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COMMENTARY

Endothelial heterogeneity shapes shear stress response: a transcriptomic perspective

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Endothelial cells (ECs) are intrinsically heterogeneous, both in their developmental origins and functional properties across different vascular beds [1]. During embryogenesis, mesodermal hemangioblasts give rise to angioblasts, which further differentiate into distinct arterial, venous, and capillary EC lineages. This lineage specification establishes a blueprint for endothelial heterogeneity that persists into adulthood. Such intrinsic heterogeneity enables ECs to meet the unique metabolic and mechanical demands of their local environment, whether in large conduit arteries, low-pressure veins, or nutrient-exchanging capillary beds [2]. Importantly, this heterogeneity also lays the groundwork for site-specific responses to physiological and pathological stimuli, including mechanical forces such as blood flow [3].

Blood flow exerts a frictional drag force called fluid shear stress (FSS) on ECs, which line the inner layer of blood vessels. FSS is a key biomechanical signal that dynamically shapes endothelial structure and function, regulating the expression of thousands of genes in a flow-dependent manner [4]. Due to vessel geometries and hemodynamic variables, shear stress directional patterns and magnitudes vary significantly across the vascular tree [5]. In straight segments of vessels, blood flow is typically unidirectional and high, generating laminar shear stress. In contrast, in the regions of vascular bifurcations and curvatures, blood flow is multidirectional, disturbed, and low, generating oscillatory shear stress [6]. The magnitude of shear stress also varies significantly among artery, venous, and capillary, and is a key regulator of vascular caliber. ECs encode an FSS set point, a preferred range of shear stress that governs vascular stability and remodeling [7]. Physiological FSS at or near the set point stabilizes the vasculature, low FSS below the set point induces inward remodeling, and high FSS above the set point induces outward remodeling [7]. Therefore, understanding how EC lineage and local hemodynamics intersect is essential for unraveling the mechanisms of vascular development, adaptation, and disease [8,9].

In this issue, Cox and Ng [10] presented a comparative analysis of transcriptional responses to graded levels of laminar shear stress among the following 3 vascular-type ECs: human umbilical vein ECs, human pulmonary artery ECs, and human microvascular ECs, which were chosen to represent venous, arterial, and capillary lineages, respectively. By subjecting these cells to a gradient of laminar shear stress and performing bulk RNA-sequencing, the authors identified a core set of flow-responsive genes (~44.2% of the total differentially expressed genes [DEGs]) commonly regulated across all EC types (Figure). These include canonical shear stress-responsive genes in ECs, such as krüppel-like factor (KLF) 2 and 4, and nitric oxide synthase 3 (NOS3), which are consistently upregulated in a shear stress magnitude-dependent manner.

However, the majority of differentially expressed genes are unique to 1 or 2 EC subtypes, highlighting vascular bed-specific responses to FSS (Figure). In line with previous findings, the authors also observed differential regulation of gene networks involved in key endothelial functions, including cytoskeletal organization [11], SMAD signaling [12,13], endothelial-to-mesenchymal transition [14], angiogenesis [15], and cell cycle control [16], suggesting that these pathways are modulated in a context-dependent manner by both shear stress magnitude and endothelial identity.

One of the most intriguing observations is the differential regulation of hemostatic and thrombotic genes under shear stress,

