. However, shear stress is not a precisely measured quantity in the microvasculature since vessel diameter can be equal to or even smaller than the diameter of a red blood cell. Besides subjected to shear stress, ECs in the lungs are also exposed to copious – and possibly injurious stretch during mechanical ventilation – due to the respiratory cycle.

Lymphatic flow is even slower than microvascular flow, averaging 0.64 dyn/cm^2 with peaks of 4–12 dyn/cm^2 (Dixon et al., 2006). Mechanotransduction and mechanosensation are less well-developed in understanding compared to the microvasculature and large vessels. However, mechanotransduction is important in lymphatic development especially valve formation and lymphatic plexus development (Sweet et al., 2015).

Lung endothelial cells are also subject to regulation of substrate stiffness. Traction forces are estimated to be much higher – typically ~5 kPa (Balaban et al., 2001) and artery wall strains ~100 kPa (Humphrey et al., 2014). This is important in pulmonary hypertension and chronic fibrotic lung diseases.

Macrovascular flow and metabolism

Cross-talk between mechanotransduction, metabolism, and disease has been most studied using *in vitro* models of large vessel hemodynamics and animal model correlates. Endothelial cells are mostly glycolytic with a relatively small contribution of ATP generation from oxidative phosphorylation, and exhibit the Warburg effect, or, utilization of glycolysis in the presence of high concentrations of oxygen (De Bock et al., 2013; Doddaballapur et al., 2015; B. Kim et al., 2017; D. Wu et al., 2017). However, mechanical forces including shear stress and surface stiffness are able to dynamically modulate metabolism by changing the proportion of ATP produced by oxidative phosphorylation (Feng et al., 2017; D. Wu et al., 2017). The metabolic activity and throughput of glycolysis and the TCA cycle have profound effects on endothelial cell physiology. In this section, we will mainly focus on atherosclerosis as the disease phenotype to summarize the metabolic regulation due to blood flow and shear stress in arterial beds. We will divide these metabolism pathways/substrates into glycolysis, mitochondria, fatty acids, and amino acids. Veins and valve formation are less well studied, especially in the context of endothelial metabolism; however, venous valve formation is under the control of lymphangiogenesis genes (Bazigou et al., 2011).

Glycolysis

Blood flow/shear stress regulates glycolysis through, at least partially transcription factors Krüppel-like factor-2 (KLF2), hypoxia inducible factor-1α (HIF-1α) and Yes-associated protein (YAP) with PDZ-binding motif (TAZ). KLF2 expression is significantly up-regulated by arterial-levels of shear stress and is anti-angiogenic, barrier protective, and anti-inflammatory and protective against atherosclerosis and acute lung injury (Atkins & Jain, 2007; Dekker et al., 2002; R.-T. Huang et al., 2017; Lin et al., 2005, 2010). HIF family of transcription factors are regulated by targeting for degradation via hydroxylation by prolyl hydroxylases (PHDs), which are sensitive to oxygen concentration (Prabhakar & Semenza, 2012; Semenza, 2012) as well as the shear stress (D. Wu et al., 2017). The Hippo pathway involving transcriptional co-activators YAP/TAZ are also flow responsive (K.-C. Wang et al., 2016; L. Wang et al., 2016) and stimulate metabolism (refs). Glycolysis is reduced by unidirectional flow in a KLF2-dependent manner, while induced by disturbed flow mainly in a HIF-1α (Doddaballapur et al., 2015; Feng et al., 2017; D. Wu et al., 2017) and YAP/TAZ -dependent manner (K.-C. Wang et al., 2016; L. Wang et al., 2016). Microvascular endothelial KLF2 expression was markedly reduced in critically ill acute respiratory distress syndrome (ARDS) patients infected with SARS-CoV-2 (Lee et al., 2021, p.). COVID-19-induced inflammation is also reported to suppress endothelial KLF2 expression, possibility contributing to the endothelialitis (S. Xu et al., 2021).

KLF2 reduces endothelial glycolysis through transcriptional repression of HK2 and PFKFB3—KLF2, induced by unidirectional flow, inhibits endothelial glucose uptake and glycolysis (Doddaballapur et al., 2015; Parmar, 2005; D. Wu et al., 2017). Both RNA silencing of KLF2 in cultured human umbilical vein endothelial cells (HUVECs) and endothelial-specific KLF2 deletion in mouse increased glycolysis as measured by extracellular acidification rate, whereas KLF2 overexpression reduced extracellular

acidification rate (Doddaballapur et al., 2015) and recapitulated the inhibitory effect of unidirectional flow on EC glycolysis (D. Wu et al., 2017). Glycolytic-suppression due to KLF2 is mainly through transcriptional suppression of key glycolytic enzymes including hexokinase 2 (HK2) and 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase-3 (PFKFB3) (Doddaballapur et al., 2015). HK2 catalyzes the phosphorylation of glucose, the rate-limiting and first committed step in glycolysis. PFKFB3 is an allosteric activator of phosphofructokinase (PFK) in the second rate-limiting reaction of glycolysis. Both of these steps are the ATP consuming reactions constituting the "investment" phase of glycolysis prior to the ATP producing steps. Decreasing HK2 (P. Yu et al., 2017) and PFKFB3 (Schoors et al., 2014; Y. Xu et al., 2014) in endothelial cells both led to reduced glycolysis and impaired proliferation. In addition to reducing proliferation, endothelium-specific PFKFB3 knockout suppressed the development of pulmonary hypertension by reducing inflammation and leukocyte adhesion (Cao et al., 2019). Also, pharmacological inhibition of PFKFB3 in high fat diet-fed $LDLR^{-/-}$ mice attenuated atherosclerosis progression and increased plaque stability, indicating an atherogenic role of this DF-induced glycolytic gene (Poels et al., 2020). In addition to KLF2, KLF4 was recently reported to suppress glycolysis in vascular endothelium under pulsatile shear stress (Y. Han et al., 2021).

KLF2 shunts glycolytic intermediates for production of glycocalyx—Besides its transcription suppression on these glycolytic enzymes, KLF2 also reduces glycolysis by inducing the biosynthesis of hyaluronan, the major structural component of glycocalyx on endothelial cell surface (G. Wang et al., 2020). Glycocalyx serves as an important structure on the surface of endothelial cells for sensation of shear stress generated by blood flow (Fu & Tarbell, 2013; Pries et al., 2000; Tarbell & Ebong, 2008; Zeng & Tarbell, 2014). The thickness of endothelial glycocalyx is associated with local shear stress (Lewis et al., 1982; van den Berg et al., 2006). Using both cultured HUVECs and *Apoe*$^{-/-}$ mouse model, Wang et al., showed that laminar shear stress induces endothelial cells to produce thicker coating of glycocalyx on the luminal surface. Specifically, this shear stress-induced hyaluronan production is through KLF2-dependent hyaluronan synthase 2 (HAS2) expression and UDP-sugar availability. KLF2 not only directly induced the transcription of HAS2, but also indirectly shuttles the glycolysis pathway (by inhibition of PFKFB3) into hexosamine- and glucuronic acid biosynthesis pathways (G. Wang et al., 2020). Consequently, the biosynthesis of UDP-GlcA and UDP-GlcNAc was increased, serving as substrates for hyaluronan production (G. Wang et al., 2020). In addition to acting as a mechano-sensor, glycocalyx also prevents endothelial permeability (Curry & Adamson, 2012; Tarbell, 2010), suppresses leukocyte-endothelium adhesion (Lipowsky, 2011; Tarbell & Ebong, 2008), and maintains potassium channel activation by blood flow (Fancher et al., 2020).

Disturbed flow-induced HIF-1α increases endothelial glycolysis—HIF-1α is associated with atherosclerosis formation by enhancing endothelial cell inflammation, proliferation, and monocytes adhesion (Akhtar et al., 2015; Feng et al., 2017; D. Wu et al., 2017, p. 1). Disturbed flow (DF) activates HIF-1α to increase endothelial metabolism beyond its baseline high glycolysis (Feng et al., 2017; D. Wu et al., 2017). There are three mechanisms which have been demonstrated related to DF-induced HIF-1α activation: (1) transcriptionally, HIF-1α is upregulated by nuclear factor NF-κB (Feng et al., 2017);

(2) post-translationally, HIF-1α protein is stabilized by deubiquitinating enzyme Cezanne (Feng et al., 2017), and also (3) post-translationally, HIF-1α is stabilized by reactive oxygen species (ROS) produced by NAD(P)H Oxidase-4 (NOX4) (D. Wu et al., 2017). HIF-1α promotes endothelial glycolysis by upregulating a cohort of glycolytic genes including lactate dehydrogenase A (LDHA), glucose transporter-1 (SLC2A1/GLUT1), HK2, PFKFB3, and probably additional glycolytic genes as the glycolysis and angiogenesis gene sets have a high degree of overlap (Feng et al., 2017; D. Wu et al., 2017). Furthermore, DF-induced HIF-1α can shift the fate of pyruvate towards glycolysis away from TCA cycle by enhancing the transcription of pyruvate dehydrogenase kinase-1 (PDK1) (J. Kim et al., 2006; D. Wu et al., 2017). HIF-1α-driven glycolytic reprogramming is required for the disturbed flow-induced endothelial inflammation and excessive proliferation, leading to atherosclerosis formation (Feng et al., 2017; D. Wu et al., 2017). Endothelial specific knockout of HIF-1α suppressed DF-induced atherosclerosis in *Apoe*$^{-/-}$ mice (Feng et al., 2017); similarly, knockdown of SLC2A1 reduced DF-induced HIF-1α expression and EC inflammation (D. Wu et al., 2017). Interestingly, HIF-1α and KLF2 are counter-regulated: KLF2 has been shown to disrupt binding between HIF-1α and its chaperone HSP90 (Kawanami et al., 2009). This suggests that there are possibly two exclusionary metabolic poles which define the metabolic state of aortic endothelial cells.

