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STEM CELLS TRANSLATIONAL MEDICINE®

TISSUE ENGINEERING AND REGENERATIVE MEDICINE

Concise Review: The Endothelial Cell Extracellular Matrix Regulates Tissue Homeostasis and Repair

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Key Words. Endothelial cell • Induced pluripotent stem cells • Microvasculature • Angiogenesis • Cell adhesion molecules • Cell interactions • Glycosaminoglycan • Tissue regeneration

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Received July 17, 2018; accepted for publication October 26, 2018; first published December 11, 2018.

http://dx.doi.org/10.1002/sctm.18-0155

ABSTRACT

All tissues are surrounded by a mixture of noncellular matrix components, that not only provide physical and mechanical support to cells, but also mediate biochemical signaling between cells. The extracellular matrix (ECM) of endothelial cells, also known as the perivascular matrix, forms an organ specific vascular niche that orchestrates mechano-, growth factor, and angiocrine signaling required for tissue homeostasis and organ repair. This concise review describes how this perivascular ECM functions as a signaling platform and how this knowledge can impact the field of regenerative medicine, for example, when designing artificial matrices or using decellularized scaffolds from organs. STEM CELLS TRANSLATIONAL MEDICINE *2019;8:375–382*

SIGNIFICANCE STATEMENT

In general, all tissues are surrounded by a mixture of noncellular matrix components, that not only provide physical and mechanical support to cells, but also mediate cross-talk between cells. The extracellular matrix of endothelial cells, also known as the perivascular matrix, forms a vascular niche that orchestrates processes required for tissue homeostasis and organ repair. This concise review describes which messages are sent by this perivascular matrix and how this knowledge can be used in the field of regenerative medicine.

INTRODUCTION

The extracellular matrix (ECM) has central roles in tissue integrity and remodeling. While collagens, laminins, and proteoglycans are the most abundant structural components of the ECM in most tissues, tissue-specific molecular complexity during repair is determined by ECM glycoproteins and the capacity to secrete specific matricellular proteins. In mammals, this comprises approximately 300 proteins, often referred to as the matrisome [1]. In particular, remodeling of ECM at the level of capillaries, in a very fundamental way, enables the interaction between endothelial cells, circulating immunocytes, and tissue that is required for homeostasis and regeneration. A lot of insight in this adaptive vascular ECM remodeling has been derived from research into developmental biology and cancer metastasis [2–7]. However, more recently these same processes have also been implicated in tissue repair [8]. From this perspective, understanding the biology and regulation of the ECM is key to the field of regenerative medicine, where the use of artificial matrices to drive stem cell maturation is an important theme. In this concise review, we will in particular discuss the microvascular ECM structure as an essential signaling platform for tissue repair and how understanding its biology may help advance the field of regenerative medicine.

THE CONCEPT OF BIDIRECTIONAL ANGIOCRINE SIGNALING IN TISSUE HOMEOSTASIS AND REPAIR

Vascularization Induces Maturation of Stem Cell-Derived Tissue and Tissue Regeneration

In addition to delivering oxygen and nutrients to cells as passive and permissive conduits, and clearing cellular waste products simultaneously, blood vessels also provide instructive signals for organogenesis. During embryogenesis, endothelial progenitor cells invade into nascent organs, develop into different endothelial phenotypes, and establish organ-specific vascular niches which release endothelium-derived growth factors and trophogens (angiocrine factors) to

promote stem cell differentiation (extensively reviewed by Rafii et al. [7]).

The relevance of this biology for regenerative medicine is illustrated by recent experiments where we demonstrated that prolonged culture of induced pluripotent stem cells (iPSCs)-derived kidney organoids failed to induce maturation of kidney beyond early embryonic tissue. However, maturation and segmental cell specification could be induced when vascularization of the organoids occurred upon transplantation in vivo, illustrating the requirement of vascular signaling for differentiation [9, 10]. Functional differentiation could also be observed in stem cell-derived beta cells upon vascularization after transplantation under the kidney capsule [9–11]. Similarly, it was recently shown that transplantation of human brain organoids into adult mouse brains resulted in progressive neuronal differentiation and maturation, gliogenesis and axonal growth of engrafted organoids. After the organoids became vascularized, neuronal activity could be demonstrated [12].

