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Review

The complex mural cell: Pericyte function in health and disease

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ABSTRACT

Pericytes are perivascular cells that can be distinguished from vascular smooth muscle cells by their specific morphology and expression of distinct molecular markers. Found in the microvascular beds distributed throughout the body, they are well known for their regulation of a healthy vasculature. In this review, we examine the mechanism of pericyte support to vasomotion, and the known pathways that regulate pericyte response in angiogenesis and neovascular stabilization. We will also discuss the role of pericytes in vascular basement membrane and endothelial barrier function regulation.

In contrast, recent findings have indicated that pericyte dysfunction, characterized by changes in pericyte contractility or pericyte loss of microvascular coverage, plays an important role in onset and progression of vascular-related and fibrogenic diseases. From a therapeutic point of view, pericytes have recently been identified as a putative pool of endogenous mesenchymal stem cells that could be activated in response to tissue injury to contribute to the regenerative process on multiple levels. We will discuss the mechanisms via which pericytes are involved in disease onset and development in a number of pathophysiological conditions, as well as present the evidence that supports a role for multipotent pericytes in tissue regeneration. The emerging field of pericyte research will not only contribute to the identification of new drug targets in pericyte dysfunction associated diseases, but may also boost the use of this cell type in future cell-based regenerative strategies.

1. Introduction

In 1873, Charles Rouget discovered a new cell type with a distinct perivascular morphology that wraps itself around blood capillaries [1]. Initially called Rouget cells and later renamed pericytes [2] they were formally described as cells with a prominent nucleus and limited cytoplasm. Pericytes are attached to the long axis of capillaries, embracing endothelial cells (ECs). Just like vascular smooth muscle cells (VSMCs) pericytes are called mural cells because of their perivascular basal membrane embedded position. In this review we discuss the biology of pericytes. We will summarize the markers that are currently used to identify pericyte cells, and we will discuss their basic physiological function. Furthermore the review will address the role of pericytes in diseases such as diabetic retinopathy and chronic kidney disease. In addition, we will also discuss the putative use of multipotent pericytes as therapeutic mediators in regenerative medicine.

2. Pericyte characteristics

Based on their perivascular position in the microvasculature, pericytes have often been considered the microvascular counterparts of VSMCs. Indeed, these two cell types are thought to be derived from the same lineage. Pericytes are found in the pre-capillary, capillary and post-capillary bed of many organs. However, coverage by pericytes is more extensive in post-capillary venules than in capillaries [3]. Similar to VSMCs, pericytes contain contractile filaments composed of vimentin and alpha-smooth muscle actin (αSMA), and are capable of vasomotion regulation. However, there are also a number of features that are more distinctive for pericytes rather than VSMCs. For example, pericytes can be primarily distinguished from VSMCs by their specific perivascular morphology. VSMCs typically maintain elongated and flattened nuclei. They also position themselves in a perpendicular fashion along the whole length of the vessel, encircling the whole endothelial surface. Layers of VSMCs are usually more dense and flat in the arterioles compared to the pre-capillary arterioles [4]. In contrast, pericytes are attached to the longitudinal axis of the capillaries. They typically maintain a rounded nuclear structure, and embrace the endothelial surface with multiple extensions.

Pericytes are also differently distributed over the vascular tree as compared to VSMCs. Pericytes are mainly localized in the

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microvasculature where they cover pre-capillary arterioles, capillaries, post-capillary venules, and collecting venules in a single layer of cells [5,6]. In contrast, in larger blood vessels that are exposed to high levels of hemodynamic stress, multiple dense layers of VSMCs and elastic fibres cover the endothelial tubule [7]. However, this distinction in the distribution of pericytes and VSMCs is not absolute. In-between mural cell phenotypes that share characteristics with both pericytes and VSMCs have also been described in the coverage of medium to small sized blood vessels [8].

