Acta Biomaterialia xxx (xxxx) xxx

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Upgrading prevascularization in tissue engineering: A review of strategies for promoting highly organized microvascular network formation ☆

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ARTICLE INFO

Article history:
Received 30 October 2018
Received in revised form 20 February 2019
Accepted 6 March 2019
Available online xxxx

Keywords:
Prevascularization
Microvascular network
Aligned microvessels
Tissue engineering

ABSTRACT

Functional and perfusable vascular network formation is critical to ensure the long-term survival and functionality of engineered tissues after their transplantation. Although several vascularization strategies have been reviewed in past, the significance of microvessel organization in three-dimensional (3D) scaffolds has been largely ignored. Advances in high-resolution microscopy and image processing have revealed that the majority of tissues including cardiac, skeletal muscle, bone, and skin contain highly organized microvessels that orient themselves to align with tissue architecture for optimum molecular exchange and functional performance. Here, we review strategies to develop highly organized and mature vascular networks in engineered tissues, with a focus on electromechanical stimulation, surface topography, micro scaffolding, surface-patterning, microfluidics and 3D printing. This review will provide researchers with state of the art approaches to engineer vascularized functional tissues for diverse applications.

Statement of significance

Vascularization is one of the critical challenges facing tissue engineering. Recent technological advances have enabled researchers to develop microvascular networks in engineered tissues. Although far from translational applications, current vascularization strategies have shown promising outcomes. This review emphasizes the most recent technological advances and future challenges for developing organized microvascular networks *in vitro*. The next critical step is to achieve highly perfusable, dense, mature and organized microvascular networks representative of native tissues.

1. Introduction

Development of highly perfusable and mature vascular networks *in vitro* holds great potential to revolutionize transplantable tissue technologies to satisfy the therapeutic needs of disease conditions that lack effective treatment options. *In vitro* fabrication of a large three-dimensional (3D) graft normally requires a system (eg. a perfusion bioreactor) that can provide nutrients and oxygen to all cells within the living construct. Unfortunately, post *in vivo* transplantation, the rate of host vessel invasion is limited to several tenths of a micron per day, leading to necrosis in the central area of the graft [1–4]. Thus, a tissue engineered graft with wall thickness greater than the diffusion limit of gases and nutrients (~150–200 μm) requires a pre-formed vascular network. This network must be able to rapidly anastomose to host vasculature in order to promote optimum graft survival [5]. Development of perfusable and functional engineered tissues may reduce mortality following myocardial ischemia (MI), limit the development of chronic ulcers, prevent bone and cartilage damage and reduce alcoholic hepatitis, among many other benefits. The Food and Drug Administration (FDA)-approved tissue engineered products developed in the past (particularly for wound healing), mostly serve as a natural reservoir of growth factors, cytokines and extracellular (ECM) proteins, but lack crucial pre-formed vasculature [6–8]. As a result, they fail to integrate with the host, and eventually undergo necrosis.

☆ Part of the Special Issue on SI: Cell & Tissue Biofabrication, organized by Professors Guohao Dai and Kaiming Ye.

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https://doi.org/10.1016/j.actbio.2019.03.016
1742-7061/

Although an extensive amount of research has been conducted to develop small diameter vascular grafts [9], major technological advances are still required for development of functional and perfusable microvascular networks that can be integrated into engineered tissues. Several vascularization strategies have been reviewed to date, mostly with a focus on single vessel or vascular network formation in engineered scaffolds using co-culture of various cell types [10,11], external growth factor provision [12], 3D bio-printing [13], use of microfabrication [14] and microfluidic techniques [15]. However, the significance of the microvessel structure and organization has been largely ignored. This review exclusively discusses current advances and challenges associated with *in vitro* development of highly organized and tissue architecture oriented microvacular networks. These strategies are categorized in five subsections including (1) electromechanical stimulation, (2) topographical stimulation, (3) microfabrication, (4) micro-patterning and (5) 3D bioprinting. Engineered structured vessels not only facilitate functional tissue regeneration post-implantation, but also augment fabrication of *in vitro* vascular disease models to understand pathogenesis of atherosclerosis, hypertension, cardiac arrest, stroke and cancer. In order to develop tissue architecture oriented microvessels *in vitro*, it is important to understand their physiological organization in native tissues.

2. Microvascular network formation in native tissues: Insights from developmental process

Vascular networks, categorized as the blood vascular and lymphatic systems, are a crucial component of biological tissue. While blood vascular networks mediate the exchange of gases, nutrients and metabolic byproducts, the lymphatic system optimizes nutrient transport between blood and tissue [16]. Hierarchically organized blood vascular networks contain a multitude of vessels with vast differences in their diameters, ranging from 3 cm to a few micrometers [17]. In this hierarchy of different sized vessels, capillaries fulfill the vital function of mass transport to cells directly, and are thereby indispensable to maintain tissue viability. Every tissue depends fundamentally upon oxygen for energy production and their oxygen requirements are dictated by their specific functions. For example, resting muscles use 1 mL of oxygen per minute per 100 g of tissue, and oxygen intake and blood flow can increase up to 30 fold during high contraction [18]. Highly organized and dense capillary networks replenish this oxygen supply due to their larger diffusion area. Notably, characterization studies of microvascular network organization in various tissues and organs, including skeletal muscle [19,20], heart [21,22], long bones [23] and skin [24–27], demonstrate that microvessels are precisely oriented in the direction of the constituting cells and ECM proteins in each particular tissue (Fig. 1C). This suggests that engineered tissues should be developed with a similar microvascular organization.

Cell-signaling mechanisms that regulate neoangiogenesis during embryonic development provide important clues that can be recapitulated to promote prevascularization in engineered tissues. For example, vascular network formation in the embryonic heart involves highly hierarchical but overlapping mechanisms of vasculogenesis, angiogenesis and arteriogenesis, as summarized in Fig. 1A. Vasculogenesis and angiogenesis regulate primitive vascular plexus formation from endothelial precursor cells and its expansion by sprouting or intussusception [28]. Arteriogenesis regulates enlargement of vessel diameter and recruitment of perivascular cells upon increased flow and sheer stress experienced by endothelial cells (ECs) [28]. Previous studies have characterized the lineage of the precursor cells that form cardiac vascular networks during embryonic development. From embryonic day (E) 9.5, the primitive microvascular network emerges from discontinuous EC patches, expands and covers the heart surface, in the dorsal to ventral direction [29]. A majority of the ECs that form the primitive coronary plexus under influence of myocardial vascular endothelial growth factor (VEGF)-A and epicardium-derived VEGF-C have migrated from the sinus venosus and endocardium [29]. Additionally, embryonic vascular smooth muscle cells (vSMCs) and fibroblasts derived from an epicardial origin under epithelial to mesenchymal transition (EMT) mediate inward migration and differentiation [30,31]. This process was found to be further regulated by platelet derived growth factor receptor (PDGFR)-β signaling [32]. The data regarding cell lineage characterization and growth factor signaling provide important information about cell source and angiogenic stimulation during embryonic growth, which can be utilized to promote similar vascular networks *in vitro* (Fig. 1A).

Notably, capillaries in mature cardiac tissue orient themselves in the uniaxial direction of myocardial fibers and are wrapped around cardiomyocytes to ensure optimum cell survival [21,22]. Although mechanisms that regulate the organization and alignment of capillary networks in the heart have not been clarified, it is possible that electrical and mechanical stimulation, such as muscle contraction, relaxation, and shear stress, may play significant roles. Insights from animal studies to investigate the organization of capillary growth in the skeletal muscle have provided important clues that verify the crucial role of mechanical and electrical stimulation in microvessel alignment. For instance, it has been observed that a scaffold undergoing cyclic stress or strain in a uniaxial direction promotes vascular growth in the same direction [33]. Shear stress generated by blood flow and electromechanical stimulation generated by muscle contraction directly regulates the expression of VEGF-A, endothelial nitric oxide synthase (eNOs) and angiopoietin (Ang)-2 in ECs, muscle cells and pericytes that promote EC survival, proliferation and migration [34–36], as illustrated in Fig. 1B. This mechanical stress reorganizes the actin cytoskeleton and focal adhesions along the stretch direction [37,38]. Upon mechanical stimulation, ECs upregulate expression of integrin $\alpha v\beta 3/\alpha v\beta 5$ to promote vessel branching, which is generally absent in quiescent ECs [37]. In addition, muscle induced mechanical stimulation regulates thrombospondin(TSP)-1, tissue inhibitor of matrix metalloproteinase (TIMP)-1 and matrix metalloproteinases (MMPs) expression. The expression profile promotes basement membrane proteolytic degradation and synthesis of "provisional ECM", which is responsible for EC sprouting. [39]. These physiological stimulations have been mimicked *in vitro* by Morin et al. to promote microvascular alignment and lumen density in a mechanically constrained cell-induced fibrin gel under interstitial flow [40]. Although promising, this strategy is not efficient for development of a mature microvascular network. In order to mimic the physiological microvascular network *in vitro*, it is crucial to analyze physiological components of microvascular networks in detail.

3. Cellular and acellular components of microvascular networks: Mimicking the physiological apparatus

Capillary structure incorporates ECs as the vessel lumen with surrounding perivascular cells, as illustrated in Fig. 1A. ECs maintain blood homeostasis, interact with immune cells and maintain molecular exchange with blood. In addition, ECs are elongated in the direction of blood flow and can increase their surface area by cell spreading to regulate shear stress generated by the flow [41]. Moreover, ECs regulate the expression of an assortment of surface molecules that can elicit a wide spectrum of effects. For example, during homeostasis, ECs express thrombomodulin, which acts as