Endothelial Cells Are Crucial for Tissue Regeneration Through Angiocrine Signaling

The angiocrine function of EC is preserved beyond embryogenesis in specialized microvascular areas such as sinusoids where ECs are in close apposition with progenitor cells or diploid epithelial cells that have preserved proliferative potential [13]. For example, capillary sinusoidal endothelial cells (SECs) within liver and bone marrow comprise phenotypically and functionally discrete populations of endothelial cells. After partial hepatectomy, liver SECs (LSECs) stimulate hepatocyte proliferation through a process of angiocrine production of hepatocyte growth factor and Wnt2 [14]. Subsequently, LSECs undergo angiogenesis to meet the demand in blood supply to regenerate liver tissue. Similarly, after chemotherapy and irradiation, activated bone marrow SECs reconstitute hematopoiesis by angiocrine expression of Notch ligands and insulin-like growth factor-binding proteins [7, 15, 16]. Pulmonary capillary endothelial cells also produce angiocrine growth factors that induce proliferation of epithelial progenitor cells thereby supporting alveologenesis [17]. There is a large variety in such angiocrine factors that can be produced by the endothelium, while the secretion is very tissue specific and still largely unknown [7].

Organotypic EC Phenotype Depends upon Instruction from Neighboring Cells and Vice Versa

Endothelial cells in turn depend for their survival and organotypic function upon instructive signaling from neighboring cells as well. For example, the highly specialized fenestrated capillary EC phenotype in the glomerulus is dependent upon vascular endothelial growth factor (VEGF) signaling from the podocytes [18], as illustrated by experiments where podocyte specific deletion of VEGF secretion results in loss of fenestrae and glomerular endothelioses. Angiopoietin 1 is another growth factor that is secreted by perivascular stromal cells such as pericytes, to maintain a stable endothelial cell phenotype [19]. Loss of angiopoietin 1 mediated Tie2 kinase signaling in the endothelium leads to endothelial cell proliferation and loss of organotypic characteristics such as fenestration. Conditional deletion of VEGF-A receptor-2 in liver ECs or bone marrow ECs [20], thus disrupting the stable EC phenotype, inhibits liver and bone marrow regeneration underscoring the necessity of these angiocrine endothelial beds to respond to signaling molecules such as VEGF to exert their angiocrine regenerative properties.

Endothelial Cell Extracellular Matrix Serves as an Important Platform for Bidirectional Signaling of Angiocrine EC to Its Neighboring Cells

The bidirectional exchange takes place at the EC extracellular matrix, where the matrix should allow for the formation of specific gradients of growth factors and subsequent engagement with surface receptors (see Figs. 1, 2). The ultrastructure of ECM that enables endothelial cells to engage with their direct surroundings through angiocrine signaling consists first of all of a very dynamically regulated subendothelial basement membrane (BM), containing collagen type IV isoforms, laminin isoforms, heparan sulfate proteoglycans (perlecan or agrin), and nidogen-1 and/or nidogen-2. Collagen type IV and laminins are the two major BM components that self-assemble to form independent networks that confer structural stability and biological activity, respectively. These two networks are connected by perlecans and nidogens [21]. Vascular endothelial cells express laminin $\alpha4$ and $\alpha5$ chains that combine with laminin $\beta1$ and $\gamma1$ chains to form laminins 411 and 511 (isotypes 8 and 10), respectively. Laminins are considered to be the major BM components responsible for the biological functions of BMs; that is, for transducing signals that control cell migration, survival, proliferation, and differentiation. Laminin α-chain distribution and expression depends on endothelial cell type, state of vessel growth, and activation state [22, 23]. Laminin $\alpha5$ chain, for example, is strongly expressed in most capillary BMs and inhibits leukocyte transmigration [24]. Laminin isoforms also bind to growth factors (VEGF, platelet-derived growth factor [PDGF], fibroblast growth factor [FGF], and epidermal growth factor [EGF]) with high affinity, through their heparin-binding domains located in the α chain laminin-type G domain [25]. In addition, membrane-bound proteoglycans and glycosaminoglycans such as hyaluronan, chondroitin sulfate, and heparan sulfate, with terminal sialic acids, contribute to binding and sequestering of growth factors and morphogens with their surface receptors. In embryology altering the proteoglycan composition of this layer results in abnormal vascular development and loss of angiocrine signaling molecules [26]. Using endothelial specific deletion of hyaluronan synthesis, we recently found that also in adult life this layer is essential for endothelial stabilization through specific binding of vascular growth factors [27].

