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Matrix-assisted cell transplantation for tissue vascularization☆

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ABSTRACT

Cell therapy offers much promise for the treatment of ischemic diseases by augmenting tissue vasculogenesis. Matrix-assisted cell transplantation (MACT) has been proposed as a solution to enhance cell survival and integration with host tissue following transplantation. By designing semi synthetic matrices (sECM) with the correct physical and biochemical signals, encapsulated cells are directed towards a more angiogenic phenotype. In this review, we describe the choice of cells suitable for pro-angiogenic therapies, the properties that should be considered when designing sECM for transplantation and their relative importance. Pre-clinical models where MACT has been successfully applied to promote angiogenesis are reviewed to show the great potential of this strategy to treat ischemic conditions.

Contents

1. Introduction

The promise of cell therapy offers much hope for the treatment of degenerative conditions [1–3]. Accordingly, the delivery of cells to

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replace and regenerate ischemic tissue has the potential to revolutionize medical treatments for many conditions including heart failure, limb ischemia, stroke, spinal cord injury and diabetes [4,5]. However, many hurdles exist that have halted the progress of cell-based therapies to the clinic [6]. One key consideration is how to deliver therapeutic cells, and ensure optimal efficacy, as poor cell engraftment and survival following transplantation are major obstacles to address. A number of factors have been identified that compromise cell survival following implantation, including mechanical forces exerted on the cells during implantation; anchorage-dependent cell death and lack of growth factors; and insufficient support from the host tissue, specifically a lack of access to vasculature [7]. Thus, the survival of transplanted cells is severely limited by the hypoxic microenvironment, which leads to a rapid loss of cells in the hours and days following implantation [8]. Typically, the benefits observed occur through intercellular paracrine signaling for the limited time the cells remain viable [9–12].

To overcome the issue of cell survival, a number of options have been suggested, including chemical and physical pre-conditioning of cells [13,14] or genetic modification [15,16]. These approaches raise safety concerns and complicate the regulatory pathway for clinical translation, perhaps explaining the limited translation for clinical applications. As a result, biomaterial systems have also been proposed as a means to enhance the survival of implanted cells *in vivo* with minimal manipulation of the cells themselves. By acting as a barrier and partially shielding transplanted cells from the harsh microenvironment, biomaterials were first proposed to immunoisolate cells and improve their survival [17,18]. However, the foreign body response and fibrous capsule formation around the encapsulated cells led to issues such as hypoxia, as diffusion of oxygen and nutrients was restricted [19]. This host response and lack of integration compromised the viability of transplanted cells.

More recently, to enhance cell survival and integration, matrix-assisted cell transplantation (MACT) has been proposed. This involves the design of semisynthetic matrices (sECM) with the appropriate biochemical and mechanical signals to promote the engraftment of cells and direct tissue regeneration. In particular, therapeutic vascularization offers the opportunity to revascularize ischemic tissue by integrating transplanted cells with the host vasculature By incorporation of the correct signals, the phenotype of transplanted cells can be guided to a more pro-angiogenic behavior [20,21]. These signals can enhance angiogenesis and direct integration with the host vasculature, ensuring perfusion of the implant [22].

Since angiogenesis is a complex and multicellular process, there are a wide array of cells to consider that can promote the formation of a neovasculature. Considerations when selecting cells include includes availability and scale up, as well as the possibility for autologous transplantation. In addition, the ideal properties of the biomaterial delivery system will vary depending on the choice of cells. In this review we first focus on the choice of cells, and on the biomaterial parameters to consider for an ideal matrix to deliver cells to promote angiogenesis following cell transplantation. Finally, we review a number of pre-clinical studies where MACT has been applied with successful results.

2. Choice of cells

The endothelium is one of the largest organs in the body, forming a semi-permeable barrier between the blood and tissue which allows for diffusion of nutrients and waste products back and forth [23]. This barrier plays a substantial role in key physiological and pathological processes, including during atherosclerosis, inflammation, diabetes and angiogenesis. At the level of individual endothelial cells, pathological conditions induce changes in cell-cell contact and the expression of adhesion ligands [24].

Neovascularization, the formation of new blood vessels, is a highly co-ordinated process involving a complex milieu of signals and cell types [25]. There are a wide range of cell types that play distinct roles in blood vessel formation and expansion. Endothelial cells are the prime component of the vessel wall involved in lumen formation and are directly involved in blood vessel formation and expansion [26–28]. Proliferation and migration of existing endothelial cells as well as progenitor cells along hypoxic gradients occur during angiogenesis to produce new vessels [29]. In addition to this, tissue-specific stromal cells and pericytes play key roles in responding to and initiating angiogenic stimuli and subsequent vessel stabilization [30,31]. This occurs mainly through paracrine support and an increase in matrix remodeling [32]. Thus, there is a variety of cell types, and indeed sources of cells, that can be considered when devising strategies to enhance vascularization, many of which are shown in Fig. 1. We discuss in detail the main cell types that may be considered for vascularization, focusing on how the cells may be sourced, and also the mechanism of action in terms of driving angiogenesis in the host tissue (See Tables 1–4.)

2.1. Human umbilical vein endothelial cells (HUVEC)

The study of blood vessel formation has relied predominantly on human umbilical vein endothelial cells (HUVEC), derived from the endothelium of umbilical cords. Much of the knowledge of angiogenic mechanisms has been derived from the study of HUVEC. In addition to basic biological study, much of the early understanding on graft vascularization has also been undertaken with HUVEC as the model cell type [33]. This includes both *in vitro* and *in vivo* characterization. For instance, the effect of various growth factors, cytokines and chemokines on endothelial cell proliferation, migration and activity has been established using HUVEC. In particular, the matrigel™ tube formation assay typically utilizes HUVECs to establish the angiogenic effect of various factors [34,35].

Despite their widespread use as a model system to study angiogenic processes, HUVEC are not the most relevant cell type to use. HUVEC are derived from the umbilical cord, an environment in which endothelial cells are exposed to a higher oxygen concentration than is typical in many organs [23]. In addition, there is a difference between venous and arterial endothelial cells, and thus some characteristics attributed to endothelial cells from the study of HUVEC may be only true of venous rather than arterial endothelial cells [36]. From a translational point of view, the complexity in donor matching the cells makes HUVEC a poor candidate for transplantation studies.

HUVECs are not the only primary endothelial cells utilized in biomedical research [33]. Endothelial cells can be extracted from many sources, and are typically named according to whether they come from: vein or artery, and the location. However, as with HUVEC they suffer from a lack of scale-up as the number of passages from primary adult cells is limited. Despite this, the use of HUVEC and other primary endothelial cells as model systems has been widespread in the context of cell transplantation and vascularization strategies. However, in recent times, there has been a shift towards cells that may be more suitable for clinical translation in terms of donor matching and scale-up potential.

2.2. Endothelial progenitors

Angiogenesis and neovascularization depends on both the migration and proliferation of existing endothelial cells, but also on the migration and differentiation of endothelial progenitors [37]. In that context, the delivery of endothelial progenitors to an ischemic microenvironment seems like an ideal approach to stimulate vascularization [38]. A wide range of endothelial progenitors have been identified, based on the mode of isolation and the expression of specific cell markers [33]. Endothelial progenitors can be isolated in a relatively simple manner from patient blood samples, and thus could prove useful as a clinically applicable autologous therapy.

