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Vascular Microphysiological Systems to Model Diseases

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Abstract

Human vascular microphysiological systems (MPS) represent promising three-dimensional *in vitro* models of normal and diseased vascular tissue. These systems build upon advances in tissue engineering, microfluidics, and stem cell differentiation and replicate key functional units of organs and tissues. Vascular models have been developed for the microvasculature as well as medium-size arterioles. Key functions of the vascular system have been reproduced and stem cells offer the potential to model genetic diseases and population variation in genes that may increase individual risk for cardiovascular disease. Such systems can be used to evaluate new therapeutics options.

Keywords

cardiovascular disease; in vitro models; endothelium; vascular smooth muscle cells; microfluidics

Introduction

Complications from cardiovascular disease (CVD) represent the leading cause of death in the United States (1) and other developed countries. The underlying cause for most CVD is atherosclerosis, in which cholesterol-laden plaques on the inner wall of the arterial lumen cause loss of vascular elasticity, reduction in blood flow, and narrowing of the arterial lumen. Risk factors for CVD include age, hypertension, type 2 diabetes, obesity, hypercholesterolemia, and smoking that induce oxidative stress resulting in modified forms of low-density lipoprotein (LDL), inflammation, and smooth muscle cell proliferation (2–5). The formation of plaque and oxidation of LDL causes endothelial cell activation and later leads to the recruitment of monocytes. In the presence of oxidative and pro-inflammatory stimuli, monocytes differentiate to macrophages and promote the formation of foam cells. The plaque may eventually rupture, which results in thrombus formation in the blood vessel, causing ischemia, heart attack, or stroke (4). Other diseases that lead to vascular damage including thrombotic disorders (deep vein thrombosis and disseminated intravascular coagulation), Marfan syndrome, aortic aneurysm, heart valve disease, congenital defects,

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and Progeria. Human immune system and inflammatory pathway activation play key roles in the initiation of atherosclerosis (6).

Mice are commonly used to study the genetic factors in vascular diseases (7). While animal models have provided crucial information about the initiation and progression of atherosclerosis, they still possess many shortcomings and cannot produce many of the features of the pathology found in humans. Wild type mice use high-density lipoprotein to transport cholesterol to tissues while humans uses LDL (8). The size of arteries in mice is much smaller compared to humans and the heart rate is much higher (9), leading to very different hemodynamic conditions. The many interacting polymorphisms identified in genome-wide association studies cannot be replicated in mice. Given these limitations, the response of treatments in mice may differ from that in humans (10, 11).

To overcome these pitfalls with animal models, human microphysiological systems (MPS) have been introduced to improve the accuracy of experimental predictions, minimize experimental time and cost, and reduce patient risk. Experiments that use MPS are highly reproducible. MPS use advanced fluidic fabrication methods to create three-dimensional models of the functional unit of tissue. These systems can be used for functional assays as well as genomic, metabolomic, and histological analysis. The major advantage of MPS is that they can be modified to test single or combination of hypotheses, which allows identification of the key factors in different model systems.

Vascular MPS use microfluidic devices with three-dimensional culture methods to recapitulate many model systems (12) (Figure 1). Furthermore, one or more MPS can be combined together to study systematic effects by the key contributing factors. To study the initiation and progression of vascular disease, tissue engineered blood vessels (TEBVs) have been designed to model the many vascular diseases, including atherosclerosis, progeria, and thrombotic disorders (13–17). The versatility of TEBVs allows the use of these models extended to vasculitis in rheumatoid arthritis and lupus or the role of oxidative stress (18). Given the different features and fabrication strategies of microvascular systems and TEBVs, each will be described separately.

In this perspective we examine the design criteria to build vascular MPS at the level of microvascular networks and as mimics of arterioles and arteries. Next, we address the various cell sources and the properties needed for adequate differentiation. Disease models are an important application area of MPS and may be used to assess the safety and efficacy of novel therapeutics.

