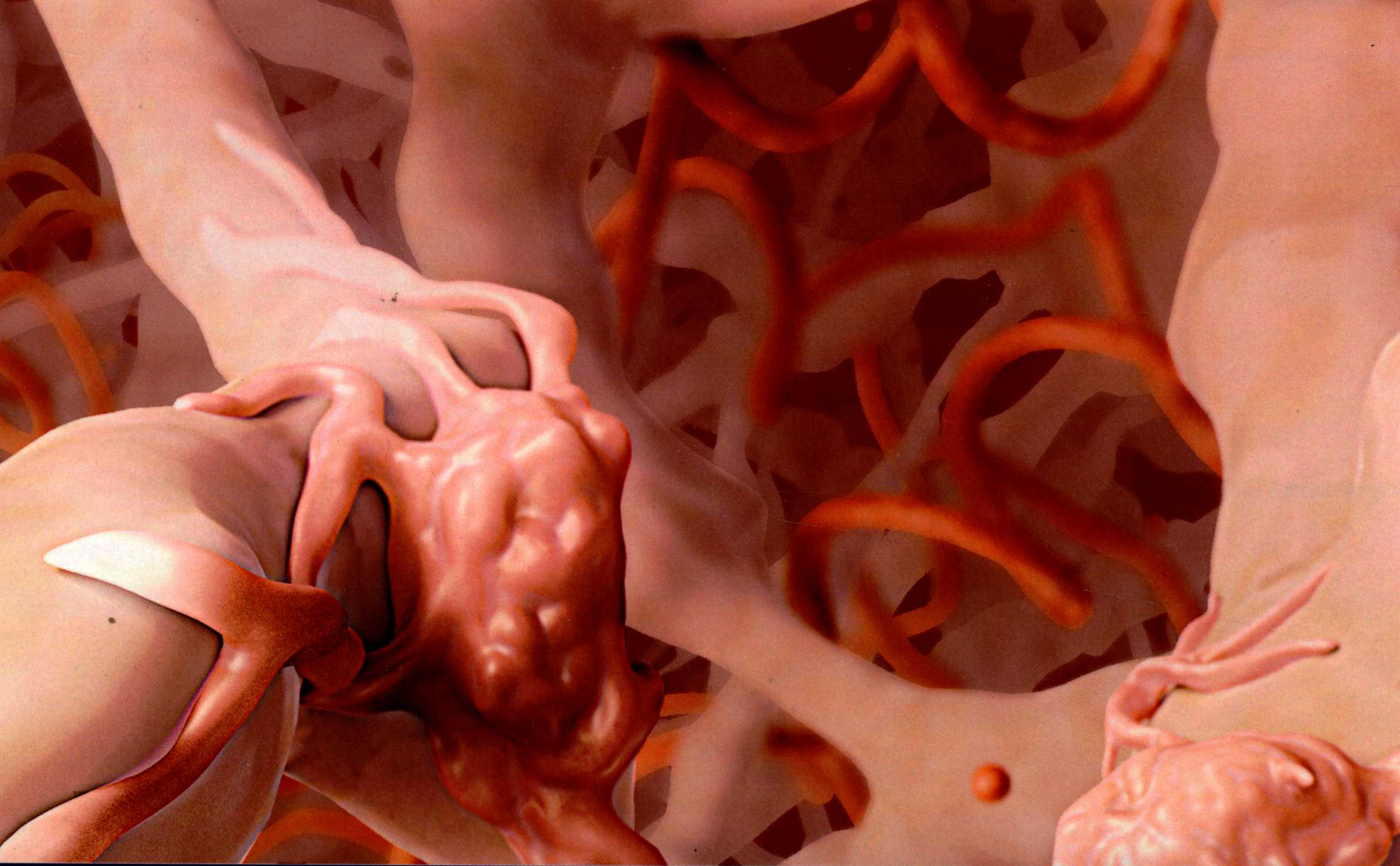
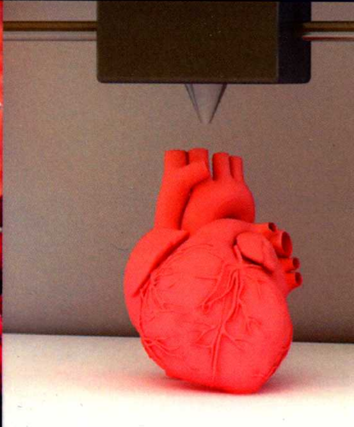


