Stem Cell Biology and Regenerative Medicine

Series editor

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Our understanding of stem cells has grown rapidly over the last decade. While the apparently tremendous therapeutic potential of stem cells has not yet been realized, their routine use in regeneration and restoration of tissue and organ function is greatly anticipated. To this end, many investigators continue to push the boundaries in areas such as the reprogramming, the stem cell niche, nanotechnology, biomimetics and 3D bioprinting, to name just a few. The objective of the volumes in the Stem Cell Biology and Regenerative Medicine series is to capture and consolidate these developments in a timely way. Each volume is thought-provoking in identifying problems, offering solutions, and providing ideas to excite further innovation in the stem cell and regenerative medicine fields.

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Epigenetic Regulation of Skin Development and Regeneration

Humana Press

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Preface

Living organisms are protected from the external environment by an integument that forms the outer body surface and permits both survival and adaptation to environmental challenges. In mammals, the integument is formed by the skin and its appendages, including feathers, hairs, and glands, and displays a high degree of evolutionary, anatomical and environmentally dependent-variability.

Mammalian skin is one of the largest organs of the body. It serves a number of critical roles, including protecting the organism from external insults, maintaining body temperature and water balance, and transmitting sensory information. To efficiently fulfill these complex functions, the skin has developed the capacity to provide a high degree of plasticity in response to changing environmental conditions, while maintaining its structural integrity. In postnatal life, the epithelial outer layer of the skin, known as the epidermis, continuously regenerates due to the ability of epithelial stem cells in its basal layer to supply progeny capable of forming all of the epidermal cell layers and generating a functional barrier. Unlike the continuously regenerating epidermis, hair follicles undergo cyclical transitions between active growth, involution, and resting phases. After skin injury, stem cells in both epithelial and underlying mesenchymal components of the skin contribute to skin regeneration, supplying progeny that repair the wounded area.

During the last two decades, tremendous progress has been made in understanding the molecular mechanisms that underlie skin development, regeneration, and both rare and common diseases. Genome-wide association studies and comparative genome analyses have provided invaluable insights into the physiological role of genetic information. Nevertheless, how the genomes of diverse populations of epithelial and mesenchymal skin cells are organized beyond their linear sequence, and the mechanisms regulating lineage-specific responsiveness of distinct genomic regions to external signals in healthy and diseased skin, remain to be clarified.

It is now widely accepted that in addition to their regulation by signaling/transcription factor-mediated mechanisms, lineage-specific gene expression programs are also controlled epigenetically by covalent DNA and histone modifications, as well as via higher-order chromatin remodeling and topological arrangement of genes and their distal regulatory elements in 3D nuclear space. Epigenetic

mechanisms play important roles in controlling cellular functions in living organisms and are considered to be a driving force of phenotypic plasticity and evolutionary adaptation. Variability in epigenetic status helps explain the relationships between an individual's genetic background and the effects of the environment on susceptibility to different diseases.

As an important and accessible source of epithelial, mesenchymal, pigmentary, and neuronal stem cells, the skin serves as an excellent model for studying how extrinsic signals coordinate gene expression by directing the activity and distribution of distinct epigenetic regulators and orchestrating the execution of lineage-specific gene expression programs and their adaptation to environmental cues.

This volume presents and summarizes recent major findings that shed light on the roles of critical components of the epigenetic regulatory machinery in the control of skin development and regeneration. Chapter 1 outlines how signaling/transcription factor-mediated and epigenetic mechanisms operate in concert to regulate skin development and regeneration, and highlights the role of the cell nucleus as a command center integrating signals received from the external environment and transforming them into distinct transcriptional outcomes.

Chapter 2 focuses on the importance of DNA methylation as a keeper of epigenetic memory in the control of skin development and physiological regeneration. Chapters 3, 4, and 5 discuss the impact of distinct post-translational histone modifications and their corresponding epigenetic regulators, including Polycomb and Trithorax genes and histone deacetylases, in the control of transcriptional silencing and activation in epithelial cells of the developing and adult skin. In Chapter 6, the role of ATP-dependent chromatin remodeling in the control of gene expression in the epidermis is discussed.

Chapters 7 and 8 highlight the roles of noncoding and micro-RNAs in regulating keratinocyte differentiation, while Chapter 9 is devoted to the emerging roles of RNA modifications in the control of epithelial stem cell activity.

Chapter 10 discusses the mechanisms coordinating three-dimensional organization of epidermal genes and their regulatory elements (enhancers) in the nucleus, while Chapter 11 describes the role of the nuclear lamina in transmitting signals from the external environment to the genome and in controlling lineage-specific differentiation programs in normal skin. Finally, Chapter 12 summarizes recent data on the functions of distinct components of the epigenetic machinery in skin regeneration after injury and during wound healing.

This collection of work offers a brief introduction to this exciting and rapidly developing area of research and provides readers with an understanding of the experimental underpinnings of current models that will aid in critical evaluation of new literature in the field. The exhilarating pace of discovery will undoubtedly ensure that significant new developments and unexpected findings will be revealed before this book is widely available.

In summary, we believe that this volume provides a useful introduction to skin epigenetics for many categories of researchers. Our hope is that this work will serve as a platform and inspiration for future research in this field that is necessary to bridge the gap between our knowledge of basic epigenetic mechanisms and clinical

practice. Progress in this direction will ultimately permit the development of novel approaches for modulating the epigenome and epitranscriptome to protect the skin against aging and environmental stressors, as well as in the treatment of skin disorders.

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