Stem Cell Biology and Regenerative Medicine 69

Firdos Alam Khan *Editor*

Advances in Application of Stem Cells: From Bench to Clinics

Humana Press

Stem Cell Biology and Regenerative Medicine

Volume 69

Our understanding of stem cells has grown rapidly over the last decade. While the apparently tremendous therapeutic potential of stem cells has not yet been realized, their routine use in regeneration and restoration of tissue and organ function is greatly anticipated. To this end, many investigators continue to push the boundaries in areas such as the reprogramming, the stem cell niche, nanotechnology, biomimetics and 3D bioprinting, to name just a few. The objective of the volumes in the Stem Cell Biology and Regenerative Medicine series is to capture and consolidate these developments in a timely way. Each volume is thought-provoking in identifying problems, offering solutions, and providing ideas to excite further innovation in the stem cell and regenerative medicine fields.

Firdos Alam Khan
Editor

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ISSN 2196-8985 ISSN 2196-8993 (electronic)
Stem Cell Biology and Regenerative Medicine
ISBN 978-3-030-78100-2 ISBN 978-3-030-78101-9 (eBook)
https://doi.org/10.1007/978-3-030-78101-9

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

Preface

The field of stem cell biology is expanding with a continuous surge of new information related to its applications. Over the past few years, stem cells have been extensively used in various biological applications, especially in cell therapy, tissue engineering, in vitro drug testing. There is no single book available that comprehensively describes the significance of stem cells' various applications derived from embryonic and adult sources from laboratory to clinics point of view. Most of the books are either written about the basics of stem cells or purely commercialized aspects separately. This book discusses the basics and advance topics of stem cells that help the researchers, students, and professionals a single source of updated information about stem cells and in various applications.

This book is divided into 12 chapters and covers topics such as in vitro cell culture, 3D cell culture, cell therapy, tissue engineering, cell factory, cell functionality, in vitro drug testing, organ development, autologous transplantation, allogeneic transplantation, adult stem cells, multipotent stem cells, induced pluripotent stem cells, a pluripotent, and embryonic stem cell. We will also discuss various stem cell-based products, commercialization, IPR, and market of stem cell-based products, challenges of stem cell therapy, current research trends, and career. As stem cell technology is expanding, we thought it is time to overview the stem cell field and write a complete book dedicated to advances in the application of stem cells from bench to clinics. This book provides comprehensive and updated information on all aspects of stem cell research. There are many books written on stem cell biology and research on different topics. Still, there is no single book available that discusses all advanced topics of application of stem cells from bench to clinics.

This book has tried to include all the topics directly or indirectly related to the stem cell field. The primary objective is to provide the students, researchers, and professionals a single source of information about stem cells' applications. There are 12 chapters in this book, and each chapter contains the updated information with beautiful illustrations. We have discussed the various topics basics of stem cell biology, types and classifications of stem cells, and the method of isolation and characterization of stem cells, differentiation of stem cells into neuronal, cardiomyocyte, and hepatocyte pancreatic lineage, and differentiation into other cell types. The book

also discusses topics such as in vivo transplantation in animal models, stem cells in regenerative medicine, clinical trials, stem cell production, and stem cell-based products in the market, and commercialization of stem cell products.

Dammam, Saudi Arabia

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Editor

Acknowledgements

First, I am grateful to the Almighty Allah, who gave me the strength to complete this book's edition on the stipulated time. I am thankful to many people, especially to Dr. Kursad Turksen, Editor-in-Chief, Stem Cell Biology and Regenerative Medicine Series, for giving me an opportunity to edit this book. I am also thankful to Dr. Gonzalo Cordova, Associate Editor, Biomedicine, Cell Biology, Molecular Biology, Biochemistry, and Biophysics, Springer Nature, who supported me to complete the task. I am thankful to all Springer Nature production team members for their support and cooperation.

I am grateful to all the authors and especially to all corresponding authors for their immense contributions and timely completion of the work. I want to thank the entire management team of the Institute for Research & Medical Consultations (IRMC), Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia, for their support, especially to Prof. Ebtesam Al-Suhaimi, Dean, IRMC, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia, for her constant encouragement.

I am thankful to all my teachers and mentors, especially Prof. Nishikant Subhedar and Late Prof. Obaid Siddiqi FRS, for their immense contributions in shaping my research career. I am also thankful to all my friends, well-wishers, and colleagues for their support and cooperation.

I am grateful to my entire family members, especially to my father Late Nayeemuddin Khan and mother Sarwari Begum, my brothers (Aftab Alam Khan, Javed Alam Khan, Intekhab Alam Khan, Sarfaraz Alam Khan), my sisters (Sayeeda Khanum, Faheemida Khanum, Kahkashan Khanum, Ayesha Khanum), my wife Samina Khan, and my sons (Zuhayr Ahmad Khan, Zaid Ahmad Khan, and Zahid Ahmad Khan) and my daughter (Azraa Khan), my father-in-law (Abdul Qayyum Siddiqi) and mother-in-law (Uzma Siddiqi). All of them, in their ways, supported me.

Enjoy reading!

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About the Editor

Prof. Firdos Alam Khan is Professor and Chairman, Department of Stem Cell Biology, Institute for Research and Medical Consultations (IRMC), Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia. In addition to his research work, he has been teaching (Cell Physiology and Biochemistry and Stem Cell Biology and Regenerative Medicine) courses to M.Sc. students. He has done his Ph.D. degree in Zoology with a Neuroscience specialization from Nagpur University, India. Over the past 25 years, he has been involved in teaching various courses such as cell biology, pharmacology, business of biotechnology, biomedicine, cell and tissue engineering, bioethics and IPR to undergraduate and postgraduate students. He was associated with Manipal University (now Manipal Academy of Higher Education) Dubai Campus, United Arab Emirates. He was Professor and Chairperson, School of Life Sciences, and served as Chairman of the Research & Development Program. He did his first postdoctoral fellowship from the National Centre for Biological Sciences (NCBS), Bangalore, India, and a second postdoctoral fellowship from Massachusetts Institute of Technology (MIT), Cambridge, USA. He has also worked with the Reliance Life Sciences as a Research Scientist in the Stem Cell Research Laboratory. He has been granted two US patents in stem cell biology and published three US patents on the use of biomaterials in cancer treatment. He has authored two books, namely "Biotechnology Fundamentals (textbook)" (1st edition 2009, 2nd edition 2014, 3rd edition 2020) and "Biotechnology in Medical Science" published by CRC Press, Taylor & Francis Group. He has also edited one book, "Application of Nanomaterials in Human Health," in 2020 published by Springer Nature. He was Associate Editor of research journal 3Biotech from 2010 to 2020. He has been a recognized reviewer for the scientific journals, Nanomedicine, International Journal of Nanomedicine, Scientific Reports, IET Nanobiotechnology, Drug Design, Development, and Therapy, Journal of Nanostructure in Chemistry, Aging, Current Pharmaceutical Biotechnology, Tissue Engineering, Nano Express. He has published more than 70 research papers in peer-reviewed journals. He is currently studying the impact of different biomolecules, biomaterials, and nanomaterials on stem cell differentiation and cancer treatment.