Disturbed flow-induced YAP/TAZ increases EC glycolysis—YAP/TAZ are transcriptional co-activators that bind primarily to enhancer elements by interacting with TEAD factors, effectors of the Hippo dependent pathway (or Hippo independent). YAP/TAZ plays a major role in transduction of mechanical signals from actin to the nucleus. YAP and TAZ have been shown to be activated in epithelial, fibroblast, endothelial cells, oncogenesis, neurons, and stem cells (Y.-A. Chen et al., 2019; Furukawa et al., 2017; Lian et al., 2010; F. Liu et al., 2015; Totaro et al., 2017).

YAP/TAZ are regulated by mechanical stimuli including shear stress (Halder et al., 2012; K.-C. Wang et al., 2016; L. Wang et al., 2016; Zhu et al., 2021). Disturbed flow increases while unidirectional flow reduces YAP/TAZ activity in endothelial cells (K.-C. Wang et al., 2016; L. Wang et al., 2016). High shear stress activates endothelial integrin and promotes integrin-Gα13 interaction, which inhibits RhoA, leading to YAP/TAZ phosphorylation thus inactivation (L. Wang et al., 2016, p.). Reduced endothelial YAP/TAZ activity has been further suggested to downregulate the expression of pro-inflammatory genes, reduce monocytes adhesion and infiltration (K.-C. Wang et al., 2016; L. Wang et al., 2016) and retard endothelial proliferation (K.-C. Wang et al., 2016), one mechanism of which is through suppression of Jun Kinase (JNK) activity (L. Wang et al., 2016). Furthermore, both *in vivo* blockade of YAP/TAZ activity either by CRISPR-Cas9-mediated endothelial-specific YAP knockdown (L. Wang et al., 2016) or by translational inhibition using morpholino oligo (K.-C. Wang et al., 2016) can reduce the atherosclerotic plaque size in hyperlipidemic *Apoe*$^{-/-}$ mice. These findings indicate that YAP/TAZ activity is partially responsible for the disturbed-flow induced atherosclerosis.

YAP/TAZ is also a key regulator of metabolism. YAP/TAZ plays an important role in the metabolism of many cell types, and acts both as an energy-sensor and energy-regulator (Koo & Guan, 2018). In brief, YAP/TAZ activity is activated when nutrient supply is sufficient,

and YAP/TAZ activity will in turn promote glycolysis, glutaminolysis, anapleurosis, and lipogenesis to regulate cell growth and homeostasis (Koo & Guan, 2018). YAP/TAZ has also been shown to regulate endothelial metabolism. RNA interference of YAP/TAZ in HUVECs decreases both glycolysis and mitochondria oxidative phosphorylation. In addition, brain endothelial cells from YAP/TAZ endothelial cell-specific knockout mice showed downregulation of genes that are involved in glycolytic and the OXPHOS pathway (J. Kim et al., 2017). Furthermore, YAP/TAZ induced endothelial glycolysis is dependent on MYC, another potent glycolysis transcription factor (J. Kim et al., 2017). Moreover, in addition to disturbed flow, YAP/TAZ is activated by increased matrix stiffness (see below, section on pulmonary vasculature). Notably, atherosclerosis lesions are also very stiff (Kohn et al., 2015).

In bone endothelial cells, YAP1/TAZ was found to repress the pro-angiogenic activity of HIF-1α, suggesting that the relationship between YAP/TAZ and HIF-1α is tissue-specific or dependent on the local chemical/mechanical microenvironment (Sivaraj et al., 2020), as in cancer cells, YAP/TAZ helps stabilize HIF-1α, preventing the latter's degradation (see below). Furthermore, whereas HIF-1α in HAECs was found to drive glycolysis and suppress oxidative phosphorylation (D. Wu et al., 2017), YAP/TAZ was found to stimulate both glycolysis and oxidative phosphorylation (Bertero et al., 2016), which suggests that HIF-1α may specifically reprogram endothelial cell metabolism for migration or inflammation, whereas perhaps YAP/TAZ stimulates endothelial cells for both migration and growth.

In cancer cell types, YAP/TAZ has been shown to increase glycolysis by binding to transcription factors and promoting glucose transporter expression. YAP/TAZ drives glycolysis by increasing lncRNA BCAR4 to increase Hedgehog signaling which promotes HK2 and PFKFB3 transcription (Zheng et al., 2017). YAP/TAZ also recruits HIF-1α at pyruvate kinase M2 (PKM2) gene promoter to enhance its transcription (Jia et al., 2019), and binds to HIF-1α to prevent HIF-1α degradation (X. Zhang et al., 2018). Transcriptomics data suggested that zebrafish embryos lacking YAP has reduced mRNA of glucose transporters SLC2A1 and SLC2A2, causing decreased glucose uptake to support nucleotide synthesis (Cox et al., 2018). In cancer cells, YAP/TAZ enhances SLC2A1 membrane translocation in an AKT-dependent manner (White et al., 2019). Additionally, YAP/TAZ/TEAD complex can promote HEK293A cells glycolysis via increasing the transcription of the SLC2A3. Knocking down SLC2A3 in cells with constitutively active YAP can partially reverses glucose uptake and lactate production (W. Wang et al., 2015).

It is noteworthy that SLC2A1 and SLC2A3 are the most highly transcribed glucose transporters in human aortic endothelial cells (D. Wu et al., 2021). SLC2A3 regulates thrombin-induced endothelial glycolysis burst and its endothelial-specific overexpression results in mouse aorta leakiness (D. Wu et al., 2021). Therefore, it would be reasonable to hypothesize and interesting to explore if disturbed flow-induced YAP/TAZ also acts as a transcriptional activator of SLC2A1/3 in endothelial cells, contributing to the glycolysis-driven atherosclerosis burden.

Endothelial cell glycolysis can play pro- and anti-atherogenic roles—Although many of the abovementioned studies revealed that disturbed flow-induced endothelial

glycolysis is detrimental to vascular health, interestingly, Yang et al. demonstrated a beneficial role of a glycolytic regulator protein kinase AMP-activated (AMPK) in protection against atherosclerosis (Q. Yang et al., 2018). Disturbed flow increased the expression of AMPK in endothelial cells both *in vitro* and *in vivo*. Selectively deleting endothelial PRKAA1, the major catalytic subunit of AMPK in vascular cells, reduced endothelial cell glycolysis and proliferation, while aggravating atherosclerosis formation in hyperlipidemic mice. In addition, overexpressing SLC2A1 rescued the impaired glycolysis in PRKAA1-deleted endothelial cells and reversed the severity of atherosclerosis, suggesting that reduced endothelial glycolysis was partially responsible for promoting atherosclerosis (Q. Yang et al., 2018). However, excessive glycolysis also triggered atherosclerosis as evidenced by overexpression of SLC2A1 in PRKAA1-intact endothelium, which increased plaque size in the partial ligation mouse model (Q. Yang et al., 2018). Thus, disturbed flow-induced endothelial glycolysis can play a double-edged sword in atherogenesis, emphasizing the importance of metabolic tuning in endothelial phenotype and therapeutic targeting. It is also important to note that the completed deletion of a metabolic enzyme, although instrumental to demonstrate the causality in animal models, rarely occurs in humans during the pathophysiological processes.

Oxidative phosphorylation

Studies from our lab and others have collectively shown that disturbed flow reduces, whereas unidirectional flow increases oxidative phosphorylation in cultured HAECs (B. Kim et al., 2014; D. Wu et al., 2017, p. 1). This is in accordance with *in vivo* data which demonstrated that increased vascular shear stress boosted mitochondrial health in rodents (B. Kim et al., 2014; J.-S. Kim et al., 2015). The unidirectional flow-induced OXPHOS in endothelial cells could be dependent on transcription factors KLF2/4. KLFs may be responsible for the unidirectional flow-increased mitochondria biogenesis in endothelial cells and other cell types (B. Kim et al., 2014; Liao et al., 2015). In addition to KLFs, the expression and activity of deacetylase sirtuin 1 (SIRT1) is also enhanced by unidirectional flow and induces mitochondria biogenesis (Z. Chen et al., 2010; J.-S. Kim et al., 2015). Unidirectional flow may also induce endothelial OXPHOS through degrading HIF-1α, as HIF-1α has been shown to promote the transcription of PDK1, which phosphorylates and suppresses pyruvate dehydrogenase (PDH) to catalyze glucose-derived pyruvate into acetyl-CoA entering TCA cycle (J. Kim et al., 2006; D. Wu et al., 2017, p. 1). Furthermore, HIF-1α has also been shown to attenuate OXPHOS through inhibiting mitochondria complex 1 activity (Tello et al., 2011).