Compared to VSMCs, pericytes are typically embedded in a basal membrane (BM) that is seamlessly merged with the BM of the ECs [9]. This shared BM encompasses the majority of the pericyte–endothelial interface. Distinct places where the BM is interrupted provide direct contact points between the two cell types. Connections that are created between pericytes and ECs are described as peg-and-socket structures. In these structures the pericytes form recognizable cytoplasmatic elongations (the so-called pegs) that are inserted in the invaginations of the endothelial membrane (the sockets). Peg-and-socket contacts are highly enriched in Connexin 43 mediated gap and (N-cadherin-based) adherence junctions [10]. Another regular type of pericyte–endothelial contact is the adhesion plaque. This structure also forms at sites where the BM is interrupted. Adhesion plaques anchor pericytes to the ECs via a matrix of fibronectin microfilament bundles that is connected to the cell's actin cytoskeleton via integrins [10]. It has been postulated that the direct transmission of biological and mechanical signals between pericytes and ECs predominantly takes place at these contact sites [6,9,10]. For example, Connexin 43 gap junctions in peg-and-socket contacts allow the exchange of ions and small molecules, whereas the adhesion plaques support the transmission of contractile forces from pericytes to ECs [10,11]. Vice versa, shear stress forces can be transmitted from the endothelium to the underlying layer of pericytes. It has to be noted that although BM embedding is a regular feature of pericytes, it remains unclear to what extent mature pericytes are embedded in the BM. Several studies have reported incomplete or absent BM microvascular coverage [11]. The lack of a distinct BM surrounding immature blood vessels in embryonic or pathologic conditions where the BM is still being synthesized or has a high turnover rate makes it impossible to apply these structural criteria in a generalizing manner. Luckily, in addition to their characteristic morphological and structural features, pericytes can also be identified by distinct molecular markers.

2.1. Pericyte identification markers

Increased interest in pericyte research has sparked the search for reliable specific markers for pericyte identification. Several reviews have composed comprehensive lists of markers that have previously been evaluated. We refer to these for a more extensive overview on this subject [6,11]. Here we will discuss the pericyte markers that have been most commonly used. A short summary of which markers for mural cells are currently used in the field and in which type of vascular structures marker expression can be detected is provided in Table 1.

Membrane bound markers for pericytes include platelet-derived growth factor receptor β (PDGFRβ), CD146, aminopeptidases A and N (CD13), endoglin, and neuron-glial 2 (NG2) [3,12–14]. Common cytosolic markers for pericyte identification include αSMA, non-muscle myosin, desmin, vimentin, and nestin.

A new cytosolic marker that appears to be promising for specific pericyte detection is the regulator of G protein signalling 5 (RGS5) [4,15]. RGS5 acts as a GTPase activating protein. RGS5 is postulated to play a role in proliferation and recruitment of VSMCs and pericytes during vascular maturation, vessel adaptation and wound healing [16]. RGS5 expression was detected in pericytes and VSMCs in large arteries and veins. It has been reported by Bondjers et al. that RGS5 expression is downregulated in PDGFβ knockout mouse embryos in comparison

Table 1
Cytosolic and membrane bound markers for the identification of mural cells.

Expressed in:	Pericytes	VSMCs	Arterioles	Capillaries	Venules	Remarks	References
Cytosolic markers							
Alpha-smooth muscle actin (αSMA)	+	+	+	−	+	Most frequently used and best characterized. Also a marker for VSMCs.	[3,12–14,18]
Non-muscle myosin	+	−	-	+	+	Present in relatively high concentration in capillary pericytes, absent in VSMCs.	[3,12–14]
Tropomyosin	Unknown	+	−	+	+	Part of the actin cytoskeleton.	[3,12–14,129]
Desmin	+	+	+	+	+	Useful marker in tissues other than skeletal muscle and heart tissue. Expressed on intermediate filament proteins in pericytes that are in direct contact with underlying endothelium. Also expressed by VSMCs.	[3,4,12,14,25,87,130]
Vimentin	+	+	+	+	+	Component of intermediate filaments.	[4,18]
Nestin	+	+	+	+	+	An intermediate filament protein that is expressed mostly in nerve cells during early stages of development. In adulthood replaced by tissue specific intermediate filaments in mural cells.	[3,12–14,131]
Regulator of G protein signalling 5 (RGS5)	+	+	+	+	+	Tested in PDGFRβ- or PDGF-β deficient mice. Marker for developing pericytes independent of PDGF-β signalling.	[4,17]
Membrane bound markers							
Platelet-derived growth factor receptorβ (PDGFRβ)	+	+	+	+	+	Expressed by developing pericytes and precursor pericytes. Also a tyrosine kinase receptor important for pericyte function.	[13,14,24]
CD146	+	+	+	+	+	Transmembrane glycoprotein. EC antigen also expressed at the surface of pericytes and in larger blood vessel types.	[13,14]
Aminopeptidases A and N (CD13)	+	+	+	+	+	Type II membrane zinc dependent metalloproteases.	[4,131,132]
Endoglin (CD105)	Unknown	+	+	+	+	TGF-β1 co-receptor required for angiogenesis. Also a marker for ECs.	[3,13–15,87]
Neuron-glial 2 (NG2)	+	+	+	+	−	Broadly expressed in pericyte population, expressed during vascular morphogenesis. Also expressed by larger blood vessel types, and by oligodendrocytes.	[3,13–15,87]