Chapter 1
Basics of Stem Cells

Dhvani H. Kuntawala and Glen J. P. McCann

Abstract Stem cells have been researched for over 100 years. It all started in 1908, when a histologist Alexander Maksimov coined the name stem cells. Many key scientists have noted the potential in researching stem cells in the following the years after. These cells have the ability to renew and differentiate themselves into a wide range of cell types. Stem cells have two classifications accordingly to their properties—pluripotent and multipotent. Pluripotent cells are able to differentiate into three germ layers while multipotent cells can differentiate into only a few limited types of cells. Hence, they are important to the repair, development, preservation and growth of many organs from the earliest stages of life. Stem cells are also obtained from many sources and found throughout the life cycle from embryos to adults. Research has also helped scientists understand stem cells in different species (animals and humans) for many years. Recognition of the value of the field has seen scientists awarded Nobel prizes on discoveries regarding stem cells. This chapter describes the basics of stem cells: their early discovery, structure, morphology, characteristics, differences, location, function, roles, sources and Nobel Prize research carried out.

Keywords Stem cells · Adult stem cells · Embryonic stem cell · Cancer stem cells · Induced pluripotent stem cells · Pluripotent cells · Multipotent cells

Abbreviations

ASCs	Adult Stem Cells
ESC	Embryonic Stem Cell
hESC	Human Embryonic Stem Cell

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F. A. Khan (ed.), *Advances in Application of Stem Cells: From Bench to Clinics*,
Stem Cell Biology and Regenerative Medicine 69,
https://doi.org/10.1007/978-3-030-78101-9_1

iPSC Induced Pluripotent Stem Cell
MSCs Mesenchymal Stem Cells.

Definition of Stem Cells

Stem cells are a different class of cells present in tissues and organs of the body at all stages of development, from an early sequential series of potent processes to adult life. They can be explained as the cellular building blocks of the body that have the potential to self-renew (make copies of themselves) and differentiate (mature into more specialized cells) over a period of time. Differentiation is essential for the growth of an adult organism. Studies have shown different forms, obtained from the embryo and the adult life (Carpenedo & McDevitt, 2013; Snoeckx et al., 2009) as these cells play specific roles, such as becoming blood, brain, bone or skin cells (Morrison & Kimble, 2006). Therefore, stem cells can replace damaged cells by acting like a repair system in organisms (Łos et al., 2019).

Stem cells have been distinguished from four sources: embryonic, germinal, those extracted from carcinomas, and somatic stem cells. They are known as adult stem cells once located in the postnatal tissues (Gonzalez & Bernad, 2012). There are four basic types of stem cells that occur at different periods of life: Adult, embryonic, induced pluripotent and diseased cells in cancers that may also exhibit quite a few stem cell properties. (Alvarez et al., 2012). Embryonic stem cells have the ability to differentiate into three embryonic germ layers (endoderm, mesoderm, and ectoderm). Furthermore, they can differentiate within the embryonic extension that leads to obtaining any of the 220 kinds of cells in an individual (Gucciardo et al., 2008).

Historical Background of Stem Cell Research

In 1908, the histologist Alexander Maksimov suggested the expression “stem cells.” He developed and introduced a theory of blood and cell origin and differentiation. Many papers were published by other researchers regarding hematopoietic stem cells after Alexander’s discovery. Evidence demonstrated functional cells could be non-specialized and were termed hematopoietic (immature cells that can grow into red, white blood cells, and platelets). These stem cells were found in the marrow in 1932 by Florence Sabin. In 1950, E. Donnall Thomas initiated his work on bone marrow transplantation to support hematopoietic stem cell actuality. He executed the first bone marrow transfer to treat leukemia. This transplant comprised of similar twins, of which one of them had leukemia. In 1957, Thomas also performed the first allogeneic transplantation. Later, evidence was building of neurons in adults being able to be produced from the neural stem cells (adult neurogenesis), and knowledge of stem cell activity in the brain was also contributed to in 1960. Ernest McCulloch

and his research team illustrated the existence of revival cells in the bone marrow of a mouse during 1963. The first HLA matched human bone marrow transfer was carried out in 1968 by Robert Good. In 1978, hematopoietic stem cells were located in human placental cord blood. Derivation of mouse embryonic stem cells from the pluriblast was achieved by Gail Martin in 1981, she invented the expression "embryonic stem cell". Bonnet and Dick located cancer stem cells in blood-forming tissue or cells, also known as hematological cancer, in 1997. Cancer stem cells usually have a normal stem cell trait, and this gives them the ability to produce many different cell types in a particular cancer sample.

James Thomson and co-workers derived the first human ESC cell line from the pluriblast (inner cell mass) of early embryos that generally go on to give rise to a foetus in 1998. A year later, adult mouse tissues were altered to give rise to various cell kinds, and this indicated that liver cells could be produced from cells obtained from the bone marrow. The first human embryo was cloned at an early stage of about 4–6 cells by researchers to generate ESCs in 2000, thereafter many articles on plasticity in adult stem cells were issued. In 2002, the first human embryonic stem cell trial took place in the USA. Government funding was banned by George W. Bush for embryonic stem cell research because of ethical (social) issues concerning the disturbance of the embryo. This ban was lifted in 2009, and the research was allowed to continue in the USA. Then biotechnology company Geron Corporation carried out a trial, hoping to trigger nerve growth in patients that have spinal cord injury by using GRNOPC1, a human embryonic stem cell-derived oligodendrocyte progenitor cells (OPCs) therapy. No formal outcomes from this trial were issued as such; preparatory conclusions of the study were addressed in October 2011 at the American Congress of Rehabilitation Medicine (ACRM) conference.

From 2004 to 2005, Hwang Woo-suk was alleged to have made many human ESC lines from human oocytes that had not been fertilized. Some of this work was later shown to have been forged. In 2006, Kazutoshi Takahashi and Shinya Yamanaka published their rat induced pluripotent stem cell work. They found the potential to encourage cellular pluripotency, and it transformed the perspective of stem cell research. During 2007, various groups reported normal skin cells being reprogrammed in mice back to an embryonic state. Mario Capecchi, Martin Evans, and Oliver Smithies in Physiology and Medicine by the end of 2007, a Nobel Prize was granted for their gene research on ESCs from mice. The researchers published the induction of pluripotent stem cells. Raymond Wong et al. resolved the part of intercellular communication connections via gap junctions in both somatic and embryonic stem cells in 2008. Vanessa Hall discovered ESCs in porcine as an origin for human cell replacement treatment in 2009, and also the genomic profiling of mesenchymal stem cells was carried out in the same year by Danijela Menicanin et al. In 2010, Yue Xu et al. revealed the importance of cell adhesion and growth factor signalling regulatory techniques for pluripotent stem cell survival and self-renewal.

