The Biology of Regenerative Medicine

Ken Muneoka

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Review and commentary on Regeneration Biology and Medicine, by David L. Stocum. Academic Press, an imprint of Elsevier, 2006, 448 pp., ISBN 13: 978-0-12-369371-6.

The field of regenerative biology evolved out of pure scientific curiosity that was based on the observation that some animals, and nearly all plants, have the ability to regrow parts of their anatomy after serious injury (*1*). As a scientific field, regenerative biology is hundreds of years old, and nearly every grant application submitted to study the regenerative capabilities of animals like the salamander contains some reference to its application in humans. In contrast, the field of regenerative medicine is relatively new and application-driven and encompasses nearly any approach that might enhance repair of the human body. The goal of regenerative medicine is to restore structure and function of human tissues not only damaged by injury but also by disease (*2*). Thus, the field is large, continues to grow, and carries with it the promise of revolutionary changes in clinical medicine. In the preface of his book *Regenerative Biology and Medicine*, David Stocum points out that there is almost no overlap between these two areas of regeneration research, and he proposes the obvious: If we are to move rapidly and effectively to modify human regenerative responses, these two fields need to join forces. This textbook, which targets an audience of beginning graduate and advanced undergraduate students, is the first step in working toward this very ambitious goal.

In chapter 1, Stocum sets the stage by outlining three mechanisms of injury-induced tissue regeneration: compensatory hyperplasia, activation of existing stem cells, and dedifferentiation to create stem cells (Fig. 1). These mechanisms are described in the context of an injury response in mature tissues consisting of multiple differentiated cell types along with reserve stem cells that function in normal cell replacement, a process Stocum calls maintenance regeneration (Fig. 1A). Compensatory hyperplasia (Fig. 1B), exemplified by the mammalian liver, involves a regeneration response in which differentiated cells respond to injury by proliferating to form additional differentiated cells; there is little involvement of undifferentiated progenitor cells, even though they exist in the tissue (*3*). A number of mammalian tissues, including bone, muscle, and epidermis, undergo regeneration to replace damaged tissues through the proliferation and differentiation of resident stem cells (Fig. 1C). In this case, stem cells are activated to proliferate and differentiate by injury, and most cell-based approaches to regenerative medicine are based on our understanding of this type of response (*4*). The final mechanism involves the dedifferentiation of adult cells to create a blastema of stem cells (*5*) (Fig. 1D). This is a mechanism that is largely restricted to lower vertebrates, such as amphibians, and is used during the regeneration of complex structures such as the limb and tail (*6*, *7*). It is this type of regenerative response (also called epimorphic regeneration) that Stocum has in mind as representing regenerative biology when he concludes that there is no overlap between the fields of regenerative biology and regenerative medicine.

Regeneration of adult tissues involves establishing a meaningful interface between the initial cellular response to injury (wound healing) and genetic programs that control embryonic development (*8*). For example, the blastema that forms during amphibian limb regeneration is equivalent to the developing limb bud (*9*), and outgrowth during regeneration is called "redevelopment" (*5*). Like wound healing and embryonic development, regeneration is regulated by cell-cell signaling; thus, it is appropriate that Stocum summarizes a number of signal transduction pathways currently known to play key roles in development, and reutilized during regeneration, to modulate such processes as proliferation, migration, adhesion, and redifferentiation. These pathways, which are briefly outlined at the end of chapter 1, include the Notch, Wnt, Hedgehog, receptor tyrosine kinase–mediated growth factor, transforming growth factor β, and JaK-STAT (Janus kinase-signal transducer and activator of transcription) signaling pathways. All of these signaling pathways are known to function in maintenance regeneration (by regulating stem cell renewal), whereas a subset has also been implicated in injury-induced regeneration. For example, Wnt, Notch, BMP (bone morphogenetic protein), and FGF (fibroblast growth factor) signaling pathways have been functionally linked to the control of regenerative responses in the limb and/or tail (*10*–*13*).

In chapters 1 and 2, Stocum develops a central theme for the book: The battle to regenerate is a war that is fought between the cells that have regenerative ability and those cells of the immune system that induce a fibrolytic response, which ultimately results in the production of scar tissues. Chapter 2 is devoted to the topic of mammalian wound healing of the skin, where inflammation-induced fibrosis in the dermis dominates the injury response while the epidermis successfully regenerates. The take-home message in this chapter is that injured human tissues have regeneration-competent cells, but their attempts at regeneration are compromised by fibrosis. Pitting regeneration against fibrosis is a theme that Stocum returns to in a number of chapters throughout the book, driving home the idea that induced regeneration not only involves the activation of competent cells but also repressing regeneration inhibitors.