Finally, a fibrillar interstitial matrix underlies the endothelial BM and serves to further interconnect the endothelium with its neighboring tissue. In general, it is composed largely of the fibrillar collagen types I and III together with chondroitin sulfate and dermatan sulfate proteoglycans such as decorin and biglycan, and again multiadhesive glycoproteins [28], although its composition may change from one capillary bed to another. The composition of this latter layer is primarily controlled by resident tissue fibroblasts, that act as a signaling hub for tissue homeostasis and repair. Like the endothelium, they have an organ-specific phenotype where anatomical localization is related to the specific transcriptome profiles, such as embryonic patterning genes, as well as function [29]. While these cells intimately communicate with tissue cells and the immune system to preserve an anti-inflammatory and trophic milieu, they can respond to injury by differentiating into proliferating myofibroblasts and eventually converting into a

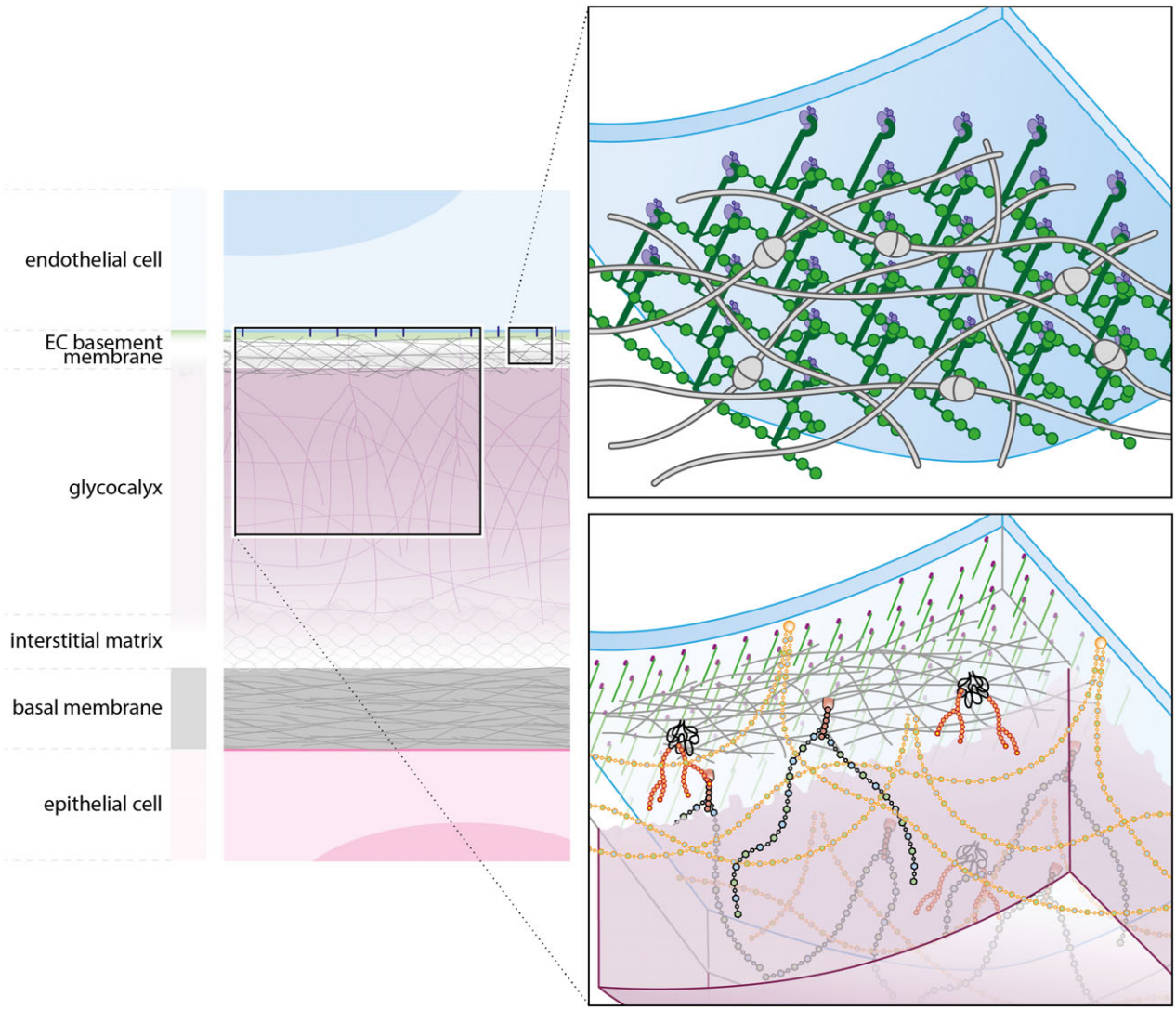

Figure 1. The endothelial basement membrane, composed of laminin and collagen IV strands which self-assemble to form an independent network crosslinked by perlecans and nidogen, is bound by the endothelial cell through integrins (right lower panel). The glycocalyx, formed by membrane-bound proteoglycans (GAGs), is able to sequester growth factors and constitutes a part of the interstitial matrix functioning as a signaling platform. Long polymeric hyaluronan (orange) crosslinks proteoglycans that carry heparan sulfate (gray) and sialated surface proteins (red), together constituting a gel like layer. Abbreviation: EC, endothelial cell.

nonproliferating, matrix-producing phenotype. Where the role of the latter in scar formation is undisputed, the way by which tissue fibroblast use and regulate their extracellular microenvironment for homeostasis is not well understood.

The Perivascular Extracellular Matrix as a Signaling Platform for Repair and Regeneration

During tissue repair and regeneration, where downstream signaling pathways such as Akt (protein kinase B) and mammalian target of rapamycin regulate endothelial cellular events, multilayered perivascular ECM remodeling can be discerned. Matrix metalloproteinases (MMPs), which normally reside in a quiescent state within the ECM can be activated upon injury, in particular inflammation, through proteolytic cleavage by proteases such as MT1-MMP on leukocytes, or by direct redox activation. The subsequent ECM degradation leads to the production and release of ECM components that further modulate ECM remodeling and set the stage to resynthesize the ECM. These include:

a. During EC injury rapid activation of latent MMPs and subsequent generation of matrix fragments occurs through activation of endothelial cells and invading immunocytes (Fig. 3). The resulting protease-mediated fragmentation of matrix proteins results in generation of matrikines. Matrikines are ECM fragments that are generated through proteolysis in a highly regulated manner and which, for example, through exposition of binding domains, can elicit specific local biological responses [30]. Collagen and fibronectin-derived peptides are well-known matrikines that have been implicated in further activation of immunocytes and fibroblasts and modulating endothelial function. For example, exposition of the terminal domain of fibronectin during ECM degradation can stimulate MMP1 formation by fibroblasts and hence further stimulate ECM remodeling [30].