Design Criteria and Fabrication of Arteriole- and Arterial-Scale MPS

The ultimate goal in designing vascular MPS is to reproduce key vascular functions *in vivo*. The minimum requirements are to allow blood flow under physiological pressures (10– 20 kPa) and shear stress (0–2.5 Pa) without inducing thrombosis or inflammation (19). Given that blood flow is generated by pressure induced by the heart, the large vessel MPS or TEBVs must process two mechanical properties, resistance to rupture (measured by burst pressure) and resistance to plastic deformation (measured by compliance) (19–21). The burst pressure of the human saphenous vein and artery are around 2000 and 3000 mm Hg,

respectively (22–24). The compliance of human vessels ranges between 1% and 6% (24–28). Hence, an ideal TEBV should possess mechanical properties similar to the natural vessels.

Other than the mechanical properties of vascular MPS, biological properties also contribute to vessel failure. Protein adsorption on the surface of vascular MPS could subsequently lead to blood clotting. Hence, the non-thrombogenic and non-immunogenic behavior is necessary for designing vascular MPS, usually by incorporating a layer of vascular endothelium. The barrier function of vascular endothelium varies considerably from impermeable in the brain microvascular network to relatively permeable in the kidneys and liver (29, 30).

Current approaches to fabricate TEBVs that are more or less similar to natural vessels can be divided into two major categories, scaffold based or self-assembly. With scaffold-based method, either synthetic polymer or nature extracellular matrix (ECM) could be utilized as scaffold for in-vitro cell seeding. The essential requirements for synthetic polymers are biocompatibility and biodegradability. Polyglycolic acid (PGA) and Poly (lactide-co-glycolide) acid (PLGA) are two of the most widely studies biodegradable polymers used in TEBVs. After a period of growth and maturation, the developing TEBVs is placed in a bioreactor with pulsatile flow and burst pressures above 2000 mm Hg can be achieved after 8–10 weeks (31). Animal studies showed great patency results of these vessels.

Natural biological hydrogels and ECM proteins such as collagen, elastin, fibrin, gelatin, and modified hyaluronic acid (32–34) have been used as scaffold materials. These scaffolds have improved biocompatibility and provide adhesion sites for binding of cell surface integrins or cleavage sites to matrix metalloproteinases (MMPs), which facilitate cell attachment, cell migration and cell proliferation (35). While fibrin scaffolds also produce high burst pressures (36, 37), collagen scaffold TEVBs typically have lower mechanical properties (20, 21, 38, 39).

Although the use of synthetic polymers as scaffold is promising, the long manufacturing time for these vessels poses a great challenge for the use as a disease model system in vitro. One way to increase the burst pressure and rapidly fabricate perfusable vessels is by plastic compression of collagen gels embedded with smooth muscle cells, which increase the collagen density and improves the TEBV (14, 15, 40). Plastic compression generates TEBVs with burst pressures around 1600 mm Hg in a few hours (14). After a one to three week maturation period, these vessels are well-suited for modeling diseases in vitro (15).

Another source of natural scaffold is to decellularize TEBVs by depleting tissue and cells from allogenic or xenogeneic sources. Decellularized scaffolds preserved the natural architecture of the ECM of the vessels (34, 35). Complete depletion of cells is required to avoid the host immune response. To overcome this challenge, two strategies have been used, either by advancing decellularization technique or inactivating immunogenic biomolecules (34).

Self-assembly is another approach to manufacture TEBVs. Self-assembly utilizes the ECM produced by seeded cells as the vessel structural supports. With this method, a confluent layer form by cells *in vitro* is rolled into a tubular structures to mimic the vessel (22, 24).

These vessels achieve a burst pressure over 2000 mm Hg. The major pitfall for TEBVs generated by this method is the long manufacturing time of several months, which makes it difficult to use as disease modeling purpose. Acellular grafts represent one approach to overcome this challenge.

Extrusion of a Matrigel solution containing endothelial cells and smooth muscle cells enabled self-organized of an arteriole-like structure, termed vesseloids (41). The vesseloids exhibit key vessel properties including a restrictive endothelial barrier and smooth muscle cell contractility. The vessels respond to inflammatory stimuli causing the endothelial cells to express the leukocyte adhesion molecules VCAM-1 and ICAM-1. The benefit of this novel approach is that vessels can be rapidly produced without a thick layer of extra cellular matrix, in contrast to most methods to produce tissue-engineered blood vessels.

