Advances in Experimental Medicine and Biology

Volume 1186

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Pluripotent Stem Cells in Eye Disease Therapy

Springer

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ISSN 0065-2598 ISSN 2214-8019 (electronic)
Advances in Experimental Medicine and Biology
ISBN 978-3-030-28470-1 ISBN 978-3-030-28471-8 (eBook)
https://doi.org/10.1007/978-3-030-28471-8

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

Preface

Stem cells have an inherent ability to regenerate tissues and organs and because of this property they constitute the core of the field of regenerative medicine. However, stem cells alone are not sufficient to bring a regenerative medicine to patients. They must be combined with other areas of biology including but not limited to tissue engineering, bioengineering, drug discovery, immunology, and surgical approaches. I have focused this book on several of these aspects of regenerative medicine by presenting examples of various interdisciplinary science currently being used for one common goal – regeneration of the entire human body.

This book mainly focuses on examples demonstrating the use of pluripotent stem cells and associated technologies in ocular research. For me, there is no better topic than eye research to provide excellent examples of research progressing in the field of regenerative medicine. The ocular research community has been at the forefront of regenerative medicine research for decades: one of first tissues successfully differentiated from pluripotent stem cells is an eye tissue - the retinal pigment epithelium; the first FDA approved gene therapy is for a monogenic childhood form of retinal degeneration; and the first cell therapy trials conducted using embryonic and induced pluripotent stem cell derived therapies are for age-related macular degeneration, a blinding eye disease. All of this happened by no accident. Various factors have contributed towards the success of regenerative medicine research in the eye: (1) blinding diseases are some of the most prevalent and devastating disorders often afflicting children and depriving patients of one of the most critical senses required to communicate with the outside world. This has led to a major push in the scientific community to develop new treatments for eye diseases; (2) several genes and gene mutations affect the eye without major effects on organismal survival. Because of this several gene mutations have accumulated that affect vision but not the overall patient health. This has sparked scientific curiosity about the role of those genes and mutations and in developing treatments for associated disorders; (3) eye is an easily accessible organ. Because of this several surgical interventions and follow up techniques have been tested and discovered over the years. All of this technology is now helping bring new regenerative medicines to patients; (4) eye is an easily accessible part of the brain, exciting neuroscientists to work on the eye. Because of all these

reasons, regenerative medicine of the eye has always gained significant attention. I have planned chapters of this book to highlight some of these factors that have contributed to the success of regenerative medicine in the eye.

I would like the readers of this book, the next generation of scientists and physicians, to appreciate the breath of research that is being conducted around the topic of regenerative medicine and the kind of research that is required to bring successful treatments to patients. Some of my favorites examples include: how patient derived iPS cells are being used to learn more about monogenic diseases but then that knowledge is applied to polygenic diseases that are not easy to study using any other model system; how evolutionary conserved immune responses regulate inflammation in the eye and control immune-response against allogeneic stem cell derived cells; combining bioprinting with stem cell technology to develop complex 3D tissues that provide a native-like environment for both disease modeling and drug testing; and co-evolution of stem cell based therapies and the surgical approaches to bring such stem cell based therapies to patients.

The time is right for such a book, because regenerative medicine is at a crossroads right now where the full potential of stem cells has been realized. Scientists are trying to harness this potential by using a multi-disciplinary approach towards solving the most fundamental problems in biology and to perform the most cutting-edge discoveries in this space. It is critical for the next generation of scientist to understand what approach is currently being adopted to bring the latest regenerative treatments to patients..

Regenerative medicine is a constantly growing field. New discoveries are happening every day. One major limitation of this book, which is perhaps a limitation for every such book, is to stay up to date with the most recent discoveries happening in the field. It took more than a year to complete this book and even though all authors did their best to continually update their chapters, it is highly likely that some of the most recent advances have not been mentioned in this book. But the purpose of this book is not to describe the latest discoveries. My goal with this book is to develop a succinct document that provides a global overview of the field and a reference document for understanding how stem cells can be used to decipher pathways involved in eye diseases and to develop treatments for such eye diseases.

For the successful completion of this work, I would like to thank all the authors who have provided their outstanding chapters. These authors have summarized their own work and the work of others. Therefore, it is only appropriate for me to extend my thanks to all of their labs and to other researchers who have spent countless hours for all the discoveries and inventions that have formed the very basis of this book. I would especially like to thank all the scientists whose vision and hard work gave birth to the field of regenerative medicine and all the associated fields. Most of all, my gratitude goes to patients who altruistically donated samples and their time for research that went into this book.

Last but not least, I would like to thank the editorial staff of Springer publisher for their help and patience (with me) while we tried to complete this work.