In 2012, a Nobel Prize was granted to Shinya Yamanaka and Sir John Gurdon to discover developed cells being reprogrammable to give rise to many different cell types (pluripotent). The first derivation of human embryonic stem cells (hESCs) by a therapeutic (designing a cloned embryo to produce embryonic stem cells with

identical DNA as the donor cell) cloning was in 2013 by Tachibana et al. The first clinical trial with human induced pluripotent stem cells (hiPSCs) was initiated in 2014. Liao et al. in 2015 reported CRISPR/cas9 technology being applied to human embryonic stem cell (hESC) gene editing; later during that year, other research was carried out by Takasato et al. on the generation of organoids from hESC for modelling foetal organ morphogenesis. During the year 2017, Jun Wu published his finding on a chimeric pig embryo populated with hIPSCs (Eguizabal et al., 2019; Kumar et al., 2010; Shihadeh, 2015).

Structure and Morphology of Stem Cells

From 2004 to 2005, Hwang Woo-suk was alleged to have made many human ESC lines from human oocytes that had not been fertilized. Some of this work was later shown to have been forged. In 2006, Kazutoshi Takahashi and Shinya Yamanaka published their rat induced pluripotent stem cell work. They found the potential to encourage cellular pluripotency, and it transformed the perspective of stem cell research. During 2007, various groups reported normal skin cells being reprogrammed in mice back to an embryonic state. Mario Capecchi, Martin Evans, and Oliver Smithies in Physiology and Medicine by the end of 2007, a Nobel Prize was granted for their gene research on ESCs from mice. The researchers published the induction of pluripotent stem cells. Raymond Wong et al. resolved the part of intercellular communication connections via gap junctions in both somatic and embryonic stem cells in 2008. Vanessa Hall discovered ESCs in porcine as an origin for human cell replacement treatment in 2009, and also the genomic profiling of mesenchymal stem cells was carried out in the same year by Danijela Menicanin et al. In 2010, Yue Xu et al. revealed the importance of cell adhesion and growth factor signalling regulatory techniques for pluripotent stem cell survival and self-renewal.

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Detailed morphology of embryonic stem cells was described by results that showed high nuclear to cytoplasmic proportion and compact colonies. Cells with prominent nucleoli and round colonies have also been seen. Additionally, these cells also have clear and smooth colony edges. When culturing hPSCs, they are grown

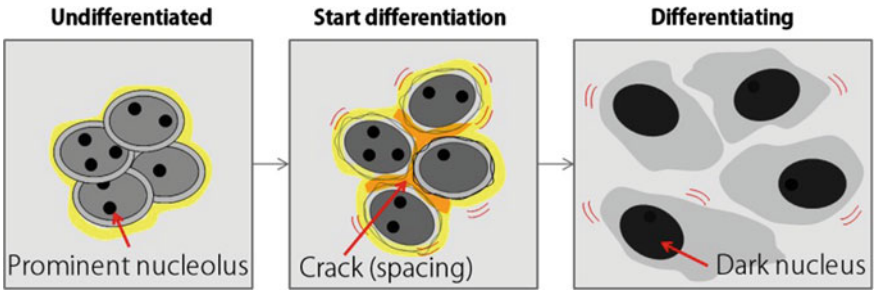

Fig. 1.1 Morphological changes in human pluripotent stem cells (hPSCs) (Wakui, 2017). Moving from left to right, as the cells specialize the nucleolus becomes harder to visualize within a dark nucleus. Cells also proceed to space themselves apart as their morphology becomes more specific

while maintaining morphological features (round, flat, and smooth edged) intact. In an undifferentiated state after reprogramming. Variations of cells usually occur in the culture due to impurities, with some cells that are not successful at reprogramming. Hence, during culture, they are selected to keep the cells that were reprogrammed and remove the unsuccessful cells. Once cells diverge from pluripotency to a differentiated condition, they have a white space that appears like a split space intercellularly. As seen in Fig. 1.1, the distance connecting the cells expands, as well as these cells develop an appearance similar to the differentiated cells. These cells slowly develop a dark and flat appearance. The differentiated cells within their nuclei have less relaxed chromatin when compared to the undifferentiated hPSCs, as chromatin undergoes an alteration in structure to heterochromatin. This will lead to a loss of translucency in the nuclei, as the nucleoli will become invisible in the course of the differentiated process under staged contrast microscopy.

Characteristics of Stem Cells

Stem cells vary in their developmental versatility or degree of plasticity. So, they can also be described according to their characteristic of self-renewal and plasticity; this is important for the renewal and recovery of the body. Other properties that allow stem cells to show their ability to exert the structure of organs and tissues are rapid proliferation and differentiation (Pavlović & Radotić, 2017).

There four main types of stem cells:

I. Embryonic stem cells—they are pluripotent stem cells obtained from the inner cell mass (ICM) of an early stage embryo called blastocyst.
II. Adult stem cells—they are any cells taken from a fully grown tissue. These include endodermal, mesodermal and ectodermal origins.
III. Cancer stem cells—these have been seen associated with nearly every type of cancer.

IV. Induced pluripotent stem cells—these types of cells have been extracted from a non-pluripotent cell, mostly from an adult somatic cell by treating mature cells with genes that dedifferentiate them to a pluripotent stage.

Stem cells are present in all multicellular living organisms. These stem cells are able to differentiate into specialized cell kinds depending on their potency. These include:

I. Totipotent cells—Morula, Spore, and Zygote; these types of cells have the possibility to give rise to any human cells (brain, liver, heart, or blood). They are also each capable of giving rise to a whole viable organism.
II. Pluripotent cells—Embryonic stem cells; cannot emerge to a whole organism; however, they are capable of giving rise to all types of tissues. Can create callus-like groups of similar cells.
III. Multipotent cells—Progenitor cells (hematopoietic and mesenchymal stem cells); they can emerge to a restricted variety of cells inside a tissue type.
IV. Unipotent cells—Specific originator cells, such as muscle stem cells (Hui et al., 2011).

Embryonic stem cells have two properties: to propagate themselves under defined conditions and to be able to differentiate into the ectoderm, endoderm and mesoderm germ layers. Human embryos have 50–150 cells at the blastocyst phase, post-fertilization (Ying et al., 2003). It is challenging to study cells in situ, so advancements in cell culture have been essential to understand cellular characteristics. For many years pluripotent cell lines have been isolated and maintained for in vitro cultures such as from mouse blastocysts (Evans & Kaufman, 1981). Also, Martin (1981) demonstrated observing these cultures that were derived from single cells that could differentiate into various cell types. This made it possible to study early mammalian development. Undifferentiated human embryonic stem cells and embryonic germ cells were cultured by James Thomson and his group in 1998. This study provides an understanding of differentiation and how human tissue functions as well as new approaches for drug discovery and analysis (Thomson & Odorico, 2000).

Adult stem cells are derived from mature tissue. Examples comprise stem cells obtained from placental tissues like human amnion epithelial cells and mesenchymal stem cells. These cells have been indicated to be able to reduce inflammation and augment repair of animal replica injury model studies. Even though these cells can segregate into tissues in vitro that are found from the separate parts of the germ cell layers in vitro, they have limited differentiation capacity. Adult stem cells benefit since cells sourced from self or family use may have reduced ethical and biological concerns (Kolios & Moodley, 2013).