Endothelial progenitors are also termed early and late outgrowth endothelial cells (OECs), depending on the timing of when they

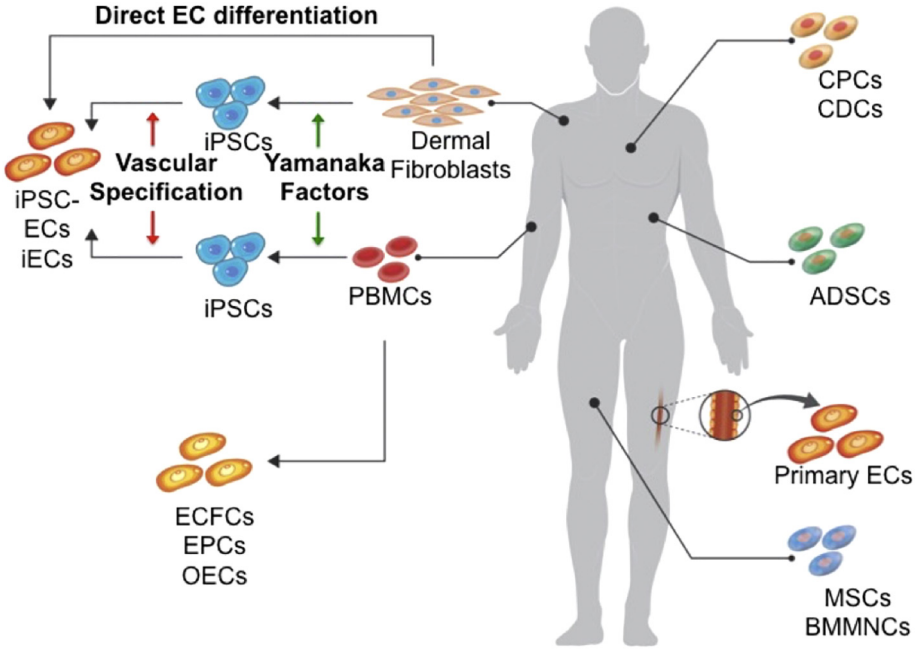

Fig. 1. Cell sources for Angiogenic Cell Therapy. A graphical depiction of a number of the cell types that are used to promote angiogenesis and the tissue source.

appear *in vitro* during the isolation procedure, while various subsets have been isolated depending on the expression or absence of a wide range of surface markers including CD14, CD31, CD34, CD45, CD105, CD133, Flk-1, KDR and vWF, amongst others [38]. Debate has continued in the literature over what combination of surface markers defines particular subsets, with recent attempts made to come to a consensus [39,40]. Two cell types that have received particular attention are blood-derived endothelial progenitor cells (EPCs) and endothelial colony-forming cells (ECFCs), both of which have shown potential in pre-clinical studies. Autologous transplantation of two separate populations of EPCs, isolated by selection of either CD31 or CD34-expressing cells from peripheral mononuclear cells, were shown to enhance capillary density in the ischemic myocardium [33]. When assessed in a matrigel™ plug assay, ECFCs have been shown to anastomose with the host vasculature of nude mice [41]. In a separate study, ECFCs integrate into the ischemic retinal vasculature, in an oxygen-induced retinopathy model [42]. Thus, there are many endothelial progenitors that can integrate with host vasculature following implantation.

However, as a therapeutic option these cells are limited given that cells isolated from diabetic patients have been shown to have reduced proliferative and vascular potential [43]. This severely limits their use as an autologous therapy for patients with cardiovascular issues. In addition, cells isolated from elderly or diabetic patients may senesce, with the reduction in proliferative capacity reducing the number of cells available for transplantation.

2.3. Human ES/iPS-derived endothelial cells

The discovery of pluripotent stem cells (PSCs) offer a potential source for the replacement of damaged cells. Embryonic stem cells (ESCs), and more recently induced pluripotent stem cells (iPSCs), allow for the derivation and production of non-proliferating cells such as cardiomyocytes or pancreatic islets. Differentiation protocols also exist for the derivation of endothelial cells from PSCs, with resulting iPSC-derived endothelial cells (iPSC-ECs) typically characterized for CD31-expression, LDL-uptake and 2D network formation on matrigel™ [44,45]. Thus, iPSC technology allows for the derivation of a range of cells from a single donor, enabling for the formation of multi-cellular tissue constructs with a homogenous genetic make-up. Endothelial cells are imperative in this context, to allow for vascularization of these constructs.

From the clinical perspective, personalized cell therapies are possible using iPSC technology. Cells such as dermal fibroblasts, keratinocytes or mononuclear blood cells may be isolated from a patient in a minimally invasive manner, and reprogrammed into iPSCs by treating with the Yamanaka factors (*OCT3/4*, *SOX2*, *KLF4*, and *C-MYC*) [46,47]. It has been shown that pluripotency may also be achieved without *C-MYC*, albeit at a lower efficiency [48]. The newly-derived iPSCs may then be differentiated to form a personalized cell therapy product. Direct reprogramming to endothelial cells (iECs) from somatic cells is also possible, and iECs have been shown to be functionally similar to iPSC-ECs in a limb ischemia model [49].

Table 1
Cell sources for angiogenesis.

Cell	Source	Autologous	Easily scalable	Primary mode of action
HUVEC	Umbilical cord veins	No	No	Vascular network formation
OECs	Peripheral blood	Yes	Depends on patient	Vascular network formation
ECFCs	Peripheral blood	Yes	Depends on patient	Vascular network formation
EPCs	Peripheral blood	Yes	Depends on patient	Vascular network formation
ES-ECs	Embryonic stem cells	No	Yes	Vascular network formation
iPSC-ECs	Induced pluripotent stem cells	Yes	Yes	Vascular network formation
MSCs	Bone aspirate	Yes	Depends on patient	Paracrine support
ADSCs	Adipose biopsy	Yes	Depends on patient	Paracrine support
Cardiac stem cells	Cardiac biopsy	Yes	No	Paracrine support and vascular network formation

Table 2
sECM systems for the delivery of angiogenic cells in pre-clinical models of limb ischemia.

Cells	Biomaterial	Mechanical properties	Adhesion ligand functionalization	Mode of degradation	Exogenous signals added	Reference
MSCs	Collagen type I hydrogel	Not defined	n/a	Enzymatic	n/a	Thomas et al. [173]
ADSCs	Methacrylated Gelatin hydrogel	Young's modulus of 8.25 kPa	n/a	Enzymatic	n/a	Li et al. [175]
MSCs	Platelet lysate hydrogel	Storage modulus of 5 Pa, Loss modulus less than 1 Pa	n/a	Enzymatic	Endogenous PDGF, VEGF, EGF and BDNF	Robinson et al. [176]
MSCs	Alginate hydrogel	Not defined	n/a	Non-enzymatic	n/a	Landazuri et al. [177]
iPSC-ECs	C7 protein polymer and 8-arm PEG	Storage modulus 15 Pa	RGD	Non-enzymatic	VEGF	Mulyasasmita et al. [179]
MSCs	Poly(NIPAAM) hydrogel	Not defined	n/a	Non-enzymatic	bFGF	Xu et al. [180]
EPCs and OECs	Alginate scaffold	Not defined	RGD	Non-enzymatic	n/a	Silva et al. [181]
Bone-marrow derived proangiogenic cells (BMPACs)	Peptide amphiphiles	Not defined	RGD	Enzymatic	n/a	Tongers et al. [182]

Differentiation protocols for the derivation of progenitor cells such as CPCs [50] and ECFCs [41] from iPSCs have recently been developed. These protocols allow for the creation of highly proliferative progenitor cells from patient-derived iPSCs. Crucially, this could overcome the problem of senescence of progenitor cells derived from elderly patients or those with cardiovascular disease or diabetes.

Despite the great promise of iPSC-ECs, there are reports that long-term culture results in endothelial-mesenchymal transition (EndMT), where iPSC-ECs lose their vascular phenotype and express more mesenchymal markers [51]. One way to avoid this may be the selective inhibition of TGF-β1, specifically signaling through activin receptor-like 5 (ALK 5) rather than activin receptor-like 1 (ALK1) [52]. This has been shown for corneal endothelial cells using SB-431542, an inhibitor of ALK5 [53].

2.4. Adult stem cells

Adult stem cells, typically support the formation and expansion of vasculature through paracrine and trophic support. For example, MSCs have been shown to support vascularization following ischemic insult [54–57], while this effect can be improved with genetic modification of the cells to enhance production of pro-angiogenic growth factors [58]. Similar effects have been observed with adipose-derived stromal cells (ADSCs) in ischemic tissues [59]. Interestingly, the capacity of human ADSCs to differentiate into ECs is much lower compared with that of rat ADSCs, emphasizing the importance of quickly moving to testing human cells rather than those of different species [60].

