Stem Cell Biology and Regenerative Medicine

Essam M. Abdelalim *Editor*

Recent Advances in Stem Cells

From Basic Research to Clinical Applications

Humana Press

Essam M. Abdelalim
Editor

Recent Advances in Stem Cells

From Basic Research to Clinical Applications

Humana Press

Editor
Essam M. Abdelalim
Qatar Biomedical Research Institute
Hamad Bin Khalifa University
Doha, Qatar

ISSN 2196-8985 ISSN 2196-8993 (electronic)
Stem Cell Biology and Regenerative Medicine
ISBN 978-3-319-33268-0 ISBN 978-3-319-33270-3 (eBook)
DOI 10.1007/978-3-319-33270-3

Library of Congress Control Number: 2016943088

Printed on acid-free paper

This Humana Press imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

Stem Cell Biology and Regenerative Medicine

Series Editor
Kursad Turksen, Ph.D.
kursadturksen@gmail.com

More information about this series at http://www.springer.com/series/7896

Preface

Stem cells, including pluripotent stem cells (PSCs) and adult stem cells (ASCs), have the ability to differentiate into several cell types, raising the hope for potential understanding and treating incurable human diseases. Despite the short history of human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs), they are already in clinical trials for some diseases, suggesting a considerable progress in the field of PSCs. The discovery of iPSC technology as well as the recent success in establishment of ESCs using somatic cell nuclear transfer (SCNT) has allowed for the generation of PSCs from somatic cells and has led to the production of in vitro patient-specific PSCs, which have several applications, such as in vitro modeling of different diseases, drug screening, and eventually providing a personalized medicine. On the other hand, ASCs have been in research use for more than 50 years and have been discovered in many organs and tissues. ASCs such as hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) have been used for transplantation-based therapies for several years. Recently, our knowledge about ASCs has greatly expanded, and there is an increased interest in their use as a therapy for certain diseases, such as blood disorders and repair of cartilage and bone defects.

This volume in the important Springer series of cutting-edge contributions in stem cell research represents a collection of chapters, focusing on some of the important topics currently being addressed in stem cell field. hESCs have a great therapeutic potential. However, there are controversies surrounding their use in research because their generation includes the human embryo destruction. This issue and others related to ethics and patents in stem research are covered in Chapter One. Stem cells can differentiate into different cell types, allowing screening and testing new drugs. This topic is covered in details in Chapter Two. Chapter Three discusses a genome editing technology, which has recently attracted more attention in the stem cell field, particularly modifying genomes in patient-specific iPSCs for disease modeling and transplantation therapy. Chapters Four and Five describe the potential use of PSCs for modeling of kidney and motor neuron diseases. The recent progress in the differentiation of PSCs into functional

pancreatic β cells in vitro as well as their use to model and treat different forms of diabetes is also covered in Chapter Six. Furthermore, how iPSCs are clinically applied in cancer is discussed in Chapter Seven. There are several chapters about ASCs. Chapter Eight summarizes the current knowledge on banking of umbilical cord blood stem cells. Chapters Nine and Ten discuss the use of MSCs for bone repair and their cellular interactions during fracture repair stages. Furthermore, the applications of neural crest stem cells are highlighted and summarized in Chapter Eleven. Finally, the recent progress in lung stem cell research is discussed in Chapter Twelve. The chapters were written by world-renowned scientists in the field of PSCs and ASCs, presenting cutting-edge studies of interest to academics, physicians, and readers with general interests in the stem cell and regenerative medicine fields. Thus, this book is valuable for a broad audience.

I would like to extend my gratitude to the authors, who contributed chapters in this volume. I would also like to thank Kursad Turksen (Series Editor) for inviting me to edit this volume. I would like to express my appreciation to Aleta Kalkstein and Michael Koy (at Springer) for assisting me to complete this project.

