Force sensing and transmission in human induced pluripotent stem-cell-derived pericytes

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Chapter 1

Introduction

abstract

Pericytes, the mural cells of blood microvessels, are important regulators of vascular morphogenesis and function that have been postulated to mechanically control microvascular diameter through as yet unknown mechanisms. Their disfunction has been implicated in several pathologies, including cerebral ischemia, Alzheimer's disease and diabetic retinopathy.

To reveal mechanisms used by pericytes for mechanical interactions within microvessels we designed models bringing human induced pluripotent stem cell (hiPSC)-derived pericytes in contact with various micropatterned substrates representing the microvascular basement membrane organization. Our findings shed light on how pericytes can mechanically regulate microvascular morphogenesis and function, and open possibilities for testing therapeutic strategies.

1.1 Pericytes and their functions

In 1873 the French scientist Charles-Marie Benjamin Rouget described a subset of contractile cells surrounding microvessels [1]. These cells were called "Rouget cells" until Zimmerman introduced the term "pericytes" in 1923 to connect to their close location to the endothelial cells (ECs) that form vessel tubes [2]. The “close location” and more precisely “embedment within the capillary basement membrane (BM)” is currently an accepted definition of mature pericytes [3]. Nevertheless, this definition is efficient only for fully developed vasculature and not applicable during angiogenesis or in some pathologic cases when pericytes tend to separate from capillaries and penetrate the tissue.

1.1.1 Morphology of pericytes and location in blood vessels

In a capillary bed, which consists of arterioles, capillaries and venules, pericytes have been found to be located mainly on pre-capillaries, mid-capillaries and post-capillaries. The morphology of the pericytes depends on their location. Mid-capillary pericytes have long cytoplasmic processes that bridge several endothelial cells. Perpendicularly to these primary branches extend thin, secondary arms that partially encircle the vessel. In contrast, pre- and post-capillary pericytes have a more stellate shape with many branches (Fig. 1.1a) [2, 4].

Pericytes are not just “embedded” within the capillary BM, they make a variety of mechanical and biochemical interconnections with ECs. Among them are: peg-and-socket contacts for direct cell signaling and communication, cell-to-cell adhesions by N-cadherins, and integrin-mediated binding of pericytes and ECs to the BM of capillaries, as featured in chapter 2 and chapter 3 (Fig. 1.1b) [5–8].

1.1.2 Identification of pericytes

So far, no single pericyte-specific molecular marker have been identified. Markers that are currently used to identify pericytes are also expressed by other cell types and/or can change their expression levels depending on external factors such as: pathological conditions, development and *in vitro* culturing [5, 10, 11]. Among validated pericyte markers are: PDGFR-β (platelet-derived growth factor receptor-beta), NG2 (chondroitin sulfate proteoglycan 4), CD13 (alanyl (membrane)