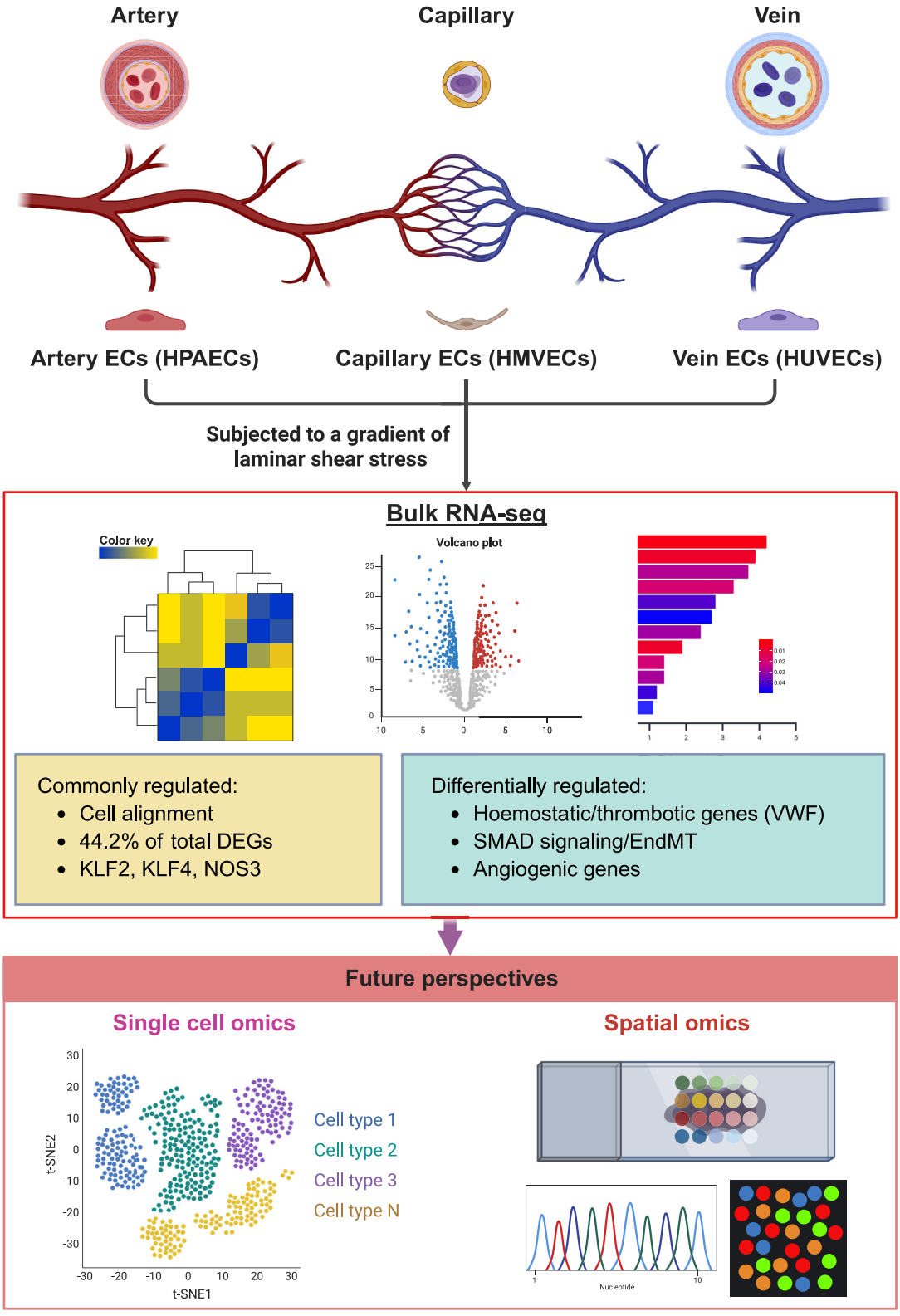

FIGURE Endothelial heterogeneity in response to shear stress. Arterial endothelial cells (ECs) (human pulmonary artery ECs [HPAECs]), venous ECs (human umbilical vein ECs [HUVECs]), and capillary ECs (human microvascular ECs [HMVECs]) were exposed to a gradient of laminar shear stress and subjected to bulk RNA-sequencing. This analysis revealed a core set of commonly regulated genes across all EC types, as well as differentially regulated genes specific to each subtype. Future studies employing single-cell and spatial omics technologies would be helpful to further elucidate mechanisms of endothelial heterogeneity in response to shear stress. This figure was created with BioRender.com. EndMT, endothelial-to-mesenchymal transition. DEGs, differentially expressed genes; KLF, krüppel-like factor; NOS, nitric oxide synthase; SMAD, mothers against decapentaplegic; t-SNE, t-distributed stochastic neighbor embedding.

including von Willebrand factor (VWF), a critical player in platelet adhesion and thrombus formation [17]. That VWF exhibits a pattern of vascular-type heterogeneity in response to shear stress underscores the translational relevance of this work, especially given the importance of endothelial VWF in conditions such as venous thromboembolism, thrombotic microangiopathies, and arterial thrombosis [18].

These findings prompt important questions: "Do arterial ECs have an intrinsically higher threshold for shear-induced prothrombotic signaling than venous ECs?" "Could microvascular ECs, with their capillary-level perfusion characteristics, modulate shear-sensitive pathways uniquely tied to their physiological role in tissue exchange?" This study opens the door for mechanistic investigations into the transcription factors, epigenetic marks, and signaling cascades that mediate these vascular-type specific responses.

Despite its strengths, this study has several limitations. First, primary human ECs in culture inevitably undergo some degree of phenotypic drift, so further *in vivo* validation would be important to confirm physiological relevance. Second, this study focused exclusively on laminar shear stress, while *in vivo* ECs are exposed to a spectrum of flow types, including disturbed flow, especially at vascular branch points and curves where atherosclerosis commonly develops. Future work incorporating these complex flow patterns will be critical for a comprehensive understanding of EC mechanotransduction across vascular types. Finally, while transcriptional profiling provides valuable insights into gene regulatory responses, changes in mRNA levels do not always correlate with protein abundance or cellular function. Thus, functional validation of key flow-responsive genes at the protein level, along with mechanistic studies linking these changes to endothelial behavior, will be necessary to establish their physiological significance.

Looking forward, these findings have broad implications for vascular biology and thrombosis research. The identification of flow-responsive genes in specific EC types provides hypotheses for why certain vessels are more thrombogenic. Future studies employing single-cell omics, such as single-cell RNA-sequencing, will be instrumental in further dissecting the cellular heterogeneity within each EC subtype, resolving transcriptional responses to FSS at single-cell resolution [19]. Moreover, emerging spatial omics technologies, including spatial transcriptomics, epigenomics, and proteomics, offer the ability to map flow-induced transcriptional, epigenetic, and translational changes in situ (Figure), while preserving the spatial heterogeneity of ECs within their native microenvironment.

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AUTHOR CONTRIBUTIONS

H.D. conceived, wrote, and edited the manuscript and illustrated the figure.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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