Cancer stem cells have many different characteristics that allow them to assist in tumourigenesis. They are discrete populations of cells within tumours. (Dalerba et al., 2007). Cancer stem cells (CSCs) have been acknowledged to be significant in leukemia and dense cancers. Researchers have suggested that cancer stem cells have the capability to self-regenerate and can then separate into distinctive forms of cancer cells. They are believed to be accountable for malignancy, evolution, metastasis,

reappearance, and drug resistance. Cancer stem cells remain pluripotent, so they can lead to tumour cells with different phenotypes, leading to the development of leading cancer and the appearance of novel cancers (Chen et al., 2013).

Induced pluripotent stem cells (iPSCs) are obtained by reprogramming grown mammalian cells by the enforced expression of DNA regions involved in pluripotency and cell multiplication (Stadtfeld & Hochedlinger, 2010). iPSCs can afterwards segregate into several specific somatic cell varieties and share identical features, including but not restricted to the morphology and proliferation of ESC, self-renewal, and the possible variation into different kinds of cells (Ji et al., 2016). This capability creates a revolutionary tool for a wider range of technical methods and reformative medication (Cantz & Martin, 2010; Reibetanz et al., 2016).

Differences Between Somatic Cells and Somatic Stem Cells

Somatic cells refer to all the body cells except sperm and egg cells (germline cells). Somatic cells are diploid and have two groups of each chromosome, one from each parent. In this sense, adult human stem cells can be considered to be somatic. These cells do not have the capability to create any progenies; instead, they shape all the organism's structures and tissues. Several types of these originator cells have been separated in adult tissues; hence most tissues have their own specific stem cells (Fig. 1.2). For example, the neural stem cells in the subventricular region (outside the lateral ventricle wall in vertebrates) contain epithelial stem cells. The spongy marrow tissue of the bone is where hematopoietic stem cells reside and function to refill cells into the blood that have deceased in function or accumulated pathological processes. These stem cells are normally located in proximity to their normal somatic cell's tissue position. In the case of blood, the unmineralized hollow bones serving as a site for this organ.

All somatic cells, both normal and ASCs, can divide through mitosis to replace and maintain the tissue continuity across a multicellular system's lifetime. The ASCs are unspecialized cells with self-renewal capacity. The source of stem cells starts with a totipotent egg, which can segregate to the placenta and all the kinds of tissue in the body. This blastocyst forms after seven to eight-cell divisions of an egg that has been fertilized. The blastocyst's outer wall will be altered to hold it to the uterine wall along with the inner cell mass, which contains the pluripotent cells that can segregate into any other cell type with their more specific functions. They are known as the embryonic stem cells that differentiate into different multipotent stem cells and progenitor-specific cells (Ramesh et al., 2009). Adult stem cells are found in a particular area of tissue in tiny numbers called a stem cell niche. An essential factor is that stem cells can remain inactive for a period of time until a signal is operated internally or externally, for example a tissue injury or diseased state (Dutta, 2020). This is very advantageous as uncontrolled cell division in these cells would be very dangerous.

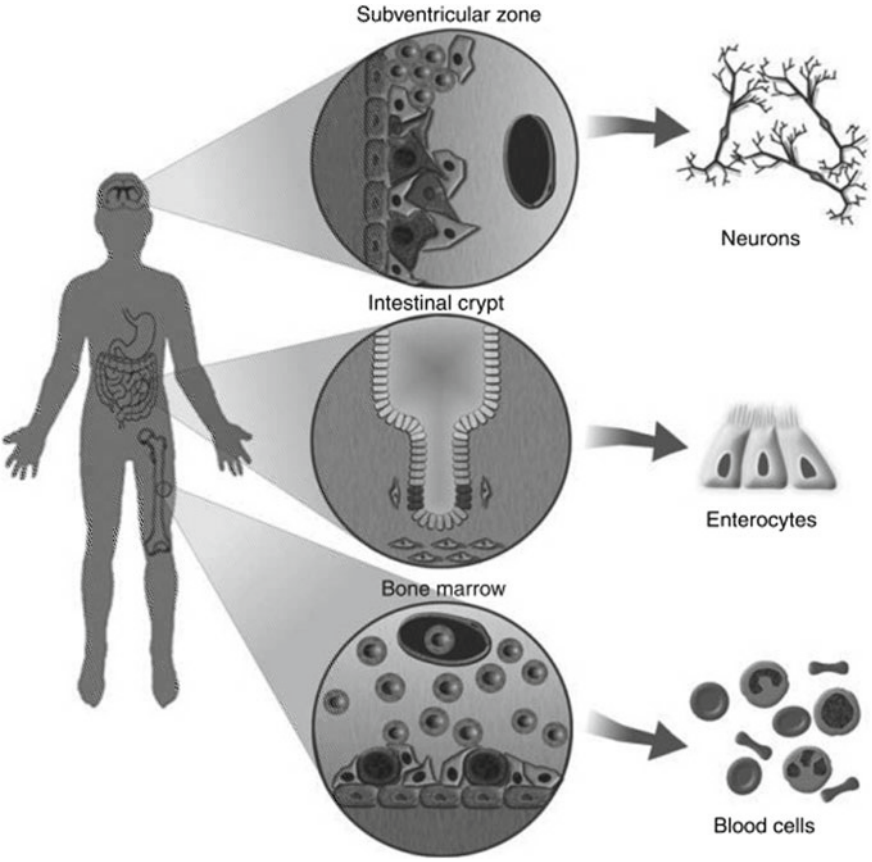

Fig. 1.2 Adult somatic stem cells (ASCs). ASCs exist in most tissues of the body. Due to most cell's dependency upon anchorage, ASCs are located close to their relevant sites. Cells of the blood being non-anchorage dependent migrate from the ASCs in bone marrow (Chagastelles & Nardi, 2011)

Normal somatic cells being differentiated and specialized in function are very often different from each other as well as from their stem cells. This is best demonstrated by studying the most extreme examples. Cells that have made the ultimate decision to terminally differentiate have become so specialized that their potency has become significantly compromised in normal circumstances. Keratinocytes in the epidermis commit to bulking up on proteins like keratin. During the latter end of the cornification process, the cell also has no need to update other structures. The cell undergoes apoptosis, and the cell morphology progresses to dead structural material. Antibody producing plasma cells upregulate endoplasmic reticulum and Golgi volume for rapid extracellular secretory protein production. Though this continued state may be undesirable if continued indefinitely. Red blood cells mature

to become denucleated and so are unable to repair themselves and require replacement. Once cells make these sorts of commitments, dramatic differences occur in cellular morphologies related to function and structural requirements. Despite exceptions, in the cited cells above, once they prioritize to this extent, it seems that their lifespan is measured within a matter of months (Andraud et al., 2012; Eckhart et al., 2013; Franco, 2012).