YAP signaling also induces OXPHOS in endothelial cells. Inhibition of YAP/TAZ in HUVECs markedly reduced OXPHOS along with decreased glycolysis (J. Kim et al., 2017). YAP/TEAD1 complex enhanced mitochondria biogenesis and oxygen consumption to support HUVECs angiogenesis, which is through promoting the transcription of peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC1α) (Mammoto et al., 2018).

A recent paper reported that plasma membrane cholesterol also plays a role linking shear stress to OXPHOS in cultured human pulmonary aortic endothelial cells (Yamamoto et

al., 2020). Shear stress reduced plasma membrane cholesterol both through efflux and internalization, leading to increased OXPHOS. Similarly, depleting membrane cholesterol using methyl-β-cyclodextrin (MβCD) mimicked shear stress-induced mitochondria ATP production, whereas addition of cholesterol to cells suppressed this shear stress-induced OXPHOS, suggesting a novel flow-activated OXPHOS mechanism mediated by membrane cholesterol (Yamamoto et al., 2020).

Nevertheless, cultured endothelial cells only generate ~15% ATP through oxidative phosphorylation, indicating that instead of as a major energy source, mitochondria in endothelial cells may play a more vital role as an organelle for signaling and metabolic intermediates production (Quintero et al., 2006). These signaling functions of endothelial mitochondria include maintaining Ca^{2+} homeostasis and regulating oxidative stress (X. Tang et al., 2014). It is worthwhile to note that multiple *in vivo* studies have suggested that increased shear stress in major vessels improves mitochondrial function (B. Kim et al., 2014; J.-S. Kim et al., 2015).

Shear stress regulates mitochondrial fusion and fission

Mitochondria are highly dynamic organelles that frequently undergo fusion and fission. Fusion and fission are important for their proper cellular distribution, inheritance of mtDNA, energy production and removal of their dysfunctional companions by mitophagy (Westermann, 2010), and are highly responsive to environmental stress (Youle & van der Bliek, 2012). In general, fusion is beneficial to complement partially dysfunctional mitochondria by mixing their contents to meet increased energy demands, whereas fission helps quality control by eliminating damaged mitochondria and promotes apoptosis (H. Chen & Chan, 2009; Y. J. Liu et al., 2020; Suárez-Rivero et al., 2016).

Shear stress has also been shown to regulate mitochondria dynamics in endothelial cells. Unidirectional flow promotes mitochondria health often by inducing mitochondria fusion, compared to disturbed flow (Chehaitly et al., 2021; L.-H. Wu et al., 2018). Unidirectional flow upregulates mitochondria fusion protein optic atrophy protein 1 (OPA1) and mitofusin 2 (MFN2) (Chehaitly et al., 2021; L.-H. Wu et al., 2018) while downregulates mitochondria fission dynamin-related protein 1 (DRP1) (Chehaitly et al., 2021) and mitochondria fission 1 (FIS1) protein (L.-H. Wu et al., 2018). Consistently, the translocation of fission protein DRP1 from cytosol to mitochondria is decreased in response to laminar shear stress. *In vivo* studies reported in an abstract seem to support this observation in mouse aorta; when compared to aortic area subjected to high shear stress, inner curvature exposed to disturbed flow had reduced OPA1 and increased DRP1 (Chehaitly et al., 2021). On the contrary, short-term laminar shear stress promoted mitochondria fission in both HUVECs and bovine aortic endothelial cells (BAECs) compared to static conditions (Bretón-Romero et al., 2014). This UF-induced mitochondria fission is dependent on enhanced translocation of DRP1 to the mitochondria membrane and the increased intracellular Ca^{2+} level (Bretón-Romero et al., 2014). Interestingly, this transient mitochondria fission induced by UF is also accompanied by reduced mitochondria bioenergetics and increased ROS production (Bretón-Romero et al., 2014). Whether the degree or time-dependence is a factor in these conflicting results is unclear.

DRP1 inhibition reduces endothelial inflammation. Interestingly, in the diabetic *Apoe*$^{-/-}$ mouse model, inhibiting DRP1 using mitochondria division inhibitor 1 improved endothelial function, reduced inflammatory makers (VCAM-1 and ICAM-1) expression and attenuated the development of diabetic-induced atherosclerosis, suggesting mitochondria fission contributes to atherogenesis in diabetes (Q. Wang et al., 2017). Moreover, inhibiting DRP1 in cultured rat aortic endothelial cells reduced TNFα-induced NF-κB activation, VCAM-1 expression and leukocyte adhesion (Forrester et al., 2020). Heterozygous DRP1-deficient mice and endothelial-specific DRP1 silencing showed reduction in inflammatory leukocyte adhesion (Forrester et al., 2020). Chehaitly et al also reported that in high fat diet-fed LDLR$^{-/-}$ mice with OPA1 or DRP1 heterozygous deletion, LDLR$^{-/-}$ OPA1$^{-/+}$ mice aggravated while LDLR$^{-/-}$ DRP1$^{-/+}$ attenuated atherosclerosis plaque formation when compared to wildtype mice (Chehaitly et al., 2021). Beyond global knockout model, it would be interesting to adopt mice with endothelium-specific mitochondria dysregulation, to further dissect the role of mitochondria fusion and fission in the context of atherogenesis in response to hemodynamic forces.

Ca^{2+} signaling—Intracellular calcium ion, or $[Ca^{2+}]_i$, acts as a key second messenger in endothelial cells in regulation of migration, proliferation, inflammation, vasodilation and cell survival (Antoniotti et al., 2003; Dalal et al., 2020; Fiorio Pla et al., 2012, p. 4; Sessa, 2005; Tsai et al., 2014; Yokota et al., 2015). An irregular endothelial $[Ca^{2+}]_i$ could lead to a variety of pathological consequences including impaired angiogenesis, barrier integrity and vasodilation (Dalal et al., 2020; Seeley et al., 2013; Yokota et al., 2015). It has been widely accepted that shear stress regulates intracellular calcium level in endothelium (James et al., 1995; Scheitlin et al., 2016; Yamamoto et al., 2000, 2018). One contributing mechanism is mediated by shear-sensitive potassium channels. In endothelium, unidirectional shear stress significantly increased the activity of inwardly rectifying potassium channels (Kir) which maintain the endothelial membrane potential, the major driving force of endothelial Ca^{2+} influx (Fancher & Levitan, 2020, p.; Fang et al., 2005, p. 2, 2006; Hoger et al., 2002; Olesen et al., 1988). Impairments of endothelial Kir channels resulted in endothelial dysfunction and vascular pathology *in vitro* and *in vivo* (Ahn et al., 2017; Boriushkin et al., 2019; Fancher et al., 2020; Mohler et al., 2007).

Shear stress was shown to induce $[Ca^{2+}]_i$, which was mainly from the uptake of extracellular Ca^{2+}(Mendoza et al., 2010, pp. 4-; Yamamoto et al., 2000), release from the endoplasmic reticulum (Jafarnejad et al., 2015; Melchior & Frangos, 2012), and release from mitochondria (Scheitlin et al., 2016), the second largest Ca^{2+} storage organelles in the cell. Besides their direct role in calcium release and uptake, mitochondria may also control endothelial calcium level through releasing ATP to induce the extracellular Ca^{2+} entry (Yamamoto et al., 2000) or ER-stored Ca^{2+} flux (C. Wilson et al., 2019).

The presence of ATP has been shown to be required for sustained induction of intracellular calcium in cultured BAECs in response to shear stress (James et al., 1995). When exposed to shear stress, cultured human pulmonary artery endothelial cells (HPAECs) induced mitochondria ATP production, which triggered caveolae ATP release, thus activating P2X4 and P2Y2 receptors-mediated extracellular calcium uptake (Yamamoto et al., 2000, 2018). This purinergic receptors-regulated calcium influx was shown to be required for

shear stress-mediated eNOS activation, PECAM-1 and VEGFR-2 phosphorylation. Mice with endothelial-specific P2Y2 deficiency showed impaired flow-induced vasodilation and hypertension (S. Wang et al., 2015).

Endothelial mitochondria can mediate $[Ca^{2+}]_i$ level through their own Ca^{2+} flux. In cultured HUVECs, mitochondria are important for shear stress-induced $[Ca^{2+}]_i$ transients, and are essential to induced $[Ca^{2+}]_i$ oscillation (Scheitlin et al., 2016). One proposed mechanism of mitochondria-controlled $[Ca^{2+}]_i$ is due to the Ca^{2+} uptake/release by mitochondria would alter local Ca^{2+} level to either activate or deactivate the IP3 receptor-mediated ER Ca^{2+} release, leading to subsequent Ca^{2+} oscillation (Scheitlin et al., 2016). This regulation was further shown to be dependent on the mitochondria calcium uptake/release but not on ATP production, since knocking down of mitochondria Ca^{2+} uniporter or inhibiting electron transport chain using Antimycin A, but not with ATP synthase inhibitor, was able to prevent the shear stress-induced intracellular calcium transients/oscillation (Scheitlin et al., 2016). However, how this ATP-independent while mitochondria Ca^{2+}-mediated endothelial $[Ca^{2+}]_i$ homeostasis contributes to vascular dysfunction has not been studied, and it would be informative to further investigate the cell signaling role of mitochondria in regulating disturbed flow-induced atherosclerosis.