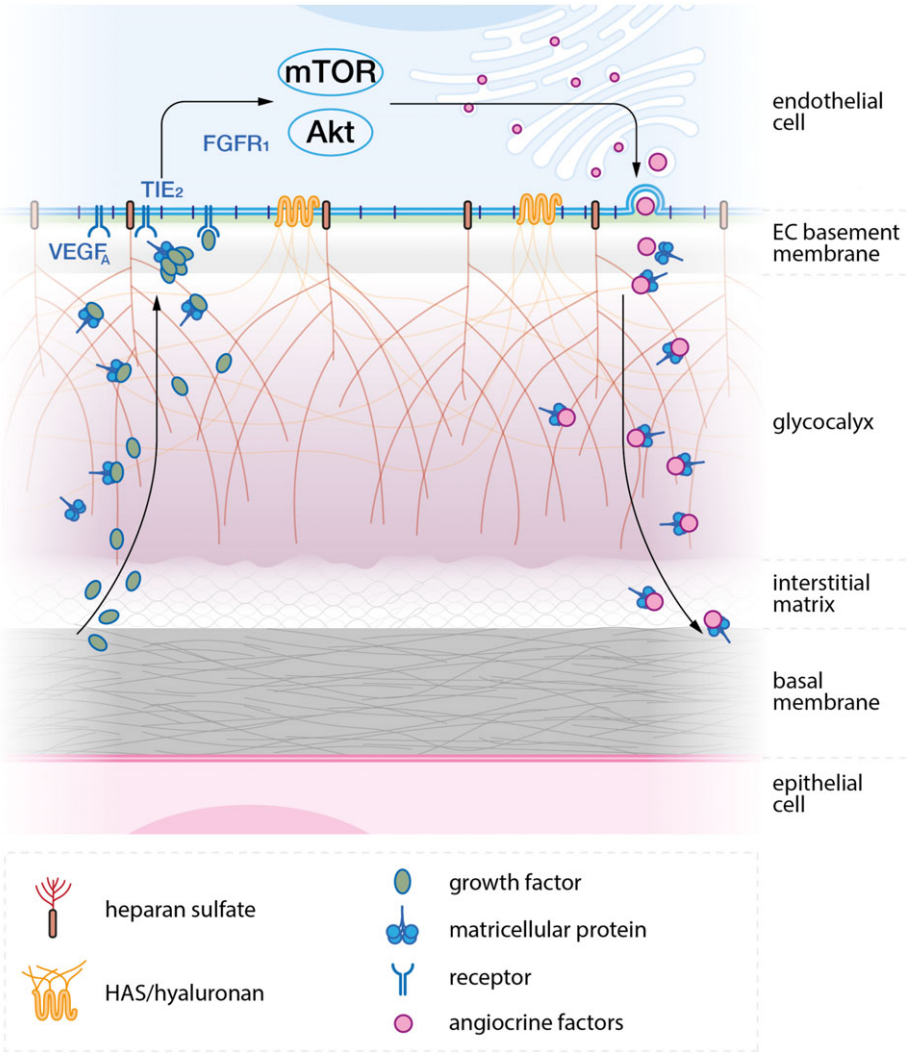

Figure 2. Matricellular proteins and glycosaminoglycans that contain heparan sulfate bind with growth factors and orchestrate receptor interaction at the endothelial cell membrane. This will elicit growth factor-induced downstream cellular events such as Akt (protein kinase B) and mTOR signaling, which define endothelial adaptive responses, such as the secretion of angiocrine factors. The transmission of angiocrine factors to neighboring cells again is governed in turn by these same endothelial extracellular matrix components. Abbreviations: EC, endothelial cell; FGFR, fibroblast growth factor receptor; HAS/hyaluronan, hyaluronan acid synthase with it's product hyaluronan; mTOR, mammalian target of rapamycin; TIE2, tyrosine kinase with Immunoglobulin-like and EGF-like domains 2; VEGF, vascular endothelial growth factor.

Another example is the proteolytic cleavage of laminin and collagen which has been shown to result in fragments that contain EGF-like repeats capable of EGF receptor transactivation and reinitiating endothelial ECM synthesis (reviewed in [31]). Together this leads to the initial remodeling of the structural ECM network in the BM and allows for resynthesis of a new provisional EC matrix. This initial step in remodeling of the perivascular matrix is important to set the stage for tissue regeneration.

