Advances in Experimental Medicine and Biology 1041

Alexander Birbrair *Editor*

Stem Cell Microenvironments and Beyond

Springer

Advances in Experimental Medicine and Biology

Volume 1041

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ISSN 0065-2598 ISSN 2214-8019 (electronic)
Advances in Experimental Medicine and Biology
ISBN 978-3-319-69193-0 ISBN 978-3-319-69194-7 (eBook)
DOI 10.1007/978-3-319-69194-7

Library of Congress Control Number: 2017959608

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

This book *Stem Cell Microenvironments and Beyond* 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. The texts are about stem cell microenvironments in different tissues and under distinct pathophysiological conditions. The authors focus on the modern methodologies and the leading-edge concepts in the field of stem cell biology. In recent years, remarkable progress has been made in the identification and characterization of the stem cell niches using state-of-the-art techniques. These advantages facilitated the identification of cellular components of the stem cell niche and the definition of the molecular basis of physical interaction between stem cells and their niches and revealed key niche signals involved in stem cell regulation. Just like the ecological niche of an organism, a stem cell niche is unique to the individual or small population and guides its dynamics. This book describes the major components of various stem cell microenvironments such as soluble factors, cell-cell interactions, extracellular matrix proteins, and physical forces. Thus, this book is an attempt to describe the most recent developments in the area of stem cell behavior regulation 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 stem cell niches in various tissues and under distinct pathophysiological conditions. Twelve chapters written by experts in the field summarize the present knowledge about the physiological and pathophysiological roles of tissue microenvironments in stem cell regulation.

Daniel Lucas from the University of Michigan School of Medicine introduces our current understanding of the hematopoietic stem cell niche and discusses some of the open questions in the field for future research. Marina Konopleva and Yoko Tabe from the University of Texas MD Anderson Cancer Center describe recent research on several key components of specific niches that provide a sanctuary where leukemia stem cells evade chemotherapy-induced death and acquire a drug-resistant phenotype. Teresa V. Bowman and colleagues from Albert Einstein College of Medicine discuss knowledge that we gained from zebrafish about niche factors critical for early hemogenic endothelial induction as well as hematopoietic stem cell

specification, migration, and expansion. Raúl E. Russo and colleagues from Instituto de Investigaciones Biológicas Clemente Estable focus on spinal cord ependymal neural stem cell niche regulation. Ilias Kazanis and colleagues from the University of Cambridge summarize the recent developments on the role of the microenvironment and how it affects neural stem cells in the brain. Akiva Mintz and his group from Columbia University Medical Center introduce the concept of glioblastoma stem cells and detail the latest findings within the microenvironment where these cells survive, proliferate, and differentiate. Christoph Handschin and colleagues from the University of Basel give an overview of the players in the skeletal muscle stem cell microenvironment and their mutual interactions with stem cells. Kiminori Sato from Kurume University School of Medicine addresses the importance of the maculae flavae of the human vocal fold as a stem cell microenvironment. Maria P. Alcolea from Wellcome Trust-Medical Research Council Cambridge Stem Cell Institute compiles recent observations on esophageal epithelial stem cell biology and how microenvironmental changes may lead to esophageal disease and cancer. Sujit K Bhutia and colleagues from the National Institute of Technology discuss the dynamic interplay between oral cancer stem cells and the tumor microenvironment in carcinogenesis. Maria Angelica Miglino and Phelipe Oliveira Favaron from the University of Sao Paulo describe the microenvironment and applications of yolk sac and amniotic membrane-derived stem cells for human and veterinary regenerative medicine. Finally, Carmine Gentile and colleagues from the University of Sydney update us with the latest technologies based on our knowledge of the stem cell niche and current approaches for engineering artificial stem cell microenvironments.

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. Sivachandran Ravanan from Springer, who helped at every step of the execution of this project.

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Chapter 1
Stem Cell Microenvironments and Beyond

Alexander Birbrair

Abstract Endogenous stem cells are indispensable to keep tissue homeostasis due to their unique ability to generate more specialized cell types in an organized way depending on the body needs. Precise control over stem cell differentiation is essential for organogenesis and tissue homeostasis. Stem cells reside in specialized microenvironments, also called niches, which maintain them in an undifferentiated and self-renewing state. The cellular and molecular mechanisms of stem cell maintenance are key to the regulation of homeostasis and likely contribute to several disorders when altered during adulthood. Extensive studies in a various tissues have shown the importance of the niche in modulating stem cell behavior, including bone marrow, skin, intestine, skeletal muscle, vocal cord, brain, spinal cord, stomach, esophagus, and others. In recent past, extraordinary advancement has been made in the identification and characterization of stem cell niches using modern state-of-art techniques. This progress lead to the definition of the main cellular components in the microenvironment where stem cells reside and the identification of molecular mechanisms by which stem cell behavior is controlled, revealing key niche signals involved in stem cell regulation. Similar to the ecological niche of an organism, a stem cell niche is exclusive to the specific type of stem cell and guides its dynamics. This book describes the major cellular and molecular components of various stem cells microenvironments in different organs and at distinct pathophysiological conditions, such as cell-cell interactions, extra-cellular matrix proteins, soluble factors, and physical forces. Although several advances have been made in our understanding of the signals that promote stem cell activation or quiescence, several components of the stem cells microenvironment remain unknown due to the complexity of niche composition and its dynamics. Further insights into these cellular and molecular mechanisms will have important implications for our understanding of organ homeostasis and disease. In this book, we present a selected collection of detailed chapters on what we know so far about the stem cell niches in various tissues and under distinct pathophysiological conditions. Twelve chapters written by experts in the field summarize the present knowledge about the physiological function and pathophysiological role of the stem cell regulation by the microenvironment.