Fatty acid uptake and oxidation—Vascular endothelial cells are exposed to plasma free fatty acids, the metabolism of which is regulated by shear stress, and ultimately occurs in the mitochondria. Fatty acids play an important role regulating endothelial functions such as inflammation, NO production and insulin signaling, contributing to pathologies of CVDs including atherosclerosis (A. Ghosh et al., 2017; X. L. Wang et al., 2006). Endothelial cells rely on passive diffusion or fatty acid translocase to import fatty acid from plasma into the cells for fatty acid oxidation (FAO) (Harjes et al., 2016). Multiple unbiased -omics studies suggest shear stress regulates lipid metabolism in endothelial cells. Using proteomics approach in HUVECs, it was discovered that high shear stress induced proteins participating in lipid metabolism including lipid transport, oxidation, catabolism and biosynthesis (Venturini et al., 2019). Specifically, atheroprone low shear stress reduced the membrane fraction of LDLR in cultured HUVECs compared to high shear stress (Venturini et al., 2019). This reduced membrane localization of LDLR is due to its hypo-glycosylation modification (immaturity) induced by low shear stress, thus causing LDLR to accumulate around the nuclei (Venturini et al., 2019). In support of this, metabolomics data showed that HUVECs exposed to low shear stress compared to high shear stress had downregulation of lipids and lipid metabolites (Venturini et al., 2019). In parallel, untargeted lipidomics in cultured HPAECs demonstrated the alteration of global lipid profile induced by shear stress (Hirata et al., 2021). Specifically, compared to static conditions, high shear stress upregulated ether-containing lipids, which is responsible for attenuating the phorbol 12-myristate 13-acetate (PMA)-induced VCAM-1 expression (Hirata et al., 2021).

Furthermore, several flow-sensitive genes/pathways regulate fatty acid metabolism in endothelial cells. For instance, NOTCH1 signaling is activated by unidirectional flow (Mack et al., 2017), and NOTCH1 signaling has been shown to promote FAO through transcriptional activation of carnitine palmitoyltransferase 1A (CPT1A) (Kalucka et al., 2018). On the contrary, DF has been shown to induce endothelial fatty acid synthesis

through sustained activation of sterol regulatory element binding transcription factor 1 (SREBP1), which enhances the transcription of HMG-CoA synthase and fatty acid synthase genes (Y. Liu et al., 2002). In concert, SREBP1 can also be increased by YAP/TAZ signaling to facilitate lipid accumulation (Aylon et al., 2016, p. 2). Expression of CD36, a scavenger receptor and fatty acid transporter, was markedly up-regulated in endothelium subjected to disturbed flow (Le Master et al., 2018), although the role of CD36 in flow-regulated fatty acid uptake remains to be determined.

In summary, these studies indicated that UF induced FAO while DF preferentially promoted lipid synthesis and accumulation in endothelial cells, suggesting a relevant role of lipid metabolism in mechanosensing and possibly mechanotransduction. Together, these data indicate that lipid metabolism is dynamically regulated in endothelial cells by different types of hemodynamic flows, which may contribute to the flow-regulated endothelial phenotypes.

FAO is dynamically modulated in endothelial cells to maintain their functions. Endothelial FAO is essential for supplementing dNTP synthesis for maintaining endothelial DNA replication and angiogenesis (Schoors et al., 2015). In addition, FAO has also been shown to benefit redox homeostasis through NADPH regeneration, thus protecting quiescent endothelial cells from oxidative-stress exposure (Kalucka et al., 2018). Inhibiting CPT1A has been shown to induce endothelial cell permeability *in vitro* and blood vessel leakage *in vivo* (Patella et al., 2015).

Another unconventional role of FAO is to regulate endothelial to mesenchymal transition (EndMT). EndMT has been considered as an atherogenic phenotype of endothelial cells and has been shown to drive atherogenesis (P.-Y. Chen et al., 2015; Evrard et al., 2016). It is widely accepted that disturbed flow induces EndMT (Andueza et al., 2020; P.-Y. Chen et al., 2015; Moonen et al., 2015), but the specific mechanism has not been well elucidated. FAO can restrain EndMT by maintaining the acetyl-CoA pool for the post-translational inhibition of the mesenchymal marker SMAD7 (Xiong et al., 2018). Inhibiting FAO in mice by endothelium-specific CPT2 deletion promoted EndMT through thickening of heart valves and increasing permeability in multiple vascular beds, suggesting the critical role of FAO in maintaining EC identity and vascular homeostasis (Xiong et al., 2018). Therefore, it is reasonable to hypothesize that FAO also acts as a metabolic link to regulate the DF-induced EndMT.

Fatty acid synthesis—In contrast to FAO, fatty acid synthesis is upregulated by DF (Y. Liu et al., 2002); however, it has not been elucidated how this DF-induced FA synthesis contributes to EC function and the atherogenic phenotype. Nevertheless, studies in other cell types have provided possible hypotheses linking FA synthesis to EC function. In cardiomyocytes, fatty acids prevented HIF-1α stabilization by decreasing succinate concentration thus enhancing HIF-1α hydroxylases (Dodd et al., 2018), suggesting that fatty acids synthesis may be beneficial to endothelium exposed to disturbed flow. On the other hand, in cancer cells, blocking monounsaturated fatty acids synthesis by inhibiting stearoyl-CoA-desaturase 1 (SCD1) reduced YAP/TAZ stabilization and nuclear localization (Noto et al., 2017), indicating fatty acid synthesis may also contribute to the hyperglycolytic phenotype of endothelium exposed to disturbed flow.

Amino acids

Glutamine is the most abundant amino acid in human plasma (Newsholme et al., 2003; Williamson & Brosnan, 1974). Glutamine serves as a major carbon source for TCA cycle in endothelial cells which contributes to EC proliferation both *in vitro* and *in vivo* (H. Huang et al., 2017; B. Kim et al., 2017). One mechanism on the glutamine-dependent EC proliferation is due to it serves as the precursor to synthesize asparagine, which is needed for protein synthesis in support of angiogenesis (H. Huang et al., 2017; Pavlova et al., 2018). Besides protein synthesis, glutamine is also important for maintenance of EC redox homeostasis by producing the antioxidant glutathione (DeBerardinis & Cheng, 2010). In addition, glutamate generated by glutamine is subsequently converted to ornithine for the synthesis of polyamine and nitric oxide, which is a critical regulator of vasodilation and angiogenesis (Kucharzewska et al., 2010; Tousoulis et al., 2012). Although glutamine is an important amino acid in ECs, its regulation by shear stress has not been thoroughly investigated. Interestingly, stiffness-activated YAP/TAZ has been shown to stimulate the transcription of glutaminase (GLS1), the first enzyme that catabolizes glutamine to glutamate and ammonia (Bertero et al., 2016). Whether a similar mechanism exists by disturbed flow-activated YAP/TAZ is unclear.

L-arginine can be converted by eNOS to synthesize NO and citrulline in vascular endothelial cells (Palmer et al., 1988). eNOS can be both transcriptionally activated (Davis et al., 2001, 2004; Tao et al., 2006), stabilized (Davis et al., 2001) and post-translationally phosphorylated by shear stress at various serine residues (Boo, Hwang, et al., 2002; Boo, Sorescu, et al., 2002), leading to increased NO production. Argininosuccinate synthetase 1 (ASS1) catalyzes the penultimate step of L-arginine synthesis, and ASS1 is transcriptionally upregulated in HUVECs subjected to high shear stress, compared to static conditions (McCormick et al., 2001; Mun et al., 2009). RNA interference of ASS1 impaired NO production in bovine aortic endothelial cells (Goodwin et al., 2004), suggesting that ASS1 takes on an essential mechano-sensitive role in key endothelial functions.

In summary, unidirectional flow is associated with an oxidative phosphorylation/ mitochondrial phenotype – promoting mitochondrial fusion, biogenesis, fatty acid uptake, oxidation, and glutamine uptake for anaplerosis and nitric oxide production. In contrast, disturbed flow is associated with a glycolytic phenotype, mitochondrial fission, and fatty acid synthesis. The metabolic switch in disturbed flow promotes atherosclerosis,

Microvasculature flow and metabolism

Capillary beds

In animal models of sepsis, microvascular flow becomes disturbed or oscillatory (De Backer et al., 2002). Microvascular flow is important in brain vascular and ear development (Q. Chen et al., 2012; D. Wu et al., 2011). Microvasculature-mitochondrial dysfunction is a well-known consequence of sepsis, resulting in dysregulated NO production, glycocalyx shedding, and barrier dysfunction (Miranda et al., 2016). Clinical therapies are focused on restoring appropriate blood flow to the capillary beds, but whether flow has a direct effect on microvascular metabolism remains poorly understood.

Brain and kidney endothelial cells—In addition to capillaries and lymphatics, different organs have distinct microvascular beds with their own metabolic specialization (Kalucka et al., 2020). Liver ECs have discontinuous basement membranes for passage of macromolecules whereas brain ECs have a tight blood brain barrier. Kidney ECs are specialized for blood filtration. Unsurprisingly, EC shear stress responsiveness in the various tissue beds has a different shear stress set point (Baeyens et al., 2015). In the brain microvasculature, physiologic shear (10–20 dyn/cm^2) upregulates expression of tight junction markers such as ZO1 and Claudin-5. However, excessive shear (40 dyn/cm^2) and/or pulsatility decreased their expression to basal levels and altered EC junctions morphology (Colgan et al., 2007; Garcia-Polite et al., 2017). This suggests a mechanism whereby atherosclerosis (increased stiff vessels) and hypertension predispose the microvasculature to endothelial dysfunction. In the brain, this would manifest as strokes. From a metabolic standpoint, measurements of glucose consumption versus lactate production showed that shear stress negatively modulated the glycolytic bioenergetic pathways of glucose metabolism in favor of the more efficient aerobic respiration and increased synthesis of TCA cycle genes (Cucullo et al., 2011). Thus, shear stress' effect on brain endothelial cells metabolism seems similar to HAECs (Doddaballapur et al., 2015; D. Wu et al., 2017).