Cardiac progenitor cells (CPCs), or cardiosphere-derived cells (CDCs), are a multi-potent population of progenitor cells isolated from the myocardium. This population of cells has tri-potential in that they can differentiate into endothelial cells, smooth muscle cells and cardiomyocytes. Thus, they have been identified as having the capacity to regenerate the myocardium following infarction. However, as with many cell therapies, minimal cell engraftment occurs following delivery to the myocardium. Furthermore, minimal differentiation into the cardiomyocyte lineage has been observed, with improvements observed typically in the growth of blood vessels in the myocardium. Studies have shown that neovessels were formed *via* differentiation of the CPCs into the endothelial lineage, [61] while other studies have emphasized the paracrine support provided by these cells [62]. Thus, it appears that these cells have a particular potency in supporting vascularization through endothelial differentiation [61]. Interestingly, studies have shown that the potency of these cells in terms of myocardial repair is enhanced when the cells are sourced from advanced heart failure patients, likely through an SDF-1α mechanism [63].

Despite this, as with all cell therapy approaches lacking a delivery matrix, only a limited number of implanted cells engraft and thus the effect of the therapy is not maximized. Furthermore, if these cells are to be used as an autologous therapy, the safety and practicality of isolating cells from the myocardium of diseased patients must be considered fully.

3. Choice of natural *vs.* synthetic materials

The choice of matrix material is paramount to successful MACT. A number of key factors must be considered, including the ease of modification, reproducibility and scale-up, biodegradation and, perhaps most importantly, the application and tissue target for which it is being developed [64,65].

Broadly speaking, biomaterials can be divided into synthetic and natural materials, although these may also be further subdivided [66]. For instance, natural materials may be subdivided into constituents of the ECM and otherwise, while ECM constituents may also be classified by whether they are derived from a specific species or tissue, or derived recombinantly.

Table 3
sECM systems for the delivery of angiogenic cells in pre-clinical models of myocardial infarction.

Cells	Biomaterial	Mechanical properties	Adhesion ligand functionalization	Mode of degradation	Exogenous signals added	Reference
CDCs	Hystem®-C™ (Hyaluronic acid/gelatin)	Elastic modulus of 200 Pa	n/a	Enzymatic	n/a	Cheng et al. [194]
CDCs	Platelet gel	Not defined	n/a	Enzymatic	Endogenous VEGF, IGF-1 and SDF-1	Cheng et al. [195]
CSCs	Agarose, Fibronectin and Fibrinogen	Not defined	n/a	Non-enzymatic	n/a	Mayfield et al. [196]
MSCs	Alginate	Not defined	RGD	Non-enzymatic	n/a	Yu et al. [197]
ESC-derived vascular cells	PEG	Not defined	RGD	Enzymatic	Thymosin β4	Kraehenbuehl et al. [199]

Table 4
sECM for the delivery of angiogenic cells in pre-clinical models of wound healing.

Cells	Biomaterial	Mechanical properties	Adhesion ligand functionalization	Mode of degradation	Exogenous signals added	Reference
ADSCs	Pluronic F127	Not defined	n/a	Non-enzymatic	n/a	Kaising et al. [202]
ADSCs	PEGylated Fibrin	Not defined	n/a	Enzymatic	n/a	Chung et al. [203]
MSCs	Pulullan- Collagen	Not defined	n/a	Enzymatic	n/a	Rustad et al. [204]
ADSCs	Pulullan- Collagen	Not defined	n/a	Enzymatic	n/a	Kosaraju et al. [205]
ADSCs	Chitosan /Gelatin	Not defined	n/a	Enzymatic	n/a	Cheng et al. [206]
ECFCs	HyA	Not defined	RGDS	Enzymatic	n/a	Hanjaya-Putra et al. [207]
iPSC-ECs	HyA	Not defined	RGDS	Enzymatic	VEGF, bFGF, ANG-1, TNF-α and SDF-1	Shen et al. [208]
Vascular resident- EPCs	Integra matrix (Collagen/GAGs)	Not defined	n/a	Enzymatic	n/a	Zhang et al. [209]

The key benefits of using natural, and specifically ECM-derived materials, is the intrinsic bioactivity of the material [67–69]. Decellularized ECM (dECM), where cells are essentially 'washed out' of the tissue using various detergent treatments, offer an ideal matrix to deliver cells and control function. Such ECM-based materials have pro-angiogenic effects when implanted *in vivo* [70,71]. Another approach involves the use of single ECM components, with collagen type I being the most common example. Collagen type I is biodegradable, contains cell adhesive sequences and intrinsically promotes angiogenesis when implanted *in vivo* [72]. However, all ECM-derived materials suffer from batch-to-batch variations, and due to the mild conditions needed to avoid denaturation can be difficult to modify chemically. Disease transmission is also a concern when using animal or human-derived products [73].

In comparison with ECM-derived materials, synthetic materials have little intrinsic biological activity due to a lack of adhesion ligands and enzymatically cleavable sites reducing the capacity for cells to invade and remodel synthetic materials. However, they can be easily modified to enhance bioactivity and biodegradation, typically through conjugation of either whole ECM-derivatives or functional peptides. [74] Scale-up of synthetic materials is less burdensome and cost-effective compared with biological materials, while there is minimal batch-to-batch variation. However, toxic degradation products may be an issue, including acid degradation products with some polymeric materials [75]. This leads to a low pH in the microenvironment, which could cause inflammation and toxicity.

By combining the best properties of natural and synthetic materials, sECM offer a tunable matrix to control cell behavior. By imparting instructive bioactivity onto polymers, sECM can be constructed with solid phase adhesion ligand and growth factor presentation, protease-sensitive crosslinkers (*e.g.*, MMP) and material moduli spanning physiologically relevant ranges (100–10,000 Pa) that can be tuned for a specific cell type or application [76]. Amongst the materials used to construct sECM, those composed of the biopolymer HyA appear most promising. HyA derived in a recombinant expression system is commercially available and widely used in regenerative medicine research [77]. In comparison with other ECM materials, modification with various chemical groups or peptide functionalization is facile, hence it's widespread use [78]. Other prominent materials used as base polymers for sECM include PEG [79] and chitosan [80], which are not part of the native ECM but are readily modified and functionalized with bioactive moieties to offer biofunctionality. With both PEG and chitosan, something of a 'blank slate' is offered on which various biofunctionalities may be decorated.

4. Properties of matrices to consider

Native ECM provides a dynamic environment, or niche, which dictates cell behavior [81]. The ECM structure and composition varies greatly between tissues and is constantly remodeled over time and in response to stimuli. A number of key biophysical and biochemical properties of the ECM control cell behavior within it [82]. Changes in any one of these parameters in the local ECM results in a change in cell behavior [83]. Thus, these key properties must be considered when designing a sECM in which cells will be encapsulated. An ideal sECM will provide a 3D environment to control cell fate and function, like the native ECM, but also protect the cells from the potentially harsh environment into which they are delivered. The properties we will consider when designing a matrix for cell transplantation are the presence of adhesion ligands (sequence, density *etc.*), the mechanical properties of the material (stiff or soft) the degradation of the material (cell-mediated or chemically-mediated) and the presentation of growth factors (passively entrapped, specifically or non-specifically conjugated), and are illustrated graphically in Fig. 2. Another often overlooked property is the physical macrostructure of the matrix, which plays a key role in the applicability of the matrix to the tissue of interest. How these properties vary over time must also be considered, the so-called 'fourth dimension' [84].