BIOLOGY AND ENGINEERING OF STEM CELL NICHES



EDITED BY
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BIOLOGY AND ENGINEERING OF STEM CELL NICHES

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Foreword

Four decades ago, James Rheinwald and Howard Green described the first long-term culture method for normal human cells. They combined freshly isolated human skin cells with irradiated mouse fibroblasts. Gradual improvements allowed them to generate large confluent sheets of epidermis, starting from relatively small numbers of primary proliferative skin progenitor/stem cells. In 1980, Green and his colleagues performed the first successful therapy of two third-degree burn patients with cultured autologous keratinocyte sheets. In a dramatic demonstration during the summer of 1983, they exhibited that large-scale use of the method was life-saving for two brothers: five-year-old Jamie Selby and six-year-old Glen; both had sustained burns over >95% of their body surface. Later studies accomplished similar spectacular results in the lab and in the clinic with a related tissue, the cornea.

Despite these early successes, it has long been held that healthy mammalian cells cannot be maintained (let alone expanded) outside the body, in a dish. This is now rapidly changing. The stem cell field has gone through a period of prolonged expansion. Many new stem cell types have been identified and characterized. However, the ways by which stem cells are nurtured by their niches still remains uncovered. Based on the new insights in understanding stem cell niches, it is now possible to culture stem cells representing virtually any tissue type in a dish. Under the right conditions, these stem cells not only simply increase in their numbers but also self-organize into organoids: miniature versions of real organs, like mini-brains, kidneys, or guts. Organoids are great experimental tools to ask basic science questions. Yet, the ease of organoid production from stem cells and their resemblance to human organs in health and disease holds great appeal for translational research and invites their almost immediate application into the clinic.

This book is written by scientists who have contributed to many of the recent stem cell discoveries. It touches on all aspects of stem cell niche research, basic and applied. It contains a wealth of information for anyone with a scientific interest in learning about newest approaches to engineer stem cells and their niches. Enjoy a good read!

Hans Clevers

Contents

List of Contributors xi
Foreword xv

I

BIOLOGY OF STEM CELL NICHES AND MOLECULAR MECHANISMS

1. The Need to Study, Mimic, and Target Stem Cell Niches

AJAYKUMAR VISHWAKARMA, JEROEN ROUWKEMA, PETER ANTHONY JONES, JEFFREY M. KARP

1. Introduction 3
2. Biology of the Stem Cell Niche 5
3. Biochemical and Biophysical Regulation of Stem Cell Behavior 7
4. Mimicking the Stem Cell Niche: Bioengineering Tools and Techniques 10
5. Bioengineering Specialized Artificial Stem Cell Niches for Clinical Therapies 12

References 12

2. Harnessing the Biology of Stem Cells' Niche

BORJA SAEZ, RUSHDIA Z. YUSUF, DAVID T. SCADDEN

1. Introduction 15
2. Components of the Stem Cell Niche 16
3. Integrative Networks Regulating the Niche 21
4. Distinct Niches for Different Stages of Differentiation 22
5. Neoplastic Transformation and Disturbance of the Tissue Ecosystem 23
6. Conclusion 25

Abbreviations and Acronyms 25
Glossary 26
References 26

3. Pluripotent Stem Cell Microenvironment

MIO NAKANISHI, MICKIE BHATIA

1. Introduction 33
2. Pluripotent Cell Microenvironment in the Early Mammalian Embryo 34
3. Microenvironment of Pluripotent Stem Cells In Vitro 38
4. Conclusion 46

Abbreviations and Acronyms 47
Glossary 47
Acknowledgment 47
References 47

4. Regulation of Hematopoietic Stem Cell Dynamics by Molecular Niche Signaling

APARNA VENKATRAMAN, MENG ZHAO, JOHN PERRY, XI C. HE, LINHENG LI

1. Introduction 51
2. Organization of Hematopoietic Stem Cell Niche in the Bone Marrow 51
3. Niche Signaling 52
4. Future Outlook and Challenges 57