Renal endothelial cells are very metabolically heterogeneous depending on their proximity to arterial oxygen and water deprivation (Dumas et al., 2020). The metabolism of renal endothelial cells is likely dominated by limited delivery of oxygen. Much like other endothelial cell types, nitric oxide production and permeability of glomerular endothelial cells are regulated by laminar shear stress (Bevan et al., 2011). In contrast to lymphatic ECs (discussed below), renal endothelial cells may be subjected to true hypoxia with $pO_2 < 20$ mm Hg (Neuhofer & Beck, 2005). Mixed venous pO_2 never reaches below 75 mm Hg in normal situations; thus, venous blood is rarely truly hypoxic. Interestingly, whereas HAECs are to some degree HIF-1α dependent for increased glycolysis in response to hypoxia in large vessels (D. Wu et al., 2017), renal ECs (and perhaps other microvasculature) also are in part dependent on SIRT3-dependent HIF-2α, in addition to HIF-1α, for glycolysis (He et al., 2017; Nauta et al., 2017).

Pulmonary vasculature—Microvascular flow dysfunction is probably prevalent in the lung. Lung diseases such as pulmonary fibrosis, acute lung injury in addition to pulmonary hypertension all have microvascular dysfunction involving pressure changes in the pulmonary vasculature due to either chronic hypoxic vasoconstriction, chronic thromboembolism, vascular obliteration due to plexiform lesions, vascular apoptosis, or heart failure causing pressure back up.

In human pulmonary microvasculature, metabolism through the HIF-2α pathway plays a role in the development of pulmonary hypertension and resolution of acute lung injury (Cowburn et al., 2016; M. C. Ghosh et al., 2021; Gong et al., 2015; C.-J. Hu et al., 2019; H. Tang et al., 2017); however, the role of HIF-2α in pulmonary microvascular mechanotransduction is unknown (in HAECs, disturbed flow also induces HIF-2α, although the consequence of this has not been studied (D. Wu et al., 2017)). Activation of HIF-2α also leads to upregulation of arginase II and ultimately lowers arginine availability for NO production, which probably occurs in the kidney microvasculature (Krotova et al., 2010).

Impairment of fatty acid synthase leads to HIF-1α de-stabilization, a reduction in HIF-1α-mediated changes in glucose transport and metabolism, and eNOS function restoration, suggesting that the inhibition of fatty acid synthesis may be beneficial for EC function in hypoxia (Singh et al., 2017). Other impacts of hypoxia, such as activation of HIF-1α, dysregulated nitric oxide and pulmonary artery metabolism, and endothelial-mesenchymal transition can be found in this review (D. Wu & Birukov, 2019).

Other endothelial beds—Retinal endothelial cells also require some degree of shear stress for quiescence involving the nitric oxide pathway (Ishibazawa et al., 2011; Lakshminarayanan et al., 2000), with lower shear stress upregulating proinflammatory pathways (Ishibazawa et al., 2013). As retinal angiogenesis is a critical factor in diabetic retinopathy (and serves as a model for developmental angiogenesis), the role of metabolism and flow-limited delivery of oxygen in retinal endothelial cell biology is ongoing (X. Han et al., 2019); like in other endothelial beds, disturbed flow likely simulates pathways mimicking hypoxia. In liver, sinusoidal endothelial cells are known to be mechanically responsive to shear stress (Braet et al., 2004), and express many classical mechano-sensitive receptors and transcription factors, but whether there is a connection to metabolism is unknown (Soydemir et al., 2020).

Lymphatics

LECs have similar metabolism to arterial-derived endothelial cells and are highly glycolytic with low mitochondrial oxidative phosphorylation in culture (De Bock et al., 2013). In some respects, this is less surprising than arterial endothelial cells, as lymphatic vasculature has about 15–60 mm Hg pO_2 compared with 80–110 mm Hg pO_2 in arterial circulation(Barankay et al., 1976; Witte et al., 1967). Furthermore, lymphatic fluid has glucose concentrations that are similar or slightly higher than arterial blood (Hendrix & Sweet, 1917). However, pO_2 limitations for mitochondria function are thought to be < 1 mm Hg and lactate production from end organs (as a sign of oxygen-limited ATP production) is thought to occur only below pO_2 values of ~15 mm Hg (Koike et al., 1994; Richmond et al., 1997; Wasserman, 1999). Therefore, it is likely that in all cases oxygen supply to the lymphatic vasculature is enough to power oxidative phosphorylation, suggesting that the Warburg effect is indeed present in lymphatic ECs, as in arterial and venous.

LECs are mechano-sensitive to hemodynamics. Low, oscillatory shear stress is sufficient to induce GATA2-FOXC2, which is a key transcriptional pathway for lymphatic vessel maturation (Sweet et al., 2015) and valve formation (Sabine et al., 2012, 2015). PROX1, another transcription factor marker for lymphatic endothelial cells, can be abolished with high amounts of shear stress (C.-Y. Chen et al., 2012). Loss of GATA2 results in lymphedema (Emberger syndrome) (Kazenwadel et al., 2015, p. 2). In LECs, the mechanosensation mechanism is thought to be through PECAM1 sensation of shear stress, phosphorylation of VEGFR2/3 which activated PI3K/AKT signaling and are held together by VE-Cadherin in the plasma membrane. Deletion of any of these components leads to lymphatic valve loss and is dependent on mechanosensation (Hägerling et al., 2018; Tzima et al., 2005; Y. Wang et al., 2016; Y. Yang et al., 2019).

During development, LEC glycolysis is critical for vasculogenesis. HK2 is essential for glycolysis. Knockout of HK2 in an endothelial cell-specific manner leads to impaired EC proliferation and migration. FGF regulates c-MYC which in cooperates with HIF-1α and regulates HK2 (J. Kim et al., 2007; Mathupala et al., 2001; P. Yu et al., 2017).

Lymphangiogenesis is also dependent on fatty acid oxidation. FAO flux in LEC is higher than in other endothelial cell types (Wong et al., 2017). Besides for energy supply, FAO are used for nucleotide synthesis in ECs (Schoors et al., 2015). Interestingly, PROX1 regulates lymphatic cell identity by causing epigenetic changes through histone acetylation via upregulation of CPT1A expression, which increases acetyl coenzyme A production, which is dependent on fatty acid oxidation (Wong et al., 2017).

Study addressing the intersection of metabolism and mechanotransduction in LECs is in its infancy. LECs from lambs exposed to increased pulmonary lymph flow are hyperproliferative, have increased expression of HIF-1α and its target genes, and demonstrate altered central carbon metabolism *in vitro* (Boehme et al., 2021).

Stretch and metabolism

Stretch is an especially important mechanical factor in lung microvascular endothelial cells. Physiologic levels of cyclic stretch are essential for endothelial homeostasis (Lehoux & Tedgui, 1998); excessive stretch leads to apoptosis and expression of inflammatory factors (Fang et al., 2019). This is an especially important topic in the pandemic era as excessive lung distention is still thought to be responsible for excess mortality during mechanical ventilation (Li et al., 2011), despite current lung protective strategies (Amato et al., 2015; The Acute Respiratory Distress Syndrome Network, 2000). From a metabolic standpoint, mitochondria are especially affected by excess stretch. Mitochondria anchor to the cytoskeleton and release ROS in response to cytoskeletal strain (Ali et al., 2006). This suggests that in endothelial cells, mitochondria and cytoskeleton together serve as a united mechanosensor and mechanotransducer (Ali et al., 2004). In a novel cellular glucose sensor experiment, it was found that glucose utilization is reduced under stretched state in endothelial cells (Peng et al., 2021). New devices that can simultaneously visualize externally applied stretch (Poulin et al., 2018) and detect single-cell metabolism (D. Wu et al., 2021) can better clarify the relationship between stretch and metabolism.

Mechano-sensitive transcription factors YAP may be active in stretch in addition to stiffness (see below). Interestingly, YAP may act to prevent stretch induced cell injury of ECs. Surprisingly, YAP knockout exaggerated vascular endothelial (VE)-cadherin phosphorylation, downregulation of vascular endothelial protein tyrosine phosphatase (VE-PTP), and dissociation of VE-cadherin and catenins following mechanical ventilation, causing endothelial barrier failure (Su et al., 2021). Although stretch is a constant feature of endothelial cells in the vasculature, its effects on cell metabolism remain under-investigated.

Stiffness and endothelial cell metabolism

As the cytoskeleton is connected to focal adhesions, it is not surprising that they play a large role in sensing stiffness. The cytoskeleton transmits the stiffness signal through

YAP and TAZ. Endothelial cells also demonstrate a strong cell shape dependence in their phenotype that is driven by surface stiffness and extracellular matrix contact (C. S. Chen, 1997). YAP/TAZ activates downstream pathways that are known to increase fibrotic pathways resulting in the synthesis of extracellular matrix (Totaro et al., 2018). The precise mechanosensing mechanism that transmits the signal from cell sensing of substrate stiffness to YAP and TAZ is poorly understood.

