Pericyte-endothelial crosstalk: implications and opportunities for advanced cellular therapies

ANITA GEEVARGHESE, and IRA M. HERMAN

BOSTON, MASS

Pericytes are mural cells of the microcirculation that have been shown to play key roles in regulating microvascular morphogenesis and stability throughout each tissue bed and organ system assessed. Of note, recent work has revealed that pericytes share several characteristics with mesenchymal- and adipose-derived stem cells, suggesting there may be lineage-related connections among bona fide pericytes and these vascular "progenitors," which can assume a perivascular position in association with endothelial cells. Hence, pericyte identity as a mediator of vascular remodeling may be confounded by its close relationships with its progenitors or pluripotent cell counterparts and yet demonstrates their potential utility as cell-based therapies for unmet clinical needs. Crucial to the development of such therapies is a comprehensive understanding of the origin and fate regulating these related cell types as well as the unveiling of the molecular mechanisms by which pericytes and endothelial cells communicate. Such mechanistic inputs, which disrupt normal cellular crosstalk during disease inception and progression, offer opportunities for intervention and are discussed in the context of the vasculopathies accompanying tumor growth, diabetes, and fibrosis. (Translational Research 2014;163:296–306)

Abbreviations: α-SMA = α-smooth muscle actin; Ang = angiopoietin; ASC = adipose-derived stem cell; DR = diabetic retinopathy; hASC = human adipose-derived stem cell; MSC = mesenchymal stem cell; NG2 = neuron-glial antigen; PDGF = platelet-derived growth factor; PDGFR = platelet-derived growth factor receptor; TGF-β = transforming growth factor β; VEGF = vascular endothelial growth factor

PERICYTES AND MICROVASCULAR REMODELING

During vascular remodeling, the blood vessel responds to hemodynamic changes to adapt and restore homeostasis. Endothelial cells comprise the inner lining of vessels whereas pericytes encompass blood microvessels such as blood capillaries, precapillary arterioles, precapillary venules, and collecting venules.[1] Pericytes use cytoplasmic processes to surround the abluminal surface of the endothelial tube.[2] They share and coproduce a basement membrane with endothelial cells, demonstrating that pericyte-endothelial interaction plays a key role in basement membrane formation, maintenance, and remodeling. Pericytes are in close proximity to endothelial cells and are typically 20 nm apart, with a single pericyte covering several endothelial cells incompletely.[1,2]

At distinct points in the basement membrane, pericytes and endothelial cells form specialized junctions with each other.[1,2] Peg-and-socket-type contacts are formed by pericyte cytoplasmic fingers that are inserted

From Program in Cellular and Molecular Physiology, Sackler School of Graduate Biomedical Sciences, Center for Innovations in Wound Healing Research, Tufts University School of Medicine, Boston, Mass.

Submitted for publication December 12, 2013; revision submitted January 15, 2014; accepted for publication January 17, 2014.

Reprint requests: Ira M. Herman, Program in Cellular and Molecular Physiology, Center for Innovations in Wound Healing Research, Tufts University School of Medicine, 150 Harrison Avenue, Boston, MA 02111; e-mail: iramherman@gmail.com.

1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2014.01.011

into invaginations within the endothelium. Adherens junctions connect the cytoskeleton of pericytes and endothelial cells, mediating contact inhibition through contractile forces. Gap junctions between the cytoplasm of pericytes and endothelial cells enable passage of metabolites and ionic currents.[3,4]

Pericytes play an important role in regulation of endothelial cell proliferation and differentiation, contractility and tone, and stabilization and permeability.[1-7] During angiogenesis, the formation of blood vessels from preexisting structures, nascent microvessels, are composed of proliferative endothelium with an immature basement membrane. This event is followed by microvascular maturation through pericyte recruitment.[2] Among the first cells to migrate to newly vascularized tissues, pericytes are located at the growing front of endothelial sprouts.[1,2] Pericyte investment of the vasculature is associated with resistance to capillary regression and suppression of endothelial growth. Thus, pericytes have a stabilizing effect on these newly formed microvessels.[1-7]