Abbreviations and Acronyms 57
Glossary 58
References 58

5. HSC Niche: Regulation of Mobilization and Homing

SAMIKSHA WASNIK, WANQIU CHEN, ABU S.I. AHMED, XIAO-BING ZHANG, XIAOLEI TANG, DAVID J. BAYLINK

1. Introduction 63
2. HSC Trafficking During Embryonic Development 64
3. HSC Trafficking in Adult Hematopoiesis 65
4. New Strategies to Enhance Homing and Engraftment of HSC 68
5. Techniques to Dissect the Mechanism of HPC Migration 68
6. Clinical Applications of the Mobilization Agents and Biochemical Factors 69
7. Conclusion 70

Glossary 70
References 70

6. Neuronal Stem Cell Niches of the Brain

JOANNE C. CONOVER, KRYSTI L. TODD

1. Introduction 75
2. Organization of the Brain's Neuronal Stem Cell Niches 76
3. Functional Role of the Brain's Neuronal Stem Cell Niches 81
4. Signaling in the Neural Stem Cell Niche 83
5. Neural Stem Cell Niche in Aging 85
6. Conclusion 87

Abbreviations and Acronyms 87
Glossary 88
Acknowledgment 88
References 88

7. Cardiovascular Stem Cell Niche

ANNAROSA LERI, MARCELLO ROTA, POLINA GOICHBERG, TORU HOSODA, TIZIANO MOCCETTI, PIERO ANVERSA

1. Introduction 93
2. Myocyte Regeneration and Cardiac Progenitor Cell Niches 94
3. Lineage Tracing of the Stem Cell Progeny 96
4. Stem Cells: Studies at the Single-Cell Level 97
5. Cardiac Progenitor Cell Classes and Their Niches 98
6. c-kit-CPCs and Their Niches 100
7. Epicardial Progenitor Cell Niches 102
8. Mesenchymal Stem Cells and Cardiac Niches 103
9. Hypoxic Niches 104
10. Cardiomyocyte Proliferation and the Notch Receptor System 104
11. Cardiac Niches and the Notch Receptor System 106
12. Conclusions 106

Abbreviations and Acronyms 107
Glossary 107
References 107

8. Intestinal Epithelial Lgr5$^+$ Stem Cell Niche and Organoids

NOBUO SASAKI, TOSHIRO SATO, HANS CLEVERS

1. Introduction 111
2. Intestinal Stem Cell 112
3. The Stem Cell Niche 113
4. Ex Vivo Intestinal Stem Cells Culture—Organoids 119
5. Application of Organoid System 120
6. Concluding Remarks 122

Acknowledgment 123
References 123

9. The Epithelial Stem Cell Niche in Skin

GÉRALDINE GUASCH

1. Introduction 127
2. The Adult Skin: A Model to Study Various Epithelial Stem Cells 128
3. The Multiple Actors in Adult Epithelial Stem Cell Niche in the Skin 136
4. Do the Niche Cells From Various Locations Regulate the Epithelial Stem Cell Fate Differently? 140
5. Conclusions 140

Abbreviations and Acronyms 141
Glossary 141
Acknowledgments 141
References 141

10. The Satellite Cell Niche in Skeletal Muscle

CAROLINE E. BRUN, FABIEN P. CHEVALIER, NICOLAS A. DUMONT, MICHAEL A. RUDNICKI

1. Introduction 145
2. The Quiescent Satellite Cell Niche 146
3. The Activated Satellite Cell Niche 150
4. Alterations of the Satellite Cell Niche 157
5. Conclusion 161

Abbreviations and Acronyms 161
Glossary 162
Acknowledgments 162
References 162

11. The Cancer Stem Cell Niche

NANIYE MALLI CETINBAS, JATIN ROPER, ÖMER H. YILMAZ

1. Introduction 167
2. Cancer Stem Cells and Niche Interactions 169
3. Cancer Stem Cell Niche Promotes Tumor Growth and Progression 172
4. The Role of the Cancer Stem Cell Niche in Metastasis 175
5. Therapeutic Targeting of Cancer Stem Cell Niche 177
6. Conclusion 180

Abbreviations and Acronyms 180
Glossary 181
Acknowledgment 181
References 181

12. Cellular Senescence and Stem Cell Niche

ARTHUR KRAUSE, MICHAEL J. CONBOY, IRINA M. CONBOY

1. Introduction 185
2. Cellular Senescence 185
3. p16^{INK4a} 185
4. Senescence-Associated Secretory Phenotype 186
5. Senescence and Tissue Repair 187
6. Stem Cell Niche 188
7. Effects of Aging and Senescence on the Stem Cell Niche 189