On the other hand, stem cells do not really require anything more than the apparatus for the correct response to cell cycle signals and the faithful copying of DNA. This is to form new daughter stem cells or forcing altered gene regulation upon daughter cells for them to specialize. Stem cells and somatic cell types can be characterized according to their specialized mixtures of morphologies, organelles, proteins, etc. A reasonable, logical correlation between microscopic observations mapped biochemical pathways and expected functions often make sense. However, those valuable observational differences are underpinned by the mechanisms that regulate the products of DNA. It is the differential use of DNA in cells that drives these differences.

The basis of DNA to mRNA to protein, while central is too basic. Cells use of transcription factors, DNA methylation, histone modifications and interfering or microRNA are used to control gene products and regulate this process. Gene promotors, often upstream of the gene, contain protein binding domains that influence the ability to make mRNA. This is through proteins binding or being removed to allow repression or promotion of the production of mRNA. These transcription factors decide how much and when mRNA transcripts can access ribosomal translation. Also, how much and when regulatory RNAs can interfere with this process is an essential factor. This cascades onwards to control more and more complex feedback loops to encourage or restrict the flow of DNA to proteins. Post-translational modifications, alternative spicing, peptide trafficking via signal peptides, and the expression of receptors with signal transduction then all go back to influence the whole process of DNA again to proteins.

The study of epigenetics and imprinting has also been able to explain further why the same genomic DNA can be controlled to give different cellular outcomes. The use of methylation of CpG rich sites in promotors can downregulate the expression of a gene. While CpG is common in DNA, it seems to be higher than expected in some promotor regions. 5′-CG-3′ on one strand of DNA forms a very short palindrome of the same on the other strand. This creates methylation on each strand's C bases, offset from each other. When DNA replication occurs, both strands contain a template with methylation on the C bases. This allows the ability to maintain a DNA methylation template to each daughter cell when the other strand is replicated. There are also enzymatic abilities to remove these methylations to change the outcome of gene expression in a cell. Stem cells and somatic cells have differential methylation patterns that are noted in these islands of CpG rich areas (Kim & Costello, 2017).

Histone protein modifications alter the readability of the chromatid by altering the density of the DNA windings upon the nucleosomes. This plays a role in the accessibility of RNA polymerase II to make mRNA and their proteins. Cellular proteins have to be produced in the correct time, place and amount to allow cell

differentiation and replication. Via these proteins, the non-proteinaceous parts of the cell can also be altered. Enzymatically cells are controlled, and they are supported by turnovers and pools of lipids, sugars, tRNA, rRNA, amino acids, cholesterol, steroids, NAD(P)H, ATP and many other supporting factors. Proteins can be are cleaved, glycosylated, switched on/off by phosphorylation, require redox supplies, interact with each other, be exported to control other cells. With this unexhausted list of factors above, an impressive array of variables is prominent. So are, therefore, why so many types of cells are possible. In summary, one set of cellular instructions can be read very many ways to produce variable and adaptive cellular outcomes.

Stem Cells in Different Species (Animals and Humans)

Animal development has been studied to help scientists understand animal biology for many years. There are many reasons for this, including personal curiosity, investigating animal welfare and farming, studying simple systems to help understand complex ones, understanding evolutionary trajectories and even exploring the potential for changing human health. Biologists have characterized animals capable of partial or full regeneration body parts for more than 100 years. So, the notion of tissue re/generation and its potential for exploitation long predates identifying the possible mechanisms. Observations in the nineteenth century were also very important. Karl Ernst von Baer's chordate embryo collections displayed some similarity to each other at early stages, but he noted they diverged in development to look dissimilar from other animals' adults. Ernst Haeckel's recapitulation theory of embryos moving through ancestral primitive forms to achieve a higher state of embryo did not provide a useful answer to this (Richtsmeier, 2018). Either way, the level of understanding at the time would have not allowed for a modern cell biology model to be formed. That is, animal stem cells acting in both very early life all the way through to the repair towards their end of life. Long before the discovery of DNA, the notion of stem cells differentiating towards specific cell types via altered access to—and regulation of their proteomes and regulatory RNAs against a backdrop of epigenetic factors—was too complex to put together.

With the right mindset, asking questions about the complex phenotypical changes that occur in frogs, many insects and butterflies, etc. alludes to a certain level of unequal pattern formation fluidity in animals. Moving forward, at the core of driving animal stem cell curiosity, there is juxtaposition in this work between offering hope to human disease, protecting rare species from extinction and the way society views what is ethical. This work has the potential to extend human life and so challenge the resources of Earth but, at the same time, perhaps provide an answer by enabling distant space travel and terraforming in other worlds. One of the simplest animals, the rotifer, can produce embryos with stem cells capable of dormancy (García-Roger et al., 2019). Germination of ancient plant embryos encased in their seed cases is also possible (Sallon et al., 2020). These two examples seem to be in extreme contrast to higher animal capabilities, but human embryos have been viable after decades of

ultralow temperature storage. This all indicates that, once understood, animal stem cell applications may be pushed into novel situations.

Multicellular eukaryotic organisms exhibit diversity in their structural complexities, genotypes, transcriptomes, proteomes, non-coding gene products, post-translational modifications and epigenetics. They also exhibit diversity in their cell biology, reproduction, gestation, life span, propulsion, food, social interactions, and the value of individual colony members, behaviours, predation, disease states and environmental parameters. All of these factors are likely to have played some role in the evolution and divergence of stem cell abilities and how they behave in animals. It is important to understand the key times when animals may need stem cell activities. Embryogenesis, homeostatic maintenance, growth/development, metamorphosis and repair. Clearly, these processes are not equal, some essential and other non-existent in certain animals. Some human cells and tissues are never subjected to remodelling or replacement, so have reduced need for stem cells. The animals that have greater levels of repair in their structures analogous to human tissues are obviously of great interest. This offers hope for learning what may stimulate analogous mechanisms in humans as some key proteins and transcription factors are highly conserved among animals and highlight routes for enhanced repair outcomes (McGurk et al., 2015).

Clearly essential to our understanding in mammalian and animal embryogenesis is to use a model of totipotent progenitor cells moving towards specialist cell types, or even terminal differentiation. Once we understand this, the next most important consideration will be in animal cells as we ask if this process may run in reverse. In situ study or harvesting stem cells for in vitro work in humans has challenges regarding ethics, legality, religion, variable clinical outcomes, cost and time taken for long term mechanisms and effects to be fully understood. Therefore, understanding stem cells both in vitro and in animals is not only beneficial for understanding those animals. It also offers potential for simple models to be created and inspire, what may be possible? Many human diseases can be understood through very simple models. Using yeast cells for modelling pathways in human neurodegenerative diseases seems unlikely but is accepted (Khurana et al., 2017). So far, simple single-celled organisms have not been so useful for studying in place of animal stem cells, but it is noted that there are sometimes similarities. The ability of animal stem cells to perform asymmetric cell division, producing either daughter stem cells or differentiated cells. This process can be seen in some single-cell organisms and organisms can influence each other demonstrating colony/multicellular-like behaviours like quorum sensing. So currently the most flexible model systems are in animals. This is useful to understand the animal itself but sometimes offers limited specific insight into the full overlapping systems in human stem cells. There are also too many variables to make use of single experiments. However, the sum of multiple data to drive computational models will hopefully make animals more redundant in this area (Zhou et al., 2019). This is a complex area, and it is important to remember the scope of animal's stem cells. Regarding what we can learn, a basic structure repair might in an animal be adequate for function and survival. However, in human medicine the expectation for full functional replacements is more likely. Presuming the regeneration of a tail

after autotomy in a lizard has been evolutionarily optimized, it is still sometimes a compromised structure and not fully identical to the original.

