Biomicrofluidics

EDITORIAL | MAY 06 2024

Organ-specific vasculature-on-a-chip systems

Special Collection: Organ-Specific Vasculature-on-a-Chip Systems

Hasan Erbil Abaci ; Mandy B. Esch

Biomicrofluidics 18, 030401 (2024)
https://doi.org/10.1063/5.0214265

Biomicrofluidics EDITORIAL pubs.aip.org/aip/bmf

Organ-specific vasculature-on-a-chip systems

Cite as: Biomicrofluidics 18, 030401 (2024); doi: 10.1063/5.0214265
Submitted: 16 April 2024 · Accepted: 16 April 2024 ·
Published Online: 6 May 2024

Hasan Erbil Abaci[1,2,a)] and Mandy B. Esch[3,a)]

AFFILIATIONS

[1]Department of Dermatology, Columbia University Irving Medical Center, New York, New York 10032, USA
[2]Department of Biomedical Engineering, Columbia University, New York, New York 10027, USA
[3]Microsystems and Nanotechnology Division, National Institute of Standards & Technology, Gaithersburg, Maryland 20899, USA

Note: This paper is part of the special collection on Organ-specific vasculature-on-a-chip systems.
[a)]**Authors to whom correspondence should be addressed:** hea2113@cumc.columbia.edu and mandy.esch@nist.gov

Anatomical differences in organ-specific vasculature have been known for decades. More recently, global gene expression analyses, such as RNA sequencing, revealed the molecular heterogeneity across endothelial cells (ECs) in different organs.[1–7] A transcriptome atlas of murine ECs based on bulk RNA-seq[4,6] and scRNA-seq of ECs from 11 mouse tissues[5] also demonstrated the heterogeneity of endothelial gene signatures between tissues. This line of research has implications for tissue-specific vascular therapies, specifically for targeting overexpressed EC genes or specific environmental signals that cause ECs to lose their tissue specialization in disease or infections. Moreover, understanding the tissue-specific vasculature can help bioengineer and regenerate human organs.

Despite the growing molecular evidence of tissue-specific vasculature, little is known about the role of organs in their specialization of the endothelium. How do the cellular and extracellular matrix components separately or together contribute to the specialization of ECs in organs? Studies of brain and liver tissues showed that signals from resident cells (e.g., WNT9 from the neuroepithelium) regulate the specialization of ECs[8–10] and also mediate intra-organ differences. Interestingly, ECs can express genes typically found in the surrounding organs,[6] such as the cardiac contractile genes expressed in the heart endothelium, suggesting that the tissue microenvironment affects the EC profile. However, it remains technically difficult to dissect the microenvironmental regulation of endothelial cells *in vivo*, raising the need for physiologically relevant *in vitro* models.

Recent advances in microfabrication techniques, biomaterials, and differentiation protocols allowed for incorporation of microvasculature into engineered organs and their integration with microfluidic platforms, i.e., tissue chips. These *in vitro* models now enable the understanding and medical utilization of tissue-specific vasculature in a human-relevant context. In the "Organ-Specific Vasculature-on-a-Chip Systems" Special Topic in *Biomicrofluidics*, Hall *et al.*[11] discuss the advances in co-culture models and organ-on-a-chip systems in different levels of complexity that are utilized for understanding and modelling tissue-specific blood and lymphatic vasculature. The authors highlight the power of microfluidics technology to mimic physical factors, such as shear stress, flow regimes, and intracellular calcium signaling, that dramatically affect endothelial cell physiology and phenotypes. In addition, they point out the role of local cues from the surrounding cell types, e.g., neurons in the brain vasculature, in recapitulating the tissue- and tumor-specific blood and lymphatic vasculature. The vascularized organ-on-chip models nicely summarized by Hall *et al.* represent *in vitro* tools that help us examine individual microenvironmental cues on the molecular profile and functions of blood and lymphatic vessels.

The vasculature plays a pivotal role in bacterial infections in various organs, such as chronic wounds in the skin and respiratory infections in the lungs. In a review paper,[12] Gaudreau and Stewart highlight the utilization of vascularized organ-on-a-chip systems for studying host-bacteria interactions and cellular responses related to bacterial infections. The model systems summarized in this review in order of increasing complexity from parallel-flow systems to complex microfluidic models demonstrate the capability of *in vitro* models to study the role of the vasculature during bacterial infections in specific organs including lung, liver, bladder, brain, and placenta.

The vasculature of the liver presents an important physical barrier that governs the uptake of nutrients, drugs, and environmental chemicals into the liver. To provide a way to investigate how the liver endothelium changes in response to its microenvironment and how the liver responds to changes in the endothelium, Ferrari *et al.*[13] have developed two microfluidic platforms that allow for endothelial cells to grow in proximity (at a 100 μm distance) or in close contact with 3D liver tissue models consisting of hepatocytes. Both platforms allow for endothelial cells to grow without the addition of artificial physical membranes that are often used in other models. Experimenting with those systems, the authors found that the presence of a model of the Disse layer

(a 100 μm gap filled with extracellular matrix components) between hepatocytes and endothelial cells enhances hepatocyte function. This model can, in the future, be used to investigate whether hepatocyte responses to toxic substances are altered due to the presence of stimulants that alter the liver endothelium, perhaps pointing the way to achieve *in vitro* responses that reflect physiological conditions more faithfully.