References 191

II

BIOCHEMICAL AND PHYSICAL CUES IN THE STEM CELL NICHE DIRECTING CELL FATE

13. Matrix Chemistry Controlling Stem Cell Behavior

CHRISTINA KLECKER, LAKSHMI S. NAIR

1. Introduction 195
2. Effect of Chemical Functional Groups on Stem Cell Behavior 196
3. Conclusions and Future Directions 211

Abbreviations and Acronyms 211
Glossary 212
References 212

14. Matrix Growth Factor and Surface Ligand Presentation

EIKE MÜLLER, TILO POMPE, UWE FREUDENBERG, CARSTEN WERNER

1. Introduction 215
2. Modulating Factor-Mediated Signaling 217
3. Cell–Cell Ligand Presentation 224
4. Adhesion Ligand Presentation 224

5. Synergistic Interaction Between Adhesion Ligands and Soluble Factors 226
6. Outlook 227
Abbreviations and Acronyms 227
References 228

15. Effect of Matrix Mechanical Forces and Geometry on Stem Cell Behavior

DEKEL ROSENFELD, SHULAMIT LEVENBERG

1. The Mechanical Microenvironment of Stem Cells 233
2. The Influence of Mechanical Forces on Stem Cell Differentiation 234
3. The Influence of Matrix Geometry and Topography on Stem Cell Behavior 238
4. How Do Stem Cells Respond to Mechanical Stimuli? 238
5. Future Directions 241
Abbreviations and Acronyms 241
Acknowledgments 241
References 241

16. Wettability Effect on Stem Cell Behavior

YINGYING LI, SHUTAO WANG, LEI JIANG

1. Introduction 245
2. The Impact of Interfacial Wettability on Cells 246
3. The Impact of Interfacial Wettability on Stem Cells 248
4. Conclusion and Future Directions 253
References 254

17. Fluid Flow Control of Stem Cells With Investigation of Mechanotransduction Pathways

BRANDON D. RIEHL, HENRY J. DONAHUE, JUNG YUL LIM

1. Introduction 257
2. Mimicking In Vivo Fluid Flow Environments 258
3. Fluid Flow Regulation of Stem Cell Function and Fate 259
4. Fluid Flow-Activated Mechanotransduction Pathways in Stem Cells 266
5. Conclusions 267
Abbreviations and Acronyms 269
Glossary 269
Acknowledgment 269
References 269

18. Hypoxia Regulation of Stem Cell: Mechanisms, Biological Properties, and Applications

YIJUN LIU, ANG-CHEN TSAI, XUEGANG YUAN, YAN LI, TENG MA

1. Physiological Relevance of Hypoxic Niche in Embryonic and Adult Stem Cells 274
2. Molecular Mechanism of Hypoxia-Mediated Cellular Response 275
3. Stem Cell Metabolic Adaptation Under Hypoxia 275
4. Influence of Hypoxia on Stem Cell Fate 278
5. Recapitulation of Hypoxia Niche In Vivo and In Vitro 282
6. Hypoxia-Preconditioning-Enhanced Therapeutic Function After Transplantation 284
Abbreviations and Acronyms 287
References 288

III

DESIGNING SMART BIOMATERIALS TO MIMIC AND CONTROL STEM CELL NICHE

19. Polymer Design and Development

CHRISTOPHER K. ARAKAWA, COLE A. DEFOREST

1. Introduction 295
2. Natural Polymers for 3D Stem Cell Culture 296
3. Synthetic Polymers for 3D Stem Cell Culture 303
4. Smart Polymer Systems for 3D Stem Cell Culture 307
5. Concluding Remarks 310
Abbreviations and Acronyms 310
Glossary 310
References 311

20. Design and Development of Ceramics and Glasses

JIE HUANG

1. Introduction 315
2. Development of Bioceramics 317
3. Design of Bioactive Ceramics and Composites 318
4. Engineering Stem Cell Niches 325
5. Summary and Future Perspective 326
References 327

21. Surface Functionalization of Biomaterials

DEEPTI RANA, KEERTHANA RAMASAMY, MARIA LEENA, RENU PASRICHA, GEETHA MANIVASAGAM, MURUGAN RAMALINGAM

1. Introduction 331
2. Surface Modifications of Biomaterials 332
3. Biological Relevance of Surface Modification for Biomaterials 338
4. Concluding Remarks 340
Abbreviations and Acronyms 341
Glossary 341
Acknowledgments 341
References 341