Design Criteria and Fabrication of Microvascular Models

In addition to models for diseases of large and medium-size arteries, microvascular systems (MVS) have been developed for drug screening, discovery, delivery, and modeling diseases in microvasculature. MVS are often combined with engineered solid organs to allow long-term maintenance (42). For example, human blood-brain barrier (BBB) tissue chips have been designed to model the BBB dysfunctions in neurological disorders (43) and Alzheimer's disease (44). Animal models do not recapitulate the whole disease state. The use of *in vitro* MVS with human cells or stem cells allows scientists to model the disease progression and drug response, which would result in better response prediction and reduce the use of live animals for disease modeling and drug testing (45, 46).

The structure of human micro-scale vessels (arterioles, capillaries and venules) are quite different from large vessels (arteries and veins). While arterioles and venules contain all three layers, the media and externa layers are very thin compared to arteries and veins, respectively. The capillaries consist of a layer of endothelial cells that function in tissue-vessel material exchanges. Pericytes are attached to the endothelium, regulating vessel dimensions and permeability.

Given the structural differences between large and medium size arteries and capillaries, strategies to manufacture MVS are different from those of TEBVs. Current approaches to manufacture MVS are either Top-Down or Bottom-Up (34, 47, 48). With the Top-Down approach, the pattern or geometry of the vascular systems are designed and then manufactured by 3D-printing (49), mold degradation (50, 51) or multilayer chip (52). While the pre-designed Top-Down approach could provide a controllable vascular structure and allow perfusions, the major disadvantage is that the resolution of these methods does not yet reach the level of capillaries.

In the Bottom-Up approach endothelial cells, pericytes or pericyte-like cells (e.g. fibroblasts or mesenchymal stem cells) are mixed together with a biological hydrogel and local chemical or physical stimuli from the various cell types induce angiogenesis and vasculogenesis. With these approaches, endothelial cells self-organized to form an interconnected network of microvessels (53–56). Growth factors such as VEGF and fibroblast growth factors are also supplemented to promote angiogenesis (57). Pericyte-like

cells are needed to stabilize the microvasculature, otherwise the vessels breakdown after 24–48 hours. These methods allow the formation of perfusable capillary-size networks (42, 58) but the structures of these networks are hard to control. Another challenge for these methods is to form perfusable networks.

Cell source

Cells are one of the major components in vascular tissue engineering. Primary autologous cells including vascular smooth muscle cells, endothelial cells and fibroblasts, harvested from the patients, showed great successes for manufacturing vascular MPS. However, there are some challenges to use these cells as source for TEBVs. First, these cells required invasive procedure to harvest. Second, primary cells lost the ability to proliferate after prolonged expansion. Third, these cells are not available or not usable in some of the patients. While primary endothelial cells, which can be isolated from blood-derived endothelial colony forming cells, and fibroblasts are relatively feasible to obtain, obtaining functional and proliferative primary SMCs retains a major challenge given the limited accessibility of donors' tissue, limited proliferation rate and donor-to-donor variation (59). Human embryonic stem cells (hESCs), mesenchymal stem cells (hMSCs) and induced pluripotent stem cells (iPSCs) show great potentials as cell sources in vascular tissue engineering. While the use of hESCs raises ethical issues, hMSCs and iPSCs seem well-suited for clinical translation and regenerative medicine. hMSCs can be easily obtained from various tissues (60) and their multipotent nature allows them to differentiate into many cell types, including smooth muscle cells (61) and endothelial cells (62). Since the discovery of iPSCs in 2006 by Takahashi and Yamanaka (63), iPSCs have been widely used (64) and showed great potential to develop vascular MPS. iPSCs could be transformed from various adult cells including fibroblasts or blood cells. The pluripotency gives iPSCs the potential to differentiate into cells from all three germ layers (mesoderm, endoderm and ectoderm) (63), which include SMCs (65) and ECs (66). The main pitfalls with iPSCs cells are their tumorigenic potential and immature differentiation. Progress has been made to reduce the risk of tumorigenicity by using non-integrating methods (67–70). Current prevailing non-viral and non-integration approaches include adenoviral vectors (68), Sendai vectors (71), episomal vectors (72), minicircle vectors (73), synthetic mRNAs (74) or small molecule cocktails (75).