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A. Birbrair (ed.), *Stem Cell Microenvironments and Beyond*,
Advances in Experimental Medicine and Biology 1041,
DOI 10.1007/978-3-319-69194-7_1

Keywords Stem cells • Niche • Microenvironment

1.1 Editorial

Endogenous stem cells are indispensable to keep tissue homeostasis due to their unique ability to generate more specialized cell types in an organized way depending on the body needs (Hall and Watt 1989). Precise control over stem cell differentiation is essential for organogenesis and tissue homeostasis (Watt and Hogan 2000). Stem cells reside in specialized microenvironments, also called niches (Schofield 1978), which maintain them in an undifferentiated and self-renewing state. The cellular and molecular mechanisms of stem cell maintenance are key to the regulation of homeostasis and likely contribute to several disorders when altered during adulthood. Extensive studies in a various tissues have shown the importance of the niche in modulating stem cell behavior, including bone marrow (Birbrair and Frenette 2016), skin (Fuchs 2009), intestine (Tan and Barker 2014), skeletal muscle (Yin et al. 2013), vocal cord (Kurita et al. 2015), brain (Koutsakis and Kazanis 2016), spinal cord (Marichal et al. 2016), stomach (Bartfeld and Koo 2017), esophagus (Alcolea et al. 2014), and others (Borges et al. 2017; Scadden 2014). In recent past, extraordinary advancement has been made in the identification and characterization of stem cell niches using modern state-of-art techniques. This progress lead to the definition of the main cellular components in the microenvironment where stem cells reside and the identification of molecular mechanisms by which stem cell behavior is controlled, revealing key niche signals involved in stem cell regulation. Similar to the ecological niche of an organism, a stem cell niche is exclusive to the specific type of stem cell and guides its dynamics. This book describes the major cellular and molecular components of various stem cells microenvironments in different organs and at distinct pathophysiological conditions, such as cell-cell interactions, extra-cellular matrix proteins, soluble factors, and physical forces. Although several advances have been made in our understanding of the signals that promote stem cell activation or quiescence, several components of the stem cells microenvironment remain unknown due to the complexity of niche composition and its dynamics. Further insights into these cellular and molecular mechanisms will have important implications for our understanding of organ homeostasis and disease.

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Acknowledgments Alexander Birbrair is supported by a grant from Pró-reitoria de Pesquisa/ Universidade Federal de Minas Gerais (PRPq/UFMG) (Edital 05/2016).

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Chapter 2
The Bone Marrow Microenvironment for Hematopoietic Stem Cells

Daniel Lucas

Abstract The main function of the microenvironment in the bone marrow (BM) is to provide signals that regulate and support the production of the billions of blood cells necessary to maintain homeostasis. The best characterized BM microenvironment is the niche that regulates hematopoietic stem cells. Efforts from many different laboratories have revealed that the niche is mainly perivascular and that blood vessels and perivascular stromal cells are the key components. In addition numerous cell types have been shown to be components of the niche. Here we discuss our current understanding of the niche and the evidence supporting the role of different types of cells in regulating hematopoietic stem cell numbers and function in vivo.

Keywords Bone marrow • Hematopoiesis • Hematopoietic stem cell • Niche • Perivascular • Niche heterogeneity

2.1 Introduction

Hematopoietic stem cells (HSC) are multipotent cells capable of giving rise to all types of blood cells and regenerating a healthy hematopoietic system when transplanted into irradiated recipients. HSC reside in the bone marrow where they tightly associate with multicellular structures that provide a unique microenvironment that supports and regulate HSC. In the bone marrow these structures are called HSC niches as defined by Schofield in 1978 who was the first to propose the existence of niches capable of regulating HSC function and differentiation (Schofield 1978).

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A. Birbrair (ed.), *Stem Cell Microenvironments and Beyond*,
Advances in Experimental Medicine and Biology 1041,
DOI 10.1007/978-3-319-69194-7_2