22. Biofunctional Hydrogels for Three-Dimensional Stem Cell Culture

JENNA L. WILSON, TODD C. MCDEVITT

1. Introduction 345
2. Hydrogel Materials 348
3. Hydrogel Material Properties 351

37. Engineering the Niche for Intestinal Regeneration

VICTOR HERNANDEZ-GORDILLO, ABIGAIL N. KOPPES,
LINDA G. GRIFFITH, DAVID T. BREAULT, REBECCA L. CARRIER

1. Introduction 602
2. Overview of Intestinal Culture Models and Regenerative Medicine Approaches 602
3. Tools and Techniques for Engineering the Intestinal Stem Cell Niche 604
4. Future Directions: Engineering the Niche for Intestinal Modeling and Development of Regenerative Medicine Therapies 610
5. Conclusions 611
Abbreviations and Acronyms 611
Glossary 612
References 612

Index 617

5. Types of Biomaterials and Their Applications 467
6. Biomaterial-Based Cardiovascular Devices 473
7. Future Direction for Cardiac Regeneration 473
Abbreviations and Acronyms 474
Glossary 474
References 474

30. Engineering Niches for Blood Vessel Regeneration

QUINTON SMITH, MICHAEL BLATCHLEY, SHARON GERECHT

1. Introduction 479
2. Elements for Recapitulating the Vascular Regeneration Niche In Vitro 483
3. Material Design Parameters for Controlling the Vascular Niche 485
4. Strategies in Engineering Artificial Niches for Vascular Regeneration 488
5. Inducing Vascularization Through Biomaterials 492
6. Conclusion and Future Directions 494
Abbreviations and Acronyms 494
Glossary 494
References 495

31. Engineering Niches for Bone Tissue Regeneration

ANGAD MALHOTRA, CLEMENS VAN BLITTERSWIJK, PAMELA HABIBOVIC

1. Introduction: The Native Bone Niche 499
2. Approaches to Control the Stem Cell Niche 504
3. Conclusions and Future Directions 511
Abbreviations and Acronyms 513
Glossary 513
References 513

32. Engineering Vascular Niche for Bone Tissue Regeneration

JOHNATHAN NG, KARA SPILLER, JONATHAN BERNHARD, GORDANA VUNJAK-NOVAKOVIC

1. Introduction 517
2. The Bone Tissue Engineering Paradigm: Scaffold, Cells, Bioreactor 518
3. Strategies to Promote Bone Vascularization 520
4. Harnessing the Inflammatory Response to Engineer Vascularized Bone 521
5. Endochondral Ossification and the Hematopoietic Niche 523
6. Conclusions and Future Directions 525
Abbreviations and Acronyms 525
Glossary 525
Acknowledgments 525
References 525

33. Engineering Niches for Cartilage Tissue Regeneration

TING GUO, KIMBERLY M. FERLIN, DAVID S. KAPLAN, JOHN P. FISHER

1. Introduction: The Native Cartilage Niche 531
2. Approaches for Engineering the Cartilage Niche 534
3. Conclusion and Future Directions 542
Abbreviations and Acronyms 543
Glossary 543
References 543

34. Engineering Niches for Stem and Progenitor Cell Differentiation Into Immune Cells

SANAYA N. SHROFF, FNU APOORVA, ANKUR SINGH

1. Introduction 547
2. Hematopoiesis and Niche Signaling 547
3. 2D Immune Cell Culture Systems 549
4. Engineering 3D Immune Niche 551
5. Future Directions and Conclusions 556
Abbreviations and Acronyms 556
Glossary 556
Acknowledgments 556
References 557

35. Engineering Niches for Skin and Wound Healing

MICHAEL W. FINDLAY, GEOFFREY C. GURTNER

Chapter Outline 560
1. Introduction 560
2. The Skin Stem Cell Niche From a Wound Healing Perspective 564
3. Engineering of Skin Stem Cell Niches for Wound Healing 571
4. Specific Targets for Niche-Based Approaches in the Skin 573
5. Conclusion 576
Abbreviations and Acronyms 576
References 576

36. Designing Stem Cell Niche for Liver Development and Regeneration

AMRANUL HAQUE, JOSHUA GUILD, ALEXANDER REVZIN

1. Introduction 581
2. LPCs Fate Selection in Developing and Injured Liver 582
3. Hepatic Stem Cell Niches 584
4. Engineering Biomimetic Liver Niches 589
5. Conclusion 595
Abbreviations and Acronyms 595
Glossary 596
References 596