The main part of the book (chapters 3 to 12) is an overview of the regenerative biology of different systems (odd-numbered chapters) alternating with chapters of regenerative medicine applied to the same systems (even-numbered chapters). Chapter 3 provides a glimpse of the epidermis and its derivatives, which are normally self-renewing and have some regenerative capabilities (for instance, hair, dental tissues, lens, and cornea), whereas the corresponding regenerative medicine chapter (chapter 4) is focused on approaches to enhance the regenerative potential of these tissues. Chapters 5 and 6 profile the regenerative biology and medicine of neural tissues; in this case, chapter 5 emphasizes regenerating systems in amphibian, fish, and mammalian

Department of Cell and Molecular Biology, Tulane University, New Orleans, LA 70118, USA. E-mail, kmuneoka@tulane.edu

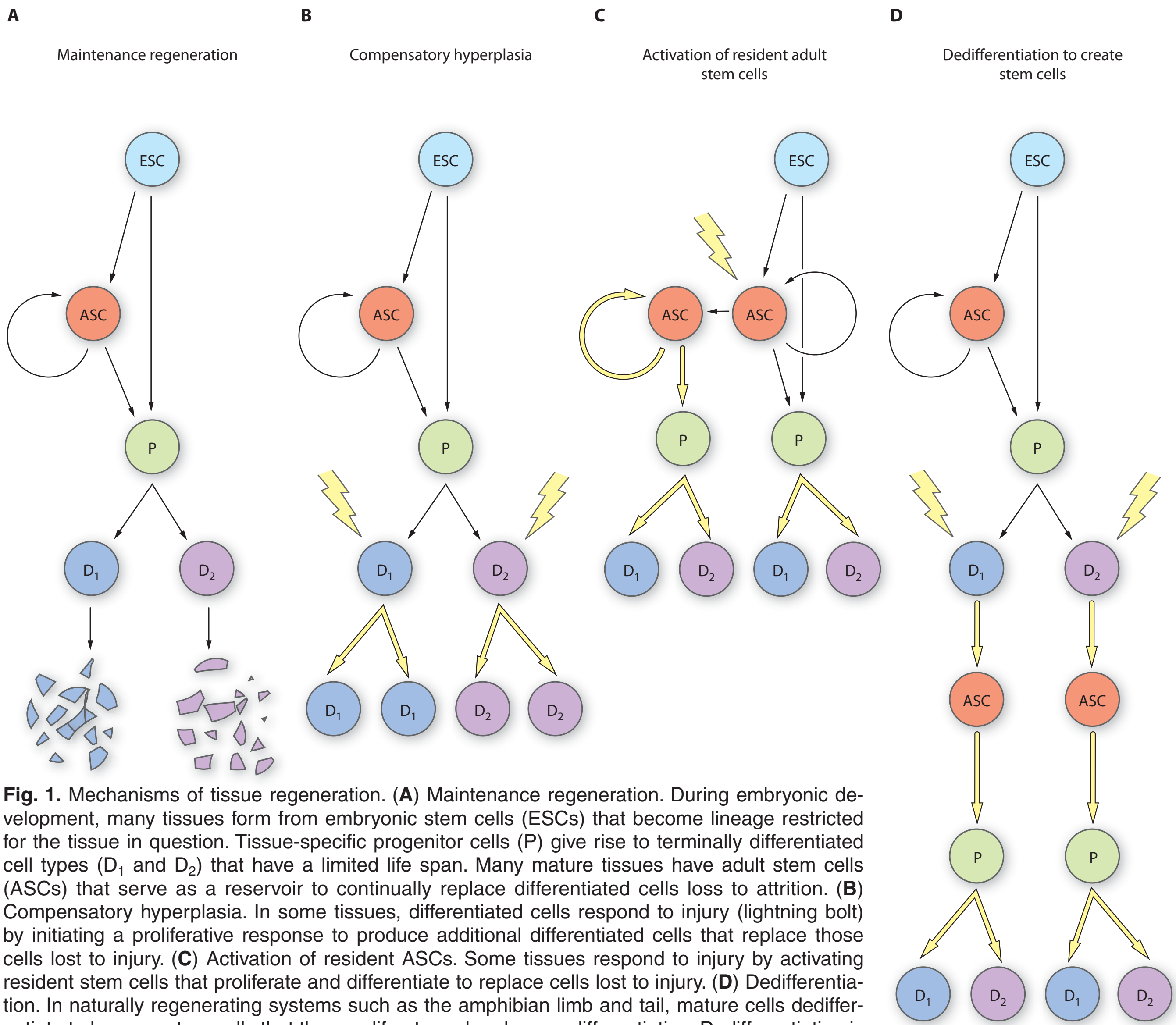

Fig. 1. Mechanisms of tissue regeneration. (**A**) Maintenance regeneration. During embryonic development, many tissues form from embryonic stem cells (ESCs) that become lineage restricted for the tissue in question. Tissue-specific progenitor cells (P) give rise to terminally differentiated cell types (D_1 and D_2) that have a limited life span. Many mature tissues have adult stem cells (ASCs) that serve as a reservoir to continually replace differentiated cells loss to attrition. (**B**) Compensatory hyperplasia. In some tissues, differentiated cells respond to injury (lightning bolt) by initiating a proliferative response to produce additional differentiated cells that replace those cells lost to injury. (**C**) Activation of resident ASCs. Some tissues respond to injury by activating resident stem cells that proliferate and differentiate to replace cells lost to injury. (**D**) Dedifferentiation. In naturally regenerating systems such as the amphibian limb and tail, mature cells dedifferentiate to become stem cells that then proliferate and undergo redifferentiation. Dedifferentiation is the reprogramming of adult cells toward an embryonic state.

systems, whereas the focus in chapter 6 switches to a summary of clinical approaches to treating spinal cord injury and neurodegenerative diseases. Chapters 7 and 8 focus on the tissues of the digestive, respiratory, and urogenital systems, which respond to injury by compensatory hyperplasia but under some conditions undergo regeneration involving stem cell activation as well. Chapters 9 and 10 describe the regeneration of musculoskeletal tissues in mammals, which regenerate injured tissues by means of tissue-specific stem cells. The hematopoietic system and cardiovascular tissues are covered in chapters 11 and 12. Regenerative medicine has been most successfully applied to the hematopoietic system; much of this success can be attributed to the identification and characterization of the hematopoietic stem cell (HSC). An understanding of HSCs provides a comparative platform to address issues such as cell enrichment, cell