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Review Article

A review article: The mysterious pericytes

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ABSTRACT

Blood vessels are composed of two types of interacting cells. Endothelial cells form the inner lining of the vessel wall, and perivascular cells referred to as pericytes, vascular smooth muscle cells or mural cells which envelop the surface of the vascular tube. They are also called Rouget cells after their discoverer, Charles Rouget. Electron-microscope analyses first revealed the morphological character of pericytes. In general, pericytes possess a cell body with a prominent nucleus and a small content of cytoplasm with several long processes embracing the abluminal endothelium wall. They are embedded within the basement membrane of microvessels, which is formed by pericytes and endothelial cells. Pericytes play an integral role in the maintenance of the blood–brain barrier as well as several other homeostatic and hemostatic functions of the brain. These cells are also a key component of the neurovascular unit, which includes endothelial cells, astrocytes, and neurons. Pericytes provide a variety of functions such as capillary blood flow regulation, clearance and phagocytosis of cellular debris, angiogenesis formation of new blood vessels and regulating blood–brain barrier permeability. Recently, pericytes have gained new attention as functional and critical involvement to tumor angiogenesis and progression. Therefore as potential new targets for antiangiogenic therapies. Pericytes are complex. Their ontogeny is not completely understood, and they perform various functions throughout the body. This review article describes the current knowledge about the nature of pericytes and their functions during blood vessel growth, vessel maintenance, and pathological angiogenesis.

1. Introduction

Pericytes also known as vascular smooth muscle cells, mural cells, or myofibroblasts, wrap around the endothelial cells.[1] Pericytes were first characterized by Eberth in 1871.[2] A French scientist Charles-Marie Benjamin Rouget, who two years later in 1873 described a population of contractile cells surrounding the endothelial cells of small blood vessels and called these cells "Rouget cells" and also coined the term "pericytes," alluding to their location in close proximity to the endothelial cells.[3] Electron-microscope analyses first revealed the morphological character of pericytes. In general, pericytes possess a cell body with a prominent nucleus and a small content of cytoplasm with several long processes embracing the abluminal endothelium wall. They are embedded within the

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basement membrane of microvessels, which is formed by pericytes and endothelial cells.[4] Pericytes play an integral role in the maintenance of the blood–brain barrier as well as several other homeostatic and hemostatic functions of the brain. These cells are also a key component of the neurovascular unit, which includes endothelial cells, astrocytes, and neurons.[5] Pericytes provide a variety of functions such as capillary blood flow regulation, clearance and phagocytosis of cellular debris, angiogenesis formation of new blood vessels and regulating blood–brain barrier permeability.[6] Recently, pericytes have gained new attention as functional and critical involvement to tumor angiogenesis and progression. Therefore as potential new targets for antiangiogenic therapies. Pericytes are complex. Their ontogeny is not completely understood, and they perform various functions throughout the body. This review article describes the current knowledge about the nature of pericytes and their functions during blood vessel growth, vessel maintenance, and pathological angiogenesis.[7]

2. Morphology and Identification of Pericytes

Pericyte morphology is characterized by a stellate appearance with long cytoplasmic processes. Pericytes may indent adjacent endothelial cells, and vice versa, in peg-and-socket contacts and encircle individual blood vessels.[8,9] Pericytes granularity is associated with extent of cytoplasmic lysosomes, and human brain pericytes appear to be exclusively granular with high content of acid phosphatase.[8] Specific immunochemical markers are use for the identification of pericytes, which originate from mesoderm. Pericytes are typically immunoreactive for α-smooth muscle actin, γ-glutamyl transpeptidase, alkaline phosphatase, nestin, vimentin, and the platelet derived growth factor-beta (PDGF-β) receptor.[10] Recent work by Bondjers et al may shed new light on pericyte identification. Using brain microvessels from mice lacking PDGF-β or the PDGF-β receptor, brain pericytes expressed the ATP-sensitive potassium channel Kir6.1. This expression seemed to be limited to pericytes of the brain. If confirmed, this would represent an important advance in the routine identification of brain pericytes using immunohistochemical or molecular markers.[10]