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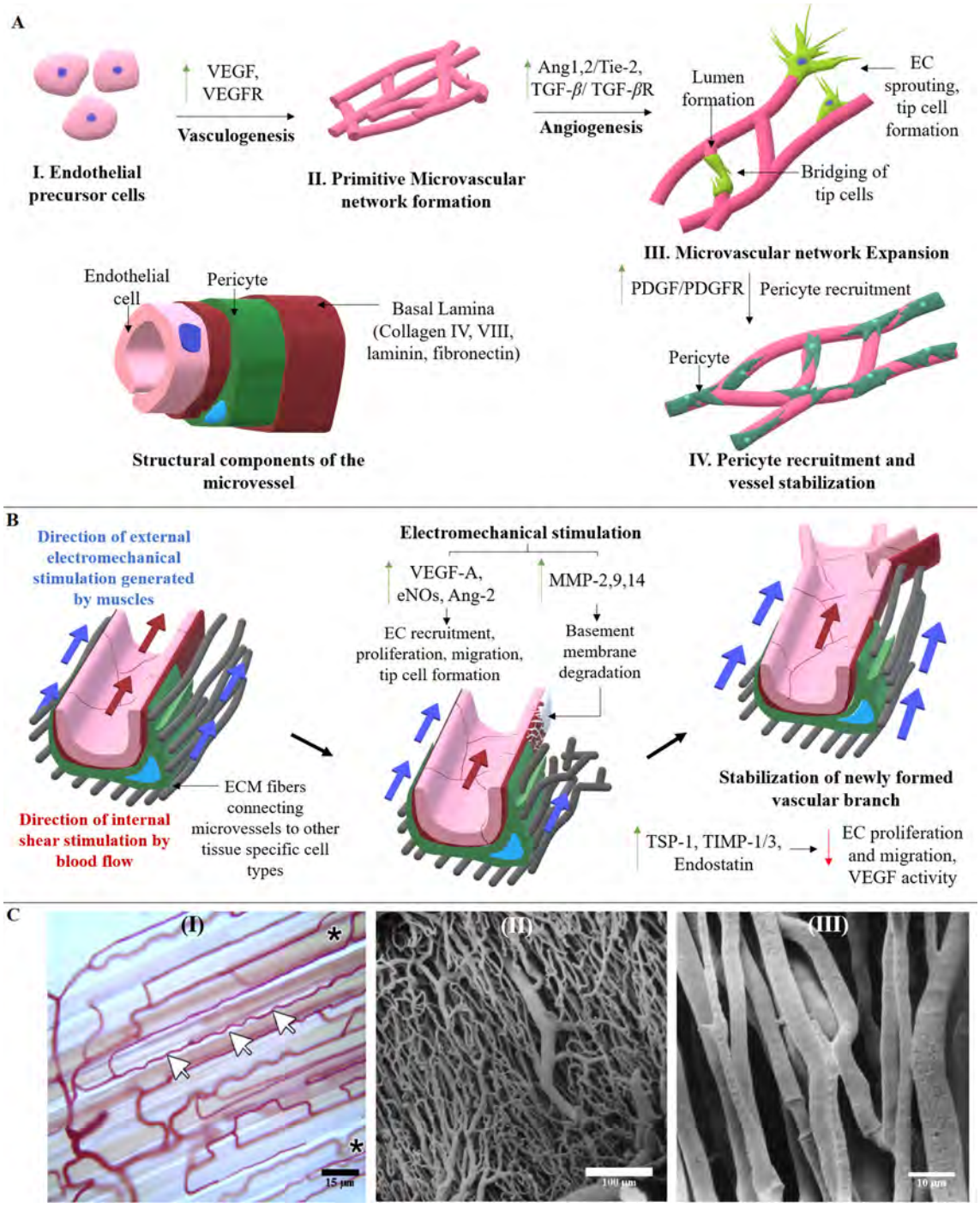

Fig. 1. Microvascular network organization in tissues. (A) Mechanism of microvascular network formation during developmental process. (B) Combined influence of electromechanical stimulation and biochemical signaling on tissue specific microvascular organization. (C) Microvascular network organization in native tissues (I) highly aligned capillaries in the porcine skeletal muscle injected with colored gelatin. (Arrows: tortuous course of the capillaries, Asterisks: anastomoses) (Image by Olfert et al.) [182]. Modified with permission and licensed under Creative Commons Attribution CC-BY 3.0: © the American Physiological Society.) (II-III) SEM images of highly aligned capillaries in adult rat heart tissue. (Image by van Groningen et al. [183]. Modified with permission from Springer.)

an anticoagulant. During injury or inflammation, ECs express adhesive surface receptors, such as selectins, to promote platelet and immune cell adhesion [42]. On the abluminal surface, ECs stimulate the contractile phenotype of perivascular cells by secretion of nitric oxide during conditions of active inflammation [43]. Therefore, it is critical to maintain a non-active phenotype of ECs in prevascularized engineered tissues for successful perfusion after transplantation. In contrast to arteries and veins that are surrounded by varying layers of vSMCs, capillaries are supported by pericytes, which attach to ECs via cell to cell and gap junctions [44]. Selecting appropriate perivascular cell types along with ECs is important to maintain the structural integrity of the engineered microvessels.

Capillaries contain a basal membrane in contact with the abluminal endothelial cell surface. In quiescent vessels, the basal membrane is primarily composed of laminins, collagen IV, nidogens,

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perlecan and heparan sulfate proteoglycan [45]. However, during early stages of angiogenesis the basement membrane is exposed to higher VEGF secretion, which causes disruption and leakage of various blood plasma proteins including fibrinogen, vitronectin, and fibronectin. This microenvironmental change facilitates the sprouting of neovessels. Moreover, enzymatic reactions convert fibrin into fibrinogen, which along with vitronectin and fibronectin transforms native collagen matrix and develops new "provisional" ECM, in order to foster pre-angiogenic sprout formation. Once these newly developed sprouts mature into vessels containing open lumens, they are stabilized by recruited pericytes. The pericytes then begin to synthesize basal lamina components and promote cells to adopt a quiescent phenotype [45,46]. Understanding the capillary structure and its construction process provides important information related to cell type, selection of appropriate proteins for scaffold fabrication and incorporation of trophic factors to regulate microvascular growth in engineered tissues.

4. Strategies to promote a structured microvascular network formation in engineered tissues

Primitive microvascular network formation by mono or co-culture of ECs and perivascular cells isolated from several sources have been extensively studied *in vitro* and *in vivo* [11]. Besides selecting appropriate cell types, external growth factors [47,48] and/or protein stimulation [49] have also been targeted to develop microvacular networks *in vitro*. Provision of angiogenic growth factors regulate several stages of angiogenesis including EC migration [50], vessel sprouting, perivascular cell recruitment and ECM production [50–52]. ECM proteins also regulate EC behavior, for example, by assembling ECs into solid cord like structures [49]. Several articles have reviewed strategies for incorporating exogenous growth factors and/or ECM protein stimulation to promote *in vitro* angiogenesis [12,47,48]. Although information obtained by these studies is of high importance, they are not sufficient to promote microvascular growth in a highly ordered manner and aligned in one particular direction. To achieve such a goal, it is important to understand native ECM architecture, their electromechanical properties, and topographical features that guide cellular behavior. These native ECM features can be mimicked *in vitro* to guide microvascular organization similar to the native tissues. Secondly, microfabrication and micro-patterning technologies can serve as a stepping-stone for the development of structured vasculature and vascular disease models *in vitro*. Lastly, recent progress in the field of 3D bioprinting, as discussed below, can be employed to produce structured vasculature in 3D scaffolds. Briefly, all of the strategies discussed here focus on the development of a highly structured and matured microvascular network *in vitro,* as summarized in Table 1.

4.1. Mechanical and electrical stimulation for microvessel formation

The ECM acts as an intermediate medium that experiences electromechanical forces exerted by attached cells, such as skeletal muscle cells. It is well known that the mechanical properties of the ECM influence cellular behavior. For example, ECs cultured on stiff substrates formed more focal adhesions and exhibited increased cell permeability [53,54]. Similarly, the cells can also alter the mechanical properties of surrounding ECM. For example, it was observed that ECM stiffness was reduced during microvessel sprouting by increased expression of MMP-2, 9, 13 and 14 [55]. However, the ECM subsequently regained its stiffness during vessel elongation by increased expression of genes responsible for ECM synthesis [55]. These studies provide evidence that microvascular growth and organization can be engineered by providing appropriate mechanical stimulation *in vitro*. In another study, microvessels cultured in 20 mm × 5 mm rectangular collagen gels while applying 6% static or cyclic stretch in the same direction aligned themselves along the major axis of the gel [33]. Constraining the gel along the long axis without additional static/cyclic stretch resulted in same amount of microvessel alignment, although there was no sign of alignment in unconstrained gels [33]. Data obtained from these studies suggest that uniaxially constrained gels show alignment of collagen fibrils due to internal traction force generated by cells. Furthermore, aligned collagen fibrils provide contact guidance for neovessels and thus form a positive feedback loop to promote alignment of newly developed microvasculatures. Chang et al. developed an aligned microvascular network in collagen gels *in vitro* using a rectangular stainless steel frame that constrained contraction along the long-axis [56]. These highly aligned microvascular network-containing gels were transplanted into immunocompromised animals with or without the steel frame to observe growth and alignment of neovessels *in vivo*. They found that highly aligned microvessels transplanted with the frame maintained their alignment even after 30 days. In contrast, unframed highly aligned vessels lost their alignment after transplantation. This highlights the need for a sustained constraint to maintain alignment after transplantation [56]. Moreover, different constraint boundary conditions elicit specific effects on microvascular organization. For example, long axis constrained constructs showed highly aligned and branched microvessel formation compared to unconstrained or short axis constrained conditions [57]. In long axis constrained gels, microvessels can align themselves in the direction of constrained axis because the gel is free to deform lateral to the long axis. However, in short axis constrained gels, the long axis experiences very high stiffness that prevents gel contraction and therefore fails to align microvascular growth in a uniaxial direction. A similar cell induced compaction concept was used to promote microvascular alignment in a constrained fibrin gel *in vitro* [58]. It was observed that serum containing media significantly promoted HUVECs and brain pericyte based microvascular alignment compared to defined cell culture medium [58]. Morin et al. developed an approach to promote microvessel alignment and lumen density in a mechanically constrained cell-induced fibrin gel under interstitial flow, leading to a prevascularized cardiac patch with highly aligned vessels and lumen density of ~650 lumens/mm^2, which is around one third the lumen density of native human myocardium (2,000 lumens/mm^2) [40]. Although effective, this approach does not promote microvessel maturation. The microvessel wall did not show complete integrity along the length of the vessels. Subsequently, the same group used laterally constrained fibrin gels to promote self-assembly of highly aligned microvessels by human blood outgrowth ECs (hBOECs) and human brain vascular pericyte (hBPC) co-culture [59]. It was observed that the mechanically constrained patch enhanced microvessel alignment and increased vessel density (940 ± 240 lumens/mm^2) compared to non-constrained gels (420 ± 140 lumens/mm^2). Transplantation of these patches onto the epicardial surface of infarcted hearts after left anterior descending artery ligation showed successful inosculation and perfusion with host vessels. However, no significant difference was found between perfused lumen formed by aligned (173 ± 97 perfused lumens/mm^2) and randomly organized microvessels (111 ± 75 perfused lumens/mm^2) [59]. Although the influence of microvessel alignment on tissue regeneration needs to be further confirmed, these studies demonstrate the significant impact of mechanical stimulation upon microvessel orientation, maturation and successful perfusion upon transplantation.

Studies have also explored the potential for electrical stimulation to promote angiogenesis. In contrast to the extensive *in vitro*

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Table 1
Prevascularization strategies and characteristics of respective microvascular networks.