b. Matricellular proteins, such as CCN (acronym of CYR61, connective tissue growth factor [CTGF], and NOV)-family of proteins, TSP-1 (thrombospondin-1), tenascin-C and SPARC (secreted protein acidic and rich in cysteine) have been identified as components of the ECM during developmental processes and organogenesis (for review see Adams [32]). The term matricellular has been applied to this group of extracellular proteins that do not contribute directly to the formation of structural ECM elements but serve to modulate cell–matrix interactions and cell function. While they usually have limited expression in adult life, they can become upregulated and released from the ECM during injury and repair [33–36]. The production and release of matricellular proteins upon injury allows for binding of these proteins to a variety of receptors, growth factors and proteases in the capillary pericellular space, generally reducing cell adhesion and proliferation, and thus tuning ECM remodeling down (Fig. 3). These effects are very specific for the various matricellular proteins [37]; for example the matricellular protein TSP-1 has been shown to act as a strong inhibitor of angiogenesis. It binds to the multiligand CD36 that is expressed on activated endothelium and that induces multiple proapoptotic antiproliferative and anti-inflammatory downstream signaling events [38, 39]. Through these effects TSP-1 can modulate response-to-injury processes. For example, during the proliferative phase of infarct healing, localized induction of TSP-1 in the ischemic zone of the myocardium prevents expansion

