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Alexander Birbrair *Editor*

Pericyte Biology in Disease

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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 Disease* 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 the biology of different organs 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. Fifteen chapters written by experts in the field summarize the present knowledge about the roles of pericytes in disease.

Ander Izeta and colleagues from Tecnun-University of Navarra discuss the role of pericytes in cutaneous wound healing. Anirudh Sattiraju and Akiva Mintz from Columbia University Irving Medical Center describe the multifaceted role of pericytes in glioblastoma and their potential use for therapeutic interventions. Jiha Kim from North Dakota State University compiles our understanding of pericytes in breast cancer. Aaron W. James and colleagues from Johns Hopkins University update us on pericytes in sarcomas and other mesenchymal tumors. Pritinder Kaur and colleagues from Curtin University summarize current knowledge on pericytes in metastasis. Mayana Zatz and colleagues from the University of São Paulo address the importance of pericytes in amyotrophic lateral sclerosis. Alla B. Salmina and colleagues from Krasnoyarsk State Medical University focus on pericytes in Alzheimer's disease. Francisco J. Rivera and colleagues from Universidad Austral de Chile introduce our current knowledge about pericytes in multiple sclerosis. Turgay Dalkara and colleagues from Hacettepe University describe pericytes role in ischemic stroke. Franck P.G. Lebrin and colleagues from Leiden University Medical Center discuss pericytes in hereditary hemorrhagic telangiectasia. Annika Keller and colleagues from Zurich University Hospital update us on pericytes in primary familial brain calcification. Katherine L. Hayes from the University of Massachusetts Medical School summarizes our current understanding on pericytes in type 2 diabetes. Volha Summerhill and Alexander Orekhov from Skolkovo Innovative Center compile our knowledge on pericytes in atherosclerosis. Bushra Shammout and Jill R. Johnson from Aston University address the role of pericytes in chronic lung disease. Finally, Sara Benedetti and colleagues from University College London give an overview of pericytes in muscular dystrophies.

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 Cutaneous Wound Healing

Shunichi Morikawa, Haizea Iribar, Araika Gutiérrez-Rivera, Taichi Ezaki, and Ander Izeta

Abstract Most of the studies on cutaneous wound healing are focused on epidermal closure. This is obviously important, as the epidermis constitutes the main barrier that separates the inner organism from the environment. However, dermal remodeling is key to achieve long-lasting healing of the area that was originally wounded. In this chapter, we summarize what is known on the stromal components that strongly influence the outcome of healing and postulate that dedifferentiation of stably differentiated cells plays a major role in the initial response to wounding, as well as in long-term wound remodeling. Specifically, we explore the available evidence implicating skin pericytes, endothelial cells, Schwann cells, and macrophages as major players in a complex symphony of cellular plasticity and signaling events whose balance will promote healing (by tissue regeneration or repair) or fibrosis.

Keywords Pericytes · Schwann cell precursors · Dermis · Dedifferentiation Remodeling · Regeneration · Scar · Revascularization · Reinnervation Macrophages · Wound healing · Injury response · Reprogramming · Neural crest Boundary cap

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This chapter is dedicated to the memory of the late Dr. Shunichi Morikawa, an original thinker and pioneering scientist who largely increased our current understanding of the role of pericytes in cutaneous wound healing.

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Shunichi Morikawa and Haizea Iribar contributed equally to this work.

Introduction

Pericytes constitute a heterogeneous group of cells, somewhat loosely defined by their perivascular location, as the mural cells of blood microvessels (Armulik et al. 2011). For this reason, the literature has to be carefully revised and different terms of search must be used to grasp the vast knowledge accumulated on their putative roles in tissue repair and fibrosis. To increase the confounding factors, adult cells may dedifferentiate and transdifferentiate in response to wounding as well as in response to tissue disaggregation and cell isolation, and the boundaries between so-called terminally differentiated cell populations blur. The consensus in the field is that pericytes are highly plastic cells (Birbrair et al. 2017). As a result, if we could sample a wound and look at the continuum of cells active at the wound bed, virtually at any time we would encounter a number of cells that may represent intermediate states among cell type A and cell type B, apart from myriad cell types that infiltrate the wound, replicate, or die. This complex picture must be carefully delineated. In this chapter, we aim to dissect the role of pericyte fate and plasticity in wound closure and remodeling. To this end, we discuss the different aspects of vascular formation, peripheral innervation, and role of macrophages in cutaneous wound healing and thus we explore the available evidence implicating pericytes, endothelial cells, Schwann cells, and macrophages as the major players in promoting wound healing or fibrosis.