Some animals demonstrate unusual forms of asexual reproduction like pathrithogenesis, haploid oocytes can undergo meiosis without subsequent cytokinesis to retain diploidy. This is of interest for the potential to make autologous high potency stem cells from gametes or even differentiated somatic cells. However, many animals form an embryo from the fertilization of oocytes. Either way, a totipotent diploid zygote is the expected outcome. The zygote in animals forms the morula ball of cells within the confines of the zygote. Changing the ratio of increasing cell numbers to decreasing cytoplasm volume perhaps serves to allow a feedback to control this process (Neurohr et al., 2019).

The next major difference in animals is the use of placenta in mammals and those that form eggs. Sometimes eggs are retained and in or near the body or left to the environment for different lengths of times. Based on this and other factors, the most obvious difference is regarding the formation of lesser or substantive yolks. These factors influence the way that the cleavage of the stem cells occurs. Cleavage methods have diversified in animals in the transition towards the blastula. In different animals, there are several directional ways in which cells perform cleavage both in relation to each other and the yolk (Houston, 2016). These differences complicate the use of some simple animals from fully modelling human stem cell embryogenesis.

Another important factor in understanding how early stage animal stem cells grow is their transition from the maternal influence of the oocyte. The oocyte contains one haploid copy of maternal DNA, the proteins, regulatory RNAs and many other factors. As the blastula develops, the diploid influence changes the landscape of proteins and these other elements. Later on, in mammals, the development of the placenta again allows further maternal influence of the stem cells of the developing embryo via molecules crossing the blood-placenta barrier. By studying these processes in diverse species like marsupials that birth early in development and the fullest range of animals, it could be possible to better characterize stem cell behaviour by compare and contrast. However, to fully understand animal stems and maximize their potential it is really important to understand the whole complex environment that they are exposed to. Despite the divergent pathways in animals, a polarity in embryogenesis generally occurs in the blastula stage. The designated area of higher activity the animal pole and the lower activity vegetal pole that develops into the extraembryonic membranous structures that provide the immediate and correct environment to protect and nourish the embryo.

In the same way as the cell membrane allows compartmentalisation, the multicellular nature of animals allows the development of layers of cells for more complex structures and functions. Many animals produce three main layers of stem cells during embryogenesis, though some simple aquatic animals only produce one or two. All triploblastic animals have three germ layers. From a human health point of view, understanding all three of these germ cell types is critical, each of them gives rise to highly functional and specialized tissue types and so can build organs. Due to this commonality, even in basic animals like worms, we can appreciate that stem cells

give rise to an analogous digestive tract, nervous system, a gas exchange/vascular system, an outer surface and other specialized tissues.

The next major distinction in animals is the presence of a notochord in chordates which give rise to the vertebrate animals we best recognize. This comes from the ectoderm during gastrulation. Gastrulation in animals does have variations but follows similar patterns of organogenesis and pattern formation of the animal from the germ layers. After this the stem cells are pluripotent and gradually differentiate towards loosing potency as the organism's tissues become more specialized.

Post Development Growth/Repair/Maintenance

Putting aside the complex metamorphosis that occurs in some animals, later development in animals is to increase complexity, size and repair. In mammals, the process of post developmental stem cell activity in maintenance is well documented via hematopoietic stem cells in their generation of a large number of blood cells from an individual kind of stem cell. This model in place by the 1960s from the study of mice but has been well documented also in humans since (Till et al., 1964). This led to offering stem cell transplants in humans for immunodeficiencies, cancers and autoimmune diseases.

From the realization that adult animals have activate stem cells, it has driven research into the possibilities that cells can increase their potency levels and whether any stem cells can be used to produce gametes. Somatic cells have been induced to become pluripotent stem cells in mice and human cells. Interestingly, this has been through the control of transcription factors. This discovery allows complex control of the genes that can increase cell potency with minimal need to understand and control every single gene and factor involved (Mullen & Wrana, 2017). More promising is that these transcription factors can be encoded transiently by introduction into cells as RNA species. If this process is then continued to make viable germ cells and gametes in mice, this transient alteration could mean that the mouse need not retain retroviral genetic modifications in offspring. So being as close to naturally wild type as possible.

So far there has been limited success in producing in vitro germ cells from mammalian embryonic stem cells for both male and female forms except in mice. This offers potential for in vitro gamete and even zygote production from stem cells. As well as for humans this offers great potential for rare and difficult to breed animals (Goszczynski et al., 2019).

Certain animals have been well represented in the understanding of stem cells in embryogenesis and adult repair. For example, the large size of the xenopus oocyte and its early discovery to translate exogenous mRNA; the mouse that has been one of the most adaptable as mammalian species; the zebrafish that demonstrates regenerative repair of tissues in humans that are incapable of repair; drosophila for their genetic homologies with development and diseases of humans; salamanders which

can regenerate highly functional limbs; and lizards which can regenerate full or partial tails after autotomy.

These organisms and systems all highlight great overlap in animal stem cell abilities and mechanisms. They also suggest that many cells can increase their potencies and then decrease them by specializing; there is also the possibility that they could even go on to form viable gametes and offspring. This offers an exciting future for not only human and animal survival but also quality of life.

Location and Function of Stem Cells in the Human Body

Stem cells have the potential to grow into any kind of the known 220 cells in the human body of an adult. Stem cells are obtained from bone marrow; however, they are also derived from the umbilical cord blood. To become erythrocytes, leukocytes or platelets, each stem cell receives chemical signals. These mechanisms are controlled by growth factors and epigenetic processes (chromatin remodelling and DNA methylation). The bone marrow space is where this growth activity takes place whereby only the mature cells are released into the bloodstream at a distant (Tuch, 2006). Tissues and organs have adult stem cells recognized in them; each tissue has a small number of stem cells present. In order to maintain a ready pool of supply for replication to take place at a controlled rate, stem cells are present in certain regions of every tissue (Kumar et al., 2010).

There Are Many Known Sites of Stem Cell Activities

Embryonic stem cells. They are particular kind of stem cells obtained from a human embryo that are about three to seven days old from the developmental phase. This blastocyst stage is known as the embryo. A blastocyst is a thin-walled globe of 150 cells, which can divide into more stem cells of an individual. Therefore, embryonic stem cells are considered to be capable to repair or revive unhealthy organs for regenerative therapeutics. Adult stem cells. The adult stem cells are found in small numbers, which makes them difficult to be found for study and harvesting. Unlike embryonic stem cells, adult stem cells have a restricted ability to provide growth to most cells. Scientists had believed that the use of AS cells could only just provide blood cells in the bone marrow. However, the scope for adult stem cells is greater and people with heart or neural diseases are being tested for the regenerative potential adult stem cells.