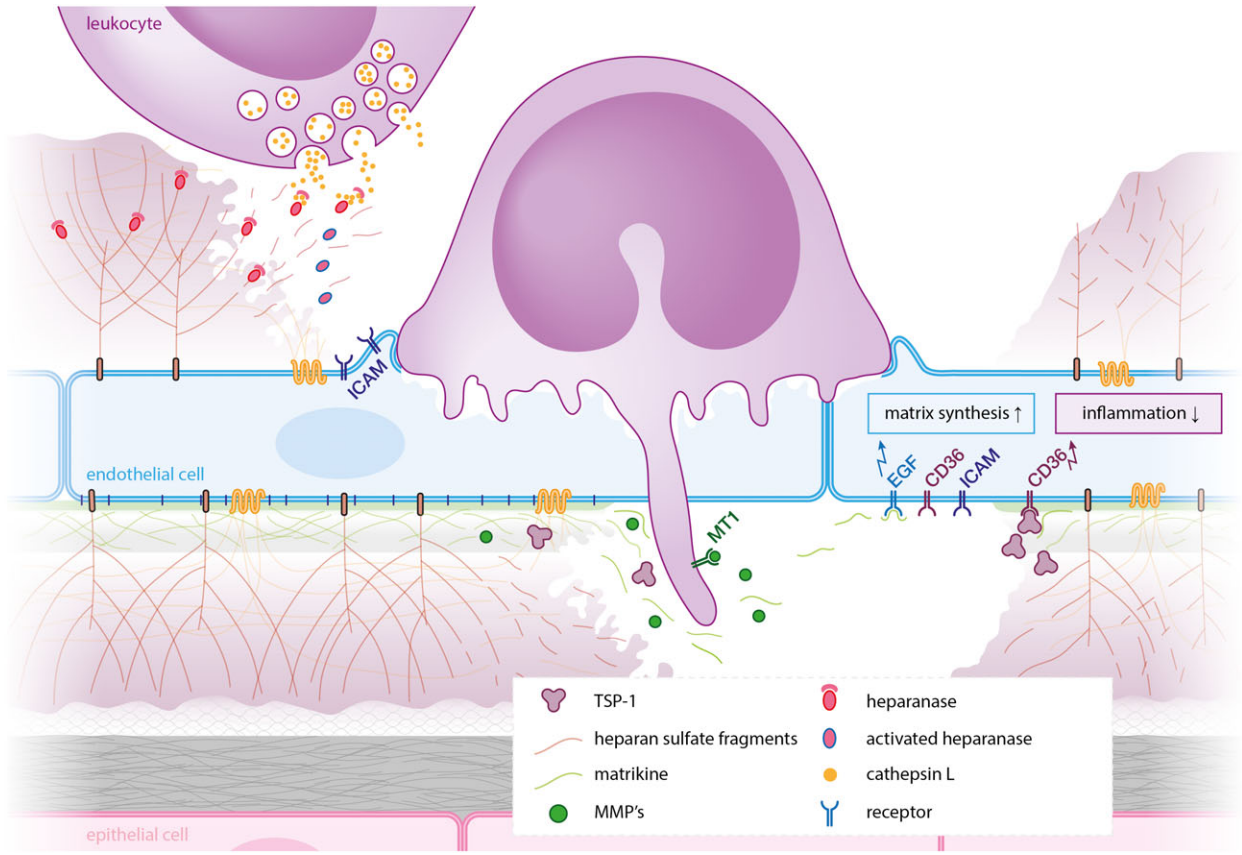

Figure 3. Activated leukocytes, through the release of Cathepsin L can activate heparanase, leading to the degradation of the luminal endothelial surface glycocalyx [43]. This allows the leukocyte to engage with endothelial surface adhesion receptors (such as ICAM-1) and form a podosome that can invade into the subendothelial matrix. The podosome delivers MT-1 leading to subsequent binding and local activation of MMPs and matrix degradation. The release of matrikines and matricellular proteins such as TSP-1 from the matrix counter-regulate matrix degradation through their respective activation of EGF and CD36 receptors on the subendothelial surface. Abbreviations: EGF, epidermal growth factor; ICAM-1, intracellular adhesion molecule 1; MMPs, matrix metalloproteinases; MT-1, membrane type I-metalloproteinase; TSP-1, thrombospondin-1.

of inflammation into viable myocardial areas through local activation of anti-inflammatory signals [40]. Another example is that TSP-1 through its modulation of endothelial function can drive lineage-specific differentiation of bronchoalveolar stem cells [41]. CCN2/CTGF, expressed by endothelial cells, plays an important role in pericyte recruitment through PDGF signaling and subsequent vascular stabilization [42]. Through integrin binding, CCN2 mediates vascular cell migration and proliferation and regulates endothelial BM formation. The general association of matricellular proteins with stem cell niches across species further suggests that matricellular proteins should be considered more closely for their potential role tissue regeneration [5, 32].

c. Finally, dynamic remodeling and chemical editing of the gel-like glycocalyx envelope of endothelial cells occurs during injury and repair (Fig. 3). The changes in this glycocalyx are probably among the most critical in controlling angiogenesis and angiocrine signaling. In particular, the ability of heparan sulfate domains to mediate binding of specific proteins is fundamental to the organization of protein–receptor interactions at the cell surface and for the creation of chemotactic gradients of growth factors and chemokines [43, 44]. For example, heparan sulfate facilitates the interaction of growth factors, such as FGF-2, VEGF and heparin-binding epidermal-like growth factor, with their respective receptors [45–49]. Upon EC injury resynthesis of membrane bound glycosaminoglycans occurs where sulfation patterns, and consequently also