Doha, Qatar Essam M. Abdelalim

Contributors

Basem M. Abdallah Molecular Endocrinology Laboratory (KMEB), Department of Endocrinology, Institute of Clinical Research, Odense University Hospital and University of Southern Denmark, Odense, Denmark

Department of Biological Sciences, College of Science, King Faisal University, Hofuf, Saudi Arabia

Essam M. Abdelalim Qatar Biomedical Research Institute, Hamad Bin Khalifa University (HBKU), Qatar Foundation, Doha, Qatar

Abdullah AlDahmash Molecular Endocrinology Laboratory (KMEB), Department of Endocrinology, Institute of Clinical Research, Odense University Hospital and University of Southern Denmark, Odense, Denmark

Stem Cell Unit, Department of Anatomy, Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia

Asma Al-Shammary Molecular Endocrinology Laboratory (KMEB), Department of Endocrinology, Institute of Clinical Research, Odense University Hospital and University of Southern Denmark, Odense, Denmark

Deanship of Scientific Research, University of Hail, Hail, Saudi Arabia

Tomoko Betsuyaku Division of Pulmonary Medicine, Department of Medicine, Keio University School of Medicine, Tokyo, Japan

Delphine Bohl French Institute of Health and Medical Research, Sorbonne University Paris, Brain and Spine Institute, France

Liuhong Cai Center for Reproductive Medicine, The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Elina Davé Union College, Schenectady, NY, USA

Neil Davey Harvard University, Cambridge, MA, USA

Sonya Davey Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Ahmed El-Hashash Stem Cells, Regenerative Medicine and Developmental Biology Program, Children's Hospital Los Angeles, Keck School of Medicine and Ostrow School of Dentistry, University of Southern California, Los Angeles, CA, USA

Jehan J. El-Jawhari Leeds Institute of Rheumatic and Musculoskeletal Medicine, St. James University Hospital, University of Leeds, Leeds, UK

NIHR, Leeds Biomedical Research Unit, Chapel Allerton Hospital, University of Leeds, Leeds, UK

Mohamed M. Emara Qatar Biomedical Research Institute, Hamad Bin Khalifa University (HBKU), Qatar Foundation, Doha, Qatar

Cecília de Souza Fernandez Institute of Mathematics and Statistics, Federal Fluminense University (UFF), Niterói, RJ, Brazil

Teresa de Souza Fernandez Laboratory Division, National Cancer Institute (INCA), Bone Marrow Transplantation Center (CEMO), Rio de Janeiro, RJ, Brazil

Peter V. Giannoudis Leeds Institute of Rheumatic and Musculoskeletal Medicine, St. James University Hospital, University of Leeds, Leeds, UK

NIHR, Leeds Biomedical Research Unit, Chapel Allerton Hospital, University of Leeds, Leeds, UK

Navin R. Gupta Division of Renal Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Ahmed E. Hegab Division of Pulmonary Medicine, Department of Medicine, Keio University School of Medicine, Tokyo, Japan

Yoon-Young Jang Department of Oncology and Institute for Cell Engineering, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Dunia Jawdat Cord Blood Bank, King Abdullah International Medical Research Center (KAIMRC), King Saud bin Abdulaziz University for Health Sciences, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia

Eui-Bae Jeung Laboratory of Veterinary Biochemistry and Molecular Biology, College of Veterinary Medicine, Chungbuk National University, Cheongju, Chungbuk, Republic of Korea

Elena Jones Leeds Institute of Rheumatic and Musculoskeletal Medicine, St. James University Hospital, University of Leeds, Leeds, UK

NIHR, Leeds Biomedical Research Unit, Chapel Allerton Hospital, University of Leeds, Leeds, UK

Hee Young Kang Laboratory of Veterinary Biochemistry and Molecular Biology, College of Veterinary Medicine, Chungbuk National University, Cheongju, Chungbuk, Republic of Korea

Moustapha Kassem Molecular Endocrinology Laboratory (KMEB), Department of Endocrinology, Institute of Clinical Research, Odense University Hospital and University of Southern Denmark, Odense, Denmark

Stem Cell Unit, Department of Anatomy, Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia

Hany M. Khattab Department of Oral Implantology and Regenerative Dental Medicine, Tokyo Medical and Dental University, Tokyo, Japan

Albert Q. Lam Division of Renal Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Harvard Stem Cell Institute, Cambridge, MA, USA

Dennis McGonagle Leeds Institute of Rheumatic and Musculoskeletal Medicine, St. James University Hospital, University of Leeds, Leeds, UK