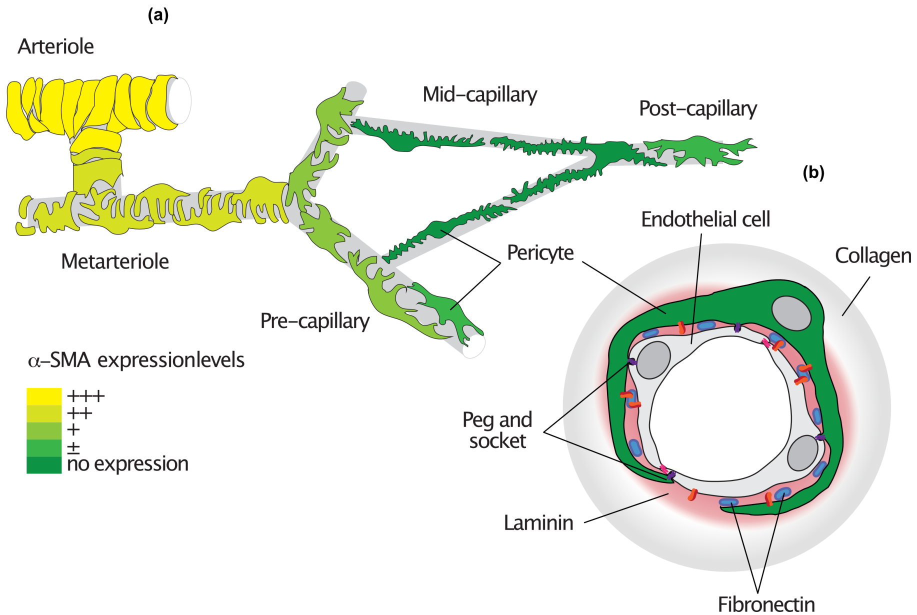

Figure 1.1: Schematic representation of the capillary basement membrane (BM). Laminin-411/511 and Collagen IV are main components that form two layers [9]. Fibronectin deposits are embedded into the Laminin part of the BM and situated in the pericyte-endothelial cell interstitia.

aminopeptidase), αSMA (alpha-smooth muscle actin), Desmin [4, 5, 10, 12].

Pericytes are frequently confused with their close neighbors – vascular smooth muscle cells (vSMCs). These also feature periendothelial location and share a vast majority of molecular markers with pericytes. Absence of specific markers, morphological heterogeneity of pericytes and a smooth transition from the pericyte phenotype to vSMCs, discussed in chapter 4, adds to the challenge of pericyte identification [4, 10, 13]. Currently, pericyte identification depends on a combination of a few factors: location on the capillary tree, morphology, two or more pericyte markers and their ability to support angiogenesis [5, 10, 14].

1.1.3 Pericyte abundance and functions

The density of pericytes and their coverage on capillaries varies across the human body. In normal tissue, the EC-to-pericyte ratio is between

1:1 to 10:1 and pericytes can cover from 10% to up to 70% of the endothelial abluminal surface [3]. It was observed that the density of pericytes depends on endothelial barrier properties, showing highest pericyte coverage in brain, then in lungs and muscle; and on orthostatic blood pressure with increased pericyte coverage in the lower body parts. Additionally, areas with high EC turnover feature lower pericyte densities.

The distribution of pericytes across the body reflects their functions. In the central nervous system (CNS) pericytes play a critical role in the development, regulation and maintenance of the blood-brain barrier (BBB). During embryo development and angiogenesis they regulate the formation and stability of newly formed microvessels, contribute to and control extracellular matrix protein expression and deposition of BM by ECs. In the mature CNS vasculature, pericytes regulate BBB-specific gene expression in ECs to maintain a high number of tight and adherens junctions between cells, and consequently establish the low level of bulk-flow transcytosis of brain ECs. Pericytes also have been reported to induce polarization and mediate proper attachment of the end-feet of astrocytes surrounding CNS capillaries [12, 15, 16]. Taken together, this explains why in the CNS the highest pericyte coverage has been found among all tissue. The barrier function of pericytes causes their lower concentration in the gas-exchange (lungs), filtration (kidney) and nutrient transport regions of the body [11]. The presence of proteins like actin, the high concentration of myosin, tropomyosin and other motors makes pericytes highly contractile cells [17–20]. In combination with their tendency to position themselves around EC junctions and to cover gaps between ECs, pericytes may provide a mechanical support for microvessel walls, preventing excessive dilation. This correlates directly with an increased concentration of pericytes in regions of high or rapidly-changing [21] blood pressure.

1.2 Pericytes and mechanobiology

Despite extensive studies of pericytes there are still many important unsolved questions regarding their mechanobiology [25]. To start with, pericytes have two states: active and mature. These two states are different in the way pericytes migrate. In their active state, pericyte migration is reminiscent of "escaping" from the vasculature and penetrating the tissue [11, 26] sometimes serving as a leading "tip-cell" for a new