4.1. Adhesion ligands

Cells exist *in vivo* in a complex ECM that provides a range of signals to control kinetics of behavior and function [85]. The ECM microenvironment provides signals to co-ordinate cell activity including processes such as tissue formation, wound healing and angiogenesis [86,87]. Principle amongst these signals are cell-matrix interactions, occurring through receptors on the cell surface and adhesion ligands of the matrix [88,89]. Integrin receptors on the cell surface govern the adhesion of the cells to ligands present in the ECM, and transmit physical and chemical signals between the ECM and the cytoplasm of the cell [90]. Native constituents of the ECM such as collagen and fibronectin contain an abundance of these ligands, and thus biomaterials based on these biopolymers promote cell adhesion and integrin engagement. However, this is not the case with many synthetic or non-ECM-derived polymers in regenerative medicine. In an effort to mimic the native ECM and confer cell adhesive properties to non-adhesive polymers, biomaterial scientists have conjugated peptides containing specific cell-adhesive sequences [91]. A key factor to consider when adding a cell adhesive peptide is the sequence to select, as each individual sequence will have a specific affinity for a specific integrin. Furthermore, the sequence adjacent to the minimal adhesive domain (*e.g.* Arg-Gly-Asp (RGD)) can play a large role in the affinity of the peptide. Fig. 3 demonstrates this, as both the length of the adjacent sequence, and the orientation of the peptide (linear, cyclic *etc.*) plays a major role in the cells affinity towards the peptide-coated surface. Integrin activation can also be altered by presentation and structural orientation, as observed by the differential activation of $\alpha_5\beta_1$ and $\alpha_v\beta_3$ on surfaces displaying a recombinant fibronectin fragment ($FNIII_{7-10}$) compared with an oligopeptide containing the RGD and Pro-His-Ser-Arg-Asn (PHSRN) motifs [92].

In addition to the choice of peptide sequence, the density or concentration of the peptide sequence plays a role in cell adhesion. Increased peptide concentration enhanced calcification of bone matrix deposited by osteoblast-like cells [93]. In the case of stem cells, the morphology of hESCs was most consistent and most equivalent to undifferentiated

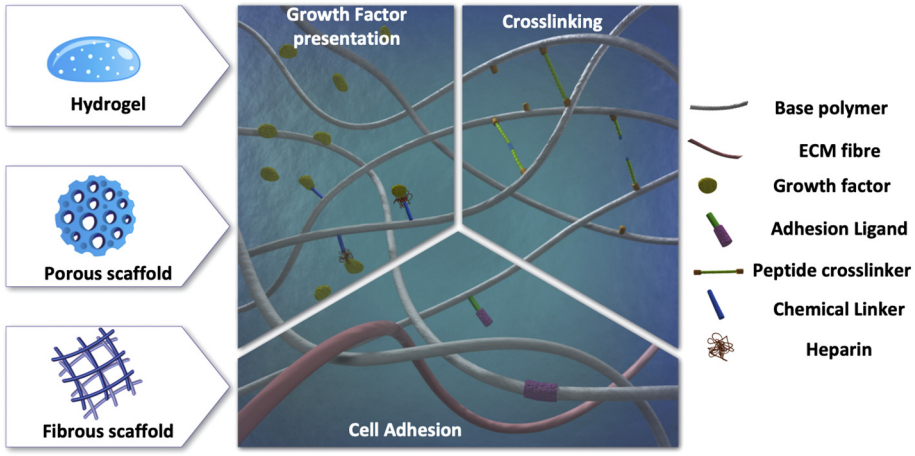

Fig. 2. Key Matrix properties of semisynthetic matrices (sECM). The parameters to consider when constructing sECM for cell transplantation are portrayed in graphical form: Growth Factor presentation, Cell Adhesion, Crosslinking (mechanical properties and degradation) and the form the sECM takes.

hESCs on hydrogel surfaces with higher densities of RGD (105 and 150 μM) than on lower density surfaces (0 and 45 μM) [94].

The most prominently studied cell adhesive sequence is the fibronectin-derived RGD sequence [95]. Early studies demonstrated the positive effect on cell adhesion and cell function of conjugating peptides such as RGD or the laminin-derived Tyr-Ile-Gly-Ser-Arg (YIGSR) to surfaces [96,97] or to thin layers of hydrogel including PEG [98] and alginate [99]. Addition of adhesion peptides (RGD and Phe-His-Arg-Arg-Ile-Lys-Ala (FHRRIKA)) to synthetic P(NIPAAm-co-AAc) hydrogels improved spreading and proliferation of encapsulated rat calvarial osteoblasts (RCO) [100]. Similarly, addition of RGD ligands to photocrosslinked PEGDA hydrogels had no effect on cell viability but did increase mineralization by encapsulated osteoblasts [101].

Engagement of specific integrin-ligand pairs plays a key role in cell behavior and fate [102,103]. In particular, the engagement of $\alpha_V\beta_3$ and $\alpha_5\beta_1$ integrins on endothelial cells has been shown to be integral to the initial stages of vascularization, specifically in terms of migration and tube formation [104–106]. Furthermore, hydrogels activating $\alpha_3/\alpha_5\beta_1$ integrins induced the formation of an organized non-leaky vasculature in response to VEGF, in stark contrast with $\alpha_v\beta_3$ activating hydrogels that stimulated the formation of leaky, tortuous vessels [107].

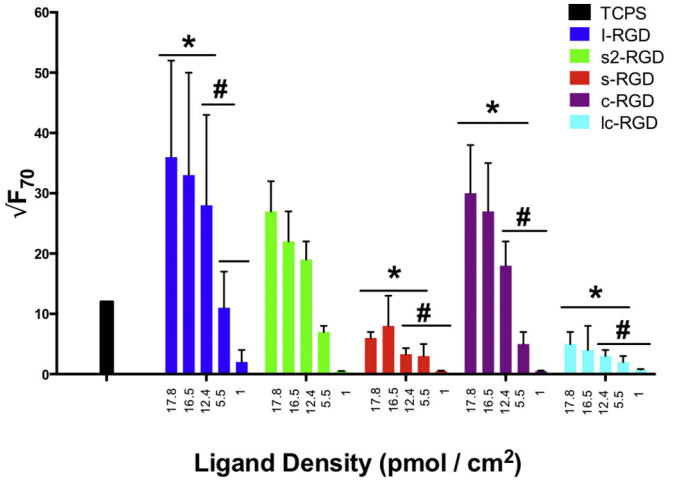

Fig. 3. Peptide sequence flanking adhesion domain plays a role in cell adhesion. Multispeed adhesion assays reveal the differences in the detachment force adhesion parameter depending on the peptide sequence flanking the RGD site [TCPS – Tissue culture plastic; I-RGD - Ac-CGGNGEP**RGD**TYRAY-NH_2, Mw 1657; s2-RGD - Ac-CGGEP**RGD**TYRA-NH_2, Mw 1332; s-RGD - Ac-CGGP**RGD**T-NH_2, Mw 803; c-RGD - Cyclic (CGP**RGD**TYG), Mw 905; lc-RGD - Ac-CGP**RGD**TYG-NH_2, Mw 966). [Modified from Harbers et al. [210]].

Many components derived from native ECM such as collagen and fibronectin naturally present adhesion ligands, including those that engage with angiogenic-associated integrins. From this it follows that many ECM-derived components intrinsically promote an angiogenic-phenotype and induce vascular network formation in cells [108]. In collagen hydrogels in particular, $\alpha_2\beta_1$ integrin was identified as a key player in lumen and tube formation [109,110]. In a fibrin matrix, endothelial cells formed vacuoles and lumen structures in an $\alpha_V\beta_3$ and $\alpha_5\beta_1$ integrin-dependent manner [111]. Furthermore, addition of a soluble RGD peptide led to regression of these pre-formed lumen structures, illustrating integrin engagement in the angiogenic process.

The addition of adhesion ligands, particularly those that engage with key integrins, to synthetic polymers is a pre-requisite to vascular morphogenesis of encapsulated cells. RGD peptide-sequences added to an alginate hydrogel enhance endothelial cell viability and cell spreading in 3D, while also allowing for increased migration into surrounding matrigel™ compared with a non-modified alginate [112]. The presence of an integrin engaging RGD sequence in an alginate/chitosan hydrogel led to increased differentiation of BMSCs into both bone and endothelial cells [113].