survival, effectiveness of cell source, and genetic intervention, allowing the therapy to be fine-tuned to maximize success rate. Rapid advances in regenerative medicine of the hematopoietic system can, in part, be attributed to the fluid nature of the system that separates physiological function from any anatomical constraints. Attaining a similar level of success in other systems where physiological function is tied to anatomical considerations will be significantly more challenging. One comment about the general organization of these chapters is that, because information about the regeneration biology versus regenerative medicine of specific organ systems is broken up between two chapters, I found myself having to search through the regenerative biology chapter to remind myself of essential information needed to fully understand selected topics in regenerative medicine. Nevertheless, these chapters contain a wealth of information that touches on the regenerative capacity of multiple systems, along with different approaches that target clinical application.

Chapters 13 and 14 address individual topics that are potentially relevant to all areas of regenerative biology and medicine.

In chapter 13, Stocum tackles the issue of pleuripotency of adult stem cells and their potential for replacing embryonic stem cells as a general source for clinical cell therapies. In a section titled "Adult Stem Cell Pluripotency: Fact or Fiction," Stocum concludes:

> Overall, the verdict is that unless the frequency can be increased significantly, lineage conversion of a single ASC (adult stem cell) type will not be a viable approach for cell therapies designed to replace damaged tissue.

This conclusion seems overly negative given that research into adult stem cells is still in its infancy and that there is much to be learned about the different populations of stem cell present (*14*), as well as the array of factors important for inducing, maintaining, and expanding lineage-converted cells. The fact that pleuripotency of adult cells exists at all represents a starting point to develop our understanding for how to direct these cells toward distinct fates (*15*).

Chapter 14 profiles an in-depth review of limb regeneration in amphibians; this is an amazing process that has been intensely studied and is Stocum's area of expertise. In the introduction, Stocum points out that this chapter is an updated version of his own recent review articles and, sadly, it reads as such. This chapter provides an overview of limb regeneration but makes little effort to integrate fundamental concepts that lie at the heart of regeneration biology in the context of current approaches to regenerative medicine that are largely stem cell driven. For example, how do stem cells at a wound site gain the information they need to know what structures need to be regenerated? The answer to this question is critically important for the future of regenerative medicine and has been addressed in regeneration biology (*16*).