EVOLUTION OF THE PERICYTE IN HISTORY

Pericytes were first described by Charles-Marie Benjamin Rouget in 1873 as cells with contractile properties that surround the endothelial cells of small blood vessels.[1] Krogh investigated capillary recruitment and vascular tone further and defined the cells adjacent to the endothelium that may be involved in these functions as Rouget cells. By 1923, Zimmermann devised the term "pericyte" because of the cell's close proximity to endothelial cells, and used light microscopy studies to elucidate their morphology further.[2] Early immunocytochemistry studies revealed pericyte expression of proteins such as actin,[8] tropomyosin,[9] and myosin,[10] among others, demonstrating their potential role as force-generating contractile elements in the regulation of vascular permeability and blood flow (Figs 1 and 2). Since then, this cell type has been studied in depth because of its crucial role in maintenance of vascular stability.

Recent research has highlighted the untapped potential of the pericyte as a critical modulator of vascular remodeling in disease states. Of particular interest is the ability of mesenchymal stem cells (MSCs) and adipose-derived stem cells (ASCs) to exhibit pericyte-like properties under specific conditions. Thus, these cell types may serve as a potential progenitor pool from which pericytes can be cultivated, or could possibly be used to restore, replace, and rejuvenate damaged, remodeling, and/or diseased tissues. This review examines the importance of pericyte-endothelial cell interactions in remodeling and restabilization of the vasculature, the use of stem cells as possible pericyte sources, and the vascular dysfunction that underlies the pathogenesis of diabetic retinopathy (DR), fibrotic diseases, and cancer.

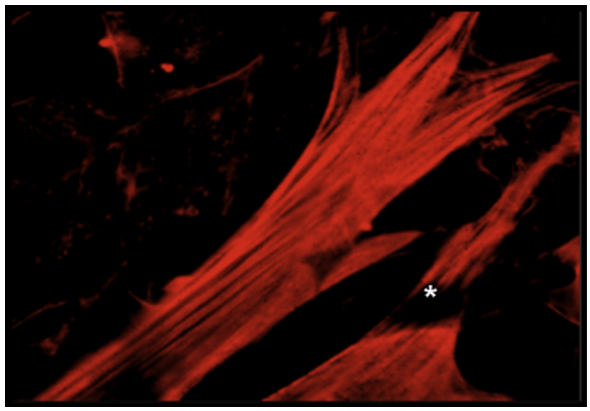

Fig 1. Discriminating between vascular cells using contractile protein isoform-specific antibodies. Cocultures of mural cells and vascular endothelial cells were fixed and permeabilized before labeling with antivascular smooth muscle actin-specific immunoglobulin G. Note the brightly fluorescent mural cells with robust stress fibers and the darkened (negative) image of the endothelial cell (*) "draping" across the pericyte.

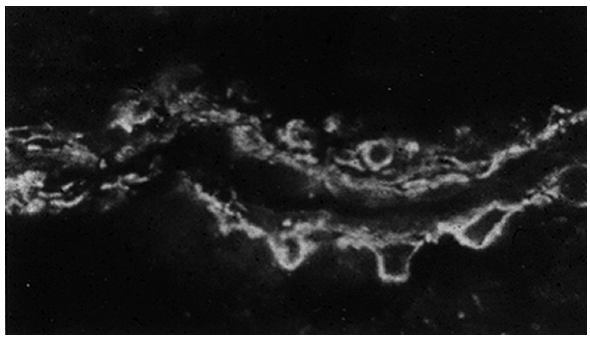

Fig 2. *In situ* localization of a mural cell-enriched cerebral microvessel. Frozen rat brain sections were prepared from perfusion-fixed specimens before treatment with fluorescently labeled antismooth muscle actin immunoglobulin G. Note the abundance of antibody-stained mural cells aligned along the length of this "muscular" venule.

PERICYTE ORIGIN

Pericytes were first evidenced by Clark and Clark[11] in 1925, who observed the development of pericytes on the capillaries of tadpole larvae from connective tissue components. Lineage tracing studies using chick-quail chimeras and cell-specific markers later demonstrated that a majority of pericytes found in the cephalic region and central nervous system was derived from the neural crest.[12,13] Fate mapping analyses in mice using genetic reporters have also shown that cells from the mesothelium give rise to pericytes in the gut, liver, heart, and lung via epithelial-to-mesenchymal transition, delamination, and migration to the aforementioned organs.[1,14-16]