In PEG hydrogel arrays a range of CRGDS peptide concentrations were assessed for their capacity to allow for vascular network formation by encapsulated HUVEC [114]. The addition of the adhesion peptide had a clear impact by improving cell viability, proliferation and tube formation in comparison with a non-CRGDS containing hydrogel. The effect of hydrogel modulus was also studied, indicating the importance of coordinating and optimizing multiple hydrogel parameters. Studies have also examined the synergy between different laminin-derived peptide sequences conjugated to a PEG hydrogel, where it was found that combinations of peptide sequences could outperform the individual peptides with regards to tube diameters and lengths [115]. The combination of YIGSR and RGDS peptides showed the greatest capacity to promote the formation of an endothelial cell network. Previous studies had identified the potency of this combination, with the YIGSR peptide promoting endothelial tubule formation and cell-cell contact, and RGDS enhancing cell attachment to the matrix [116].

HyA is a non-sulfated polysaccharide present in the ECM. Due to its lack of adhesion sequences, HyA must be decorated with ligands to enhance cell adherence to a HyA-based matrix. In fact, vacuole formation in encapsulated ECFCs was found to be dependent on RGD concentration, with a control sequence greatly retarding vacuole and lumen formation [117]. Vacuolation of ECFCs in an RGD-decorated HyA hydrogel could be stopped by blocking integrins $\alpha_V\beta_3$ and $\alpha_5\beta_1$, but not $\alpha_2\beta_1$ [114]. In the context of CPCs, addition of an RGD sequence derived from bone sialoprotein to a HyA hydrogel led to increased cell survival and vascular network formation both *in vitro* and *in vivo* [118].

4.2. Mechanical properties

Cells responds to the ECM that supports them, and the mechanical properties of the ECM plays a key determining role in the behavior of cells that interact with it [119–121]. This is also the case regarding vasculogenesis [122]. The mechanosensitivity of vascular development has been demonstrated in a bone defect model, with early loading of the defect inhibiting vasculogenesis [123], while Mammato et al. have shown that ECM stiffness controls VEGFR2 expression and subsequent capillary morphogenesis *in vitro* and *in vivo* [123]. Thus it is clear that modulus is a vital consideration when designing sECM for cell-based therapies.

An *in vitro* assessment of the effect of matrix density on angiogenic outgrowth from microvessel fragments found that collagen concentration plays a key role in neovessel formation and angiogenic sprouting [124]. A lower collagen concentration (2 mg/ml) allowed greater vessel length, interconnectivity and branch points compared with higher concentration (3 mg/ml and 4 mg/ml). Interestingly, computational simulations of these experiments accurately demonstrated the same effect. Critser et al. demonstrated with ECFCs that increased collagen hydrogel concentration resulted in reduced vessel density but an increase in vessel cross sectional area [125]. The authors postulated that this change in network characteristics was due to increased mechanical properties of the hydrogels; however, increased collagen concentration would also increase adhesion ligand density, while reducing pore size and the rate of degradation, all of which would also have a direct impact on cell behavior. A similar study revealed that fibrinogen concentration played a key role, with lower fibrinogen concentration (2.5 mg/ml) allowing increased network formation in a fibrin hydrogel compared with higher concentrations (5 mg/ml and 10 mg/ml) [126]. While mechanical properties likely play a role in this difference, the authors also demonstrate that concentration affects diffusion and nutrient transport in the gel. These studies highlight the importance of using systems that allow independent control over mechanical properties without otherwise modifying properties of the gel.

Yamamura et al. generated collagen hydrogels of the same concentration but with different mechanical properties by polymerizing the collagen at various pH values. It was found that network length varied based on stiffness or flexibility, with particular differences observed on the depth of the network into the hydrogel [127]. Differences in vinculin expression were also detected between so-called 'soft' and 'rigid' hydrogels. In a HyA-gelatin hydrogel system, EPCs formed capillary-like structures of increased length, thickness and area on a soft substrate ($E = 10 \pm 2$ Pa) compared with a stiff substrate ($E = 650 \pm 180$ Pa) [128]. The authors also demonstrated that substrate mechanics regulated the formation of vacuoles and lumen, with TEM images revealing the formation of many open lumens and complex lengthening cellular structures on yielding structures. In comparison, EPCs formed many vacuoles on rigid surfaces, with an intermediate behavior on firm surfaces with the presence of enlarged vacuoles and some lumen formation.

The importance of mechanical properties on network formation using ECFCs was demonstrated by Blatchley et al. Using a hybrid hydrogel system composed of modified gelatin and dextran, the authors were capable of independently tuning oxygen tension and mechanical properties of the hydrogel [129]. By controlling the number of phenolic moieties (both conjugated and unconjugated), as well as controlling crosslinking density with a secondary crosslinking mechanism, precise control of oxygen concentration and mechanical stiffness was achieved. It was found that when the effect of these two key parameters was assessed on network formation by ECFCs, the effect of mechanical properties was dominant over oxygen tension. That is that the encapsulated ECFCs formed robust vascular networks in softer hydrogels regardless of oxygen tension, but in stiffer hydrogels ECFCs demonstrated minimal network formation [129]. By modifying the crosslinking mechanism of an RGDS decorated PEGDA hydrogel, a softer hydrogel (storage modulus 1.64 kPa) enhanced network formation of a co-culture of HUVEC and human brain pericyte cells (HBVPs) in comparison with a stiffer PEGDA hydrogel (storage modulus 5.31 kPa). In a bioinspired HyA hydrogel, encapsulated CPCs demonstrated extensive endothelial differentiation and vascular network formation depending on the mechanical properties of the hydrogel [118]. In this case, a storage modulus of 850 Pa was optimal for differentiation of CPCs into endothelial cells and the formation of a vascular network, compared with a lesser effect in hydrogels with a storage modulus of 15 Pa or 170 Pa. In addition, response surface methodology (RSM) revealed that hydrogel stiffness played a much greater role in cellular proliferation of CPCs than adhesion ligand density.

Chaudhuri et al. have developed stress-relaxing hydrogels that more closely mimic the native behavior of the ECM [130]. By varying the molecular weight and density of calcium crosslinking of alginate, and using a PEG spacer, the stress relaxation could be controlled independent of initial stiffness. Faster stress relaxation increased cell spreading and proliferation, as well as enhancing differentiation of encapsulated MSCs. A similar effect on cell spreading was also reported recently in a HyA collagen sIPN, in which the encapsulated cells could readily remodel and align the collagen in a fast-relaxing hydrogel compared with a slow relaxing hydrogel [131]. While vasculogenesis is not explored in either of these studies, it would be interesting to see how organization and capillary morphogenesis of endothelial cells is influenced by stress relaxation of hydrogels.

4.3. Structure/architecture

The form or structure that a synthetic ECM takes is often overlooked, but is a crucial parameter to consider. This can greatly influence the mode of application or implantation and the timing of cell implantation. In fact, the choice of structure to use will often depend on the application to which it will be applied. The most common materials systems for cell delivery involve *in situ* forming hydrogels [132]. In this case, the cells are mixed throughout the polymer solution pre-gelation, taken into a syringe and applied *in vivo* where gelation occurs due to addition of a crosslinking agent or stimulus (Temperature, UV light, *etc.*). This allows for easy application of the cells to readily accessible tissues (skin, subcutaneous muscle, fat, *etc.*). In the case of internal organs such as the heart, access to the internal wall of the myocardium may be achieved through a catheter. However, this requires careful matching of catheter design and properties of the polymer solution. For instance, the viscosity of the hydrogel must be such that it can pass through a catheter, while the timing of gelation must be allowed for also. This is further complicated if the hydrogel is thermo-responsive, as then the catheter must have a cooling mechanism to prevent gelation prior to injection. An innovative development involves the use of the so-called 'HeartLander' [133]. Under the control of a surgeon, a mobile miniature robot crawls along the surface of the beating heart to a precise location where an injection can be made. Systems such as these may be combined with a cooling mechanism to precisely deliver thermoresponsive hydrogels to the heart [134].