growth factor and morphogen binding, are modified to adapt to the altered microenvironment (for review see Rabelink et al. [43]). Several lines of evidence support the concept that such perivascular ECM remodeling favors tissue regeneration. For example, in newts, cardiac regeneration following injury was preceded by formation of a matrix network comprising tenascin-C, fibronectin, and hyaluronan. This specialized matrix network may serve as a path for progenitor cells as well as play an active role in activation of a regenerative program [50].

Implications for Regenerative Medicine

Mimicking the Regenerative Endothelial ECM

Understanding the biology of the provisional perivascular EC matrix during repair has implications for biomaterials that are currently being developed for regenerative medicine and tissue engineering in particular. Today, many micro/nanofabrication technologies have been developed for tissue engineering applications. These technologies can be used to create geometrically

defined matrix structures that enable interactions with a specific matrix topography. However, still little knowledge is available as to how to engineer the qualitative characteristics of these materials, such that they mimic the regenerative properties of the perivascular EC matrix. Recently, synthetic neoproteoglycans (neoPGs) with affinity for FGF2 were synthesized, thus mimicking an essential component of the EC glycocalyx envelope. These neoPGs were introduced into plasma membranes of ESCs deficient in HS biosynthesis. Here, they assumed the function of native heparan sulfate proteoglycans, rescued FGF2-mediated kinase activity, and promoted neural stem cell specification [51]. A 2018 study described the covalent incorporation of laminin heparin binding domains into fibrin matrices, thus recreating components of the BM in a hydrogel [24]. This addition improved retention of growth factors and significantly enhanced the efficacy of VEGF and PDGF to promote wound healing in vivo, under conditions where the growth factors alone in fibrin are inefficacious [25]. Another example, where insight in the biology of the EC matrix was used was a biomolecular engineering approach, which introduced cell-instructive peptide motifs of the matricellular protein CNN within a recombinant elastin-like protein polymer. This polymer elicits integrin-specific endothelial cell survival and function, and would therefore serve as a promising biomaterial for tissue regeneration [52].