3. Pericyte Localization

Pericytes are present on the abluminal surface of endothelial cells of capillaries, as well as arterioles and venules.[11] Pericytes cover 22-32% of cerebral capillary surface (more than skeletal and cardiac muscle, but less than retina), and post capillary venules tend to have more pericytes than do capillaries.1 Capillary pericytes, contained entirely within basal lamina on the endothelial cell abluminal surface, tend to be localized over endothelial tight junction regions.[12] One layer of basement membrane separates pericytes from endothelial cells, while another basement membrane layer serves to compartmentalize pericytes from astrocyte end feet in the neurovascular unit.[13]

4. Pericytes Function

4.1. Control of blood flow by pericytes

In the retina, cerebellum and cerebral cortex, spatially isolated contractile pericytes were found to alter the capillary diameter in response to depolarization, neurotransmitter action or neuronal activity. Notably, in the cerebral cortex in vivo, almost as many capillaries dilated to neuronal activity as did penetrating arterioles, the capillary dilation occurred before the arteriole dilation and the occurrence of capillary dilation correlated with the presence of a pericyte on the vessel. This implies that capillary dilation is caused by an active relaxation of pericytes, rather than being a passive response to an increase of local blood pressure produced by arteriole dilation.[14]

5. Vascular Development and Angiogenesis

Pericytes have an active role in newly blood vessel proliferation. Blood vessels develop early during embryogenesis and are derived from mesodermal precursors called angioblasts.[15] Additionally, it is believed that endothelial cells share a common precursor with hematopoietic cells; this precursor is called a hemangioblast. This hypothesis of a common precursor is supported by the observations that developing hematopoietic and endothelial cells share common surface markers and that hematopoietic cells can bud from major embryonic blood vessels. Pericytes have an important regulatory role in angiogenesis, orchestrating initiation, sprout connection, and termination via expression of transforming growth factor-β(TGF-β), vascular endothelial growth factor(VEGF), and angiopoietin-1 and -2.[16]

6. Immune and Phagocytic Function

Brain pericytes constitutively express low levels of adhesion molecules (intercellular adhesion molecule-1 and vascular cell adhesion molecule-1), with pericyte expression up regulation induced by inflammatory cytokines; moreover, pericytes have the capacity to present antigen to T-lymphocytes.[17] Robust expression of acid phosphatase by pericyte lysosomes implies phagocytic function of pericytes.[18]

7. Migratory Function

Pericyte movement to endothelial cells during vascular development is mediated by endothelial-derived PDGF-β and PDGF-β receptors expressed by pericytes.[19] Pericyte-to-endothelial migration is readily demonstrable in cell culture preparations using in vitro capillary-

like structures.[20] Following traumatic brain injury, approximately 40% of brain microvascular pericytes migrate from a microvascular to perivascular location, probably mediated by pericyte expression of urokinase plasminogen activator receptor.[21]

8. Pericytes Act as Stem Cells

A number of recent studies suggest that pericytes may constitute multipotent stem and/or progenitor cells, such as mesenchymal stem cells (MSCs) , white adipocyte progenitors, muscle stem cells and even neural stem cells.[22]To discuss this issue, we need to go back 40 years, when MSCs were identified as fibroblast-like cells, called CFU-F (colony- forming unit fibroblastic) in human bone marrow cell cultures seeded at clonal density.[23] These single-cell-derived cartilage, bone, adipose, and fibrous tissue. The cells were later named bone marrow mesenchymal stem cells (BM-MSCs), whereas cells with similar lineage potential for in vitro differentiation (adipocyte, osteoblast, chondrocyte) subsequently identified in other tissues were referred to as MSCs.[24]

9. Conclusion

The pericytes are essential components of the microvessel wall, with important metabolic, signaling, and mechanical roles that support endothelial cells in a manner that depends on tissue and angiogenic stage. Pericytes are also proposed to be important contributors to the regulation of pathological angiogenic processes like diabetic retinopathy and tumor angiogenesis. During tumor propagation, pericytes, in spite of having structural abnormalities, still appear to provide functions necessary for vessel maintenance and endothelial-cell survival.

10. Source of Funding

None.

11. Conflict of Interest

None.

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