Porous pre-formed scaffolds typically require surgical implantation, or the addition of a suture to keep them in place. The invasive nature tends to reduce enthusiasm for these types of materials. However, while this is certainly a drawback, there are a number of benefits associated with using pre-formed scaffolds. Typically, pre-formed scaffold will be mechanically more robust than a hydrogel, and thus more useful in load bearing applications such as bone, or ligament/tendon in the case of fibres. In addition, pre-formed scaffolds may be cultured *in vitro* prior to implantation. This allows for cells to remodel the scaffold and create their own matrix prior to implantation. Furthermore, stimuli such as hypoxia can be applied to the scaffold to influence cell behavior and prepare the cells for the microenvironment in which they will be implanted [135].

Highly porous scaffolds composed of hydrogel microspheres as building blocks have recently been developed [136–138]. A dense paste of microspheres may be injected and forms a gel *via* secondary crosslinking between adjacent microspheres. The void space between packed microspheres creates a highly porous structure that promotes rapid cell infiltration and motility. This system has shown it can promote angiogenesis *in vivo* and is likely to prove useful in controlling the behavior of transplanted angiogenic cells [137,138].

4.4. Degradation

Cell-mediated degradation of biomaterial systems is a crucial aspect of vascularization and tissue replacement. Allowing cells to remodel a matrix using MMPs, as well as the rate of matrix degradation, plays a crucial role in cell behavior [139]. In the context of angiogenesis, MMP-mediated degradation of the basement membrane is a key early step, allowing for the migration of endothelial cells and expansion of the vascular network. Studies have shown that encapsulation of endothelial cells in an MMP-cleavable HyA hydrogel with appropriate signals allows for vascular network formation [140]. Specifically, the importance of an MMP-degradable sequence was demonstrated, with limited network formation when an MMP-insensitive sequence was used [117]. Similarly, it was found that hydrogels containing non-degradable secondary crosslinks, generated using a photoinitiator and UV light, were not permissive to vascular network formation [141]. With secondary non-degradable crosslinks, encapsulated ECFCs could only undergo vacuole and lumen formation but not progress to sprouting and network formation. The authors attributed this to non-degradable polymer chains created by UV crosslinks. However, this secondary crosslinking also dramatically alters the mechanical properties of the hydrogel, which cannot be ignored in the context of altering cell behavior, as has been discussed previously.

Miller et al. assessed a number of MMP-cleavable sequences in an RGDS decorated PEGDA hydrogel system [142]. A highly degradable, less degradable and a native collagen sequence were tested, and it was observed that the highly degradable sequence allowed for greatest ingrowth into the hydrogel from a chick aortic arch ring explant, indicating the importance of tailoring the degradation rate of the MMP-sequence. In addition, replacement of the RGDS peptide with a non-adhesive RGES peptide dramatically reduced sprouting, signaling the necessity of controlling and coordinating multiple hydrogel parameters to control cell behavior. Jha et al. assessed crosslinking peptides exhibiting varying MMP-sensitivities in a cell-laden bioinspired HyA hydrogels [143]. Peptides with differing Michaelis–Menten parameters (k_{cat}/k_m) were found to differentially support CPC survival and vascularization, with the slowest degrading peptide (QPQGLAK) providing greatest support for the implanted cells. A slower rate of degradation allows prolonged mechanical support of the implanted cells, and is offered as a reason behind the improved outcome *in vivo*.

A different approach to assess the effect of cell-mediated degradation rate is to use peptides with different MMP-specificity or containing multiple MMP-cleavable sites [144]. *In vitro* vessel invasion from a HUVEC/Smooth muscle cell spheroid into a PEGDA hydrogel revealed that an increased number of cleavage sites resulted in more rapid degradation and increased cell invasion [141]. Interestingly, some of these studies have outcomes that may appear contradictory, with some indicating rapid degradation is superior and others suggesting a more delayed degradation it appropriate. In fact, the effect of the degradation rate must be considered in a number of contexts. One key factor to consider is the type of cells used, as different cells will have different MMP expression profiles. Another consideration when comparing different systems is the relative degradation rate, as what is considered a 'slow' degrading peptide in one study may be considered a 'fast' degrading peptide in another. One potential solution to avoid this may be for authors to define and directly compare parameters such as the Michaelis–Menten kinetics for any degradable peptides used. This will allow for direct comparison of peptide degradation rates by selected MMPs. Combining this with the knowledge of MMP expression from the cells of interest will allow for more accurate comparisons and more definitive conclusions.

4.5. Presentation of growth factors

Growth factors, peptides and cytokines play a key role in directing cell behavior. The process of angiogenesis has been extensively studied, and a number of key factors identified. Typically, these factors play a role in key cellular activities such as cell proliferation, migration and vascular network formation or maturation. For example, VEGF and bFGF are involved in cell proliferation, migration and network formation, while factors such as PDGF and TGF-β1 are typically more associated with the later stages of vessel stabilization. Thus, selection of the appropriate factors is vital, specifically related to the timing of presentation. For example, VEGF has a key role in early stages of vascularization, but VEGF alone can result in the formation of an abnormal, unstable vessels [145]. Many biomaterial systems have been developed to deliver multiple factors to overcome this issue and improve outcomes [146–148]. Thus, a range of strategies exists to present key factors to cells encapsulated within matrices. This includes simple encapsulation in the matrix, non-specific sequestration and specific chemical conjugation [127]. The most basic means of presenting factors to encapsulated cells involves the simple loading of the factor within the matrix without any modification of the factor or matrix. The factor will be released from the matrix by diffusion, which may be delayed if there is any electrostatic affinity between the factor and the matrix. For example, in the case of an *in situ* forming hydrogel, the factor would be added to the gel forming solution prior to gelation, or loaded to a scaffold prior to implantation. Other material strategies involve the use of microparticles and hydrogels to prolong retention kinetics [149–151].

In the natural ECM growth factors are typically sequestered to the matrix rather than being free in solution [152,153]. Sulfated proteoglycans play a key role in the sequestration of growth factors to the ECM, with changes in the sulfation patterns effecting growth factor binding and activity in the tissue [20,154]. Thus, the idea of conjugating growth factors to a synthetic matrix is inspired by components of the natural ECM such as heparin sulfate [155,156]. Conjugation of heparin enhances retention of added growth factors, as has been shown with VEGF in a collagen scaffold [157]. VEGF was more potent in terms of stimulating cell proliferation when heparin was conjugated to the collagen scaffold. Heparin-starPEG hydrogels have been developed to prolong the release of angiogenic growth factors [158,159] and also as model systems to study cell-growth factor interactions [160]. In another study, addition of heparin to a HyA hydrogel enhanced the effect of sequestered TGF-β1 on encapsulated CPCs, increasing endothelial cell differentiation and network formation [161]. In this study, the molecular weight and weight percentage of heparin in the hydrogel also proved to be of great importance in relation to retention of exogenously added and endogenously produced growth factors. Using this growth factor sequestering HyA system, hCDC also assembled into vascular networks [162]. It was shown that the mechanism of vascular differentiation and network formation of hCDC was dependent on TGF-β1 signaling through the CD105 co-receptor.

The heparin-binding domain of fibrinogen has also been shown to enhance growth factor retention [163]. The addition of this domain to a synthetic matrix enhanced retention of two growth factors (FGF-2 and PlGF-2) and subsequent angiogenesis in a wound model. Another approach is to fuse ECM-binding sequences to growth factors to ensure they are retained within a matrix containing natural ECM components [164]. These super-affininty growth factors showed enhanced binding to ECM-derived proteins such as collagen, fibrinogen and fibronectin. These approaches create growth factor rich environments that control the behavior of encapsulated cells.