Prevascularization strategies	Scaffold materials	Endothelial cell sources	Mural cell source	Microvessel characterization				Potential applications	Refs.
				Vessel orientation	Lumen formation	Vessel diameter (μm)	Intercapillary distance (μm)		
Mechanical and electrical stimulation									
Static/cyclic stretch	Collagen gel	Rat fat pads	Rat Fat pads	Aligned	Yes	5–15	10–50	Complex tissue fabrication	[33]
Gel constrainment	Collagen gel	Rat fat pads	Rat Fat pads	Aligned	Yes	5–20	10–50	Complex tissue fabrication	[57]
	Fibrin gel	hBOEC	hBPC	Aligned	Yes	5–7	50–100	Cardiac tissue engineering	[58]
DC current	Matrigel	hMEC, HUVEC	MASMC, BPAF	N/A	N/A	N/A	N/A	Unidirectional cell migration	[63]
Nano-micron scale topographical features									
Porous scaffolds	Silk fibroin and fibrin	HUVEC	N/A	Random	No	10–50	Cannot be regulated	Prevascularized tissue fabrication for diverse tissue regeneration	[74]
	PDLLA and silk fibroin	HUVEC	N/A	Random	No	10–15			[75]
	Fibrin/PEG	hAFSC	hMSC	Random	Yes	40–50			[76]
	GelMA	ECFC	hMSC	Random	Yes	20–50			[77]
	Calcium phosphate; hydroxyapatite; nickel–titanium	hdMEC	hOS	Random	Yes	25–40			[78]
Fibrous scaffolds	Silk fibroin	hdMEC	hOS	Random	Yes	N/A	N/A	Fabrication of tissues having highly aligned and dense microvessels	[84]
	Collagen	hCMEC HUVEC	N/A	Aligned	Yes	10–20	10–15		[86]
	hDF-based ECM		hDF, hMSC	Aligned	Yes	10–12	10–20		[88,89]
Soft lithography based topographical features	Dextran, HA, agarose	HUVEC	hNSF	Aligned	Yes	15–17	Arbitrary	Development of arbitrarily organized transplantable microvascular networks	[90]
	PDMS, collagen	Bovine MEC, HUVEC	N/A	Aligned	Yes	20–50	Arbitrary		[92]
	PDMS, fibrin, collagen	HUVEC	Hepatocytes	Aligned	Yes	20–50	Arbitrary		[93]
Microfabrication									
Master-mold casting	PLGA,	Bovine EC,	N/A	Arbitrary	No	50–80	Arbitrary	Complex tissues with structured microvessels	[94]
	Silk	HUVEC	BMSC	Aligned	Yes	5–10	Arbitrary		[102]
	Fibrin/PMMA/PC	RAEC, HUVEC	NRCF, NRVC	Aligned	Yes	~60	Arbitrary		[103]
	Fibrin	EPCs	No	Aligned	Yes	<50	50		[133]
Electrochemical replica deposition	Chitosan	Mouse EC (MS1)	N/A	Arbitrary	Yes	300–500	600–900		[101]
Laser micromachining	PLGA	Bovine EC	N/A	Arbitrary	No	N/A	Arbitrary		[96]
Interfacial polyelectrolyte based technique	Chitin and alginate	HUVEC, hMVEC	HepG2, hMSC	Aligned	Yes	~5 to 15	~10 to 70	Prevascularized hepatic tissue engineering	[104]
	Chitin doped with galactose and collagen	iPSC-EC	iPSC derived Hepatocytes	Aligned	Yes	~5 to 10	Arbitrary		[105]
Soft lithography based microfluidic device	Collagen	HUVEC	HBVPC, HUASMC	Aligned	Yes	~100	Arbitrary	*In vitro* disease models and pharmaceutical screening	[109]
	PDMS	HUVEC	N/A	Arbitrary	Yes	100–150	Arbitrary		[110]
	PDMS	HUVEC	HES3-derived pericytes, hDf, hLF, HL-60	Aligned	Yes	50–150	Arbitrary		[111,112,113]
Surface Patterning									
Photo-crosslinking for microvessel guidance	GelMA	HUVEC	hMSC	Aligned	Yes	Arbitrary	Arbitrary	Bone tissue engineering	[159]
	PEGDA containing MMP-sensitive domains	HUVEC	SMC	Aligned	Yes	N/A	N/A		[121]
	PEGDA	HUVEC	N/A	Aligned	Yes	Arbitrary	Arbitrary	*In vitro* angiogenic studies	[160]
	PEG	HUVEC	SMC	Random	Yes	500–1500	Arbitrary	Complex multilayer tissue	[120]
Laser photolithography	MMP-sensitive and RGD conjugated PEGDA hydrogel	HUVEC	Mesenchymal progenitor cells	Arbitrary	No	10–50	Arbitrary	Guiding vessel growth with precision of few microns	[123,129]

(*continued on next page*)

Table 1 (*continued*)

Prevascularization strategies	Scaffold materials	Endothelial cell sources	Mural cell source	Microvessel characterization				Potential applications	Refs.
				Vessel orientation	Lumen formation	Vessel diameter (μm)	Intercapillary distance (μm)		
Cell sheet stacking	Scaffold free approach	HUVEC	NHDF	Random	Yes	10–20	N/A	Thick 3D tissue by multiple cell layers	[132]
		HUVEC	NHDF	Aligned	N/A	Arbitrary	Arbitrary		[134]
		HUVEC	Cardiac cell	Random	Yes	N/A	N/A		[135,136]
3-D bioprinting									
Indirect 3D printing	Fibrin, collagen	HUVEC	hMSC, hNDF	Arbitrary	Yes	100–410	Arbitrary	Physiological scale prevascularized tissue fabrication	[143]
	GelMA	HUVEC	hNDF, 10 T1/2 fibroblast	Arbitrary	Yes	200	Arbitrary		[161]
	Alginate, collagen, gelatin, fibrin	HUVEC	hDF	Arbitrary	Yes	200–1000	Arbitrary		[162]
Direct 3D printing									
Extrusion bioprinting	GelMA, alginate	HUVEC	MDA-MB-231, MCF7, NIH/3T3	Arbitrary	Yes	300–500	Arbitrary	Complex prevascularized tissue fabrication and *in vitro* cancer modeling	[163]
	GelMA, alginate	HUVEC	Cardiomyocytes	Arbitrary	Yes	100–300	Arbitrary		[164]
	GelMA, PEGTA	HUVEC	hMSC	Arbitrary	Yes	400–1000	Arbitrary		[165]
Light/laser based bioprinting	PEGDA	N/A	HELA, 10 T1/2	Arbitrary	Yes	25–120	Arbitrary		[158]
	GelMA	HUVEC	10 T1/2	Arbitrary	Yes	50–250	Arbitrary		[166]
	PEG-DMA	N/A	NIH/3T3 fibroblast	Arbitrary	Yes	100	Arbitrary		[156]
Droplet based bioprinting	GelMA, collagen	HUVEC	hMSC	Arbitrary	Yes	<50	N/A	Patterned cellular constructs	[167]
	ULGT-agarose	N/A	HEK-293 T cells, MSC	Arbitrary	N/A	120–160	N/A		[154]

DMA: Dimethacrylate; **hAFSC**: human amniotic fluid stem cells; **hBVPC**: human brain vascular pericyte; **HEK**: human embryonic kidney cells; **HES**: human embryonic stem cells; **HL-60**: human promyelocytic leukemia cell; **hLF**: human lung fibroblast; **hMVECs**: human microvascular ECs; **hNDF**: human neonatal dermal fibroblasts; **hNSF**: human neonatal skin fibroblasts; **NHDF**: normal human dermal fibroblast; **NRCFs**: neonatal rat cardiac fibroblasts; **NRVCs**: neonatal rat ventricular cardiomyocytes; **RAECs**: rat aortic endothelial cells; **ULGT**: ultra low gelling temperature.

studies that have confirmed the role of mechanical stimulation in prevascularized engineered tissue fabrication, most of the electrical stimulation based studies are preliminary and largely focused on angiogenesis *in vivo*. Early animal studies indicated that electrical stimulation promotes the expression of VEGF, Ang-II and Ang-I receptors [60–62]. In another study, different vascular cell types including human microvascular endothelial cells (hMECs), HUVECs, bovine pulmonary artery fibroblasts (BPAFs) and murine aorta SMC (MASMC) were tested for alignment, elongation and migration under directional electrical fields of 150–400 mV/mm [63]. Among these cell types, hMECs showed the highest migration in the direction of direct current (DC), with a rate of 100 μm/h. These studies highlighted the potential influence of electrical stimulation in directing microvascular growth in a desired direction. Recently, Ud-Din et al. tested degenerate waveform based electrical stimulation on cutaneous wound healing in 40 healthy individuals. Their results indicated that electrical stimulation enhanced wound healing and increased angiogenic activity by promoting VEGF-A and placental growth factor (PLGF) expression [64]. Although promising, further studies focusing on the use of electrical stimulation for microvascular organization, especially in tissue engineered scaffolds, are required. Moreover, the optimum force intensities of this electomechanical stimulation and their target signaling pathways needs to be further explored in order to design novel bioreactors that can stimulate vascular cell organization and microvessel alignment *in vitro*.

4.2. Nano-micron scale topographical features for microvessel formation

ECM proteins are usually assembled into 3D structures *in vivo* with typical surface topographies in the range of nano- to micrometer scale sizes [65]. One of the elementary components of natural ECM, a helical collagen I fibril, has a diameter in the range of 20–200 nm [66,67]. These fibrils are assembled into larger collagen bundles, with a diameter of ~1–20 μm [68]. Similarly, vascular basement membranes contain typical topographical features, such as pores and fibers, that have dimensions in the range of 100–1000 nm [69]. Studies have shown a significant influence of these surfaces topographical features on cellular behaviors, irrespective of external biochemical stimulation [70,71]. It has been found that the basal lamina remains intact even after tissue injury and severe necrosis, acting as an architectural map to establish spatial relationships between new cells and angiogenic sprouts during regenerative processes [72]. Therefore, scaffolds mimicking native ECM based topographical features may translate spatial and mechanical cues to guide the orientation of microvascular network *in vitro*. In this section, the influence of three types of topographical features including porous, fibrous and soft lithography based surface topography on highly-organized and structured microvessel formation are reviewed.

4.2.1. Porous topographical features for microvascular network formation

Surface topography of the basement membrane as revealed by scanning electron micrographs (SEM) of different tissues, including descending aorta, left common carotid, left saphenous vein, inferior vena cava and cornea of the rhesus macaque, as well as porcine aortic valve and human cornea, contain a porous structure with pore sizes ranging from ~38 to 92 nm [69]. Scaffolds designed with these porous topographical features control EC behavior by regulating integrin binding and focal adhesion complex formation, which further results in cytoskeletal re-organization. Several natural, synthetic and hybrid scaffold materials designed with bone ECM mimicking porous topography have been tested as potential scaffold candidates to develop and sustain microvascular networks

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in vitro. Importantly, this 3D porous topography provides structural support and promotes a uniform colonization of vascular cells into the scaffold. One of the natural polymers, submicron-scale pore sized silk fibroin, has been wildly used for bone tissue engineering [73]. Silk fibroin combined with a fibrin gel supported highly dense capillary network formation upon human umbilical vein endothelial cell (HUVECs) and human foreskin fibroblast co-culture [74]. Silk fibroin containing a salt-leached poly (D, L lactic acid) (PDLLA) sponge mimics both porous and fibrous topographical features of natural ECM with pore sizes ranging from a few hundred nanometers to a few hundred micrometers providing a good scaffold platform to promote vascularization [75]. It was observed that hybrid (PDLLA + silk fibroin fibers) sponge showed enhanced stiffness, EC retention and an increased rate of vascularization compared to a synthetic (PDLLA only) sponge [75]. It is possible that incorporation of fibers provided a coherent surface for EC attachment, which might have produced the increased rate of vascularization. Another polymer combination that contains micron scale porous surface topography is fibrin- poly ethylene glycol (PEG) scaffolds [76] and gelatin methacrylate (GelMA) hydrogels [77]. The hybrid polymers have been demonstrated as appropriate scaffold materials for promoting dense capillary networks along with distinctive lumen formation by co-culture of ECs and perivascular cells (i.e. bone marrow derived mesenchymal stem cells (MSCs)). For prevascularized bone tissue engineering, various scaffolds having porous topography such as, hydroxy apatite (HA), calcium phosphate, and nickel–titanium, were tested for their ability to sustain microvessel formation during long term co-culture of human dermal microvascular endothelial cells (HDMEC) and primary human osteoblast cells (HOS) [78]. These materials formed and sustained microvessel assembly for 42 days without external growth factor stimulation (Fig. 2A(IV)) [78]. The microvessels formed on different porous scaffolds had vessel diameters from a few microns up to ~60 μm. Importantly, microvascular networks