The cytoskeleton plays a critical role in force transmission as the nuclear translocation of YAP/TAZ was mitigated by inhibitors of non-muscle-myosin II in a study on matrix stiffness and its effects on the transcriptional output of epithelial cells (Dupont et al., 2011). Interestingly, osmotic forces affect intracellular crowding and stiffness, which in turn affects cell differentiation (Guo et al., 2017), and can cause both nuclear translocation (Hong et al., 2017) and phase separation of YAP, which when condensed are active sites of gene transcription in HEK293 cells (Cai et al., 2019). It remains to be seen if these affects play out in endothelial cells.

The cytoskeleton engages in mechanical-metabolic crosstalk through YAP/TAZ. Pulmonary vascular stiffness causes YAP to bind to GLS1 promoter sequence in response to matrix stiffening, and hence conversion of glutamine to glutamate in pulmonary artery endothelial cells. As glutamate enters the TCA cycle as alpha-ketoglutarate, YAP/TAZ therefore stimulates synthesis of biosynthetic growth and proliferation intermediates (Bertero et al., 2016). YAP also increases transcription of LDHA to promote glycolysis and cell migration (Bertero et al., 2016). YAP/TAZ accelerates lipid accumulation via activation or dysregulation of SREBP2 (Aylon et al., 2016; Jeong et al., 2018).These growth signals are thought to drive the plexiform lesions and thickening of the vasculature leading to the clinical phenotype found in pulmonary hypertension. Furthermore, YAP/TAZ coordinates EC proliferation and metabolic activity by upregulating MYC signaling (J. Kim et al., 2017).

In vascular development, YAP/TAZ promotes cell migration and barrier function by linking mechanical signals with bone morphogenetic protein (BMP) signaling to establish functional network formation of blood vessels during angiogenesis (Neto et al., 2018). BMP family regulates VEGFR2 and NOTCH signaling via TAZ-Hippo pathway (Pulkkinen et al., 2021). Furthermore, YAP/TAZ constrain HIF-1α target gene expression *in vivo* and *in vitro*. Surprisingly, YAP/TAZ suppresses bone angiogenesis in hypoxia (Sivaraj et al., 2020). Upstream kinase signaling components of YAP/TAZ (such as Wwc2, which activates LATS) are also critical for vascular development (Hermann et al., 2021, p. 2). YAP and TAZ are also important for lymphatic plexus patterning and postnatal lymphatic valve maintenance by negatively regulating PROX1 (Cho et al., 2019).

YAP/TAZ and stiffness are instrumental to endothelial-adjacent cells in the microvasculature. YAP is induced after injury and promotes wound healing (proliferation, migration) which provides evidence for tension sensing at wound fronts (Kimura et al., 2016; X. Wang et al., 2012). Stiffness-activated YAP/TAZ has also been found to regulate metabolism in fibroblasts (cancer-associated) by increasing glutamine metabolism in response (Bertero et al., 2019). Matrix sensing/remodeling is responsible for smooth muscle growth in pulmonary hypertension models (Bertero et al., 2015; Dieffenbach et al.,

2017; Kudryashova et al., 2016) and *in vitro* models of idiopathic pulmonary fibrosis (F. Liu et al., 2015). Interestingly, YAP inhibition causes resolution of scars and prevent the formation of keloids, an excessive scarring process (Mascharak et al., 2021).

Cytoskeletal regulation of metabolism

In addition to external mechanical forces, metabolism is regulated cell-autonomously by internal mechanical cues largely in response to cytoskeletal remodeling. ATP and GTP hydrolysis drive actin and tubulin filamentation; ATP hydrolysis drives myosin-dependent formation of actin stress fibers in many cell types. Thus, it is not surprising that changes in cell internal mechanics through cytoskeletal reorganization can autonomously regulate metabolism and energy production.

The cytoskeleton can regulate energetic demand by sequestering enzymes that can regulate glycolysis. Tripartite motif containing-21 (TRIM21) is sequestered by F-actin, which hides a protease that degrades phosphofructokinase (PFK), making it more active (Park et al., 2020). Glycolytic enzymes aldolase A has a catalytic site right next to its actin binding site (J. Wang et al., 1996). Filamentation of actin is therefore thought to regulate aldolase A activity (J. Wang et al., 1997). Insulin-dependent activation of PI3K/PIP3 recruits and activates Rac which promotes actin fiber monomerization, causing release of aldolase A which increases glycolysis (H. Hu et al., 2016).

Cells exhibit structural and functional compartmentalization of ATP production

The cell has segregated pools of energy production and consumption and is far from equilibrium. The nucleus has its own pool of glycolytic enzymes (Y. Liu et al., 2018; Vega et al., 2016; H.-J. Wang et al., 2014, p. 5; Yalcin et al., 2009) (most of uncertain function (Boukouris et al., 2016)) and can perform glycolysis on its own (Rechsteiner & Catanzarite, 1974; Siebert & Humphrey, 2006). In dividing hepatocytes, glycolysis is more active in the nucleus than in the cytosol (Kuehl, 1967). Data suggest that plasma membrane Na/K ATPase is tightly coupled with cytoplasmic glycolysis and receives almost no ATP from mitochondria (Sepp et al., 2014). Structural barriers prevent free diffusion of ATP in muscle cells (Vendelin et al., 2004). Muscle cells exhibit regular patterns of glycolytic enzymes that align spatially and functionally with sarcomeres (Sullivan et al., 2003; Wojtas et al., 1997). Spermatozoa have glycolytic enzymes regularly organized along flagella and exhibit cytoplasmic droplets enriched with glycolytic enzymes which and are critical for sperm maturation (Yuan et al., 2013). Studies in red blood cells, which lack mitochondria, suggest that glycolytic proteins compartmentalize near the plasma membrane and that their subcellular organization is important for the regulation of cellular cation pumps (Chu et al., 2012; Mercer & Dunham, 1981).

Stress affects the spatial distribution of glycolytic enzymes. Hexokinase (HK) exists in both cytoplasmic and mitochondrial membrane bound phases(Roberts & Miyamoto, 2015; J. E. Wilson, 1978). HK transits to its membrane bound form during periods of ischemia (Knull et al., 1973, 1974). In this way, cells use spatial distribution to control enzyme function: diversion of critical glycolytic intermediates may be used to prevent intracellular

competition for ATP (Ottaway & Mowbray, 1977) or to divert energy between anabolic or catabolic processes (John et al., 2011).

Several glycolytic enzymes were among the first actin-binding proteins identified (Masters, 1984), which suggests an intimate relationship between cytoskeletal organization and energy production (Pagliaro, 1995). Glycolytic enzyme aldolase has separate sites for actin binding and isomerase activity; reorganization of cytoskeleton is thought to activate glycolysis by freeing aldolase from its bound state (H. Hu et al., 2016; Lew & Tolan, 2013). Aldolase and other glycolytic enzymes glyceraldehyde 3-phosphate dehydrogenase (GAPDH), pyruvate kinase (PK), and lactate dehydrogenase (LDH) also bind to tubulin; binding of these enzymes to tubulin cytoskeleton changes their activity *in vitro* (Kovács et al., 2003; Marmillot et al., 1994; Volker et al., 1995), suggesting active cytoskeletal regulation of glycolysis.

Teleologically, these observations fit a globally parsimonious view of cellular energy production/consumption as (some) cells do not have excess pools of freely diffusing ATP and in fact have developed sophisticated mechanisms to sense energy stress, demand, and anabolic requirements (Hardie et al., 2012; Herzig & Shaw, 2018; J. Kim & Guan, 2019; Saxton & Sabatini, 2017). Whether these observations can be applied to ECs is unknown.

Subcellular metabolic heterogeneity in migrating ECs

More recently, “glycolytic metabolons” have been suggested in ECs. An enrichment of glycolytic enzymes such as PFKFB3 in lamellipodial ruffles may drive increased ATP in the lamellapodia, which may in turn drive migration (De Bock et al., 2013; Eelen et al., 2018). In thrombin-stimulated endothelial cells, glycolysis is more active near the contracting lamella and co-localizes with actin turnover, which again suggests cell autonomous subcellular organization of energy production (D. Wu et al., 2021). Targeting local ATP supply with ATP/ADP exchange enzyme adenylate kinase-1 enhances cell migration in embryonic fibroblasts (van Horssen et al., 2009).

The cytoskeleton regulates glycolysis in response to increased energy demand and cell migration—Obeying basic laws of physics, there is a strong correlation between cellular work (distance migrated) and cellular energy production (Kondo et al., 2021; D. Wu et al., 2021). In breast cancer cells, cellular ATP/ADP ratio correlates with leader-cell invasion (J. Zhang et al., 2019). Furthermore, in cell migration, there is acute energy demand that should be heterogeneous within a cell, as some parts of a cell active extend while other part are stationary. It follows that there should be a way to upregulate energy intake at the subcellular level. Using single cell metabolism assays, it was recently discovered that RhoA in response to thrombin stimulus stimulates SLC2A3 to uptake more glucose in HAECs. The resultant glycolysis is spatially heterogeneous within a cell and only occurs in areas of the cell which are actively contracting (D. Wu et al., 2021). Interestingly, intracellular pH, which is largely determined by the subcellular glycolytic rate, is regulated by integrin-mediated cell spreading, and thus cellular tension may also regulate metabolism autonomously (Schwartz et al., 1989, 1990, 1991). SLC2A3, which has a lower

Km for glucose than SLC2A1, is thus a promising candidate for rapid glucose uptake (Burant & Bell, 1992); whether SLC2A3 is spatially regulated within ECs is unknown.