Function	Organ/Process	Details	Referen-ces
BBB integrity control	CNS	Regulation of tight and adherens junctions & bulk fluid flow transcytosis	[12, 15]
Astrocyte end-feet polarization	CNS	pericytes induce polarization and mediate proper attachment of the astrocyte end-feet surrounding CNS capillaries	[15]
Blood flow regulation and vascular tone maintenance	CNS, mature vasculature	pericytes may dilate and constrict capillaries in response to vasoactive substances and neurotransmitters	[11, 21–23]
Vessel stabilization	Angiogenesis, embryonic vascular development, mature vasculature	Contacts between pericytes and ECs promote EC survival, regulate EC migration, proliferation, differentiation and branching	[10, 12, 24]
Basement membrane (BM) synthesis and deposition	Angiogenesis, embryonic vascular development, mature vasculature	pericytes together with ECs produce and deposit extracellular matrix (ECM) proteins necessary for vascular BM formation	[5]
Participation in immunologic defense	CNS, mature vasculature	pericytes have macrophage-like properties and/or can convert into macrophages. They act as antigen-presenting cells for primed T-lymphocytes and are the first line of defense in the brain	[11, 12]
Contribution to tissue regeneration	Vascular niche	pericytes may represent mesenchymal stem cells, white adipocyte progenitors, muscle stem cells and neural stem cells. They were shown to promote tissue regeneration	[10, 11]

Table 1.1: General functions of pericytes

vessel branch. In that state they retract processes, degrade the BM and penetrate the tissue. This active state is specific for tissue healing and generation. In the mature state, pericytes are tightly located around the vessel, stably built-in to the vessel BM, and develop numerous contacts with ECs. Migration in the mature state is described as "sliding" along the vessel, and spreading across newly formed vessels. Both states can be simultaneously observed during active angiogenesis.

The ECs of protruding vasculature release the protein PDGF-B, attracting PDGFRβ positive pericytes [27–30]. When cells are in close proximity, an initial cell-to-cell contact leads to protein EphrinB2 engagement by EphB membrane receptors. Subsequent EphrinB2 phosphorylation starts a reverse-signaling program promoting cell-to-cell adhesion formation [31, 32].

Let us take a closer look at the cell-to-cell adhesion types that may allow mechanical communication between pericytes and ECs. One of them is mediated by N-cadherins [7]. N-cadherins directly link the cytoskeleton of pericytes with that of ECs, promoting direct mechanotransduction between these two cell types [33]. Yet, it has been shown that with vessel maturation and the formation of a BM, the expression of N-cadherins by ECs is downregulated in favour of VE-cadherin binding between the ECs [34, 35]. The next mechanical type of coupling is represented by peg-and-socket contacts. They are known to contain gap-junctions for direct communication and signaling between pericytes and the ECs [6]. The structure of these insets of pericytes into the cytoplasm of ECs is reminiscent of mechanical hooks, that potentially are established to pull on the ECs [36, 37]. Another type of adhesion dominates in mature vasculature. It involves integrin binding of both cell types to the extracellular matrix of the BM [8]. Pericytes are located within a layered BM between collagen type IV on the outer side and laminin (LM)-411/511 on the pericyte-EC interstitium [9, 38]. Electron microscopy analysis shows that the laminin layer also contains small deposits of fibronectin (FN). These FN deposits are $0.2 - 2\mu m$ wide and occur only between pericytes and ECs. The vast majority of focal adhesions, for both cell types, are formed on top of these FN deposits, suggesting that those FN deposits are the points of mechanotransduction between pericytes and ECs. Nevertheless, mechanotransduction pathways between pericytes and ECs are not fully discovered by now.

One of the most interesting topics related to the mechanobiology of

pericytes is their ability to control vascular blood flow [22, 23, 39–41]. Pericytes have many features that would allow them to fulfill this function. They express contractile proteins that allow them to apply forces on the vessel tube [17–20]. The actin fibers of pericytes are oriented axially in the primary processes and circumferentially in the secondary processes. Taking into account that fiber orientation reflects the main direction of cellular force application, circumferential orientation of the fibers in the secondary processes suits to the idea of a role of pericytes in capillary diameter modulation [42]. Additionally, pericytes are often located at capillary branching points – an ideal place for control and redirection of the blood flow, thus working as a switch [43]. In the CNS pericytes have been shown to be capable to react on neuronal activity, resulting in active relaxation and thereby capillary dilation [39, 41]. How pericytes decrease or increase a vessel lumen by constriction through normal forces, general wall stiffening or thinning by tangential contraction or deformation of the underlying ECs, however remains to be discovered [25].

1.3 Pericytes and pathology

Pericytes play an important role in the microvasculature and, thus, are involved in many pathological conditions [44]. The role of pericytes in pathology shall be divided between pathologies: that are caused by deficient pericytes, and those that are caused by impairment of the functions of healthy pericytes due to other factors.