Understanding how ECM components induce cell differentiation is also critical to the field of stem cell and organoid culture. Stem cell-derived organoids recapitulate multiple aspects of real organs making them promising models to study organ development, function, and disease. However, the full potential of organoids has remained unrealized, owing to the poorly defined animal-derived matrices in which they are grown. Typically, such organoids are grown in Matrigel, which is a solubilized BM preparation extracted from the Engelbreth-Holm-Swarm mouse sarcoma, a tumor rich in such ECM proteins as laminin (a major component), collagen IV, heparin sulfate proteoglycans, entactin/nidogen, and growth factors. A 2014 study showed that such a Matrigel environment can be recreated by using enzymatically crosslinked polyethylene glycol hydrogels that include the RGD (Arg-Gly-Asp) peptide of fibronectin [53]. It appeared that in addition to the presence of ECM components mechanical properties of the hydrogel were of relevance as well: matrix stiffness significantly enhanced stem cell expansion through a yes-associated protein 1-dependent mechanism [54]. Stem cell differentiation and organoid formation, on the other hand, required a soft matrix and laminin-based adhesion [55, 56].

The Use of Decellularized Matrices as Regenerative Matrix

Another approach to capitalize on the regenerative and instructive potential of the ECM in general and that of the vasculature in particular, is to use decellularized ECM obtained from organs. This field was pioneered by Ott and coworkers who developed a standard process for pressure-controlled perfusion decellularization of whole organs for generating acellular 3D scaffolds with preserved ECM protein content, architecture, and perfusable vascular conduits [57]. By applying antegrade perfusion of detergents and subsequent washes to arterial vasculature at low physiological pressures, successful decellularization of complex organs (i.e., hearts, lungs, and kidneys) can be performed [57–59]. The resulting scaffolds can be used in ex vivo culture models where the ECM may provide important information to repopulating cells through retention of growth factor or niche-specific cues. For example, it was shown that hepatic SECs maintained their differentiated state longer when cultured on ECM- from the liver than on ECM-derived from the urinary bladder or the small intestine, emphasizing the crosstalk and organ specificity of the ECM and SECs [60]. The instructive capacity of decellularized matrix on differentiation of early progenitor or stem cells into endothelial cells has proven successful. For instance, embryonic stem cells or human nephrosphere-derived PAX2 positive cells differentiate into endothelial cells when cultured on decellularized kidney scaffolds [61–63]. The challenge here is to unravel the culture conditions during which the interaction between early progenitor cells and decellularized matrix scaffolds are optimal. For example, we could recently demonstrate that decellularized scaffolds of human kidney's still contain endothelial glycosaminoglycans that can be reloaded with EC growth factors, and which subsequently resulted in improved adherence of iPSC-derived ECs and functional recellularized vascular conduits [64].

In addition, it was recently demonstrated [65] that the recellularization of decellularized rat gut using both epithelial and endothelial iPSCs showed functionality after 4 weeks, indicating the therapeutic potential of this approach.

Conclusion

Further insight into the matrisome, at the very critical interface between the perivascular capillary EC and niches of tissue with proliferative capacity (progenitors cells) may prove to be key in developing successful biomaterials for tissue engineering. At the same time, the complexity of the biology of glycosaminoglycans and matricellular proteins is daunting, incompletely understood and currently hard to resynthesize and recreate in vitro. Given the central role of the endothelial cell matrix in coordinating tissue homeostasis, we argue that focusing on understanding the dynamic regulation and composition of this matrix is of particular relevance.

Acknowledgments

The work of the authors is supported by RECellularizing ORgan Donors for KIDney bioengineering (RECORD KID, Dutch Kidney Foundation, 15RN02). We thank M. Zuurmond for preparing the illustrations.

Author Contributions

F.M.R.W and T.J.R. wrote and finalized the manuscript. C.W.v.d.B, B.M.v.d.B, M.A.E, commented and improved the manuscript writing.

Disclosure of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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