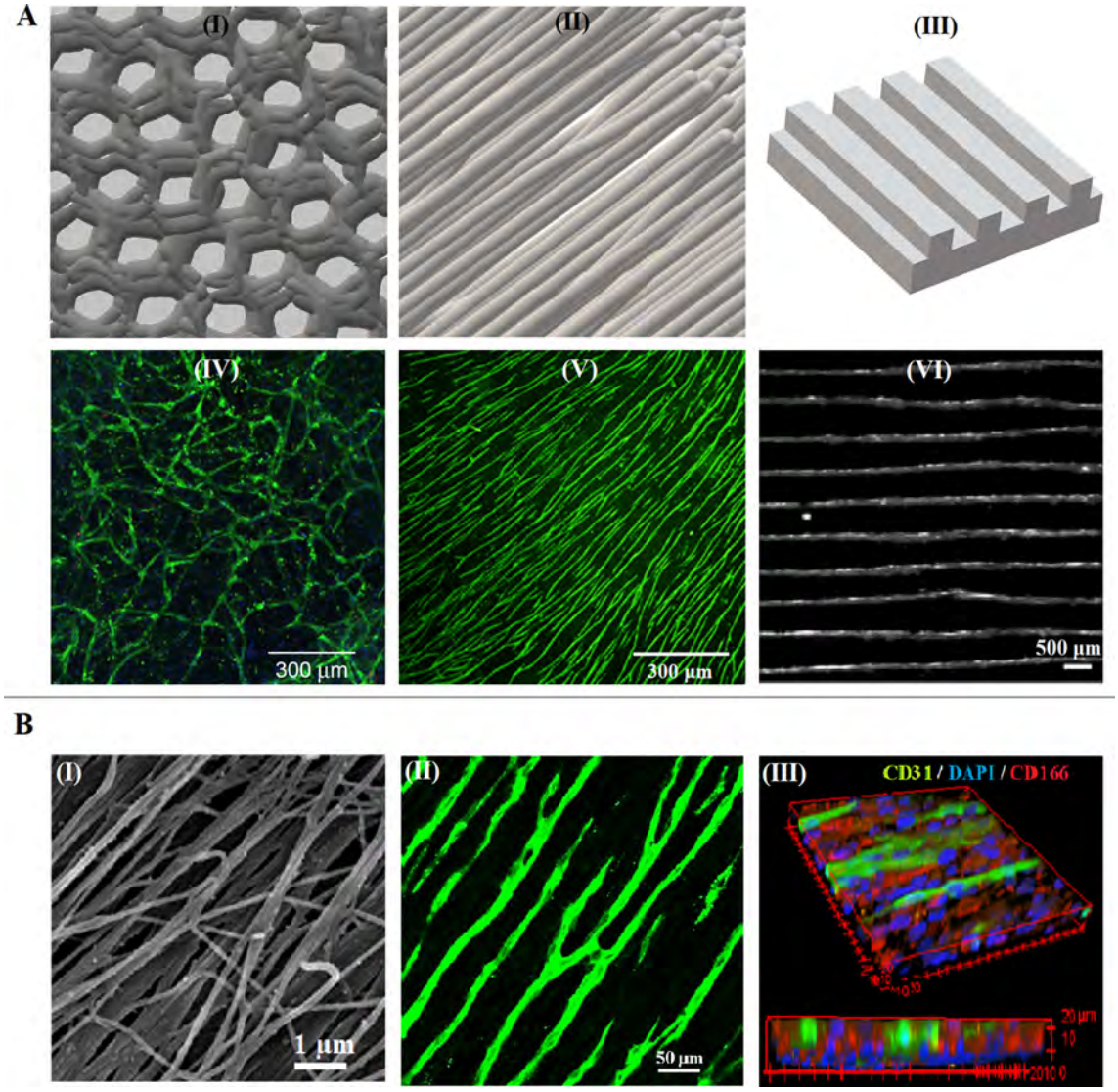

Fig. 2. Influence of topographical features on microvascular network formation. (A) The first penal illustrates (I) porous, (II) fibrous and (III) soft lithography based materials. The second penal shows microvascular network formation on respective surface topography. (IV) Randomly organized microvascular network formation on porous calcium phosphate scaffolds by HDMEC - HOS co-culture stained by EC-specific PECAM-1 (green) and DAPI (blue). Image reused and modified from [78] with permission of Elsevier. (V) Highly organized and dense microvascular network formation by hMSCs and ECs co-cultured on hDF-derived aligned nanofibrous ECM sheets stained by anti-CD31 antibody (green) [89]. (VI) Aligned microvessels formed by ECs grown in collagen filled aligned PDMS grooves (50 μm width and 50 μm height). Image reused and modified from [93] with permission of PNAS. (B) Mechanism of highly aligned ECM directed microvessel formation. (I) SEM micrograph of highly aligned ECM nanofibers derived from decellularized hDF sheets. (II) Highly aligned microvascular network formed by hMSC-EC co-culture on aligned ECM sheet. (III) CD166 guided aligned and random microvascular tracks [89]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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developed on GelMA *in vitro* successfully formed functional anastomoses with host vasculature in an immunodeficient mouse model [77]. Although microvascular networks formed on these porous materials showed open lumens, a mature vessel phenotype and improved vessel characteristics such as length, branching and density, the vascular structures are randomly organized. In contrast, as mentioned earlier, tissues such as cardiac and skeletal muscles have highly organized and aligned microvascular networks (Fig. 1C) [21,22]. To obtain similar highly organized microvascular architecture *in vitro*, fibrous topographical features have been utilized that can guide uniaxial cell migration and vessel assembly.

4.2.2. Fibrous topographical features for microvascular network formation

Akin to porous materials, several natural, synthetic and hybrid fibrous materials have been developed that can support high-density microvascular network formation without using external biochemicals. As aforementioned, collagen fibrils (20–200 μm in diameter) in native ECM are hierarchically organized into the larger collagen bundles that are few microns in diameter [67]. These native ECM fibers provide nano-micron scale contact guidance that influences cell polarity as well as migration through regulation of integrin binding, focal adhesion complex formation and cytoskeletal re-organization [79]. Several studies have shown that fibrous surface topography can regulate orientation and density of microvessel formation. Electrospun fibers, due to the ease of fabricating aligned and nano-scale topography [80], have been widely used as scaffold materials for engineering blood vessels, skin and bone tissues [81,82]. Nowsheen et al., have reviewed strategies for the development of *in vitro* and *in vivo* vascularization in surface modified electrospun scaffolds that incorporates co-cultures, growth factors and small molecules [83]. However, the majority of the studies have not put a high emphasis on the development of highly oriented and organized tissue architecture in mature microvascular networks *in vitro*. The strategies summarized here purely focus on the influence of fibrous topographical features on the development of highly organized microvascular networks. Fibrous scaffolds prepared from natural polymers, for example, fibrous silk fibroin nets (~75 μm fiber diameter), when co-cultured with HDMEC and primary HOS, showed self-assembly of randomly organized micron scale, capillary like structures with an open lumen [78]. These prevascularized silk fibroin scaffolds, when subcutaneously transplanted into an immunodeficient murine model, showed rapid and successful anastomosis with the host vasculature [84]. As a major component of native ECM, alignment of collagen-I fibers may play a crucial role in regulating the direction of microvessel growth [85]. It was observed that compared to randomly organized collagen fibers, highly aligned collagen fibers promoted more aligned and branched microvessels with an average length of ~300–500 μm and open lumen structure [86]. It is possible that ECs have different mechano-sensing ability for aligned fibers compared to randomly organized fibers, resulting in differential vessel length and branching. This possibility was further confirmed by addition of focal adhesion kinase (FAK) and rho-associated protein kinase (ROCK) inhibitors, which reduced microvessel growth on highly aligned collagen fibers, but not on randomly organized fibers [86]. In order to utilize properties of not only collagen but the blend of native ECM protein components, our group has created a highly aligned nanofibrous scaffold by decellularizing aligned human dermal fibroblast (hDF) cell sheets [87] (Fig. 2B(I)). The highly aligned ECM sheet contained fibronectin, collagen I and elastin, with a fiber diameter of approximately 80 nm, which is similar to the diameter of collagen fibers *in vivo*. hMSCs and HUVECs co-cultured on these decellularized ECM sheets formed highly organized, dense, branched and mature microvascular networks with the expression of both endothelial and perivascular cell specific phenotype (Fig. 2A(V)) [88]. Capillaries in native cardiac tissues have diameters in the range of ~10 μm or less, and intercapillary distance typically between 10 and 20 μm [21,22]. Importantly, microvascular network formed on aligned ECM sheets by hMSC-EC culture displayed similar intercapillary distances and vessel diameters (Fig. 2B(II)) compared to native myocardium as shown in Fig. 1 [89]. By investigating underlying mechanisms, it was observed that hMSCs cultured on ECM sheets orient themselves by following the topographical features of the scaffold. hMSCs further created cluster of CD166 tracks to guide EC assembly into microvessels in the same orientation and also enhanced the maturity of the microvessels as described in Fig. 2B (III) [89]. These prevascularized cell sheets with highly aligned microvessels can serve as potential building blocks in the development of physiological scale 3D cardiac patches, which may promote positive cardiac remodeling after MI. It is always important to design strategies that can tune interconnectedness, branching and density of microvascular network throughout the scaffold materials and also allow anastomosis with host vasculature. However, there are a few, but important, translational issues that need to be resolved including improvements in prevascularized cell/ECM sheet stacking methods to develop thicker prevascularized tissues and the development of functional anastomosis between the engineered microvascular network and the host vasculature upon transplantation.

4.2.3. Soft lithography for microvascular network formation

Highly structured nano- and micro- scale topographical features have been created on substrate surfaces using soft lithography. Several studies have demonstrated that soft lithography enables both natural and synthetic materials to tune their structures, which could further regulate directions and dimensions of microvessels by integrating the spatial, biochemical and biomechanical factors in the microenvironment. For example, Jiang et al., combined soft lithographic and micro- molding techniques to develop micro- patterned hyaluronic acid (HA)–dextran hydrogels having 20 μm-high parallel grooves with varying widths (30, 50, 100 and 200 μm). The microchannels in these hydrogels were filled with collagen [90]. HUVECs seeded in these microchannels displayed self-assembly of microvessels in grooves with a width narrower than 50 μm. Moreover, delayed addition of stromal fibroblast further stabilized preassembles EC cord like structures by wrapping them outwardly [90]. In another study, nano-patterned polydimethylsiloxane (PDMS) substratum with 350 nm groove width, 250 nm groove depth and 700 nm groove pitch coated with collagen was used to perform tri-culture of hDF, human pericytes from placenta and HUVECs [91]. This study indicated that compared to a flat surface, nano- scale surface topography significantly promoted cellular alignment and capillary like tubular structure formation with increased vessel length and total vessel area [91]. Although soft lithography based topographical features provide a highly controlled microenvironment to study spatio-mechanical crosstalk between cells and surfaces, they are unsuitable to develop physiological scale 3D prevascularized tissues. Moreover, large engineered tissues normally require longer vessels that can span throughout the scaffold ensuring overall transport of nutrients and gases. To address this issue, Raghavan et al., developed a soft lithography based technique to fabricate microvessels whose length can be extended up to 1 cm [92]. ECs seeded in collagen filled aligned PDMS grooves having 50 μm width and 50 μm height formed aligned microvessels with distinctive open lumens (Fig. 2A(VI)). These collagen supported EC cord structures can be removed from the PDMS grooves and then be transferred onto another hydrogel, making this technique more translational for engineering 3D tissues [92]. When implanted into

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nude mice, these vascular cords formed rapid anastomosis with host vasculature within 3 days [93]. Interestingly, these implanted cords acted as template and guided neovasculature formation in the host tissue. In addition, implanted highly organized vascular cords containing primary rat and human hepatocytes in a construct showed better hepatic survival [93]. These studies indicated that various surface topographical features, irrespective of external growth factor stimulation, significantly regulate characteristics of microvascular networks including microvessel maturation, length, density, and most importantly, vessel orientation, in order to comply with tissues with highly organized microvasculatures. However, issues related with development of thicker prevascularized tissues and functional anastomosis with host vasculature still need to be addressed.