Vascular Formation in Wound Healing

The Circulatory System in the Skin

The blood supply to the skin stems from arteries in the subcutis layer. Branches from these arteries run upwards to form two plexuses of anastomosing vessels, one sitting deep in the dermis (the cutaneous plexus) and the other more superficial (the subpapillary plexus) (Braverman 2000; Young et al. 2014). The venous and lymphatic drainages run parallel to the arterial supply (Fig. 1.1).

The deep cutaneous plexus or *rete cutaneous* (Sorrell and Caplan 2004) sits at the junction between the dermis and hypodermis. It supplies blood to the dermal fat layer as well as the reticular dermis and epidermal appendages (hair follicles, sebaceous and sweat glands). The superficial subpapillary plexus or *rete subpapillare* lies just beneath the dermal papillae, and supplies the capillaries in the dermal papillae.

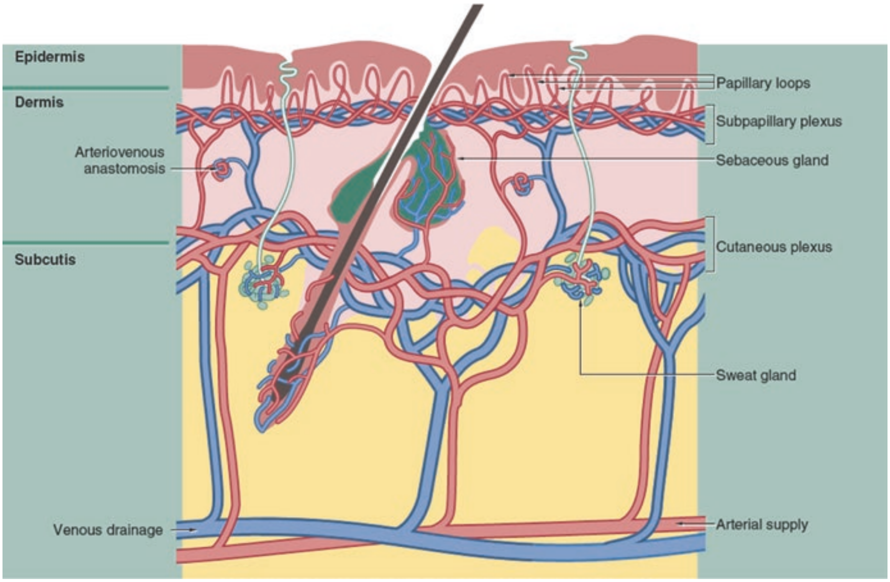

Fig. 1.1 The skin circulation system. The arteries supplying the skin are located deep in the subcutis, from which they give rise to branches passing upwards to form two plexuses of anastomosing vessels. The deeper plexus lies at the junction of the subcutis and dermis and is known as the cutaneous plexus; the more superficial plexus lies at the junction between papillary and reticular dermis and is known as the subpapillary or superficial plexus. The venous drainage of the skin is arranged into plexuses broadly corresponding to the arterial supply. The skin has a rich lymphatic drainage which forms plexuses corresponding to those of the blood vascular system. Reprinted from Young et al. (2014) with permission

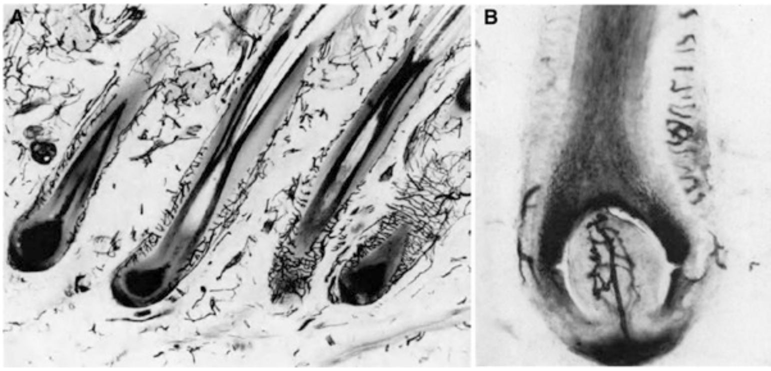

Fig. 1.2 Vascularization of hair follicles. Parallel, longitudinally oriented vessels extend from the base of the bulb to the pilary canal. (**a**) Numerous capillary networks around eyebrow hair follicles demonstrated with alkaline phosphatase. (**b**) A tuft of blood vessels inside the dermal papilla of an eyebrow follicle demonstrated with the alkaline phosphatase technique. Reprinted from Montagna and Parakkal (1974) with permission