PART I

BIOLOGY OF STEM CELL NICHES AND MOLECULAR MECHANISMS

CHAPTER

1

The Need to Study, Mimic, and Target Stem Cell Niches

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OUTLINE

1. Introduction 3
1.1 The Stem Cell Niche in Health and Disease 3
1.2 Components of Stem Cell Niche 4

2. Biology of the Stem Cell Niche 5
2.1 Behavior of Stem Cells: Hierarchical Versus Stochastic Model 5
2.2 Embryonic and Adult Stem Cell Niches 6

3. Biochemical and Biophysical Regulation of Stem Cell Behavior 7
3.1 Extracellular Matrix and Biochemical Cues 7
3.2 Soluble Growth Factors and Ligands 9
3.3 Physical Cues and Matrix Mechanics 9
3.4 Oxygen and Metabolism 10
3.5 Immune Cells, Inflammation, and Immunomodulation 10

4. Mimicking the Stem Cell Niche: Bioengineering Tools and Techniques 10

5. Bioengineering Specialized Artificial Stem Cell Niches for Clinical Therapies 12

References 12

1. INTRODUCTION

1.1 The Stem Cell Niche in Health and Disease

As opposed to single-celled organisms, cells in complex multicellular organisms are associated with a tissue-specific physiological environment. Different cell types differ in morphology and function; yet, they are genetically identical. This variation, caused by differential gene expression, is controlled by intrinsic mechanisms and by extrinsic signals from the local environment, thereby controlling distinct cellular behavior, or "phenotype." The local physiological microenvironment supporting the cell and driving extrinsic cues from outside the cell is known as the "cell niche," which is composed of extracellular matrix (ECM) components for attachment/anchorage, diffusible biomolecules for cell signaling, cell surface ligands for signal transduction, and essential cell–cell interactions.

Studies of cell populations during embryonic development have led to the identification of stem cells that possess the capacity to produce a full organism from a fertilized egg.[1] Stem cells are functionally defined as undifferentiated embryonic or adult cells, which can self-renew and generate differentiated cell types with varying degrees of potency. The fundamental replicative feature of stem cells, along with their generation of differentiated progeny, accounts for the origin of the

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word "stemness." However, whether stem cells need a special environment that controls stem cell renewal, maintenance, and survival, and what is the nature of such microenvironment are pertinent questions many researchers continue to explore. With growing evidence, there is a growing consensus that in vivo function and the fate of stem and progenitor cells are regulated by the interplay of various extrinsic signals of tissue-specific microenvironments, often referred to as "stem cell niches."

The concept of a stem cell niche was first proposed by Schofield in the late 1970s as a physiologically restricted microenvironment that supports stem cells.[2] The initial concept of anatomically distinct sites that regulate hematopoietic stem cell (HSC) activity and self-renewal was later extended to acknowledge the discovery of stem cells and their niches in multiple tissues.[3] Stem cells are often linked with asymmetrical cell division, and the niche maintains a stable number of stem cells during homeostasis, and removal of the niche induces differentiation. Extrinsic signals interact and integrate to ensure that one cell remains in the niche, while another escapes it by receiving a differentiation signal. It is now clear that in high-turnover systems, such as in the gut and blood, the behavior of stem cells is not uniformly quiescent, and the various niche components may govern their relative proliferative activity.[4–6] Also, it is emerging that stem cell performance is not only dependent on factors promoting stemness but is also a result of factors inhibiting differentiation pathways. Hence, in homeostasis, the underlying relationship between stem cell and niche accommodates nuances and involves various elements influencing the stem cell functional parameters: replicative capacity and potency. However, when tissue is injured or diseased, the niche actively engages stem cells; guides their proliferation, migration, and differentiation; and regulates their participation in tissue regeneration and repair. Therefore, the niche should be regarded as a dynamic participant controlling stem cell number, fate, and behavior in the health and disease of the tissue and the organism.

1.2 Components of Stem Cell Niche

The stem cell niche is a complex, heterotypic, and dynamic structure, which includes supporting ECM, neighboring niche cells, secreted soluble signaling factors (such as growth factors and cytokines), physical parameters (such as shear stress, tissue stiffness, and topography), and environmental signals (metabolites, hypoxia, inflammation, etc.) (Fig. 1.1).[7,8] Stem cell niches are highly innervated and densely vascularized, thus are directly or indirectly influenced by vascular and neural inputs.