Induced pluripotent stem cells. It is possible to alter the genes in adult stem cells to give rise to induced pluripotent stem cells in the laboratory. This alteration is done by reprogramming the cells to perform like embryonic stem cells. Reprogramming techniques (a procedure used to revert fully grown cells into induced pluripotent stem cells) may allow an alternative of embryonic stem cells and put an end to immune

system rejection of the newly grown stem cells in allogenic transplants. Yet, it has not been confirmed if using altered adult cells will cause any risky effects in humans. In several cases, connective tissue cells have been reprogrammed to become efficient heart cells. New heart cells have been injected to animals having a heart failure, leading to an improvement to the heart function and increased survival period. Perinatal stem cells. Researchers have discovered stem cells in both umbilical cord blood and placenta. To protect a growing foetus in the uterus a liquid called amniotic fluids fills the sac. Stem cells have been seen in samples of amniotic fluid from pregnant women. Amniocentesis is carried out to examine possibilities of developmental.

Role of Stem Cells in Human Development and Embryology

Section "Stem Cells in Different Species (Animals and Humans)" describes the common roles of stem cells in animals and humans leading up to the generation of three germ layers in triploblasts. After this, human stem cells are still highly active on the formation towards a foetus. However, over time with the final body pattern in place, stem cells can reduce in potency, becoming more specific in their roles. Loss of potency obviously is not the same as loss of activity. This is complex and human tissues must always balance the pulls from cell cycle repression, growing in size, growth in complexity, housekeeping, mechanical tissue repair, infection, DNA repair, endogenous and exogenous chemical signals, tumourigenesis, epigenetic regulation, oxidative damage, ageing and apoptosis. To remain functional certain tissues must also resist the urge for both stem cell and sometimes also immunological cellular activities to occur. This is because remodelling or repair may limit functionality of the tissue. In humans, it may be too simplistic but useful to consider stem cell activities to be related to either the structural or functional natures of the tissue types. The stem cells giving rise to dermal fibroblasts or neurones, for example not requiring the same level of activities in adults and embryos. It is this lifetime compromise in the needs of embryo development differing from ageing that can lead to disease in later life. Attempting to change the nature of this balance of compromise is what offers hope for stem cells correcting disease states and, perhaps, monitoring and preventing problematic embryogenesis. This starts with understanding embryogenesis.

After gastrulation forms a cavity globe of cells, the stem cells of the developing embryo's three germ layers are highly active and potent. They have lost the ability to form any type of cell, but each layer still retains potency to form the great number of cells and tissues specific to its layer. The outer layer of cells as the external facing ectoderm, mesenchymal cells as a central connecting layer form the mesoderm and the inner cells of the developing gut from the endoderm. This early pattern of cellular organization is transferred through to structures retained throughout life. The endodermal gut development process forms a pathway from the buccal cavity to the anus. As well as the obvious structures of the digestive system, the lungs terminate off this branch, glands and organs such as the liver that interact with the digestive system and endocrine also form from this layer.

From the mesoderm, a connectivity of motor-related and spatial matrices forms bones, joints, muscles and connective tissues and so their ultimate proteinaceous depositions such as collagen and others in the dermis. The vascular system including heart and the tubes of the urinary and reproductive systems also originate from the mesoderm. The mesoderm also gives rise to the dorsal midline. This gives the body a symmetrical and central axis point based on the notochord which then goes on to form the vertebrae of the spinal column. The mesodermal stem cells' areas of activity are organized into blocks. These blocks called somite's and arrange themselves either side of the notochord in discontinuous segments along the length of the notochord. The blocks allow corresponding levels of regional muscles to form in situ, but they also have migratory abilities.

The ectoderm goes on to form the skin epidermis but is also able to form the central nervous system. The mesodermal derived notochord is externally covered in ectoderm which is several cells thick and forms a neural plate. This then pulls itself up from a flat layer of cells to meet together, forming a central hollow neural tube above the notochord and below a new layer of sealing ectoderm. This neural tube gives space to form the spinal cord and brain. Between the neural tube and the ectoderm, a grouping of ectodermal cells forms a neural crest. The cells from this area are able to move through the mesoderm and populate it with cells of the peripheral nervous system (PNS). However, in the head they are also able to form bones, joints and connective tissues. A further complexity is the three sense organs of the head are not all derived from the same germ layers (Alberts, 2017).

The key points in the ongoing development of the germ layers are that some of these processes occur in three dimensions through extensions and elongations, respecting a directional governance. Also, that the origin of the stem cells in a region may have originally migrated from another germ layer. The applications attempting to use the stem cells in medicine are complex. For example, to repair significant damage to the spinal cord itself and also re-joining it to peripheral nerves is problematic as they did not have the same origins. Compared to embryogenesis, such an attempted repair may lack respect for the natural directional abilities, migratory origin of the cells and the cell signalling that initially gave rise to neurulation. Attempts to use scaffolding may mitigate some of these problems (Katoh et al., 2019).

As well as the mesodermal somites arranged around the rear of the embryo, the lateral plate mesoderm separates the rest of the endoderm from the ectoderm around the rest of the forming body. The final external body pattern of the embryo is not in place until the limb buds of the body develop from this lateral plate. During and after this, regional stem cells produce many layers of compartmentalisation and tissue types required for development towards near the final body pattern in miniature to form a foetus. The foetus is formed towards the end of trimester one.

The high level of the potency in very early embryo development is evident as it can sustain loss of cells to create twins or repair a cell lost. This level of potency is required as the cells that distinguish the germ layers transition to different and specialized tissues and organs have yet to form. Stem cells do not retain their full potency as part differentiated but as lower potency role specific stem cells. It could be that a reversible lower potency state could be controlled only by general gene and

transcription factor regulation. However, this is perhaps risky and a degree of cellular memory and commitment to not normally revert is held in place as specialized stem cells. In the developing embryo, cells must maintain their differentiated states. The reversal of state or migration of higher potency stem cells without the context of their original spatial and chemical signals could lead to a non-viable embryo or structures in compromised positions.

In post embryo humans, an increase in potency or retention of stem cells may be desirable against disease, ageing and damage repair. However, the consequences of retaining cells potentially able to form a full repertoire of tissues out of context, capable of rapid cell division and migration might be a step too close to tumourigenesis (Wuputra et al., 2020).

Accepting this model and the risks of embryo interference, recent stem cell harvesting from the placenta to retain hematopoietic progenitor and hematopoietic stem cell populations for autologous use against certain blood cancers and autoimmune diseases seems to provide potential for a low risk for high rewards. Placental tissue also contains mesenchymal stem cells that can form a very diverse range of cells in the laboratory when given specific cell signalling reagents (Wang & Zhao, 2010).