4.3. Microfabrication for structured microvessel formation

Advancements in microfabrication technology have opened up possibilities to create micro-size scaffolds with nanoscale surface features. During recent years, microfabrication has been employed to develop micron scale 3D scaffolds that directly support structured microvessel formation. However, it is crucial to select appropriate natural or synthetic biomaterials that not only support microvessel formation *in vitro*, but also are suitable for transplantation.

4.3.1. Engineered micro-scaffold based prevascularization

Photoresist master molds have been widely used to developed micron sized casts of biodegradable microstructures that supports highly organized microvascular network formation (Fig. 3A(I)) [94,95]. In one such study, poly (lactide-co-glycolide) (PLGA) microchannels with internal diameter of ~60 μm were casted from a master mold and seeded with bovine ECs to promote endothelialization [94]. However, inappropriate endothelialization was observed during dynamic cell seeding as it causes severe cell flushing out of the microchannels [94]. Femtosecond laser micromachining is another system that can create micron scale pillared scaffolds from a biodegradable material such as polylactide (PLA) and PLGA [96,97]. The major advantage of this technique is that it enables engineers to modulate size, shape, orientation and internal diameter of the microstructures at the micron-scale level. Using this technique, Wang et al., developed PLGA scaffold with rectangular branches having a width and depth of 80 μm and 50 μm, respectively [96]. This technique further created surface roughness at the level of nanometers (~226 nm) that promoted successful adhesion and proliferation of ECs that covered the scaffold branches completely. Although promising, this technology requires studies regarding long-term vessel integrity and intact lumen formation after polymer degradation. Importantly, selection of appropriate perivascular cell type for co-culture can further enhance stability of the microvascular networks, especially after scaffold degradation [98]. Microfabrication has also been used to develop microchannel structures, which allows a high level of control over scaffold features [99]. The preformed channels can increase oxygen and nutrient transportation along the length of scaffold to enhance endothelialization and cell viability [100]. In one such study, different regularly-oriented micro-channels with the same diameter (500 μm) but different inter-channel spacing (600, 700, or 900 μm) were produced by electrochemical replica-deposition of chitosan and subsequent cross-linking [101]. Compared to randomly oriented micro-channels, the scaffold with symmetrically organized microchannels having 700 μm inter-channel spacing enhanced mouse EC attachment, proliferation, migration and the formation of ~100 μm ID microchannels. Besides chitosan, regularly-oriented micro-channels fabricated from silk and [102] and fibrin [103] have also been tested for their ability to support *in vitro* vascularization and successful anastomosis with host vasculature after transplantation. Leong et al., developed a novel approach to construct prevascularized adipose and hepatic tissue with aligned vasculature using water-soluble chitin and alginate based fibers based on an interfacial polyelectrolyte method [104]. They constructed a structure containing central HUVEC laden algi-

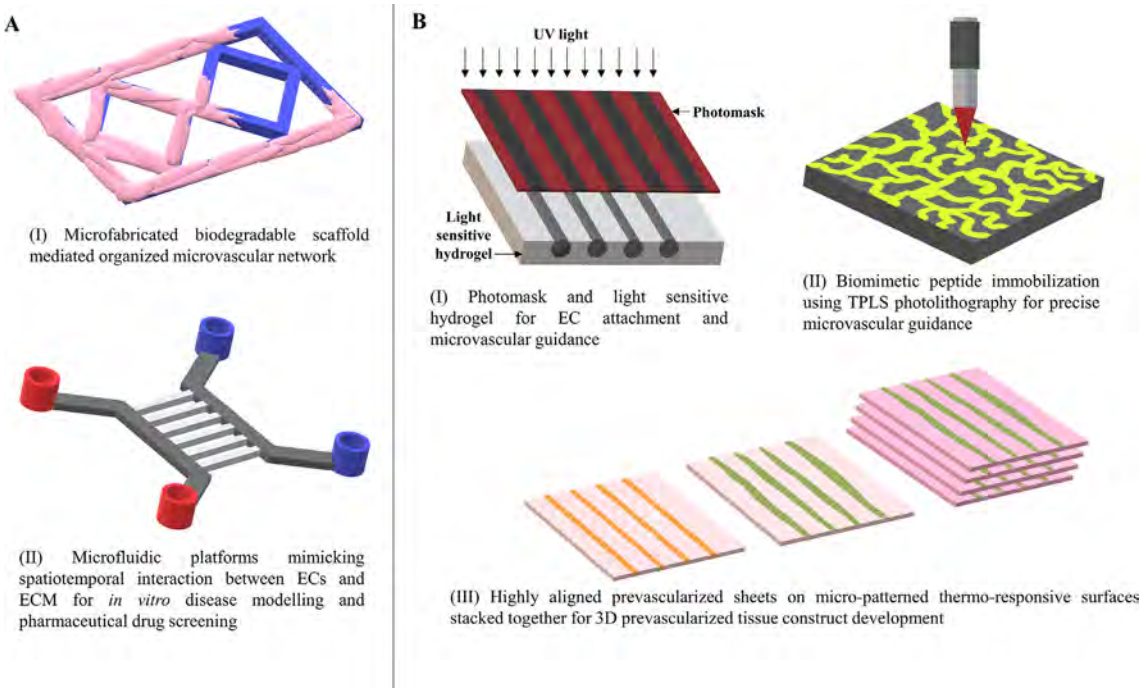

Fig. 3. Microfabrication strategies for structured microvessel networks. (A) Micro-scaffolding for structured microvessel formation. (I) Engineered micro-scaffold based prevascularization, (II) Microfluidics devices for structured microvessel formation. (B) Surface-patterning for microvascular guidance. (I) Photo-crosslinking, (II) Laser photolithography, (III) Micro-contacting and cell sheet stacking.

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nate fibers surrounded by eight hepatocytes (HepG2) cell laden fibers. These structures were further assembled into other higher order structures by multiple stacking to create highly aligned prevascularized tissue with an average intercapillary distance between ~10 and 50 μm [104]. Similarly, water-soluble chitin doped with galactose and collagen has shown to support induced pluripotent stem cell (iPSC) derived hepatocyte as well as EC growth [105]. This construct containing EC channels in the center surrounded by hepatocytes promoted vascularization upon mouse partial hepatectomy model transplantation [105]. Taken together, these micro-scaffolding strategies, including master-mold casting, laser micromachining, electrochemical replica-deposition and interfacial polyelectrolyte based microfiber formation have enabled researchers to create microscale structures that allow primordial vascular structure formation *in vitro*, which can be transplanted into animal models to test their potential. Although primitive, these strategies have served as initial stepping-stones in the direction of higher order structured microvessel network formation *in vitro.*

4.3.2. Microfluidics devices for structured microvessel formation and in vitro bio-mechanism detection

In vivo angiogenesis assays including cranial window and dorsal skin chamber preparation have been widely used for understanding the angiogenic process. However, these methods are costly, time consuming, labor intensive and therefore, are unsuitable for high throughput test studies [106,107]. Alternatives *in vitro* angiogenic assays also have been challenged for their reliability because they do not mimic essential micro-environmental features of native tissues. Therefore, *in vitro* assays can lead to inaccurate conclusions being drawn. Microfluidics devices can provide a potential platform that mimics spatiotemporal interaction between cells and surrounding ECM [108]. To explore this possibility, Zheng et al., have developed microfluidics-based functional vascular structures that can provide an *in vitro* platform to study angiogenesis and thrombogenesis related phenomenon [109]. They created type-I collagen gel based aligned channels with cross section area of 100 μm × 100 μm using soft lithography and seeded ECs and/or perivascular cells. The ECs in these channels showed typical barrier function along with expression of focal adhesion junction [109]. Experiments further proved that these EC lined channels closely mimicked certain physiological characteristics of microvessels and therefore, may be used as a potential disease model. In another study, simple microfluidic devices containing geometrical channels were coated with type-I collagen and matrigel [110]. These devices offered ability to create endothelialized lumens with ~100–150 μm diameter and tubular EC branches in different geometries (Fig. 4A). ECs seeded in these devices showed normal barrier function and responsiveness toward angiogenic stimuli [110].

Microfluidic devices with array or tubular capillaries of various dimensions on a single chip can provide a good platform to understand cellular behavior in different sized vessels in a spatiotemporal fashion [111]. For example, microfluidic device containing different sized capillary channels between 50 and 150 μm in diameter and between 100 and 1600 μm in length, were created. ECs seeded in these microchannels showed characteristic tight junction protein expression and barrier function. Interestingly, these chips were compatible with live cell microscopy, which made this model more advanced for studding angiogenesis [111]. Same group developed a microfluidic platform that sustained perfusable normal and tumor vasculatures by spatially controlling co-culture of ECs with fibroblasts, pericytes and cancer cells (Fig. 4B) [112,113]. These simple microfluidic devices very efficiently mimicked the physiological microenvironment of native microvessels and therefore, provided a reliable *in vitro* model to understand phenomena associated with angiogenesis, thrombosis and inflammation. As mentioned earlier, these models can be very helpful in studying underlying mechanisms of various diseased conditions as well as pharmaceutical screening for atherosclerosis, hypertension, cardiac arrest, stroke and cancer. Recent progress in microfluidic platforms will enable researchers to create successful anastomoses between host vessels and engineered microvasculature formed *in vitro*. Although somewhat primitive, these advancements will be milestones in the development of physiological scale prevascularized tissues as well as for organ fabrication. One such study showed a successful connection between a capillary network that was developed in a fluidic chamber and adjacent EC lined microfluidic channels, mimicking arteries and veins [114]. Physiological fluid transport and ability to connect with host vasculature makes these devices an appropriate tool for *in vitro* disease models and organ-on-chip applications.

4.4. Surface-patterning for microvascular guidance and organization

In recent years, rapidly evolving surface-patterning techniques have enabled researches to regulate cellular behavior, tissue self-assembly and mechanics. Micro-patterning techniques, such as photo-crosslinking, laser photolithography, micro-stamping and cell sheet stacking, have been used to develop highly structured 3D microvascular networks in engineered tissues (Fig. 3B).