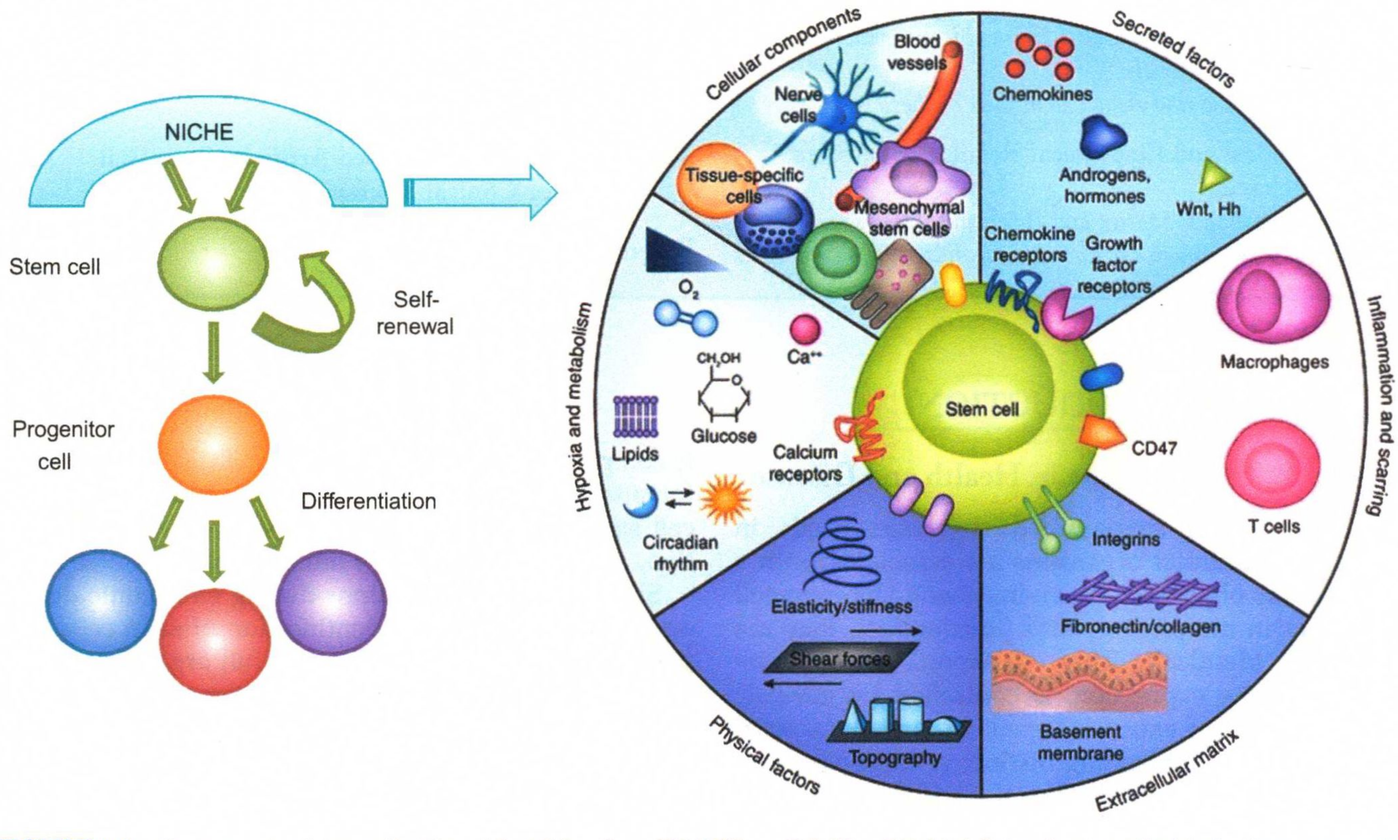

FIGURE 1.1 Components of stem cell niche. *Adapted from Lane SW, Williams DA, Watt FM. Modulating the stem cell niche for tissue regeneration.* Nat Biotechnol *2014;***32***(8):795–803.*

In addition to matrix and cell signaling elements mentioned above, niche cells form functional units within the stem cell niche. These are neighboring tissue-specific stem or somatic cell populations that interact with resident stem cells to regulate cell fate. For example, mesenchymal stromal/stem cells in the HSC niche or parenchymal hepatocytes in liver. In addition to stem cell themselves, niche cells provide a source of physical and biochemical signals within the niche microenvironment by building extracellular matrix and producing cell surface or soluble signaling factors.