Apart from a constant general growth in size and brain complexity throughout childhood and towards adulthood, puberty leads to rapid changes in cellular activities. However, compared to embryogenesis the changes are slight and slow. Throughout the process though, there appears to be a theme that cells have a built-in memory for retaining correct potency levels and some kind of clock activity for timing change. On the route from foetus to adult, it is clear that there are reducing needs for stem cell potencies but still great need for stem cell activities. In adults, it is noted that most cells have finite lifespans requiring turnover. Some cells like the heart muscle are also seemingly mechanically and functionally expected to need turnover yet they are not capable of doing so. It is also expected to think of skin, muscles, and connective and synovial tissues of having high need for stem cell turnover for repair just from normal mechanical stress. Yet these cells often form scar tissue and joints demonstrate little ability to renew from arthritis.

The best documented example of ongoing stem cell activities in adults is in the generation of blood cells. The necessity being the expiration of the nonnucleated red cells incapable of dividing and repair. The white immunological cells also require strict control of their levels of activities. The liver is also well-known for its regenerative capacity, it can receive a lot of oxidative damage from ethanol metabolism via cytochrome P450 CYP2E1, a great deal of functional stress (Abdelmegeed et al., 2017). In adults, the regenerative capacities of tissues would appear to be sometimes illogical. It may be expected that stem cell regeneration of the hip joints to prevent osteoarthritis and allow food gathering would be of evolutionary advantage over the detoxification of exogenous compounds in the food. However, humans have had the ability of social cooperation to share the social needs of food gathering. Humans have also been able to elongate the gap between reproductive age and death, reducing the drive for adaptations to counteract ageing. This contrasts against the level of systemic sickness that can occur from liver damage and can cause premature death.

If the biological evolutionary aim for human life is to reach an age of securing the independence of the next generation, then we may consider the natural evolutionary use of stem cells beyond maintenance and repair evolutionary redundant within a generation of reproductive age.

Multipotent Stem Cells Versus Pluripotent Stem Cells

Multipotent stem cells only segregate into certain cell kinds once they perceive signals, such stem cells known as hematopoietic, neural and mesenchymal. The hematopoietic stem cells transform into various blood cells; neural stem cells into astrocytes, oligodendrocytes and neurons; mesenchymal stem cells can give rise to adipocytes, osteoblasts and chondrocytes. Hematopoietic stem cells become an oligopotent cell after differentiation and later differentiate into many cell types. An example of this is a myeloid stem cell that can split into white blood cells excluding red blood cells. Found in small numbers, multipotent stem cells are available in specialized tissues mostly in adult tissues and are able to restore cells that are damaged.

Pluripotent stem cells are categorized into perinatal, induced pluripotent and embryonic stem cells. The embryonic stem cells are harvested inside the range of the first four cell division of the embryo, they are called totipotent. Totipotent cells can differentiate into extraembryonic tissues in a constant direction with germ layer obtained tissues. Another specialty of embryonic stem cell is that they are able to split up in vivo, this is different from the adult stem cells that split separate from each other during death of the cell or tissue damage. The pluripotent stem cells play a vital role in forming endoderm, ectoderm and mesoderm (germ layers) except for the structures located outside the embryo.

Unlike pluripotent stem cells, multipotent stem cells can adapt to separate into cells of very many given cell descents. Hematopoietic stem cell is an example of this adaption, this kind of stem cell can give rise to many kinds of blood cells by hematopoiesis. Multipotent stem cells can further become an oligopotent cell after differentiation. The ability to differentiate will be restricted to cells of its derivation. Yet, these cells are able to convert into discrete cell kinds, which leads to identifying them as pluripotent cells (Fig. 1.3.) (Zakrzewski et al., 2019).

All cell types that can form an adult are *pluripotent*. From zygote to very early embryo and formation of the extraembryonic tissues of the foetus are *totipoten*t. In adults, stem cells can be limited to being multipotent. If a tissue has cells off a single differentiated lineage and stem cells are used to maintain this lineage, they are called *unipotent.* Adult stem cells can be reprogrammed to pluripotency by somatic nuclear transfer. Practical applications of inducing/reversing pluripotency in adult cells have become evident, with the formation of iPSCs. The transcription factors (TF) Oct4, Sox2, KLF4 and Myc are greatly expressed in ES cells. So, upregulation of such TF and so their target genes are thought to lead cells like fibroblasts (cells that produce collagen and fibres) to become pluripotent (Watt & Driskell, 2010).

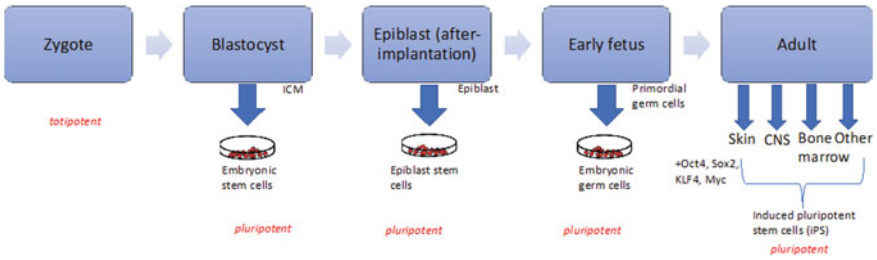

Fig. 1.3 Origin of stem cells

Both pluripotent and multipotent stem cells have pros and cons in their potential for exploration. Firstly, the ability of pluripotent cells to develop to any cell kind could be a curative benefit such as treating unhealthy or ageing tissues in which multipotent stem cells are inadequate. Secondly, proliferation of pluripotent stem cells is rapid, leading to a level of cellular production that may not be useful (Drukker et al., 2002). The benefit of this work is that the material is regarded as self. The immune system responses to particular epitopes presented on the surface of cells via the major histocompatibility complexes for immune cells to sample for signals as to if a cell is infected or has acquired non-self peptides and haptens. Self-confirming epitopes can also be displayed. Cells derived from the same (autologous) multipotent stem cells comprise of the patient's own particular proteins on the surface that permit it to considered self by the immune system of the host. Pluripotent stem cells are partly immune privileged and do not normally display the same signals for the immune system to form a rejection response. So, their use to treat other people as allogenic transplants may be valuable (Biehl & Russell, 2009). However, this is not well understood and seemingly even autologous iPSCs have been noted to be targeted by the immune system.

Nobel Prize Research on Stem Cells

In 2012, Sir John Gurdon was presented with a Nobel Prize when he was able to modify a frog egg cell so that it could grow into a typical tadpole. This was by substituting the nucleus of a Xenopus frog zygote cell with a nucleus from a tadpole enterocyte. Moreover, his work led to this sort of concept of animal cloning and modified the field of cell specialization and growth. Larry Goldstein also mentioned how Sir John Gurdon's work will be vital to teach how reprogrammed adult cells can behave like embryonic stem cells, including how to utilize the full repertoire of DNA instructions to form many kinds of adult cells. During the 1960s, it was unsure of what the future of the curative applications of this information might be.

Later in 2006, a researcher named Shinya Yamanaka helped respond what the future held for this field. He demonstrated how to reprogram a whole and transformed