4.4.1. Photo-crosslinking for microvessel guidance

Light sensitive hydrogels polymerize when exposed to certain wavelength of the light by free radical induced chemical reaction between the photo-initiator and the photosensitive polymer [115]. The use of a photomask can prevent hydrogel polymerization in pre-designed areas. The unexposed, non-polymerized areas can be washed off to create open channels which can be subsequently seeded with ECs to develop microvascular networks. GelMA hydrogels, due to their photo-crosslinking abilities and biological properties including the presence of arginine-glycine–aspartic acid (RGD) peptide and MMP responsive peptide motifs, have been widely used as a scaffold material for the development of vascular networks *in vitro* [77,116]. GelMA can promote microvascular network formation upon co-culture of human blood-derived endothelial colony-forming cells (ECFCs) and bone marrow derived MSCs. The capillary network formed within these gels showed an average vessel diameter between ~5 and 20 μm and a total vessel length of ~5 mm/mm^2 with typical lumen structure [77]. However, the capillary network formed on these hydrogels was randomly organized. In order to create highly aligned capillary-like network in a 3D scaffold, Nikkhah et al. used HUVEC-laden GelMA hydrogels, which were poured in between spacers with different heights of 50, 100 and 150 μm [117]. This cell-laden hydrogel was further photo-crosslinked under ultraviolet (UV) light with photomasks to develop 8 mm long and 50 μm wide highly aligned rectangular channels. It was observed that hydrogels with 100 μm height provided optimum microenvironment for the development of highly aligned and stable capillary cord like structures with circular lumens [117]. Poly(ethylene glycol) (PEG)-diacrylate (PEGDA) is another photoactive polymer that has been explored to create microvessels through a simple surface patterning method [118]. Although, PEGDA hydrogel is resistant to cell and protein adhesion, immobilization of ECM mimicking peptides, such as arginine-glycine–aspartic acid -serine (RGDS), can guide cellular migration and growth in particular direction. Photolithographic masks can be used to create hydrogel surfaces patterned with acryloyl–PEG–RGDS in precise geometrical patterns upon UV photo-crosslinking. These acryloyl–PEG–RGDS patterned surface successfully guided human dermal fibroblast adhesion in the hydrogel [118]. However, similar technology can be applied to create highly aligned capillary cord like structures [119]. To achieve this goal,

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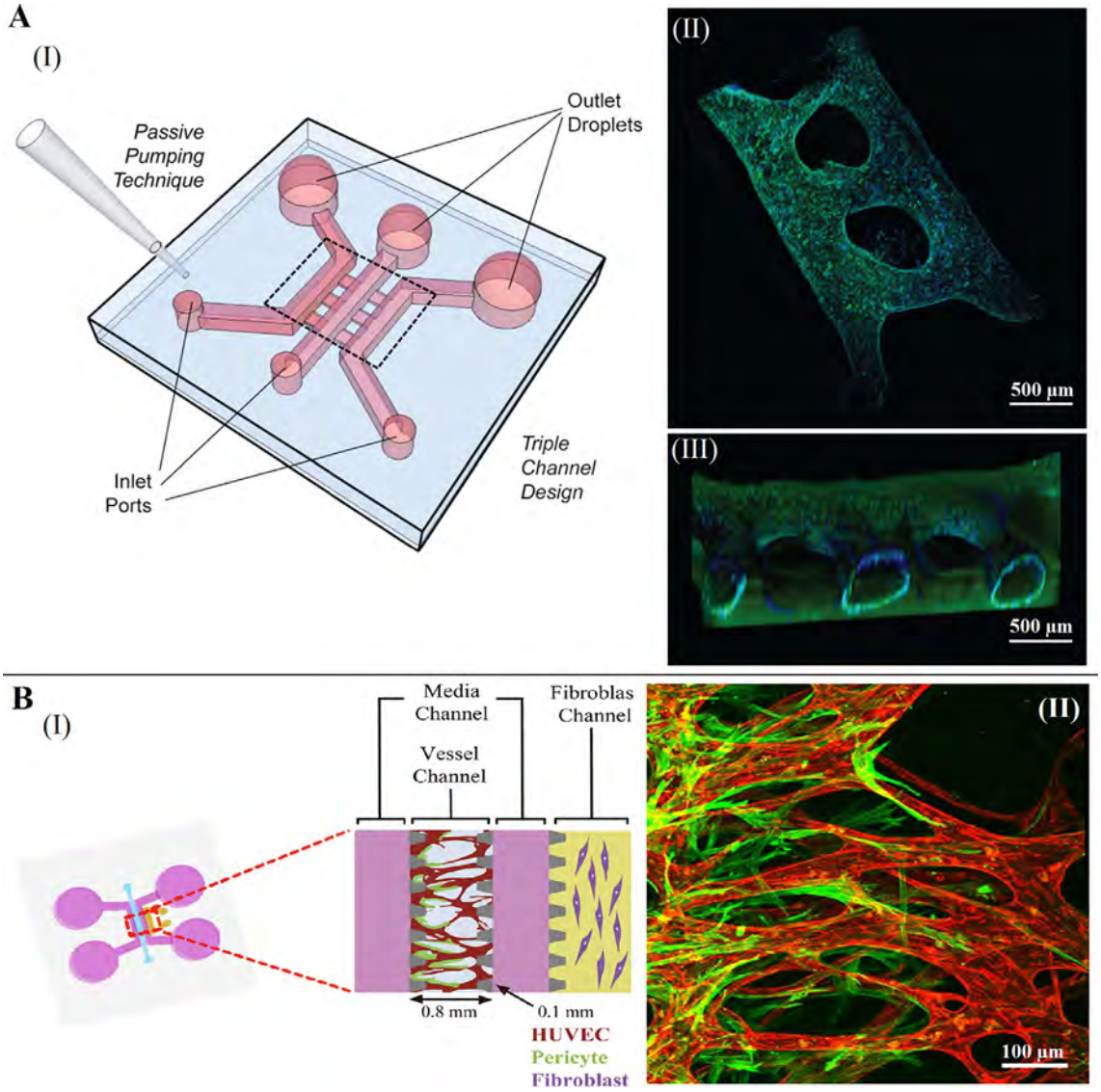

Fig. 4. Microfluidics based platforms for prevascularization. (A) (I) Microfluidic design with connected microchannels, (II and III) A double microchannel containing interconnected endothelialized lumens with volume-rendered cross-sectional view (Image reused and modified from [110] with permission of Elsevier). (B) (I) Microfluidic device design (II) EC patterning and microvascular networks wrapped by mature pericytes (Image reused and modified from [113] with permission of PLoS One).

RGDS peptides were immobilized in different concentration (2, 4, 20, 100 μg/cm^2) and geometries (aligned stripes with width in the range of 50–200 μm) using photolithography to control HUVEC adhesion, migration and morphogenesis. It was observed that ECs self-assembled into highly aligned capillary cord like structure while cultured on 50 μm wide and 20 μg/cm^2 RGD immobilized stripes. Interestingly, increased RGD concentration negatively affected capillary like structure formation, possibly by restricting EC migration [119]. In another study, 3D PEGDA constructs with defined internal microchannels were created using UV photolithography [120]. An array of these hydrogels were further stabilized by secondary UV exposure to create interconnected constructs with wall thickness of 450 μm, internal diameter of 100–400 μm, and a length of 3.6 mm. These constructs may be seeded with ECs and SMCs for rapid and cost effective construction of vascular structures [120]. Perfusion based photopolymerization has been employed to develop gradients of elastic modulus, immobilized MMP-sensitivity and YRGDS (Tyr-Arg-Gly-Asp-Ser) peptides in PEGDA hydrogels to guide microvessel growth [121]. Gradients of different stiffness, MMP-sensitive peptide presentation and YRGD concentration successfully promoted highly regulated and longer (maximum ~2,700 μm) microvessel growth upon HUVECs and human umbilical artery smooth muscle cells (HUASMCs) co-culture [121]. Although photo-crosslinking methods are efficient in creating microvascular structures with precise size and orientation, the majority of the studies are only applicable for *in vitro* applications. Moreover, selection of photo-crosslinkable materials and UV light exposure needs to be precisely controlled otherwise it may induce cytotoxicity. The UV light penetration is also limited to certain depth, which can be a significant hindrance for development of 3D channels in thicker hydrogels.

4.4.2. Laser photolithography for precise microvascular guidance

Scaffolds fabricated via solvent casting, lyophilization and porogen leaching have been developed for tissue engineering. However, these techniques lack control over pore geometry as well as porous interconnectivity in the scaffold. In sharp contrast, laser photolithography is a highly precise method that can create microchannels with defined geometrical parameters in the scaffold, which can be subsequently vascularized. Two-photon laser scanning (TPLS) photolithography can create 3D microstructured scaffolds with increased precision and fidelity. One such geometri-

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cal porous scaffold having a 2.5 mm^3 cube size and 250 μm pitch size between two geometrical pores was developed using TPLS photolithography to sustain cell culture. Primary hepatocytes seeded in these scaffolds showed higher levels of liver specific function over 6 days of culture period compared to a 2D monolayer culture [122]. This technology can also be used for the development of highly organized microvessel growth into millimeter scale scaffolds. In another study, TPLS photolithography was used to precisely immobilize RGD peptides in micro-patterns within collagenase-sensitive PEGDA hydrogels [123]. Human dermal fibroblasts cultured in fibrin clusters, when encapsulated with these RGD immobilized collagen sensitive PEGDA hydrogels, showed precise RGD guided migration [123]. This approach has a potential application in guiding EC growth on a predefined path to create highly aligned microvascular network in 3D scaffolds. Due to recent advancements in high-resolution microscopy and image processing techniques, 3D architectural maps of microvascular networks in various native tissues are available [22,124–128]. These architectural maps can be used as explicit blue prints to develop biomimetic microvascular networks *in vitro*. Culver et al., used photo-crosslinkable, MMP-sensitive and RGD conjugated PEGDA to create such biomimetic microvascular networks [129]. Confocal images of microvascular network organization from different tissues (heart, retina and cerebral cortex) were used as a templet to immobilize RGD conjugated PEG via 3D TPLS lithography on the cell-encapsulated hydrogel. HUVECs and mesenchymal progenitor cells were chosen as endothelial and perivascular cell sources respectively, in order to develop microvascular networks. Results obtained from this study showed precise microvascular growth following RGD patterning with vessel diameter of ~10–50 μm [129]. Although closely biomimetic vascular growth was obtained by this study, the microvessels lacked vessel wall integrity and typical lumen formation. Laser photolithography based techniques are highly efficient in regulating microvessel growth in a particular direction. However, future advancements are required to promote microvascular maturation, perfusion and long-term stability for translational applications.

4.4.3. Micro-contacting and cell sheet stacking for thick prevascularized tissue fabrication

One of the major questions that still needs to be addressed is how to develop physiological sized, thick prevascularized tissues with highly organized in-built microvascular networks. One of the potential solutions to resolve this issue is the development of microvascular networks in 2D cell sheets and then stack them into thicker tissues. Cell sheet stacking manipulator coated with millimeter thick fibrin gel provides a possible solution to stack multiple cell sheets detached from thermo-responsive polymers [130,131]. This approach was used to stack three cell sheets, containing layers of hDF and/or HUVECs into different orders to promote vascularization [132]. It was observed that a HUVEC sheet covered with two hDF cell sheets developed a microvascular network with typical open lumen structure of 2–10 μm diameter [132]. However, this technique does not provide control over regulating microvessel growth in a desired direction. To achieve this goal, PDMS substrates with aligned microgrooves (width ranging from 2.5 μm to 70 μm) were used to stamp patterned fibrin coatings on a glass slide, which was subsequently seeded with endothelial progenitor cells (EPCs). This EPC containing slides were inverted and placed on top of another fibrin gel layer. Thus, the EPCs were sandwiched between the fibrin gel layer and the cover slip to promote aligned microvascular growth [133]. EPCs cultured on fibrin coatings having a width less than 20 μm did not assemble into capillary cord like structures, while 50 μm wide fibrin strips showed successful 3D microvascular tube formation with positive expression of CD31, VEGF receptor (VEGFR)-2 and vascular endothelial cadherin (VECAD). Although promising, this technique did not produce a continuous lumen open throughout the length of the capillary cords [133]. In another approach, highly aligned thermo-sensitive poly(N-isopropylacrylamide) (PIPAAm) surfaces were used to develop highly aligned EC and hDF sheets [134]. When the aligned EC sheet was sandwiched between aligned hDF sheets in the same orientation, ECs developed a vessel like structure in the same uniaxial direction [134]. However, changing hDF orientation significantly hindered ECs ability to form capillary like structures, indicating that the orientation of co-cultured cell types significantly influences vessel alignment.

