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Alexander Birbrair *Editor*

Pericyte Biology in Different Organs

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Preface

This book's initial title was "Pericyte Biology: Development, Homeostasis and Disease." However, due to the current great interest in this topic, we were able to assemble more chapters than would fit in one book, covering pericyte biology under distinct circumstances. Therefore, the book was subdivided into three volumes entitled *Pericyte Biology - Novel Concepts*, *Pericyte Biology in Different Organs*, and *Pericyte Biology in Disease*.

This book *Pericyte Biology in Different Organs* presents contributions by expert researchers and clinicians in the multidisciplinary areas of medical and biological research. The chapters provide timely detailed overviews of recent advances in the field. This book describes the major contributions of pericytes to different organs' biology in physiological and pathological conditions. Further insights into the biology of pericytes will have important implications for our understanding of organ development, homeostasis, and disease. The authors focus on the modern methodologies and the leading-edge concepts in the field of cell biology. In recent years, remarkable progress has been made in the identification and characterization of pericytes in several tissues using state-of-the-art techniques. These advantages facilitated the identification of pericyte subpopulations and definition of the molecular basis of pericytes' role within different organs. Thus, the present book is an attempt to describe the most recent developments in the area of pericyte behavior which is one of the emergent hot topics in the field of molecular and cellular biology today. Here, we present a selected collection of detailed chapters on what we know so far about the pericytes in various tissues and under distinct pathophysiological conditions. Thirteen chapters written by experts in the field summarize the present knowledge about the roles of pericytes in different organs.

Herbert A. Reitsamer and colleagues from Paracelsus Medical University/SALK discuss the role of pericytes in the retina. Limor Landsman from Tel Aviv University describes pericytes in the pancreas. Lynn M. Schnapp and colleagues from the Medical University of South Carolina compile our understanding of pericyte biology in the lung. Jyoti Gautam and Yao Yao from the University of Georgia update us with what we know about skeletal muscle pericytes. Mercedes Fernandez and colleagues from the University of Barcelona summarize current knowledge on gut

pericytes. Yuya Kunisaki from Kyushu University Hospital addresses the importance of pericytes in the bone marrow. Martin Canis and Mattis Bertlich from the University Hospital Munich focus on cochlear pericytes. Maria Angelica Miglino and colleagues from the University of S*ã*o Paulo introduce our current knowledge about placental pericytes. Enis Kostallari and Vijay H. Shah from the Mayo Clinic discuss the roles of pericytes in the liver. Motohiro Komaki from Kanagawa Dental University introduces what we know about pericytes in the periodontal ligament. Linda L. Lee and Vishnu Chintalgattu from Amgen Inc. talk about pericytes in the heart. Clifford L. Librach and colleagues from the University of Toronto focus on umbilical cord pericytes. Finally, Michail S. Davidoff from the *University Medical Center Hamburg-Eppendorf* gives an overview of pericytes in the testis.

It is hoped that the articles published in this book will become a source of reference and inspiration for future research ideas. I would like to express my deep gratitude to my wife Veranika Ushakova and Mr. Murugesan Tamilsevan from Springer, who helped at every step of the execution of this project.

This book is dedicated to the memory of my grandfather Pavel Sobolevsky, PhD, a renowned mathematician, who passed away during the creation of this piece.

My grandfather Pavel Sobolevsky z"l, PhD (March 26, 1930–August 16, 2018)

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Chapter 1
Pericytes in the Retina

Andrea Trost, Daniela Bruckner, Francisco J. Rivera, and Herbert A. Reitsamer

Abstract Pericytes (PCs) are specialized cells located abluminal of endothelial cells (ECs) on capillaries, embedded within the same basement membrane. They are essential regulators of vascular development, remodeling, and blood-retina-barrier (BRB) tightness and are therefore important components to maintain tissue homeostasis. The perivascular localization and expression of contractile proteins suggest that PCs participate in capillary blood flow regulation and neurovascular coupling. Due to their ability to differentiate into various cell types in vitro, they are regarded as potential cells for tissue repair and therapeutic approaches in regenerative medicine. Altered function or loss of PCs is associated with a multitude of CNS diseases, including diabetic retinopathy (DR). In this chapter, we will provide a short overview of retinal vascular development, the origin of PCs, and focus on PCs in retinopathy of prematurity (ROP) and in the diabetic retina. Further, animal models to study the fate of PCs and the potential role of (retinal) PCs in regeneration and wound healing will be discussed.