A challenge with iPS-derived smooth muscle cells has been limited differentiation which reduced mechanical strength of the TEBVs (76, 77). Optimizing the differentiation protocol (65, 78) or applying cyclical mechanical stimulation (65)promotes SMC differentiation and increases the TEBV mechanical strength. Self-assembled microvascular networks have been developed using human brain microvascular endothelial cells and pericytes have been derived from iPSCs and exhibit the low permeability and high levels of tight junction proteins found *in vivo* (79).

Transdifferentiation of human adult cells to ECs and SMCs provides another cell source for vascular MPS. Transdifferentiation eliminates the intermediate step of generating iPSC cells and reduce the risk of tumorigenicity and can be achieved by small molecules (80, 81) targeting certain signaling pathways, activation and overexpression of key genes (82, 83) or

CRISPR/Cas9-based transcriptional activator systems that force expression of key endogenous transcription factors (84). The introduction of cDNAs or CRISPR/Cas9 systems for gene editing can be achieved by either viral systems or non-viral/non-integration systems (85). In the context of vascular MPS, several groups have shown success in transdifferentiating human fibroblast cells to ECs (80, 82, 83, 86, 87) and SMCs (88) or ECs to SMCs (89).

Disease Models

iPSC cells and transdifferentiated cells offer great potentials for regenerative medicine and personalized medicine with minimum ethical issues. iPSC differentiated smooth muscle cells have been derived from patients with progeria (15), supervalvular aortic stenosis (90), and fibrillin 1 mutations in Marfan syndrome (91). Endothelial cells have been derived from individuals with pulmonary hypertension (92). iPSCs enabled discovery of new biology of these diseases, although only a few have been converted to three-dimensional models. Atchison *et al.*, used Hutchinson-Gilford progeria syndrome (HGPS) patient derived TEVBs and these vessels could reproduce key features of HGPS and the response to drug treatment (15). A recent study used HGPS patient derived TEVBs and identified the contribution of endothelial dysfunction to the progression of atherosclerosis in HGPS (78). A tissue-on-a-chip and bottom-up self-assembly model of the neurovascular unit using primary or iPSCs derived from individuals with various neurological diseases, showed that these disease states alter the blood brain barrier permeability and could be suitable testbeds to assess drug candidates (43, 44).

Translational Insight

The development of vascular MPS provides an effective platform for the investigation of vascular development, vascular disease modeling, and evaluation of drug safety and efficacy. The vascular MPS create physiologically relevant microenvironments that closely model the *in vivo* environments. By incorporating recent advances in stem cell differentiation, vascular MPS could also be used in tailored medicine to model diseases individually and provide personalized information for each patient. Microvascular systems have already been used to study angiogenesis (54), (93), and the blood-brain barrier (42). Furthermore, the easy modification of vascular MPS enables deconvolution of the complex *in vivo* systems and testing hypotheses one by one. For example, high levels of LDL, monocyte activation, and accumulation and inflammatory environments all contribute to the initiation and progression of atherosclerosis. However, it is extremely difficult to identify which contributes more to the early stages of atherosclerosis by in vivo system. By using vascular MPS, each factor could be tested individually or combined with other factors to give more information about the underlying mechanisms. Gene editing technology allows creation of specific acquired changes to examine complex conditions such as aging (94) and interactions among polymorphisms associated with CVD. The future of vascular MPS relies on new techniques to 1) manufacture vascular MPS with shorter manufacturing time and more closely mimicking the natural vessels, 2) promote complete cell differentiate from iPSCs or hMSCs to functional ECs and SMCs, and 3) integrate different scales of vessel (artery to capillary) in the same system.