Bethesda, MD, USA Kapil Bharti

Introduction

Developmental biologists have long known about the ability of pluripotent stem cells to differentiate into various cell types. These early observations led to a quest that led to successful culture of mouse embryonic stem (ES) cells and coining of the term ES cells in the year 1981 by Gail Martin. This discovery completely revolutionized the scientific approach towards understanding of gene function. Scientists were able to generate transgenic mice with a gene specific knockout to better investigate gene function, to identify phenotypes associated with specific gene knock out and correlate them with patient phenotype associated with specific diseases. Perhaps even more relevant discovery for human biology was the discovery of human embryonic stem cells by Jamie Thompson in the year 1998. This advancement for the first-time allowed scientists to make human tissues in a dish and to study human developmental biology in vitro. The scientific community also realized the potential of human ES cells to provide replacement tissues as treatments for degenerative diseases. This formed a new field of regenerative medicine with a focus on replacement tissues.

In parallel another scientific endeavor was ongoing to better understand the biology of ES cells. Scientists were trying to convert a somatic human cell into an ES-like cells. This work was originally sparked by a 50 years old observation by Sir John Gurdon, who had demonstrated that the cytoplasm of an egg was sufficient to reprogram the nuclear genome of a somatic cell such that the derived cell could now behave like an ES cell. The work led by Dr. Thompson and Dr. Yamanaka led to the discovery of human induced pluripotent stem (iPS) cells: ES-like cells derived from any somatic cell of the body with the capability to differentiate into any other cell or tissue type of the body. This work was even more exciting for the scientific community because it allowed scientist to develop patient specific cells and tissues in vitro and investigate disease pathogenesis in a dish. Furthermore, it provided a possibility of developing autologous cell therapies that might get around the immune-rejection concerns associated with ES cell derived cell therapies. Discoveries of both ES cells and iPS cells have led to major breakthroughs in different aspects of regenerative medicine. This book focuses on such breakthroughs with highlights of both the disease-in-a-dish and the cell therapy aspect of pluripotent stem cells.

The main emphasis of the book is on the use of stem cells in retina research as remarkable progress has occurred in various aspects of eye research using pluripotent stem cells. The three main retinal cell types that have been successfully derived from both ES cells and iPS cells are the retinal pigment epithelium (RPE), the light sensing photoreceptors, and the retinal ganglion cells. RPE is a monolayer of pigmented epithelial cells, located in the outer retina. It is a polarized tissue with specialized microvilli located towards its apical side and a proteinaceous membrane called the Bruch's membrane towards its basal side. RPE interacts with photoreceptor outer segments via its microvilli and performs several functions to maintain health and integrity of photoreceptors throughout its life. RPE also forms the outer blood retina barrier and regulates nutrient and metabolite flow between the choroidal blood supply on its basal side and photoreceptors on its apical side. RPE dysfunctions lead to choroidal atrophy and photoreceptor cell death leading to vision loss.

Photoreceptors are the main light sensing unit of the retina. There are two main types of photoreceptors: rods and cones. Rods are primarily responsible for dim light vision and cones are responsible for bright light and central vision. Rhodopsin and cone opsins located in the outer segments of these two photoreceptor cell types absorb light photons and transmit those signals to the interneurons of the retina. Through the interneurons, electrical signals are transmitted to retinal ganglion cells (RGCs). RGCs are one of the main neuronal cell types of the retina that carry electrical signals to the visual cortex of the brain where the electrical signal is converted into an image. Different types of RGCs carry signals from different areas of the retina, thus regulating dim light and bright light responses.

Clearly, all three cell types are quint-essential for vision and some of the most prevalent blinding eye disease are associated with degeneration of these three cell types. Successful RPE differentiation from stem cells was achieved a few years before the differentiation of photoreceptors and other cell types of the retina. Overtime researchers have further optimized the RPE differentiation protocols developing RPE monolayer as a functionally validated fully polarized and mature tissue derived from both ES and iPS cells. This has allowed researchers to develop relevant disease models and cell therapies using stem cell derived RPE cells. These advances are reflected in three chapters that are focused on the RPE. Photoreceptor and retinal ganglion cell differentiation initially started in 2D cultures but with seminal discoveries of late Dr. Yoshiki Sasai 3D retinal organoid cultures were also established. Current efforts in the photoreceptor field utilizes both 2D and 3D cultures. However, in neither culture methods researchers have been successful in developing fully polarized photoreceptors that contain opsin protein harboring outer segments or demonstrate light responses similar to what is seen in the native retina. This has limited the use of stem cell derived photoreceptors in disease modeling. But efforts continue in the photoreceptor transplantation field because the thinking is that transplanted photoreceptors will continue to mature when present in the in vivo eye environment. RGC research community has been able to develop neurons that contain several key RGC markers and demonstrate an action potential. This has allowed researchers to simulate RGC diseases using

patient specific iPS cells. The importance of these three cell types for vision has long stimulated vision researchers to study their basic developmental biology, to explore disease-inducing pathways, and to develop cell therapies to replace degenerated cells in the eye. This book covers research performed in all these areas on all three cell types. In fact, it goes beyond the work directly performed on these cell types and covers advanced tissue engineering approaches used by stem cell researchers to develop 3D eye tissues containing a capillary network and provides a more native-like environment to study tissue-tissue interaction under healthy and diseased conditions. The book also provides a discussion on surgical approaches that have been developed to transplant cell therapies in the eye. A brief synopsis of all the chapters is provided below.

