

Preface

The last decade has witnessed significant progress in understanding the organization and regulation of regenerative cells in the adult lung. The development and refinement of multiparameter flow cytometric cell sorting protocols and *in vitro* clonogenic assays has enabled the identification, prospective isolation, and characterization of candidate adult lung stem and progenitor cells. Powerful gene labelling technologies, cell lineage tracing and cell fate mapping protocols, and genetically engineered mouse models have revealed critical regulatory molecules, mechanisms, pathways, and cellular interactions important in building the lung during fetal development; and in maintaining lung function and rebuilding the lung in adulthood. This in turn has advanced the understanding of the pathophysiology of lung diseases; and how endogenous lung stem and progenitor cells, exogenous stem cells, and bioengineering technologies might be harnessed to attenuate or reverse intractable, life-threatening respiratory diseases.

This is the more remarkable considering that until relatively recently the lung was generally considered a conditionally renewing organ with limited growth potential and regenerative capacity in adult life [1, 2]. Why this paradigm remained so entrenched for so long is puzzling given compelling lung cell kinetic analysis that showed that lung epithelium was continuously replaced, albeit at a very slow rate overall, that could only be explained by continuous renewal [3, 4] of postulated subsets of cells with much higher rates of turnover than the average for the organ [5]. This failure to fully appreciate that the extremely slow turnover of cells in the adult lung was not inconsistent with the existence of continuously renewing endogenous lung stem and progenitor cells able to replace senescent cells in the steady state, and regenerate functional lung cell lineages lifelong following insult or injury “blinded” the field to the potential of stem cells as therapeutic targets for adult lung regeneration and repair. Rather, research predominantly focused on understanding the pathophysiology of intractable lung diseases, and on the development of essentially palliative pharmacologic interventions to resolve inflammation and attenuate fibrotic responses induced by infectious agents, toxicants, or injury. This bias is patently obvious on interrogation of the Pubmed database as of May

7, 2015. Whereas 185,890 publications were retrieved using the search term “lung inflammation OR lung fibrosis,” only 6688 publications were retrieved using the search term “lung stem cell OR lung progenitor cell,” and 3228 using the search term “lung regeneration.” Comparison with an archetypal continuously renewing stem cell hierarchy is also illustrative in this context, showing that 87,492 publications were retrieved in the same period using the search term “hematopoietic stem cell OR hematopoietic progenitor cell.”

Interest in the potential of stem cell-based therapies in lung regenerative medicine was initially motivated by studies in the early 2000s purporting to show that various adult and embryonic stem cell populations could be respecified or reprogrammed to express lung epithelial cell lineage markers when cultured in defined media, or engrafted in the lung. Concurrently, various research groups intensified their efforts to develop best-practice tools, assays, and models to identify, isolate, and characterize endogenous adult lung stem and progenitor cells, determine their spatial location(s) in the airway, and assess their regenerative potential. In particular, these studies aimed to determine whether the organization and regulation of these putative stem and progenitor cell compartments conformed with, or deviated from, the organization of classical continuously renewing stem cell hierarchies [6].

The reductionist approach was predominantly concerned with determining and defining the intrinsic properties of adult lung epithelial stem and progenitor cells. But, according to the niche hypothesis first articulated by Schofield in 1978 [7], “stemness” is determined by anchorage of the stem cell to a complex and malleable anatomical niche comprising a matrix scaffold, adhesion molecules, soluble and insoluble factors, and contiguous fixed and circulating cells which engage in crosstalk with the stem cell to specify its fate and constrain its proliferation and differentiation. The importance of these critical niche interactions, and mesenchymal–epithelial crosstalk in particular, have long been appreciated in lung developmental biology, and are likely recapitulated in regeneration and repair of the adult lung [8]. The analysis of mesenchymal–epithelial interactions has also long been a major focus of research in the pathogenesis of fibrosis and airway remodeling in intractable lung diseases such as allergy and asthma [9]. However, the lung is a complex organ comprising as many as 60 cell lineages and less is known about the role of interactions of many of these diverse cell lineages with lung epithelial stem and progenitor cells, and with each other, in regulating lung development and in maintaining, regenerating, and repairing the lung in adulthood. Significant advances have recently been made in understanding the process of vasculogenesis and angiogenesis in the lung, and in the crosstalk with lung epithelial cells. In comparison, the important role of neuronal cells in the regulation of lung development, and in lung regeneration and repair is less well determined and a worthy and fertile subject of further study.

This monograph presents a comprehensive overview of the current understanding of the organization and regulation of endogenous lung stem and progenitor cell compartments during fetal and perinatal lung development, and in the adult and ageing lung. The chapters on fetal lung development aim to elucidate the integrated

role of epithelial, stromal, vascular, and neural cell elements in building a functional lung. These chapters provide a basis for identifying critical factors and pathways regulating lifelong lung regeneration and repair, and understanding the fetal and neonatal origin of lung disease. The chapters on adult lung regeneration describe the organization and properties of epithelial stem and progenitor cell compartments distributed along the proximal–distal axis of the airway tree and how they are affected with age. The chapters on lung regeneration and repair describe the role of crosstalk between regenerative cells and cellular and biomatrix elements of their niche in the adult lung in maintaining organ integrity in the steady state, and regulating lung regeneration.

The chapters on cellular therapies for lung disease provide an overview of emerging therapies utilizing exogenous mesenchymal stromal cells, and vascular endothelial cells to repair the diseased lung; and also review studies in animal models exploring the potential of pluripotent stem cells in lung regenerative medicine. The monograph concludes with an overview of recent progress in lung bioengineering describing the challenges in engineering acellular biomatrix scaffolds to replace damaged or diseased airways, or reconstruct a functional lung *ex vivo*.

It remains for me to thank the many authors at the cutting-edge of the field who enthusiastically contributed the lucid and authoritative chapters in this volume. I also thank Kursad Turksen (Series Editor) for the invitation to edit this volume; and acknowledge Brian Halm and Aleta Kalkstein and their team at Springer for their advice and assistance in developing and preparing this volume for publication.

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Stem Cells in the Lung

Development, Repair and Regeneration

Bertoncello, I. (Ed.)

2015, XIV, 366 p., Hardcover

ISBN: 978-3-319-21081-0