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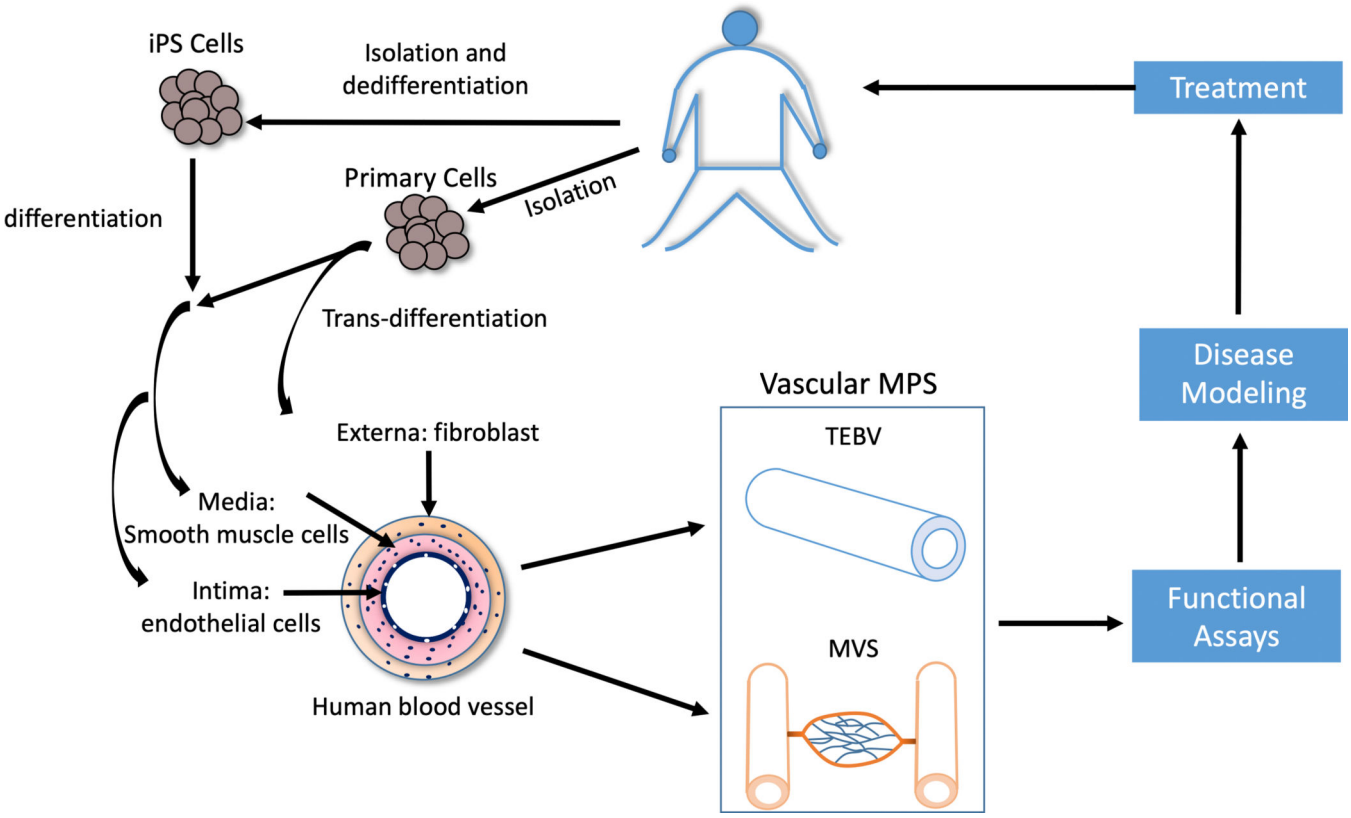

Figure 1.

Overview of *in vitro* human vascular system. Fibroblasts, smooth muscle cells and endothelial cells that resemble the externa, media and intima layers, respectively, of human blood vessel could be obtained by isolation, differentiation from stem cells, or transdifferentiation from other cell types. Human vascular MPS including TEBV and MVS manufactured from these cells could be applied for functional assays, disease modeling and treatment discovery. These results could potentially translate back to patients.