Metabolic memory is encoded in epigenetic modifications and the cytoskeleton—Metabolic changes are critical for changing cell phenotype. This occurs functionally in the production of metabolites but also provides a basis for cellular differentiation or creation of memory in the form of epigenetic modifications. Fatty acid-derived acetyl-CoA was found to be critical for maintaining lymphatic differentiation through acetylation of histones (Wong et al., 2017). Acetylation requires the key intermediate metabolite acetyl-CoA, the sole donor of acetyl groups for acetylation (Choudhary et al., 2014). In addition to epigenetic modifications, the cytoskeleton is also acetylated: α-tubulin promotes microtubule stability (Szyk et al., 2014). Thus it can be said that the cytoskeleton also possesses some metabolic memory.

Acetylated tubulin improves EC barrier function. Histone deacetylase 6 (HDAC6) phosphorylation, which deacetylates microtubules (MTs) and reduces barrier function, exacerbates EC barrier dysfunction in a cigarette smoke/LPS animal and Staphylococcus aureus model and of lung injury (Borgas et al., 2016; Karki et al., 2019; Kratzer et al., 2012), whereas hyper-acetylated tubulin is protective against LPS-induced ALI (Y. Zhang et al., 2008). Selective HDAC6 inhibition by tubastatin A also reduced TNFα-induced lung endothelial cell hyperpermeability (J. Yu et al., 2016).

In acute lung injury models, multiple studies invoke a final common pathway of RhoA-induced activation of myosin light chain, causing EC contractions and pulmonary vascular leak. Microtubules modulate RhoA activity in an LPS-dependent manner via oxidative-stress induced release of GEF-H1(Kratzer et al., 2012). GEF-H1 bound to MTs is dependent on microtubule acetylation. Mechanically, stiffness can activate GEF-H1 expression and thereby exacerbate LPS-induced lung inflammation (Mambetsariev et al., 2014).

In addition to microtubules, acetylation is important for stable adherens junctions. β-catenin HDAC6-dependent deacetylation causes β-catenin nuclear translocation and disassembly of adherens junctions (J. Yu et al., 2016, p. 6); on the contrary, β-catenin acetylation promotes its membrane localization thus stabilizing adherens junctions (Iaconelli et al., 2015), although these studies are not in endothelial cells. Thus, acetyl-CoA, a key mitochondrial-derived metabolite, may be critical for vascular permeability in lung injury. As mitochondria activity of ECs is enhanced by unidirectional flow and suppressed by disturbed flow (D. Wu et al., 2017), it is now possible to speculate that shear stress-induced mitochondria function affects cytoskeleton and junctional stability and hence is protective against lung injury.

Discussion

Mechanical forces drive changes in endothelial cell phenotypes which can lead to disease states. Mechano-transduction mechanisms result in changes to endothelial phenotypes such as production of matrix, expression of inflammatory markers and TNFα signaling, changing barrier properties, and endothelial-mesenchymal transformation. Continued endothelial transformation at a large enough scale in tissue or organ beds leads eventually to

pathological disease processes such as atherosclerosis, pulmonary hypertension, and capillary leak syndromes.

These changes require rewiring cellular biomass and energetics to support new cellular functions instead of maintaining cellular quiescence. All major metabolic pathways become altered including glucose, amino acids, fatty acid metabolism. Glucose is diverted from synthesis of glycocalyx into fueling cell migration. Amino acids and fatty acids are diverted for synthesis of nucleic acids in preparation for cell division.

Metabolic byproducts have a profound impact on cellular identity and act to preserve the state of the cell in accordance with the nutrient microenvironment. While transcription factors are central actors in promoting differential transcriptomic identities, metabolic products are central to preserving the epigenetic change of cells including methylation, acetylation, and lactylation. These changes occur via one-carbon metabolism, the production of acetyl-CoA from pyruvate, and through lactate dehydrogenase from pyruvate to lactate, respectively. Production of these metabolites thus changes the chromatin state and fundamental identity of the cell.

Not only are cellular level epi- and transcriptomic memories created from metabolic products, but also the structural fabric of endothelial cells. Microtubules and cell-cell junctions are acetylated, which stabilizes the cell integrity. This is especially important since the cytoskeleton is an integral and necessary component of mechanical signaling. Mechanical forces are often transient, whereas nutrient supply changes are much slower; buffering against sudden mechanical changes prevents rapid signaling changes which may be counter-productive. Acetylation of the cytoskeleton, as well as changes to chromatin, require significant integration of time-dependent mechanical forces prior to cellular decision making and cellular memory formation.

However, there are certain instances where quick sensation of nutrients is important, namely, such as during ischemia and reperfusion. While not discussed in depth in this current review, hypoxia can act digitally in an on-off manner through the action of HIF-1α. Degradation of HIF transcription factors through prolyl hydroxylases requires alpha-ketoglutarate and thus TCA metabolism plays a central role in regulation of the hypoxia response. Longer term, the reduction in acetyl-CoA via shutting down pyruvate dehydrogenase acts to reverse cytoskeletal and chromatin memory. Nevertheless, since O_2 plays such an important role in ATP generation and ROS signaling in ECs, its role as a digital switch makes sense in that regard.

The interaction between mechanical forces and nutrient flux must be further clarified both *in vitro* and *in vivo*. One often unrecognized difficulty with mechanotransduction and metabolism experiments is that due to fundamental thermodynamic principles, mechanical forces and nutrient delivery are co-dependent variables. Much like the thermoelectric effect where current necessarily produces changes in temperature through Onsager reciprocal relations, changes in mechanical flux, be it shear stress, pressure, stiffness, or stretch, will necessarily change the inbound flux of nutrients and outbound flux of waste products. For instance, in disturbed flow there is no net shear stress and therefore no net flux; in this case,

the delivery of O_2 is only reliant on diffusion and not convective flow. Therefore, the rate of consumption of nutrients must also be considered. Mitochondrial oxygen consumption, for example, may outstrip its diffusion-limited supply in the absence of convectional flux. Thus, mechanical forces, nutrient flux and nutrient gradients are inexorably linked through basic mass transport mechanisms.

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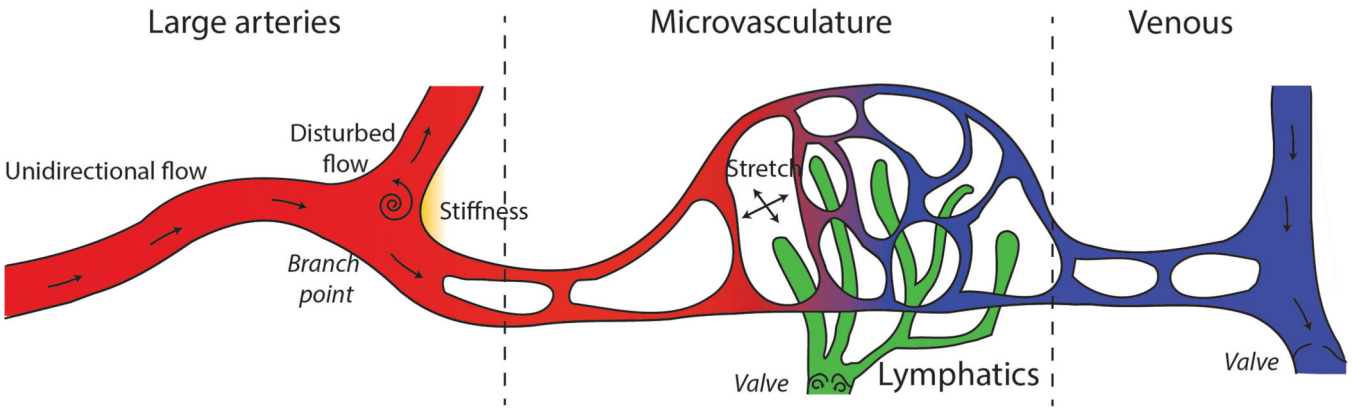

Figure 1: Major mechanical forces in vasculature.

(Left) In large arteries, endothelial cells in the straight vessels are subjected to unidirectional flow, whereas endothelial cells in the branch points and curvatures are subjected to disturbed flow and stiffness, leading to atherosclerosis formation. (Middle) Microvascular flow occurs in vessels, capillaries, and lymphatics. Shear stress is critical for lymphatic valve development. Stretch in the lung modulates capillary barrier function. (Right) Veins have valves which are under the control of lymphangiogenesis genes, but how metabolism plays a role is unclear.

Table 1.

Summary of studies on mechanical forces cooperating with metabolic changes in driving endothelial phenotypes.