The first chapter by Dalvi et al presents a "classical" use of iPS cell technology for disease-in-a-dish approach focusing on inherited forms of retinal degenerative diseases. One of the key requirements for developing in vitro disease models is the ability to develop functionally validated RPE cells from iPS cells. Authors discuss various human disease models that have been developed using patient-derived iPS cells and discoveries performed using such human disease models both for better understanding of disease pathogenesis and for discovering potential treatments that can be brought back to patients. Authors also address the potential of stem cells for better understanding of more complex diseases such as age-related macular degeneration.

The second chapter by Greene et al demonstrates an application for stem cell derived wild type cells in studying the fundamental biology of RPE cells. Authors use pluripotent stem cell derived RPE cells to better understand the epithelial phenotype of these cells. Loss of RPE epithelial phenotype associated with eye injuries leads to a condition called proliferative vitreoretinopathy (PVR). Authors present an in vitro PVR model developed using iPS cell derived RPE cells, and also discuss high throughput screens that can be performed using iPS cell derived primary cells.

The third chapter by Ben M'Barek et al covers an important topic of stem cell derived cell therapies. Authors discuss in depth how functionally validated RPE cells are differentiated from ES and iPS cells and used to develop cell therapies for retinal degenerative diseases. Currently, two approaches are being tested to deliver RPE cell therapy in the eye: cells in suspension and cells on a scaffold. Authors discuss differences between these two approaches and how synthetic and natural scaffolds are used to develop an RPE-patch for transplantation. Furthermore, they discuss preclinical efficacy data from animal models used to demonstrate functionality of RPE cell therapies and also discuss preliminary safety data from ongoing human trials using stem cell derived RPE.

The fourth chapter by Kramer et al focuses on photoreceptor-based cell therapies and challenges faced during ES or iPS cell derived photoreceptors transplantation in preclinical animal models. Authors discuss challenges with the integration of transplanted photoreceptors in the host retina and the role played by the host retina microenvironment and the immune system in transplant survival and integration. Authors describe genetic and immune modulatory strategies to overcome the immune response against stem cell derived photoreceptors in an allogeneic host.

The success of this work will help bring stem cell-based treatments to a large number of patients.

The fifth chapter by Ohlemacher et al deals with vision restoration downstream of photoreceptors in retinal ganglion cells. These authors explain how functionally authentic RGCs have been differentiated from ES and iPS cells. They discuss gene expression and electrophysiology readouts used to validate ES or iPS cell derived RGCs. Furthermore, authors review advances in developing optic neuropathy and glaucoma disease models using stem cell derived RGCs, approaches used to discover potential new drugs using stem cell derived RGCs, and an ambitious future challenge to develop a cell therapy to replace degenerated RGCs.

The sixth chapter by Stanzel et al highlights a critical example of associated technologies that must be developed to successfully bring stem cell-based therapies to patients. Here authors demonstrate elegant methods that have been developed to transplant stem cell derived RPE cells in suspension, RPE-monolayer patch, photoreceptors, and retinal sheet grafts. Surgeons are trying such transplants through the front of the eye (going through the vitreous) or the back of the eye (going through the sclera). Authors also discuss various preclinical animal models, their advantages and disadvantages for developing surgical techniques for transplantation in the eye.

The seventh chapter by Boutin et al discusses a next generation technology that combines different stem cell derived cells with bioprinting technology to develop a 3D RPE/choroid tissue. Authors discuss how iPS cell derived endothelial cells when bioprinted on one side of a scaffold are capable of forming a capillary network. This capillary network interacts with the RPE monolayer that is grown on the other side of a scaffold. Similar to the native RPE/choroid, the in vitro 3D choroid tissue depends on the RPE for its survival. Authors demonstrate that this 3D tissue can be used to develop advanced 3D models for complex diseases like AMD. This work shows the power of stem cell technologies when combined with tissue engineering.

The work presented in this book summarizes state-of-the art eye research that is being conducted world-wide using stem cells. The success of this work will lead to improved understanding of human eye development and of diseases that affect the eye. Furthermore, this work will lead to the development of potential therapies to treat these blinding eye diseases.

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