NIHR, Leeds Biomedical Research Unit, Chapel Allerton Hospital, University of Leeds, Leeds, UK

André Luiz Mencalha Laboratory of Cancer Biology (LABICAN), State University of Rio de Janeiro (UERJ), Roberto Alcantara Gomes Biology Institute (IBRAG), Rio de Janeiro, RJ, Brazil

Na Xu George Washington University School of Law, Washington, DC, USA

Zhaohui Ye Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

About the Editor

Essam M. Abdelalim is a Scientist at Qatar Biomedical Research Institute (QBRI) in Doha, Qatar, and an Assistant Professor at Hamad Bin Khalifa University (HBKU) in that city. He is also Associate Professor at the Suez Canal University in Ismailia, Egypt, where he received his B.Sc. degree and his M.Sc. degree. He received his Ph.D. in Medical Science from Shiga University of Medical Science in Otsu, Japan, and was later appointed Assistant Professor at that university. Dr. Abdelalim was awarded a Postdoctoral Fellowship from the Japan Society for Promotion of Science, where he studied the roles of natriuretic peptides and p53 in the regulation of self-renewal, pluripotency, and differentiation of embryonic stem cells (ESCs).

Dr. Abdelalim's research interests focus on understanding the molecular mechanisms controlling unique characteristics of pluripotent stem cells (PSCs) and establishing their differentiation into specific cell types. His current research focuses on the potential use of PSCs to study diabetes, insulin resistance, and pancreatic beta cell development.

Contents

Chapter 1
Ethics and Patents in Stem Cell Research

Elina Davé, Na Xu, Neil Davey, and Sonya Davey

1.1 Introduction

Henrietta Lacks was a poor African-American woman born in Roanoke, Virginia in 1920 [1]. When she was 31, she had abnormal pain and bleeding and felt a mass in her cervix. She became a patient at Johns Hopkins' Hospital where physicians diagnosed her with cervical cancer [1]. During one of Henrietta's radiation treatments, a doctor removed samples of her cancer cells, without her knowledge. Despite receiving radiation and transfusions, she died of uremic poisoning while at the hospital at the age of 31 [1].

Henrietta's cancer cell samples were taken to Dr. George Gey's lab. Gey noticed that these cells, when preserved under appropriate conditions, did not die, giving them an "immortal" characteristic [1]. The cells were named HeLa. Gey continued to distribute HeLa cells to other scientists to help them make advances in their research [1]. These cells were cloned and shared with many scientists across the

E. Davé
Union College, Schenectady, NY, USA
e-mail: dave.elina@gmail.com

N. Xu
George Washington University School of Law, Washington, DC, USA
e-mail: naxu.mail@gmail.com

N. Davey
Harvard University, Cambridge, MA, USA
e-mail: ndavey@college.harvard.edu

S. Davey (✉)
Perelman School of Medicine at the University of Pennsylvania,
3400 Civic Boulevard, Philadelphia, PA 19104, USA
e-mail: Sonya.davey@uphs.upenn.edu; davey.sonya@gmail.com

E.M. Abdelalim (ed.), *Recent Advances in Stem Cells*, Stem Cell Biology and Regenerative Medicine, DOI 10.1007/978-3-319-33270-3_1

world [2, 3]. HeLa cells are commercially available and are the basis for 60,000 research papers as well as medical achievements including the polio vaccine created by Salk.

The telomeres in HeLa cells are not incrementally shortened during cell division, thereby circumventing the Hayflick Limit and not undergoing senescence. Although there is much debate about how to classify HeLa cells, various studies have been conducted to identify cancer stem cell-like populations within HeLa cells [4]. The story of Henrietta Lacks introduced the complicated and delicate topic of ethics in immortal cancer cell lines and stem cells.

Lacks' family was unaware of all the research that involved the usage of HeLa cells [2, 3]. Later in 2013, without the Lacks family's knowledge, researchers sequenced and published the complete genome of the HeLa cell line [2, 3]. Because of concerns from the Lacks family, the data was initially withheld until the Director of the National Institutes of Health [5] reached an agreement with the family—the HeLa Genome Data Use Agreement—where the genome sequence could be accessed by approved researchers (National Institutes of Health).