After successful development of highly organized microvessels *in vitro*, the further challenge lies in the translational applications. It is critical to find novel solutions that can promote successful anastomosis between engineered microvascular networks and host vessels. To address this issue, two different approaches, which involve either natural femoral muscle or a synthetic collagen-gel based vascular bed, have been developed to provide oxygen and nutrient transport to prevascularized cell sheets [135,136]. In a collagen gel based vascular bed design, cardiomyocyte-EC co-cultured sheets were cultured on the top of a collagen gel containing ~300 μm wide microchannels [136]. Co-cultured ECs formed microvascular networks within the cell sheets as well as inside the collagen gel based microchannels. The anastomosis between newly formed vasculature in cell sheets and collagen microchannels was confirmed by continued flow of blood [136]. Although the cell sheet based microvessels formed an anastomosis with engineered collagen channels, the challenge remains open for creating successful anastomosis between host vessels and collagen microchannels. Moreover, maintaining vascular integrity of these collagen microchannels after transplantation and biodegradation is still an open question that needs to be addressed. In the second strategy, three cell sheets fabricated by EC-cardiac cell co-culture were stacked upon rat femoral muscle containing artery–vein (AV) loop to form an anastomosis between a cell sheet based capillary network and the AV loop based microvascular bed. Prevascularized cardiac tissues developed by this method showed beating cardiac muscle cells and successful anastomoses with host vessels within two weeks of transplantation [135]. Although promising, this approach needs to address translational issues associated with immune rejection, as animal-based AV loop transplantation in humans could promote severe chronic inflammation.

4.5. 3D bioprinting for precisely organized microvascular network formation

Over the course of the last decade the potential impact of 3D printing, also known as additive manufacturing, has attracted much attention within the scientific community for largely the same reasons that it has become so popular in manufacturing and hobbyist circles. These include ease and speed of iterative prototyping, low cost of production, and the ability to create nearly any geometry developed using readily available modeling software [137]. The ability to translate these production characteristics to the creation of tissues for the purposes of medicine and biology would be highly advantageous. However, progress in this area has been slow, because many of the materials and practices, which are common in industrial and recreational settings, need extensive modification to be applicable to biological systems in addition to being case specific based on requirements for strength, permeability, and other factors of the tissue [138]. Despite these challenges, the substantial impacts which this technology could have on the personalization and efficiency of research and medicine have continued to drive the development of 3D printing in recent years, with a number of research groups developing systems for creating objects ranging from custom implants to organs and tissues [139].

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Organized or directed vascularization of engineered tissue is one such research area that could benefit from 3D printing techniques, as additive manufacturing systems can be designed to create any pattern in either 2D or 3D forms [140]. As opposed to other methods for developing structured tissue constructs with vascular networks, 3D printing allows for precise and directed placement of cells into any pattern without the need for intermediate steps such as the creation of molds, cutting or etching of an existing material, or the manufacturing of microfluidics [13,140]. If support structures are required, multi-material printers can accomplish this with relative ease in a single step. The challenge for applying these 3D printing systems to highly organized vascular networks is in finding a way to create an environment, in which the cells will adopt the desired structure. This is generally performed in two ways: indirect vessel creation and direct cell printing. In indirect printing, the printed material serves as a guide for cells that are seeded at some point after initial material deposition. In direct printing, the material extruded or deposited by the printing technique contains cells that will form the vessel network [13,140,141].

4.5.1. Indirect printed vasculature

For indirectly casting vessels within certain matrices, a model is prepared that represents the desired vessel structure. This model is printed and used as a sacrificial material to cast the chamber out of a second material. This sacrificial material must then be removed via heating/cooling, solvent, or some other means that will not impact the surrounding matrix. After casting the second material around the model, the model is removed, leaving open lumens. These lumens can then be perfused with cell suspension, resulting the lining of the lumen with cells (Fig. 5B). This method was demonstrated recently by Justin et al. using a 3D sacrificial model printed in a polyester based thermo-polymer [142]. A template was created around this model out of alginate, followed by heating and subsequent removal of the liquid thermo-polymer. Gelatin was added to the channels in the alginate, bonding to the surface of the tubes. Removal of the surrounding alginate via chelation left only the gelatin structures, which were used as a temporary and removable fugitive template for the creation of highly organized microvessles with diameters of approximately 200 μm, spaced approximately 1000 μm apart within an extracellular matrix hydrogel [142]. Injecting HUVECs through the channels resulted in the endothelialization of the inner walls of the channels and the initiation of tight junction formation after 8 days [142]. The multiple steps and materials in this process are required in order to accommodate the material properties of the original 3D printed polyester, and to allow for each material to be removed without disturbance to the surrounding structure, or vessel constructs. A similar approach was used by Koleski et al. to create a highly organized vascular network using a fugitive ink printed from Pluronic F127, which can be removed as a liquid when cooled. This network was surrounded by a castable ECM which, following removal of the fugitive ink, provides the structure for injected HUVECs to form a vessel network within the structure [143,144]. The experiment was expanded upon through controlled printing of hMSCs throughout the vessel structure. hMSCs were observed to have migrated from the surrounding area toward the vessels, eventually surrounding them circumferentially. This technique was able to support the tissue construct throughout the course of the 6-week experimental period, promoting transport of nutrients and waste evenly across the geometry [143].

Indirect vessel printing is effective in creating complex geometries, however it could be challenging to precisely dictate cell seeding as they are not delivered directly in the material. Moreover, it is relatively labor intensive, requiring multiple steps and materials before the final cell laden vessel structure is created. The sacrificial material or materials must be considered in addition to the matrix in which the cells will be deposited. With each material the complexity, time and cost increases as a number of considerations, such as porosity, stiffness, cytotoxicity, gelation mechanism, and interactions with the other polymers or hydrogels, must be made for each. For these reasons, other systems are desired, which are less complex, require fewer steps and materials, and could also directly print the cells in the required location.

4.5.2. Direct printed vasculature

While indirect vascularized matrix creation can be useful for creating clearly defined and highly organized structures, the ability of direct printing techniques to limit the number of intermediary

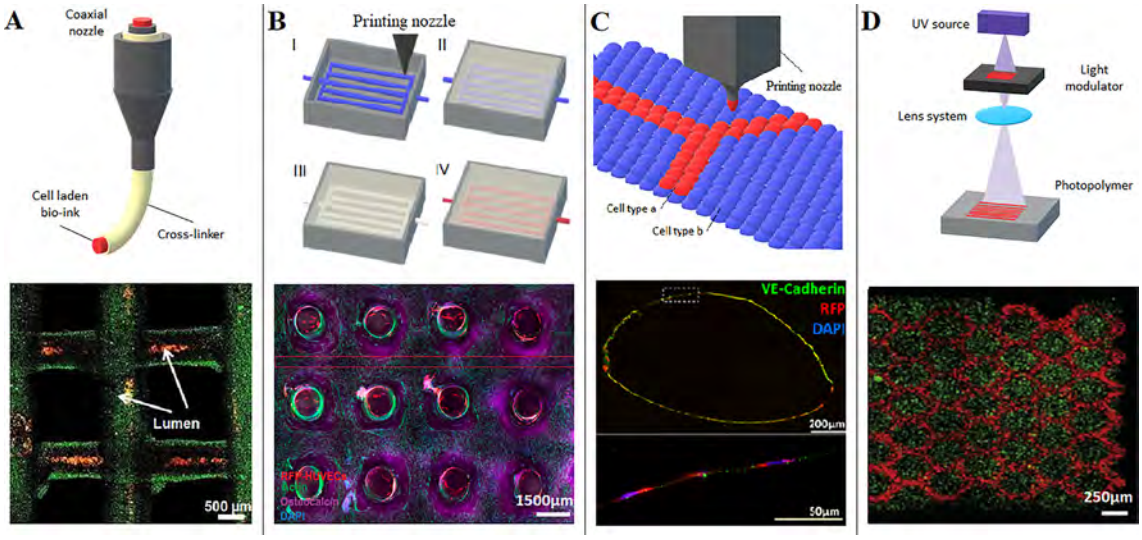

Fig. 5. 3D Printing based approaches for vascularization. Generalized diagrams of various 3D bioprinting techniques for creating vascularized tissues along with adapted examples of their products (A) Extrusion Printing utilizing a coaxial needle system to crosslink the bio-ink while printing. Image reused and modified from [146] with permission of Elsevier. (B) Indirect Printing system creates a network out of fugitive material that is removed after a casting material is formed around it. Image reused and modified from [143] with permission of PNAS. (C) Droplet based systems use printing nozzles to deposit small drops of various materials to create intricate designs. (Image by Lee et al. [155]. Modified with permission of Elsevier. (D) Light based solutions use a projection of the desired geometry to crosslink specific regions of a polymer, creating channels through the cell laden photopolymer. Image reused and modified from [157] with permission of Elsevier.

Please cite this article as: D. Sharma, D. Ross, G. Wang et al., Upgrading prevascularization in tissue engineering: A review of strategies for promoting highly organized microvascular network formation, Acta Biomaterialia, https://doi.org/10.1016/j.actbio.2019.03.016

steps and place cells in specified locations could make it more desirable. This printing style has many iterations with a variety of materials and deposition techniques, but generally involves printing a vascular bed out of cell laden bio-inks, potentially followed by seeding of other cell types [145–149].

4.5.2.1. Extrusion bioprinting. Extrusion printing is most like traditional 3D printing, which generally employs a thermoplastic polymer passing through a hot end, softening it for printing. For applications in biological systems, this material, also called filament or ink, can use a variety of methods for conversion from liquid to solid and contains the cells of interest [150,151] (Fig. 5A). Studies performed by both Colosi et al. and Jia et al. utilize coaxial needles to extrude ionically crosslinked, cell laden bio-ink layer by layer, constructing complex 3-D networks. This structure also contains GelMA photo-initiator to allow for further crosslinking, following exposure to a UV light source [145,146]. The cells are distributed throughout the hydrogel fiber at deposition, and, as shown by Colosi et al. using HUVECs, over time there is migration to the edges of the fiber to create a cellular tube with high CD31 signaling. Nevertheless, too much or too little crosslinking could inhibit the ability of cells to migrate and spread. Live/dead staining after 10 days showed that cell viability was highest when UV crosslinking time was controlled to achieve a modulus between 15 and 25 kPa [145]. Jia et al. used an additional component in the bio-ink to produce a blend of polymers for fine tuning the crosslinking-process. 4-arm poly(ethylene glycol)-tetra-acrylate (PEGTA) was added to the sodium alginate and GelMA because of its ability to achieve high crosslinking density while maintaining more porosity to enhance the cell's ability to spread and migrate [146]. This allowed for a more desirable balance between mechanical properties and cell behavior. Additionally, this study applied a 3-material coaxial with calcium being outputted from the inner and outer most channels so that a stable, hollow tube could be printed directly with inner diameters ranging from 400 to 1,000 μm, as well as a custom printing channel for potentially extruding multiple cell types individually for more complex structures. Following removal of the alginate, and subsequent perfusion with cell culture media, samples showed the ability to maintain cell viability through day 7 with steady spreading through day 14 to form confluent multilayer cell coatings with open lumens. In both cases, benefits to viability as well as increases in proliferation, spreading, and migration were observed with UV crosslinking exposure times below 30 s [146].