The first group is relatively small, as deficient pericytes usually result in death already during embryo development due to deficient vessels and hemorrhages [12]. The second group includes, for instance, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy and diabetes related erectile dysfunction. These diseases are partially caused by pericytes vulnerability to uncontrolled, high glucose levels in patients suffering from diabetes [44].

Another example of pericytes involvement in the pathophysiology is that of ischemia. Myocardial or renal ischemia promote pericytes to contribute to fibrosis and scar formation in heart and kidneys [45, 46]. In cerebral ischemia, pericytes have been shown to enhance brain damage by actively blocking capillaries in response to prior lack of oxygen and glucose supply [39].

Alzheimer disease (AD), one of the main reasons of cognitive decay in elder humans, appears to induce pericyte contraction, followed by the small vessel disease and cerebral blood flow reduction. The conditions of AD further lead to a decreased pericyte vessel coverage and final BBB breakdown. Combination of both factors further accelerates AD progression and dramatic neurodegeneration [47, 48].

In cancer, pericytes are considered to be progenitors of glomus tumor and myopericytoma [49]. Yet, all tumors lead to impaired functions of pericytes and ECs in general, in particular in the tumor proximity. Various conditions may alter the recruitment of pericytes to newly formed tumor vessels, resulting in high or low pericyte coverage of the tumor microvasculature. Both settings lead to either nourishing the cancer cells resulting in aggressive tumor growth, or in intravasation of cancer cells into the bloodstream and formation of metastasis [44].

All together, during the past decade pericytes have been recognized as important players in pathobiology. An accurate identification of the general role of pericytes, their respective signaling programs and their mechanobiology is needed to understand the mechanisms that pericytes play in pathology. Such novel insight may lead to a more on-target treatment in a diverse range of disease.

1.4 Outline of this thesis

To allow the study of pericyte mechanobiology I focused on *in vitro* modelling of the capillary basement membrane (BM) in **chapter 2**. The part of BM in between pericytes and endothelial cells (ECs) supposedly acts as a mediator of the mechanical interaction between these two cell types. To mimic the BM I developed a technique using microcontact printing (μCP) of proteins on surfaces of largely varying stiffness. Thereby I reproduced the BM rigidity-range and it's unique spatial organization of the two main ECM components in the pericyte-endothelium cell interstitium – laminin (LM)-411/511 and fibronectin (FN).

In **chapter 3** I then used the *in vitro* BM-model together with human induced pluripotent stem cell (hiPSC)-derived pericytes on flexible PDMS micropillar arrays. I showed that mid-capillary pericytes indeed preferred FN-plaques, and I was able to demonstrate that these plaques indeed act as sites for exquisite stiffness sensing and regulation of contractile forces and cell spreading. My findings will open opportunities

for testing therapeutic strategies that target the mechanical properties of capillaries in disease.

In **chapter 4** I assessed the mechanical signals that potentially influence α-SMA expression in pericytes. I used the *in vitro* BM-model approach to investigate vessel diameter, BM composition and the effect of stiffness on the α-SMA recruitment to stress fibers in hiPSC-derived pericytes and compared my findings to those for human smooth muscle cells (SMCs). To quantify the results I developed an automatic image analysis. I showed that α-SMA recruitment was mainly affected by the spatial organization of FN and LM, and to a lesser extend to the stiffness or the ECM contact area. Those findings for pericytes significantly differ to those of SMCs, which were more affected by the rigidity and spreading area, rather than by the protein arrangement in the BM.

In **chapter 5** I investigated the opportunity to study the behaviour of pericytes in pathological conditions *in vitro*. I integrated flexible PDMS micropillar arrays into fluid-flow channels to examine mechanoresponse of pericytes to compromised oxygen and/or glucose supply that permits to mimic pathological conditions like hypoxia and ischemia *in vitro*. My approach will allow us to monitor cellular forces simultaneously with morphological changes, and dynamic protein behaviour in rapidly changing conditions of the microenvironment. Such instrumentation will have a broad applicability for potential *in vitro* testing of drugs or treatment strategies in pathological conditions.

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