In addition, there are 11,000 patents involving HeLa cells. The issue of commercializing a person's cells was brought to the Supreme Court of California in the case Moore versus Regents of the University of California, where the court ruled that a person's discarded cells are no longer the property of that person and can be commercialized [6].

Overall, HeLa cells have raised many ethical questions. While scientists dispute their categorization as a cancer stem cell, they provide an excellent test case of the first usage of "immortal" cell lines in research.

1.2 Stem Cell Research

1.2.1 Types of Stem Cells

Stem cells are defined as a class of undifferentiated cells that can differentiate into various specialized cell types. Noncancerous human stem cells can be categorized into human embryonic stem cells (hESCs), induced pluripotent stem cells (iPSCs), and human parthenogenetic stem cells (hpSCs) [7]. hESCs come from 4 to 5-day-old human embryos that are in the blastocyst phase of development. iPSCs are generated from adult somatic cells through the induction of four transcription factors (Oct4, Sox2, cMyc, Klf4) [7]. hpSCs are formed by parthenogenesis (chemical stimulation of an ovum without fertilization of oocytes that form blastocysts) [7]. iPSCs and hpSCs do not involve the destruction of human embryos, and for this reason the usage of hESCs has specifically been ethically questioned.

1.2.2 History of Stem Cell Research

In 1981, Martin Evans from the University of Cambridge located the first ESCs in mice [8]. Evans was able to demonstrate that embryonic cells were able to regenerate fertile breeding mice from tissue culture cells and could carry out mutations that were introduced to the cells [8]. This concept is the basis of targeted genetic manipulation and newer developments that have created unique ways to experiment with mammalian genetics.

In 1998, James Thomson and John Gearhart individually isolated hESCs and grew hESCs in a lab [9]. Thomson was able to derive and maintain hESCs from human blastocysts that were produced through in vitro fertilization [9]. Gearhart was able to derive embryonic germ cell lines [10]. Thomson and Gearhart furthered their research by conducting animal studies on mice and monkeys, respectively, using hESCs. hESCs are particularly useful as they can be differentiated into all cell types in the body.

Embryonic stem cells have various therapeutic potentials including the creation of tissue that is immunocompatible with the recipient. In January 2009, the Food and Drug Administration (FDA) approved the first Phase I clinical trial of hESC-derived tissues for the transplantation of oligodendrocytes derived from hESCs into spinal cord injured individuals [11].

Later in 2006, Shinya Yamanaka discovered a way to bypass the destruction of human embryos, and invented iPSCs [12]. Yamanaka converted somatic cells into iPSCs by insertion of specific transcription factors into skin fibroblast cells [12]. In 2014, Masayo Takahashi successfully began conducting the world's first ever trial of a therapy based on iPSCs, in hopes to treat age-related blindness [13]. Overall, all of these discoveries have opened many doors for new therapies, but have also raised interesting ethical questions.

1.2.3 Ethics of Stem Cell Research

Stem cells offer great promise for new medical treatments as they generate viable cells to replace diseased cells and thus this principle can be applied to regenerate damaged tissue in humans. However, there is controversy on both the research and patentability of hESCs. A hESC is extracted from an embryo when it consists of approximately 250 cells in the trophoblast. The hESCs are taken from the 40 cells located in the inner layer of the blastocyst. To access the cells, the trophoblast must be removed, thus preventing further development of the embryo. The notion of destroying an embryo invited opposition to the research of hESCs because opponents believed that an embryo is a human life. Questions about stem cell research have subsequently been raised. For example, is a human embryo at 5 days old equivalent to a human life? When does a life begin—is it at fertilization, in the womb, or at birth? Will the potential use of hESCs to cure many human diseases

justify the destruction of single embryos? Will such hESCs be patent-eligible even though US patent law has no morality ban on patenting biological materials? The three key parts behind the ethics of stem cell research are divided into destroying the human embryo, using the human embryo in research, and creating human embryos [14].