Keywords Pericyte · Retina · Origin · Pericyte marker · PDGFRb · NG2 · tbx18 · Diabetic retinopathy (DR) · Retinopathy of prematurity (ROP) · Wound healing · Regeneration

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Abbreviations

Angs	Angiopoietins
BBB	Blood-brain barrier
BM	Bone marrow
BRB	Blood-retina barrier
CNS	Central nervous system
DME	Diabetic macular edema
DR	Diabetic retinopathy
ECs	Endothelial cells
INL	Inner nuclear layer
IPL and OPL	Inner and outer plexiform layer
MSCs	Mesenchymal stem cells
NG2	Neuron-glial antigen 2
NVU	Neurovascular unit
ON	Optic nerve
ONL	Outer nuclear layer
P0	Postnatal day 0
PCs	Pericytes
PDGFRb	PDGF-receptor beta
RPE	Retinal pigment epithelial cells
tbx 18	T-box family transcription factor 18
TGF-b	Transforming growth factor beta
VEGF	Vascular endothelial growth factor
vSMCs	Vascular smooth muscle cells

1.1 Retinal Structure and Function

The human eye is composed of three different layers. The outermost layer is formed by the cornea and sclera. The middle layer is divided into an anterior part (iris and ciliary body) and a posterior part (choroid). The light-sensitive organ, the retina, forms the innermost layer and lines the inner surface of the eye, extending from the papilla to the ora serrata. In the center of the retina, axons of the ganglion cells are bundled within the optic nerve (ON) running to the visual cortex in the brain. In addition to cells of the oligodendroglial lineage, the ON contains incoming blood vessels, that vascularize the inner retina. Temporal of the ON, the blood vessel free fovea, the sharpest point of vision and most essential part of the retina for human vision, is located (Fig. 1.1a). The retina can be divided into the neurosensory retina and the retinal pigment epithelium. The neurosensory retina is composed of three layers of nerve cell bodies and two layers of synapses. The outer nuclear layer (ONL) contains cell bodies of the rods and cones. Bipolar, horizontal, and amacrine

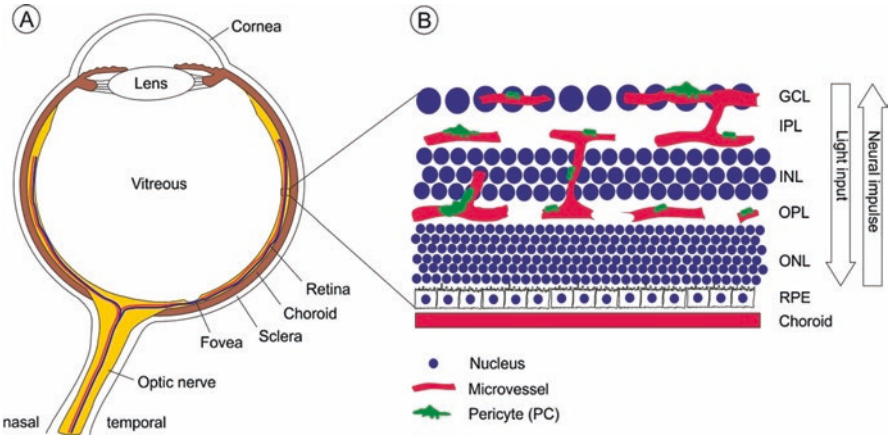

Fig. 1.1 (**a**) Schematic drawing of an eye cross section. (**b**) Schematic drawing of a retinal cross section: the neurosensory retina is composed of three layers of nerve cell bodies and two layers of synapses. The outer nuclear layer (ONL) contains cell bodies of the rods and cones. Bipolar, horizontal, and amacrine cells are located in the inner nuclear layer (INL). The innermost layer, the ganglion cell layer, contains cell bodies of ganglion cells and displaced amacrine cells. Within the inner and outer plexiform layer (IPL and OPL), located between the nerve cell layers, synaptic contacts occur. Nutrition to retina is provided by the choroid and the inner retinal vasculature: the three retinal vascular plexi are located in the GCL (superficial), in the IPL (intermediate), and in the OPL (deep)