Direct conjugation of growth factors to polymer scaffolds is a more specific way to ensure enhanced retention of a factor. Conjugation of VEGF to a thermoresponsive acellular hydrogel improved recovery in an MI model, with enhanced capillary density in comparison with VEGF that was simply added to the hydrogel [165]. However, in the context of cell encapsulation, conjugation to a polymer matrix leads to an increased interaction between encapsulated cells and the factor. Multiple examples exist showing that sequestration of a range of factors including VEGF [166,167], bFGF [168] and PDGF [169] enhances endothelial cell proliferation, migration and network formation. Rather than conjugate the entire protein, some studies have simply used a short peptide sequence that mimics growth factor function. Chan et al. conjugated the VEGF-mimetic peptide QK to a collagen scaffold and observed increased cell proliferation and tube formation [170]. A similar effect occurred when QK was conjugated to methacrylated gelatin [171]. However, as the conjugation used the same chemistry as gel formation, there was a reduction in mechanical properties and an increase in pore size of the hydrogel. While a control peptide did not show the same effect on endothelial cells, it is unclear if the QK peptide and these changes in material properties combined synergistically to promote enhanced vascular network formation, or if simple addition of the peptide alone is enough to enhance network formation.

While direct conjugation of an angiogenic factor to a sECM is an effective means by which to assess the propensity of a specific factor to promote vasculogenesis, it has its limitations. This approach allows only for the retention of specific exogenously added factors, rather than endogenous cell-secreted factors that would be retained with heparin or other sulfated glycosaminoglycans. Thus, non-specific approaches that allow for the retention of both exogenously added and endogenously secreted factors is favored.

5. Relative importance of matrix parameters

We have described five key parameters when designing a sECM for cell therapy. Each parameter plays an important role in enhancing cell survival and function, in this case enhancing vascularization. Furthermore, these design parameters act synergistically to control cell function, and each parameter must be thought of in terms of how it will co-ordinate with the other material parameters to control cell behavior. For example, the presentation of adhesion ligands is altered by the mechanical properties of the material to which they are conjugated – emphasizing the importance of coordinating multiple material properties. When considering the mechanical properties of a material, one must also consider how this will change over time as a result of biodegradation – again emphasizing the senselessness of considering parameters individually rather than synchronously.

In terms of relative importance, it is difficult to pinpoint the key parameter when designing a sECM. However, an order of preference when designing a sECM should be considered. Initially, it is important that cells are provided with appropriate adhesion ligands to ensure cell adhesion, and potentially engagement with integrins associated with angiogenesis. Once a suitable ligand is identified, mechanical properties, and how these change with the rate of biodegradation over time, should be considered. Furthermore, matching biodegradation with the rate of tissue formation should be considered. The addition of exogenous growth factors to the hydrogel system, in order to enhance angiogenesis, is a further consideration of any angiogenic cell delivery system. The means of adding any factor (entrapment, specific or non-specfic conjugation) and its spatiotemporal retention within the system is also a crucial consideration. Finally, the form any sECM takes is of great importance, and most crucial when considering translational. The form any sECM takes will have a great effect on the mode of delivery *i.e.* can the sECM be injected, or must it be surgically implanted?

The approach described above for designing a sECM can be followed to allow for informed decision-making. It ensures that parameters that complement one another are selected. Response surface methodology can be used to further optimize the system, identifying combinations of variables that result in the greatest angiogenic cell function. This is critical to developing efficacious therapies when transplanting cells to a harsh and challenging ischemic environment. Indeed, identification of the correct combination of matrix parameters is a key step to successful MACT for revascularization of ischemic tissues in a range of pathological conditions (Fig. 4).

6. Therapeutic applications of encapsulated cells

Many clinical conditions suffer from insufficient tissue perfusion, including cardiovascular diseases such as critical limb ischemia (CLI) and myocardial infarction (MI) as well as wound healing application. These conditions will benefit greatly from cellular therapies to enhance vascularization. Engineered matrices that promote cell survival and tissue vascularization hold much promise as a therapeutic modality for these clinical conditions. The assessment of sECM in relevant pre-clinical models is imperative to identify those with greatest clinical potential. We will now review sECM approaches that have displayed potential in pre-clinical models.

6.1. Critical limb ischemia

Critical limb ischemia (CLI) is a severe form of peripheral arterial disease (PAD) which involves severe blockage of major arteries serving the lower extremities. CLI is a major burden on healthcare worldwide [172].

A range of materials have been developed and assessed as sECM to promote stem cell-derived vascularization in pre-clinical models of CLI. Encapsulation of hMSCs in a type I collagen microgel system 'primed' the cells to secrete pro-angiogenic growth factors and cytokines [173]. In an immunocompromised hindlimb ischemia model [174], this treatment enhanced capillary density and reduced necrosis of the limb. The cells were alive at day 7 following retrieval from the implant site, indicating the capacity of the engineered microgel system to sustain cell survival *in vivo*. A similar gelatin microcryogel system showed that encapsulated ADCSs outperform ADSCs delivered without a matrix [175]. ADSCs within the microcryogel system outperformed a higher number of ADSCs delivered without a sECM, emphasizing the power of an appropriate sECM for cell delivery. A novel platelet lysate (PL) gel enhanced the revascularization potential of MSCs. The PL is composed mainly of fibrin, but also contains many pro-angiogenic factors (VEGF, EGF, PDGF, BDNF *etc.*) that contribute to enhance the MSCs angiogenic capacity [176]. Even MSCs within unmodified alginate capsules increased perfusion of ischemic limbs [177]. This indicates that by simply physically entrapping the cells, their therapeutic capacity is improved, most likely by improved retention and subsequent paracrine support rather than any biological enhancement of the cells function.

Synthetic mixing-induced two-component (MITCH) hydrogels have been developed for cell delivery with mild gelation conditions [178]. Composed of PEG and the C7 peptide (with an RGD motif), VEGF retention was enhanced through manipulation of mesh size [179]. Injection with MITCH hydrogels protected iPS-ECs from shear forces compared with PBS delivery, and enhanced recovery in a limb ischemia model. A NIPAAm-based hydrogel, with a sol-gel transition temperature of 26.5 °C, encapsulated bFGF and MSCs which activated the KLF4 survival signaling pathway and increased angiogenic growth factor production [180]. Furthermore, bFGF incorporation triggered endothelial differentiation of MSCs, along with improving cell survival, proliferation and perfusion of the ischemic limb, demonstrating the potency of growth factors to direct cell survival, fate and function. A similar effect was observed with OECs and VEGF in an RGD-decorated alginate hydrogel, while the effect was further improved by co-culturing OECs and EPCs [181].

Self-assembling peptide ampiphiles with an RGD-presenting epitope enhanced functional repair by bone-marrow derived angiogenic cell [182]. The presence of the RGD sequence activated integrin