Stocum sums things up in a final chapter entitled "Research Issues in Regenerative Medicine." He returns to three strategies of regenerative medicine that were briefly introduced in chapter 1—cell transplantation, bioartificial tissues, and induction of regeneration in situ—and discusses some of the practical challenges encountered in applying these strategies to regenerative medicine, for instance, defining an appropriate cell source, expansion of the appropriate cells to achieve a therapeutic dose, inducing vascularization of bioartificial tissues, and so on. The book ends with a colorful discussion of bioethical issues with references to Mary Shelley's novel *Frankenstein* and H. G. Wells' story *The Island of Dr. Moreau*, bringing a sober reality to how sensitized the public might be in its response to successes in regenerative medicine.

Overall, this is a seminal contribution that will influence new, as well as seasoned, members of the regeneration field. Hopefully, this book will serve as a seed to initiate conceptual cross-talk between those actively involved in the biology of regeneration and those targeting its clinical application. For my part, I value the availability of an excellent reference textbook that offers an updated review of a diverse array of regeneration efforts, and this text will be forever on my bookshelf. For anyone contemplating a move into this field, Stocum's book is a good place to start.

References

1. C. E. Dinsmore, *A History of Regeneration Research* (Cambridge Univ. Press, Cambridge, 1991).
2. I. V. Yannas, *Regenerative Medicine II* (Springer-Verlag, Berlin, 2005).
3. M. H. Walkup, D. A. Gerber, Hepatic stem cells: In search of. *Stem Cells* **24**, 1833–1840 (2006).
4. C. A. Gregory, J. Ylostalo, D. J. Prockop, Adult bone marrow stem/progenitor cells (MSCs) are preconditioned by microenvironmental "niches" in culture: A two-stage hypothesis for regulation of MSC fate. *Sci. STKE* **2005**, pe37 (2005).
5. S. V. Bryant, T. Endo, D. M. Gardiner, Vertebrate limb regeneration and the origin of limb stem cells. *Int. J. Dev. Biol.* **46**, 887–896 (2002).
6. P. A. Tsonis, *Limb Regeneration* (Cambridge Univ. Press, Cambridge, 1996).
7. D. L. Stocum, *Wound Repair, Regeneration, and Artificial Tissues* (R. G. Landes, Austin, TX, 1995).
8. M. Han, X. Yang, G. Taylor, C. A. Burdsal, R. A. Anderson, K. Muneoka, Limb regeneration in higher vertebrates: Developing a roadmap. *Anat. Rec. B New Anat.* **287**, 14–24 (2005).
9. K. Muneoka, S. V. Bryant, Evidence that patterning mechanism in developing and regenerating limbs are the same. *Nature* **298**, 369–371 (1982).
10. M. Han, X. Yang, J. E. Farrington, K. Muneoka, Digit regeneration is regulated by Msx1 and BMP4 in fetal mice. *Development* **130**, 5123–5132 (2003).
11. C. W. Beck, B. Christen, J. M. Slack, Molecular pathways needed for regeneration of spinal cord and muscle in vertebrate. *Dev. Cell* **5**, 429–439 (2003).
12. Y. Kawakami, C. Rodriguez Esteban, M. Raya, H. Kawakami, M. Marti, I. Dubova, J. C. Izpisua Belmonte, Wnt/beta-catenin signaling regulates vertebrate limb regeneration. *Genes Dev.* **20**, 3232–3237 (2006).
13. G. P. Taylor, R. Anderson, A. D. Reginelli, K. Muneoka, FGF2 induces regeneration of the chick limb bud. *Dev. Biol.* **163**, 282–284 (1994).
14. F. Anjos-Afonso, D. Bonnet, Nonhematopoietic/endothelial SSEA-1+ cells define the most primitive progenitors in the adult murine bone marrow mesenchymal compartment. *Blood* **109**, 1298–1306 (2007).
15. A. J. Engler, S. Sen, H. L. Sweeney, D. E. Discher, Matrix elasticity directs stem cell lineage specification. *Cell* **126**, 677–689 (2006).
16. D. M. Gardiner, Ontogenetic decline of regenerative ability and the stimulation of human regeneration. *Rejuvenat. Res.* **8**, 141–153 (2005).

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