cells are located in the inner nuclear layer (INL). The innermost layer, the ganglion cell layer contains cell bodies of ganglion cells and displaced amacrine cells. Within the inner and outer plexiform layer (IPL and OPL), located between the nerve cell layers, synaptic contacts occur (Fig. 1.1b) (Kolb 1995). One of the main functions of the retina is the conversion of light into an electric impulse, the first stage of image processing. The light passes through the entire retina, to reach the pigment molecules in the photoreceptors. The light signal is converted into an electrical impulse and transmitted to the bipolar cells and the ganglion cells where the signal is finally sent through the ON to the visual cortex. Photoreceptor cell metabolism and functioning of the visual cycle is maintained by a monolayer of retinal pigment epithelial cells (RPE), located in direct contact to the ONL.

1.2 Retinal Vascular Development

Nutrition of the metabolically highly active neural retina is provided by two vascular beds: the outer retina, including photoreceptors and RPE cells, is supplied by diffusion from the choriocapillaries. The inner retina is nourished by retinal blood vessels (Fig. 1.1b). During embryonal development, the inner retina is metabolically

supported by the hyaloid vasculature, an arterial network in the vitreous. In humans, the hyaloid vasculature is replaced by retinal vasculature around 15 weeks of gestation and by the formation of the primary plexus. This remodels into three parallel connected vascular networks located in the nerve fiber layer and the inner and outer plexiform layer, until retinal vascularization is completed by 38–40 weeks of gestation (Lutty and McLeod 2017). In mouse, however, retinal vascular development starts by sprouting of vessels out of the optic nerve head at birth (P0). At this time point, a cellular network of astrocytes, already developed, provides a template for blood vessel sprouting and for the establishment of the primary vascular network. Within the first 3 postnatal weeks, the three vascular plexi are developed (Dorrell et al. 2002; Fruttiger 2002, 2007; Selvam et al. 2017): the vessels spread along the inner retinal surface to the ora serrata until the inner vascular layer is completed at postnatal day 7 to 10 (P7–P10). They subsequently spread into the retina and form the deep capillary layer. Finally, the intermediate capillary is formed from P14–P21.

The mammalian retina is dedicated to the central nervous system (CNS) since it derives from the neural tube and is formed through evagination from the diencephalon. Like in other CNS tissues, paracellular and transendothelial transport from the vasculature to the surrounding retinal tissue is highly regulated by the BRB, ensuring an optimal chemical composition of the neuronal microenvironment. The BRB is composed of the inner BRB (retinal capillary endothelial cells) and the outer BRB (retinal pigment epithelial cells). Although BRB tightness is mainly mediated by tight and adherent junctions between ECs, PCs have been proven to be an essential constituent of the BRB and blood-brain barrier (BBB). The contribution of PCs to the BRB/BBB is discussed in the subheading entitled: “Pericytes and their impact on the blood-retina barrier (BRB).”

1.3 Identification of (Retinal) Pericytes (PCs)

Currently, there is an urgent need to study and determine the role of retinal PCs in health and disease. To achieve this goal, the proper identification of this barely explored cell type is essential. However, following the gene and protein expression pattern, an identification of a specific PC molecular signature has been quite challenging. Up to now, no unique PC marker has been identified. Currently, the established marker panel for PC characterization comprises PDGF-receptor beta (PDGFRβ), neuron-glial antigen 2 (NG2, Cspg4, Fig. 1.2a), CD13 (brain PCs), Desmin, Vimentin, and RGS5 (Armulik et al. 2011). More recently, additional markers like Gli1 (Kramann et al. 2015) and Tbx18 (Guimaraes-Camboa et al. 2017) were proposed to identify PCs. A recent comparative single-cell transcriptomal study identified genes specifically expressed in (brain) PCs: in addition to the known markers Pdgfrb, Cspg4, Rgs5, and Anpep, Kcnj8, Cd248, Abcc9, Vtn, and S1pr3 were identified (Vanlandewijck et al. 2018). Of note, many markers used to identify PCs (e.g., NG2/Cspg4, PDGFRb) are also positive in vascular smooth