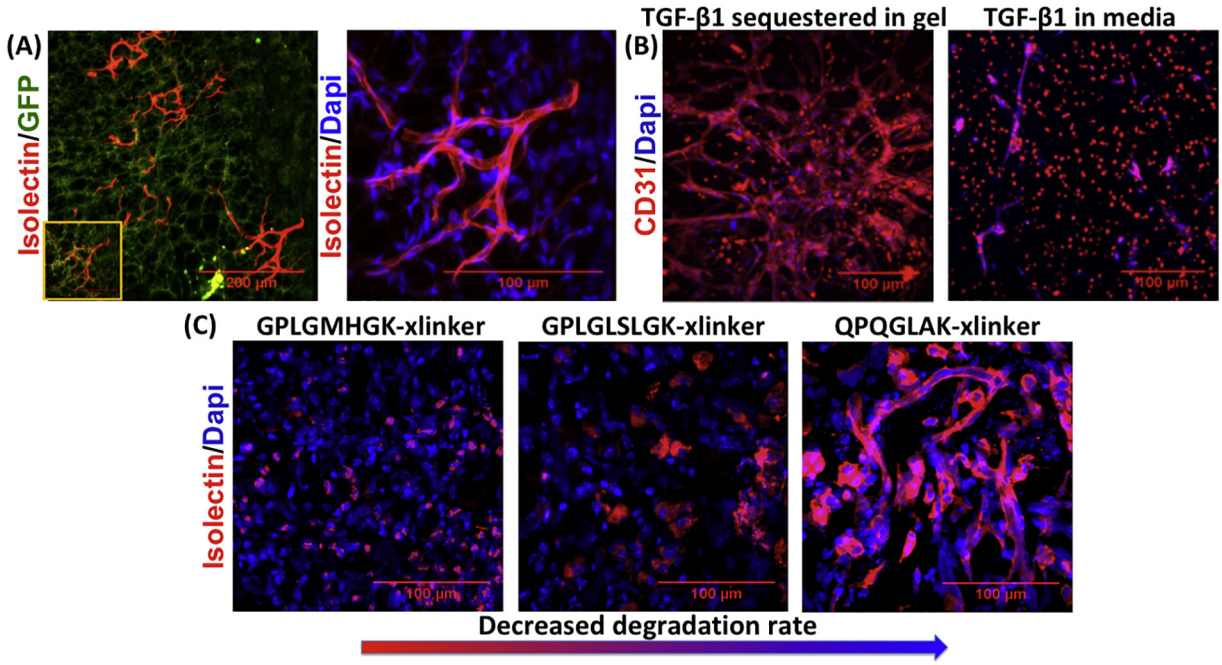

Fig. 4. Vascular Network Formation in sECM. (A) Integration of vascular networks derived from GFP-labelled cardiac progenitor cells (CPCs) in growth factor-sequestering hyaluronic acid (HyA) hydrogels with host vasculture, confirmed by Isolectin perfusion [118]. (B) TGF-β1 presentation in growth factor-sequestering HyA hydrogels plays a key role in vascular network formation by CPCs [161]. (C) The selection of an MMP-cleavable peptide with appropriate degradation rate plays a role in vascular integration of CPCs transplanted in growth factor-sequestering HyA hydrogels [143].

signaling cascades and improved cell survival, and limb perfusion *in vivo*. Peptide-based gels are modular in nature, and can be modified with various functionality, including the incorporation of VEGF-mimetic sequences that would further enhance cell function particularly in ischemic tissue [183].

6.2. Myocardial infarction

Coronary heart disease is a major health and economic burden, and is attributed as the cause of one in seven deaths in the United States [172]. MI is a manifestation of coronary heart disease where blood supply to the myocardium is interrupted. Unfortunately, the myocardium has low endogenous capacity to regenerate, leading to fibrosis of the infarct and surrounding tissue [184].

Promotion of angiogenesis in the infarct area has been shown to improve recovery [185–188], while the survival of any implanted cells will be heavily dependent on blood supply to the infarct. The benefit of cell therapy in the myocardium has been widely attributed to paracrine support offered by transplanted cells [189,190]. Furthermore, the implantation of a biomaterial can support the infarcted myocardium, whether the material is a synthetic [191,192] or natural material [193]. Thus, the use of biomaterials to enhance cell survival in the myocardium has a synergistic benefit in terms of supporting cell survival but also supporting the infarcted myocardium.

A commercially available hyaluronic acid/gelatin hydrogel (Hystem®–C™) enhanced engraftment of hCDCs in a mouse MI model [194]. Enhanced cell retention improved functional recovery of the myocardium and angiogenesis, while dual staining of human nuclear antigen (HNA) and von Willebrand factor (vWf) provided evidence of endothelial differentiation of the engrafted hCDCs. A similar effect was observed following delivery of hCDCs in a platelet gel, which is composed mostly of fibrin and contains high levels of endogenous growth factors including VEGF, IGF-1 and SDF-1α [195]. An agarose capsule supplemented with fibronectin and fibrinogen increased retention of implanted CSCs [196]. However, while the number of HNA positive cells was increased, the percentage of differentiated cells was the same, indicating that the capsule simply increased cell retention rather than directing cell differentiation or function.

RGD-conjugated alginate microspheres enhanced the survival and efficacy of encapsulated hMSCs up to day 7 [197]. Furthermore, encapsulation of hMSCs upregulated mRNA expression of bFGF compared with 2D cultures, although no difference was observed in arteriole density between non-encapsulated hMSCs or alginate microspheres alone.

Roche et al. [198] compared a number of biomaterial systems for the delivery of MSCs to the myocardium – two injectable gels (chitosan and alginate) and two implantable patches (alginate and collagen). After 24 h no difference was observed between the biomaterial groups, with all biomaterial carriers showing enhanced retention compared with saline delivery. While not shown, it is likely that differences would emerge between groups after 24 h when the different degradation rates and other material properties would begin to effect the loaded cells.

hES-derived vascular cells were delivered to the myocardium in an MMP-responsive PEG hydrogel with the pro-survival and angiogenic factor thymosin β4 incorporated [199]. Although survival of cells was not directly measured, there was an increase observed in tissue angiogenesis, indicating an increase in the cell survival.

6.3. Wound healing

Impaired wound healing leading to chronic wounds is a major burden in global healthcare. This results in reduced life quality and a great financial cost [200]. Vascularization of the wound bed is a key stage in wound healing, with disruption to angiogenesis playing a key role in non-healing wounds [30]. Amongst the strategies to enhance compromised wound healing, increased blood vessel formation is a key target to promote regeneration [201].

The angiogenic effect of ADSCs in full thickness wounds in diabetic rats was enhanced by the use of a hydrogel carrier, in this case the synthetic and thermoresponsive Pluronic F-127 [202]. There was an increase in wound vascularization from use of the hydrogel, suggesting increased potency simply by retention at the wound site. A PEGylated fibrin gel combined with ADSCs also enhanced neovascularization of the

wound bed, with the presence of ADSCs in the wound bed confirmed at two weeks [203]. Pullalan-collagen hydrogels containing ADSCs enhanced wound healing and vascularization [204]. This was shown to occur through a mechanism of attracting endogenous progenitor cells to the wound bed [205]. *In vitro*, conditioned media collected from these hydrogels had greater angiogenic stimulatory capacity than cells seeded on tissue culture plastic, as measured in an *in vitro* angiogenesis assay. In a chitosan hydrogel, addition of gelatin significantly increased the survival of encapsulated ADSCs in a wound model [206]. There was also a significant increase in CD31+ staining in the wound bed. This supports the suggestion that that ECM-derived materials support encapsulated cells, likely to be primarily through integrin engagement with specific sequences and cell-mediated remodeling.

In a HyA hydrogel system containing RGD sequences and MMP-cleavable crosslinks, ECFCs formed a vascular network in a full-thickness wound model [207]. However, there was no significant effect on wound closure compared with a HyA hydrogel without ECFCs, possibly due to the regression of blood vessels observed at 14 days. A similar study assessed the effect of ECFCs and iPSC-derived ECs in a diabetic wound model [208]. Addition of cells significantly improved vascularization and wound healing, with ECFCs performing best. Interestingly, there was no difference observed between iPSC-ECs derived from healthy patients and those derived from diabetic patients. Thus, iPSC technology may be suitable as an autologous therapy for wound healing and ischemic conditions in diabetic patients.

Integra™ is a commercially available matrix derived from bovine tendon that is used to treat various wounds. Composed of collagen and GAGs, Integra™ was seeded with Vascular-resident EPCs from the myocardium and applied to a full-thickness wound model [209]. This increased the vascularization of the wound bed compared with Integra™ alone, but no evidence of enhanced wound closure or dermal regeneration was provided.

7. Conclusions

Cell therapies provide an exciting opportunity to transform healthcare for a number of degenerative conditions. In particular, stem cell and iPSC-derived therapies provide the chance to develop personalized therapies. However, key to the successful translation of cell therapies to the clinic is the development of material systems to ensure delivery and survival of therapeutic cells. Much progress has been made in the design of systems for MACT. This has resulted in the creation of a range of sECM to deliver various cell types to promote tissue revascularization. Ideal sECM properties necessitates the use of systems that allow for independent tuning of the parameters discussed in this article. Furthermore, considering these parameters in isolation is insufficient, with a mechanistic understanding of the interplay between them vital. Increased levels of complexity of sECM are required to tailor multiple matrix properties for optimal cell performance. However, from a translational and regulatory standpoint, the importance of simplicity of design and composition cannot be overstated [76]. Thus, a balance must be maintained between optimizing the matrix for cell encapsulation while at the same time respecting the current translational environment, as well as considering scalability of the product. This will ensure the widespread adoption of suitable matrices in the regenerative medicine space to facilitate angiogenic cell therapies to revascularize ischemic tissues.

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