By introducing rat cardiomyocytes after endothelialization of a similar alginate/GelMA vascular structure, Zhang et al. showed that this technique could be used to create a 3D muscle tissue with organized vascularization that could function through synchronous and spontaneous contraction. While this technique has only been applied a handful of times, it does demonstrate the ability to create samples for study of viable prevascularized tissue constructs *in vivo* or *in vitro* [149].

4.5.2.2. Droplet based bioprinting. By depositing small drops from the printer head, designs with very fine features and high fidelity can be achieved for mimicking *in vivo* vasculature [152,153] (Fig. 5C). Tubes and grafts on larger scales (>1,000 μm) have been produced previously with some success, and more recently this technique has been adapted to form smaller features and complex vascular networks [152]. Graham et al. have recently created features under 200 μm [154]. By depositing the cell-laden bio-ink comprising of culture medium, agarose, gelators, and collagen I, while submerged in oil, this group was able to increase the resolution by reducing the spreading caused by gravity when the droplet comes in contact with the surface. The designs are then transferred from the oil to a culture medium where they can undergo further culture and/or analysis [154]. This process shows promise in that it has precision and ability to create a large number of geometries on many scales. However, it is a complex process with a number of intermediary steps and creating larger networks would take a significant amount of time. Similar to the other prevascularization strategies, microvascular networks developed by 3D printing needs to be perfusable after transplantation. Therefore, strategies that can develop functional anastomoses with host vessels is critical. To resolve this issue, Lee et al., constructed two larger fluidic microchannels (~1 mm diameter) by 3D printing adjacent to the capillary bed in between [155]. EC seeding in these microchannels resulted in intact lumen formation (Fig. 5C). The capillary bed was attached with these microchannels by the natural process of capillary sprouting from larger channel edges [155]. This method has great potential in fabricating thicker prevascularized tissues that can form successful anastomoses with the host vasculature.

4.5.2.3. Light/Laser based bioprinting. Using lasers or focused UV images to polymerize or heat material is another additive manufacturing technique that has been used to create specific patterns or structures in the creation of vessel networks [156] (Fig. 5D). One example of this system utilizes digital masks, or other masking techniques to project UV images onto a bed of liquid photopolymer. Zhu et al. used this technique to first create a polymerized structure with an open network of channels ranging from 50 to 250 μm across a sample of approximately 100 mm^2. The negative of the first mask was then used on a second polymer containing HUVECS to create the vascular structure through photopolymerization [157]. Following 2 week implantation in mice, prevascularized samples showed significant increases in both vascular area density and average vessels per area (0.17–3.24% and 7.66/mm^2–66.1/mm^2 respectively). This technique is relatively limited in vascular network complexity and 3D tissue construction, but can create fine features. Similar techniques construct objects layer by layer by projecting a series of images in order to deposit material in desired locations as demonstrated by Huang et al. [158], which could be applied to create more complex structures, though the current applications in this field where directly printing vascular networks are limited.

In summary, both indirect and direct methods of printing appear to be able to demonstrate similar results regarding vessel diameter and matrix material. However, each method has its own unique advantages and disadvantages, meaning that no single method can satisfy every need. The simplicity of direct methods such as extrusion bioprinting is very attractive, and the ability to directly create cell laden vessels with open lumens in only a couple steps while creating 3D structures which could support other cell types could make it applicable for a wide variety of tissue engineering applications. Although droplet and light-based methods have potential for creating structures with extremely high accuracy and fidelity, they are limited by low efficiency and limited ability to create complex/multi-material structures, respectively. Future developments in materials or techniques will likely allow these printing systems to be more competitive moving forward.

5. Conclusion remarks and future perspective

An enormous amount of research data associated with the understanding of angiogenic and vasculogenic processes is currently being translated into tissue engineering applications to further develop perfusable and functional vascular networks that can re-vascularize ischemic tissues. Controlled delivery of angiogenic growth factors or appropriate cell types can promote

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re-vascularization in ischemic tissues via therapeutic angiogenesis. Although phase I and II human clinical trials involving VEGF, bFGF and HGF delivery showed promising outcomes, larger randomized studies failed to demonstrate significant benefits [168]. Different stem cell types including hMSCs, cardiac stem cells (CSCs) and embryonic stem cells (ESCs) have also been tested in clinical trials to treat cardiovascular diseases. Among these cell types, bone marrow derived hMSCs are considered the most attractive stem cell type to-date [169]. Results obtained from the BOOST clinical trial has shown that intracoronary (IC) infusion of autologous bone marrow derived hMSCs in patients with acute MI showed a 6.7% increase in left ventricular ejection fraction (LVEF) compared to the control group [170,171]. In addition, the POSEIDON trial showed that post-MI patients receiving either autologous or allogenic bone marrow derived hMSCs experienced an improved ejection fraction compared to control groups [172]. In other clinical trials, patients at high risk of heart failure were treated with CSCs (SCIPIO phase I [173]) or fibrin gel embedded ESCs (ESCORT [174]). Both of these cell types promoted an improved LVEF and decreased infarct size. These early phase clinical trials have proved that cell therapies have potential to regulate positive cardiac remodeling. Although promising, these cell therapies still suffer from several limitations such as a heterogeneous cell population, time consuming *ex vivo* autologous cell expansion and very low engraftment efficiency due to apoptosis, inflammation and inappropriate cell homing [168]. Cells embedded in tissue engineered constructs that mimic native ECM architecture can avoid some of these limitations, particularly inappropriate cell homing, and can effectively contribute to positive therapeutic angiogenesis. Moreover, successful development of biomimetic, perfusable microvacular networks can revolutionize the field of physiological scale tissue fabrication as well as organ engineering. Microvascular networks present in native tissues follow tissue architecture for optimum diffusion of molecules. Therefore, the current review specifically focuses on strategies that can be used for development of highly organized, dense, mature and perfusable microvascular networks in engineered tissues either for translational applications or for disease models.

The ideal prevascularized tissue should mimic the hierarchical order of the vascular tree, containing arterioles, venues and capillaries. Although several studies reviewed here have shown success in developing highly organized, dense and mature microvascular network, it is equally important to calculate and optimize the volume of fluid that can be perfused though these engineered vascular networks. Initial studies associated with microvascular network formation highly relied upon angiogenic growth factors to promote extensive vessel growth. One of the studies associated with Delta-like ligand 4 (DLL4), a negative-feedback VEGF regulator, showed that uncontrolled expression of VEGF activated ECs to create highly dense and branched microvessels. However, these microvessels were defined "unproductive" as they were poorly perfused and promoted hypoxia in the tissue microenvironment [175]. Therefore, it is critical to regulate external growth factor stimulation, if provided, to maintain vessel growth and perfusion. Another important aspect is ensuring vessel maturation by focusing on endothelial barrier function, their quiescent phenotype and perfusion ability. Fabrication of macro-sized vessels in a scaffold that can connect with both engineered microvascular network and host vasculature via microsurgery can greatly ensure transplant survival. As an alternative approach, tissue inosculation by natural angiogenesis can also form anastomosis between preformed vascular networks in the engineered tissues and host vasculature [176]. Constantly emerging in-depth insights into angiogenic process and its regulatory mechanisms as well as advancements in the microsurgery process will provide solutions for successful connection of engineered and native vasculatures.

Next, mechanical properties of the scaffold must be finely tuned in order to promote development of intact and perfusable microvessels. It was observed that hydrogels with high mechanical strength significantly hindered ECs' migration and self-assembly into capillary like structures [177]. Secondly, biodegradation rate of the scaffold material needs to be finely tuned as change in mechanical compliance upon degradation can significantly influence maturation and organization of microvessels. On the other hand, maintaining mechanical properties of the EC structures is equally important for appropriate perfusion of fluid from the engineered vascular networks. Moreover, effects of perfusion-induced shear stress on the behavior of newly assembled ECs after anastomosis is also significant. Selection of appropriate cell type is another critical issue to deal with, as ECs are strongly immunogenic due to presenting class II human leukocyte antigen (HLA) molecule [178]. Therefore, appropriate HLA matching between patient's cells and the cells used for transplant construction can result in lower immune-suppression doses. Some of the suggested solutions to solve this problem include development of universal donor cells by knocking out HLA gene or genetically engineered cells that can secrete immunosuppressive molecules in small amount [179]. Use of immunomodulatory perivascular cells, such as hMSCs, can also reduce risk of immune rejection. For example, transplantation of prevascularized hMSC sheets into immunocompetent rat full-thickness wound model significantly enhanced wound healing with least immune cell infiltration [180].

Although biomimetic scaffold materials such as polymers and hydrogels provide a good platform for *in vitro* tissue culture and pre-assembly of microvacular networks in an arbitrary orientation before implantation, they and their biodegradation products might significantly inhibit successful anastomosis with host vessels. In a recent study, it was observed that preassembled microvascular networks formed in a GelMA hydrogel via ECFC and MSC co-culture failed to anastomose to host vasculature [181]. On the contrary, an unassembled ECFC-MSC cell suspension successfully formed anastomosis with host vasculature in nude as well as immunocompetent mice [181]. This study proved that cells that were pre-assembled in the microvessels had significantly lower expression of cytokines that can recruit host specific polarized (N2) neutrophils, which played a critical role in successful anastomosis. Moreover, blocking Notch signaling during pre-assembled microvessel culture for at least 24 h can significantly increase the number of perfused vessels [181]. Therefore, it is crucial not only to suppress the activity of pro-inflammatory cells but also to harness the power of anti-inflammatory immune cell types. This strategy will not only preserve the highly organized structure and high density of engineered vasculatures, but also promote their successful perfusion upon implantation. To summarize, although significant advancements need to be achieved to translate prevascularized tissue engineering into clinical practices, knowledge gained from extensive research in the past few years has increased hope for the development of functional, perfusable and physiological scale engineered tissues in near future.

Acknowledgements

This study was supported by the National Institutes of Health (1R15CA202656 and 1R15HL115521-01A1) and the National Science Foundation (1703570) to FZ.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.actbio.2019.03.016.

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Please cite this article as: D. Sharma, D. Ross, G. Wang et al., Upgrading prevascularization in tissue engineering: A review of strategies for promoting highly organized microvascular network formation, Acta Biomaterialia, https://doi.org/10.1016/j.actbio.2019.03.016

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Please cite this article as: D. Sharma, D. Ross, G. Wang et al., Upgrading prevascularization in tissue engineering: A review of strategies for promoting highly organized microvascular network formation, Acta Biomaterialia, https://doi.org/10.1016/j.actbio.2019.03.016

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