Importantly therefore, stem cell microenvironments are highly dynamic and display temporal variations. Such variations in direct cell–cell contacts and ECM components, as well as their interaction with regulatory molecules secreted by stem or niche cells and the spatial organization of niche components, ultimately enable the regulation of stem cells to render tissue homeostasis and regeneration.[9]

2. BIOLOGY OF THE STEM CELL NICHE

2.1 Behavior of Stem Cells: Hierarchical Versus Stochastic Model

Understanding developmental biology is an important approach to fully comprehend the structure and function of the human body developed from a single totipotent stem cell, the zygote. The potency of a given cell to differentiate into many specialized cells is defined by the degree of its plasticity and versatility at various stages. Totipotent stem cells are those with the greatest differentiation potential and can differentiate into any and all cells in an organism, plus the extraembryonic or placental cells. Pluripotent stem cells can differentiate into any cell within the three germ layers (endoderm, mesoderm, and ectoderm). Embryonic stem cells (ESCs) are pluripotent and can divide and differentiate into cells of various types found in the body. Multipotent stem cells are progenitor cells that can differentiate into numerous cell types but within a similar "family" or lineage. Lastly, unipotent stem cells, the most restricted precursor, can only result in one cell fate. Unlike ESCs, stem cells from adult tissues are multipotent or unipotent.

During development and in the healthy body, stem cells can divide to produce new cells. This is a carefully controlled process that allows the body to grow and to replace lost or damaged cells during adult life. For the body to maintain homeostasis, stem cells proliferate before differentiating into a specific lineage, such that the generation of differentiated cells and the maintenance of stem/progenitor pools are balanced. Two distinct models have been proposed to explain the lineage choices of stem cells (Fig. 1.2). The hierarchical model suggests a discrete arrangement of cells consisting of slow-cycling stem cells that can self-renew extensively, which also give rise to short-lived transit amplifying progenitor cells that then further differentiate into committed nondividing cells. The stochastic model suggests that each stem cell chooses at random between self-renewal and differentiation. In this model, each individual clone will vary in size.

Recent lineage tracing studies have supported the findings of the hierarchical model of stem cell behavior,

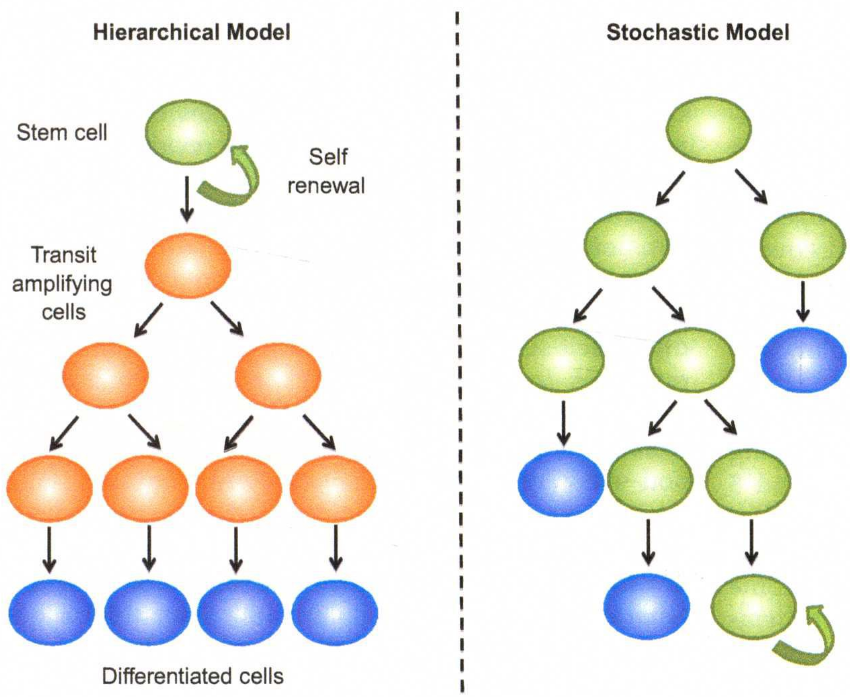

FIGURE 1.2 Hierarchial versus stochastic model for behavior of stem cells.