Wang *et al.* also present a microfluidic system in which endothelial cells and hepatocytes can interact with each other. Some of the results obtained after exposing this model to acetaminophen (APAP) and nicotine indicate that the presence of endothelial cells can alter the hepatic response to drugs and xenobiotics.[14] Besides affecting albumin production, the presence of human umbilical vein endothelial cells (HUVEC) in the model increased the CYP3A4 activity in response to acetaminophen. Challenges with nicotine caused irregularities in endothelial cell adherens junctions, decreased GTP cyclohydrolase 1 expression, and impaired angiogenesis. The study demonstrates how an endothelialized liver model can be used to investigate the potentially compounding effects of xenobiotics that affect the endothelium when investigating drugs that are metabolized by liver cells.

A comprehensive review by Varma and Fathi[15] summarizes recent efforts to build vascularized kidney, heart, and skin tissues. Together, the review papers and the studies published in the "Organ-Specific Vasculature-on-a-Chip Systems" Special Topic lead the way towards the development of microfluidic cell culture technologies that allow us to combine organ mimics with their organ-specific endothelial cells within close proximity (or in direct contact with each other). Microtechnology is also known for its ability to replicate some of the accompanying microarchitecture that appropriately reflects *in vivo* conditions. In the future, we expect that the vasculature will also be incorporated into multi-organ microphysiological systems to better simulate drug uptake, metabolism, and excretion.

In conclusion, this special issue will serve as a valuable resource for researchers who are interested in building and investigating organ-specific vasculatures and who are evaluating the transport of drugs and xenobiotics across the endothelial barrier within the context of their immediate surroundings. The membrane-less liver models and experimental strategies presented here can serve as a starting point for investigating the effects of the presence of endothelial cells on other on-chip organ models. In the future, investigators will likely also use such models to illuminate how to better treat bacterial infections in organs such as the lung. Using *in vitro* models of organ-specific vasculatures and their microarchitectures may help with identifying additional factors and pathways that may play a role in organ-specific cancer metastasis and its prevention.

REFERENCES

[1]D. J. Nolan *et al.*, "Molecular signatures of tissue-specific microvascular endothelial cell heterogeneity in organ maintenance and regeneration," Dev. Cell **26**, 204–219 (2013).
[2]J.-T. Chi *et al.*, "Endothelial cell diversity revealed by global expression profiling," Proc. Natl. Acad. Sci. **100**, 10623–10628 (2003).
[3]R. Marcu *et al.*, "Human organ-specific endothelial cell heterogeneity," iScience **4**, 20–35 (2018).
[4]A. C. A. Cleuren *et al.*, "The in vivo endothelial cell translatome is highly heterogeneous across vascular beds," Proc. Natl. Acad. Sci. **116**, 23618–23624 (2019).
[5]J. Kalucka *et al.*, "Single-cell transcriptome atlas of murine endothelial cells," Cell **180**, 764–779.e20 (2020).
[6]A. Jambusaria *et al.*, "Endothelial heterogeneity across distinct vascular beds during homeostasis and inflammation," Elife **9**, e51413 (2020).
[7]D. T. Paik *et al.*, "Single-cell RNA sequencing unveils unique transcriptomic signatures of organ-specific endothelial cells," Circulation **142**, 1848–1862 (2020).
[8]L. He *et al.*, "Single-cell RNA sequencing of mouse brain and lung vascular and vessel-associated cell types," Sci. Data **5**, 180160 (2018).
[9]J. M. Stenman *et al.*, "Canonical Wnt signaling regulates organ-specific assembly and differentiation of CNS vasculature," Science **322**, 1247–1250 (2008).
[10]A. Desroches-Castan *et al.*, "Bone morphogenetic protein 9 is a paracrine factor controlling liver sinusoidal endothelial cell fenestration and protecting against hepatic fibrosis," Hepatology **70**, 1392–1408 (2019).
[11]E. Hall, K. Mendiola, N. K. Lightsey, and D. Hanjaya-Putra, "Mimicking blood and lymphatic vasculatures using microfluidic system," Biomicrofluidics **18**, (2024).
[12]L. I. Gaudreau and E. J. Stewart, "Vasculature-on-a-chip technologies as platforms for advanced studies of bacterial infections," Biomicrofluidics **18**, 021503 (2024).
[13]E. Ferrari *et al.*, "A method to generate perfusable physiologic-like vascular channels within a liver-on-chip model," Biomicrofluidics **17**, 064103 (2023).
[14]E. Wang, M. J. Andrade, and Q. Smith, "Vascularized liver-on-a-chip model to investigate nicotine-induced dysfunction," Biomicrofluidics **17**, 064108 (2023).
[15]A. Rama Varma and P. Fathi, "Vascularized microfluidic models of major organ structures and cancerous tissues," Biomicrofluidics **17**, 061502 (2023).