Mechanical Force	Vasculature (cell type)	Regulation Mechanism	Metabolism	EC Phenotype	Disease	Ref
Shear stress (high/static, UF/DF)	HUVEC, ApoE-KO mouse, LDLR-KO mouse	↑KLF2 (↓PFKFB3, ↓HK2)	↓Glucose uptake, ↓Glycolysis	↓Proliferation, ↓migration, ↓inflammation, ↓monocyte adhesion	Pulmonary hypertension, atherosclerosis, thrombosis, pathological angiogenesis	*1–6*
Shear stress (UF/DF and long/short)	HUVEC, BAEC, RFPEC, ApoE-KO mouse	↑KLF2 (↑HAS2 for glycocalyx)	↓Glycolysis (↑Hexosamine and glucuronic acid biosynthesis)	↓Permeability, ↓monocyte adhesion	Atherosclerosis	*7–16*
Shear stress (DF/UF)	HAEC, HUVEC, mouse, ApoE-KO mouse	↑HIF-1a (↑SLC2A1, ↑HK2, ↑PFKFB3, ↑LDHA, ↑PDK1, ↑*NDUFA4L2*)	↑Glycolysis, ↓OXPHOS	↑Proliferation, ↑inflammation	Atherosclerosis	*6, 17–19*
Shear stress (DF/UF)	HUVEC, HAEC, mouse brain EC, mouse, ApoE-KO mouse	↑YAP/TAZ (↑JNK, ↑MYC, ↑PGC1α)	↑Glycolysis, ↑OXPHOS, ↑Mitochondria biogenesis	↑Proliferation, ↑inflammation, ↑migration, ↑monocyte adhesion	Atherosclerosis	*20–25*
Shear stress (DF/UF)	HAEC, mouse	↑SLC2A1/3 (possibly by YAP/TAZ)	↑Glucose uptake and glycolysis	↑Migration	Aorta leakiness	*26*
N/A	Mouse bone EC	↑YAP/TAZ (↓HIF-1a)	↓Glycolysis	↓Proliferation	Angiogenesis, osteogenesis	*27*
Shear stress (DF/UF)	HUVEC, MAEC, ApoE-KO mouse	↑PRKAA1	↑Glycolysis	↑Proliferation	Atherosclerosis	*28*
Shear stress (high/static and UF/DF)	HAEC, HUVEC, mouse	↑SIRT1 (↑PGC1α)	↑Mitochondria biogenesis	↑NO bioavailability		*29–31*
Shear stress (high/static)	HPAEC	↓Plasma membrane cholesterol	↑OXPHOS	↑Ca^{2+} signaling		*32*
Shear stress (UF/DF)	HUVEC, RAEC, mouse, LDLR-KO mouse, ApoE-KO mouse	↑OPA1, ↑MFN2, ↓DRP1, ↓FIS1	↑Mitochondria fusion, ↓Mitochondria fission	↓Inflammation, ↓monocyte adhesion	Atherosclerosis	*33–36*
Transient shear stress (high/static)	HUVEC, BAEC	↑DRP1, ↑$[Ca^{2+}]$i	↑Mitochondria fission, ↓OXPHOS, ↑mitochondria ROS			*37*
Shear stress (high/low)	HPAEC, HUVEC	↑Mitochondria ATP (↑Purinergic receptors)	↑Ca^{2+} influx	↑Vasodilation, ↓inflammation	Hypertension	*38–40*
Shear stress (high/low)	HUVEC	↑Mitochondria Ca^{2+} release/uptake	↑ER Ca^{2+} uptake/release			*41*

Mechanical Force	Vasculature (cell type)	Regulation Mechanism	Metabolism	EC Phenotype	Disease	Ref
Shear stress (DF/UF)	HUVEC	unknown	↓Lipid metabolism, ↓LDLR			*42*
Shear stress (high/static)	HPAEC	unknown	↑ether-containing lipids	↓Inflammation		*43*
Shear stress (UF/DF)	HUVEC	↑NOTCH1 (↑CPT1A)	↑FAO	Possibly ↓EndMT, ↑dNTP synthesis	Angiogenesis	*44–46*
Shear stress (DF/UF)	BAEC	↑SREBP1	↑FA synthesis ↑Lipid accumulation			*47–48*
Shear stress (high/static)	HUVEC, BAEC	↑ASS1	↑L-arginine synthesis	↑NO production, ↑viability		*49–51*
Shear stress (capillary-like/static)	HBMEC	↑TCA enzymes such as PDH, ↓LDHA	↑OXPHOS, ↓Glycolysis	↓Proliferation		*52*
Shear stress (high/static)	HGEnC	↑ENOS	unknown	↓Permeability		*53*
Hypoxia/normoxia (unknown in mechanotransduction)	HMVEC, mouse	SIRT3 (↑HIF-2a, ↑PFKFB3)	↑Glycolysis, ↓OXPHOS	↑Proliferation	Diastolic dysfunction	*54–55*
Hypoxia/normoxia (unknown in mechanotransduction)	HPAEC	↑FA synthase (↑HIF-1a)	↑Glycolysis	↑Proliferation, ↓eNOS	Pulmonary hypertension	*56*
Hypoxia/normoxia (unknown in mechanotransduction)	HMVEC	↑HIF-2a (↑Arginase II)	↓L-arginine for eNOS	↓NO production	Pulmonary hypertension	*57*
Long-term shear stress (high/static)	HRMEC, BRMEC	↑ENOS, ↑TM, ↓ET-1	unknown	↑Vasodilation, ↑Antithrombotic		*58–59*
Shear stress (low/static)	HRMEC	↑E-selectin, ↑ICAM-1, ↑Cytokine/chemokine, ↑Procoagulant factors	unknown	↑Inflammation		*60*
Shear stress (DF/UF)	HLEC, mouse	↑FOXC2-PROX1 (↑Connexin37, ↑calcineurin)	unknown	↑Lymphatic identity	lymphatic-valve morphogenesis	*61–62*
Shear stress (low/static)	HDMLEC	↑GATA2-FOXC2	unknown		lymphatic vessel maturation, lymphedema	*63–64*
Shear stress (high/static)	HLEC	↓PROX1 (↓CPT1)	↓FAO (↓dNTP synthesis)	↓Lymphatic identity	Lymphangiogenesis	*65–66*
Shear stress (chronic low/static)	LLEC	↑HIF-1a	Altered metabolomics	↑Proliferation		*67*
Stretch	BPAEC, HUVEC	Actin filaments	↑Mitochondria ROS	Possibly ↑focal adhesion kinase signaling; ↑Inflammation		*68–69*
Stretch	HUVEC	unknown	↓Glucose utilization			*5*
Stretch	MLEC, mouse	↑YAP/TAZ (↓VE-PTP)	unknown	↓Permeability, ↓inflammation	Ventilator-induced lung injury	*71*
Stiffness	RPAEC, rat	↑YAP/TAZ (↑GLS1, ↑LDHA)	↑Glutamate (↑TCA intermediates), ↑glycolysis	↑Proliferation, ↑migration	Pulmonary hypertension	*26*

Mechanical Force	Vasculature (cell type)	Regulation Mechanism	Metabolism	EC Phenotype	Disease	Ref
Cytoskeleton	HUVEC	↑PFKFB3	↑Glycolysis	↑Filopodia formation (↑Migration)	Vessel sprouting	*72–73*
Cytoskeleton	HPAEC	↑HDAC6 (↓Microtubule)	Acetyl-CoA	↑Permeability	Acute lung injury	*74–76*
Cytoskeleton	HAEC	↑RhoA (↑SLC2A3)	↑Glucose uptake	↑Migration		*77*

Abbreviation list of Table 1:

BAEC: bovine aortic endothelial cell

BRMEC: bovine retinal microvascular endothelial cells

HAEC: human aortic endothelial cell

HBMEC: human brain microvascular endothelial cell

HDMLEC: human dermal microvascular lymphatic endothelial cell

HGEnC: human glomerular endothelial cell

HLEC: human lymphatic endothelial cell

HPAEC: human pulmonary arterial endothelial cells

HRMEC: human retinal microvascular endothelial cell

HUVEC: human umbilical endothelial cell

LLEC: lamb lymphatic endothelial cell

MLEC: murine lung endothelial cell

NDUFA4L2: NADH dehydrogenase [ubiquinone] 1 alpha subcomplex, 4-like 2

RAEC: rat aortic endothelial cell

RFPEC: the rat fat pad endothelial cell

RPAEC: rat pulmonary arterial endothelial cells

Reference directory of Table 1:

1. (Doddaballapur et al., 2015)

2. (Parmar, 2005)

3. (Yu et al., 2017)

4. (Xu et al., 2014)

5. (Schoors et al., 2014)

6. (D. Wu et al., 2017, p. 1)

7. (G. Wang et al., 2020)

8. (Pries et al., 2000)

9. (Tarbell & Ebong, 2008)

10. (Fu & Tarbell, 2013)

11. (Zeng & Tarbell, 2014)

12. (Curry & Adamson, 2012)
13. (Tarbell, 2010)
14. (Lipowsky, 2011)
15. (Lewis et al., 1982)
16. (van den Berg et al., 2006)
17. (Feng et al., 2017)
18. (Akhtar et al., 2015)
19. (Tello et al., 2011)
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21. (L. Wang et al., 2016)
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23. (Koo & Guan, 2018)
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25. (Mammoto et al., 2018)
26. (Bertero et al., 2016)
27. (Sivaraj et al., 2020)
28. (Yang et al., 2018)
29. (B. Kim et al., 2014, p.)
30. (J.-S. Kim et al., 2015)
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32. (Yamamoto et al., 2020)
33. (Chehaitly et al., 2021)
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