1.2.3.1 Ethics of Destroying Human Embryos for Research

An argument in favor of hESCs is that there are many therapeutic benefits, in which case the value of research exceeds the destruction of the embryo. The most basic argument for why it is unethical to destroy human embryos is that it is equivalent to the destruction of a human being because of the embryo's capacity to become a human being. This has led to various debates about what constitutes a human being, ranging from fertilization of a one-cell zygote to 15 days after (when monozygotic twinning occurs) to birth [14]. Right to life groups in the United States believe that embryonic stem cell research violates the embryo's sanctity of life. An opposing argument for why early human embryos are not human beings is that the cells that constitute the early embryo are homogeneous and within the same membrane, therefore not a human being. Overall, there is no clear conclusion about when an embryo becomes a human being [14].

1.2.3.2 Ethics of Using Human Embryonic Stem Cells in Research

There are many situations in which researchers are not directly involved in the destruction of embryos—in fact, the embryos used in the USA for research today are from in vitro fertility clinics where the embryos were created but not used [14]. However, there is a concern that research on hESCs will lead to future mass destruction of embryos as the results from therapeutic research could lead to possible breakthrough medical treatments and thereby increase the demand for hESCs.

1.2.3.3 Ethics of Creating Stem Cell Banks

Most hESCs are derived from leftover embryos which were not utilized during infertility treatments. However, these leftover embryos are not genetically diverse enough to address the issue of immune rejection by recipients of stem cell transplants [14]. There could be ways to create embryos by cloning technologies and through the creation of stem cell banks. However, both these approaches have ethical concerns. In the case of stem cell banks, for example, there is a concern that there will be a need to obtain thousands of eggs to prepare cloned embryos, which in turn could result in abuse of women who provide the eggs [14].

1.3 US Governmental Guidelines on Stem Cell Research

The ethical debate over research involving embryonic stem cells began in 1973 when the Supreme Court ruled in *Roe vs. Wade*, 410 U.S. 113 (1973), that a fetus is not considered a person with rights, under the 14th Amendment, and legalized abortion [15]. This historic decision activated opponents as they considered abortion to be destruction of life and later opposed stem cell research. In 1974, Congress initiated a temporary suspension on federally funded clinical research that used human embryos until national guidelines could be established [15]. The U.S. Department of Health and Human Services also mandated regulations and denied funding for therapeutic research using human embryos. Federal government policymakers provided limited funding for any research with human embryos due to the conception and birth of the first "test tube" baby, Louise Brown, by in vitro fertilization (IVF) in 1978 [15].

Almost two decades later, under the National Institutes of Health Revitalization Act, President Clinton and Congress gave the NIH direct authority to fund human embryo research for the first time in 1993 [16]. NIH established a Human Embryo Research Panel consisting of scientists, ethicists, public policy experts, and patient advocates to establish the eligibility criteria for providing federal funding [16]. The panel proposed that federal funding should be provided for research to obtain stem cells from the destruction of spare embryos from fertility clinics. President Clinton, however, rejected parts of these recommendations; he directed NIH to allocate no funding for experiments that would create new embryos specifically for research. In 1996, due to the Dickey–Wicker Amendment, the U.S. Congress passed a rider attached to the appropriation bill banning the use of federal funds for either creating or destroying human embryos [16]. President Clinton signed this bill, thus limiting embryo research to the private sector.

In 1998, James Thomson of the University of Wisconsin and John Gearhart of Johns Hopkins University successfully cultured and created the first hESC lines using private funds [16]. This was an historic achievement and the NIH realized the value of this milestone to revolutionize the practice of medicine to treat conditions like Parkinson's, heart disease, diabetes, and spinal cord injury [16]. However, the research to treat these conditions required long-term federal funding, which was blocked by the Dickey–Wicker Amendment.

Harriet Rabb, the General Counsel at the Department of Health and Human Services, provided a legal opinion to the NIH in favor of the funding of human stem cell research [16]. She maintained that if the derivation of the hESC lines was funded privately, then federal funding of later research would not pose a problem regarding the creation of embryos. She concluded that a hESC was not legally an organism, as it cannot develop into a viable embryo outside the uterus, and therefore not covered by the Dickey–Wicker Amendment [16]. In 1999, President Clinton strongly endorsed the new guidelines and the NIH began to accept research proposals from scientists. Therefore, the Clinton Administration first opened the door for federal funding at this time [16].