Stem Cells: The Foundation of Regenerative Medicine

FATIMA AZAM[1*], SABA[1], AFNAN RASHID[2], AFSAH PERVAIZ[3], WAJEEHA AFZAL[1], AMIR KHAN[4], AYESHA BINTAY FAROOQ[5], RIMSHA JAMIL[1], SEHRISH GUL[6]

[1]Department of Zoology, Wildlife and Fisheries, University of Agriculture, Faisalabad, Pakistan
[2]Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan
[3]Institute of Microbiology, University of Veterinary and Animal Sciences, Lahore, Pakistan
[4]Department of Animal Sciences, Faculty of Biological Sciences, Quaid-e-Azam University Islamabad, Pakistan
[5]Department of Physiology, Government College University Faisalabad, Faisalabad, Pakistan
[6]Institute of Microbiology, University of Agriculture, Faisalabad, Pakistan
[*]Corresponding author: azam.ffatima@gmail.com

SUMMARY

This chapter reviews the present status in research on stem cell biology and its future prospects. The chapter encompasses topics from the biology of stem cells (SCs) to their application in therapy, ethical issues and future directions. They possess two definitive properties: self-renewal and pluripotency, which define them as unspecialized cells with the potential to differentiate into any cell type of their host. The review encompasses the wide sources of SCs, starting from embryonic and induced pluripotent SCs to statistical sources, adult tissue-derived SCs, explaining in detail their different characteristics and possibilities for application in therapy. These applications of SCs can be made for the treatment of several diseases and injuries, like neurodegenerative disorders, pinpointing Parkinson's and Alzheimer's diseases, ischemic heart disease, myocardial infarction, among many others and bone and joint injuries. This review is on the promise and problems associated with stem cell-based therapeutics; it, therefore, considers recent advances in the field, including improved knowledge of conditions for cell growth and novel options for cell delivery systems. It also includes discussion on ethical issues in stem cell research, problems in using embryonic SCs and ethical issues arising from the use of new technology CRISPR/Cas9.

INTRODUCTION

The SCs are undifferentiated cells that may grow into specialized organs or tissues, and with their capabilities of self-renewal, quite a bit of interest has been generated for biomedical research. The study related to SCs started in the 1960s when some Canadian researchers discovered hematopoietic SCs (HSCT). The following developments took place when (Thomson et al., 1998) isolation of embryonic SCs in the year 1998, and (Takahashi & Yamanaka, 2006) the identification of induced pluripotent SCs (iPSCs) in 2006. A review by (Trounson & DeWitt, 2022) separates promises from difficulties in translating treatments based on SCs into new clinical practices. Lin et al. (2023) takes one more step toward improving the stem cell transplant method by seeking fresh ways. Overall, given the historical perspective of this article and further discoveries afterward, the field of stem cell biology is in flux, opening up new ways to health and health technologies (Trounson & DeWitt, 2016).

DISCOVERY AND MILESTONES

Stem cell science has achieved some huge discoveries and achievements that have had considerable influence in the area of medical science. As for the analysis, there have been huge developments in the progress of this field in the two or three preceding years. Very astonishingly, the introduction of Takahashi and Yamanaka's (2006) induced pluripotent SCs was great news for personalized therapy in 2006. CRISPR-Cas9 gene editing by Doudna & Charpentier (2014) in SCs turned out to be efficient for both the improvement of accuracy and enabling genetic manipulation more effectively. Besides, the recent works, like those concerning muscle SCs by Sacco et al. (2008) have given evidence for the realization of tissue-specific SCs and therefore, gave an important impulse to the field of regenerative medicine.

IMPORTANCE OF SCS IN REGENERATIVE MEDICINE

Regenerative medicine will involve new methods of replacing or renovating damaged parts of the body to restore normal function. Some of the technologies that will be used for accelerating healing and regeneration include stem cell treatment, tissue engineering and gene therapy (Andersson & Lendahl, 2014). SCs remain important and among the most identified possible platforms for creating personalized therapies have been iPSCs. Newer advancements have

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included the manipulation of CRISPR-Cas9 gene editing to further enhance the efficiency of cell therapy with minimal immunological limitation. Among the relevant works are "Challenges in Regenerative Medicine" by Umemura & Morrison (2021) "Stem Cell Therapies for Tissue Repair" by Kou et al. (2022) "CRISPR-Cas9 in Regenerative Medicine" and "Advances in Tissue Engineering" and "Immunomodulation in Regenerative Therapies (Bahrami et al., 2021).

Significance in medical advancements

In the area of medicine, SCs are very important; for the future of medicine, they appear to be one of the most promising methods of therapy because they bear specificity, in that they are capable of growing into a lot of cell types. Its properties for self-renewal and differentiation have brought about advancements in the fields of regenerative medicine, tissue engineering and the treatment of a large form of diseases (Rai et al., 2020). Available research also mentioned the use of SCs for treating degenerative diseases, such as Alzheimer's and Parkinson's diseases. Such cells helped in restoring diseased tissues and organs, hence new methods of treatment were developed (Rai et al., 2020).

The works of Takahashi and Yamanaka, which became known in 2006, presented induced pluripotent SCs that would later turn adult cells into embryonic ones; thus, they are of great significance for regenerative medicine or disease models. Furthermore, in the year 2019, the study by Bargehr et al. (2019) introduced the use of SCs in cardiac repair and opened a new way toward heart disease treatments. Moreover, novel improvements in the genetic editing tools, such as the CRISPR-Cas approach described by Doudna & Charpentier (2014) allow for more effective targeting of therapeutic SCs. Certain research mentioned above underlines changes in the relevance of SCs that contribute to continuous development in biomedical science and propose new approaches for solving complicated healthcare problems.

TYPES OF SCS

Embryonic SCs (ESCs)

The ESCs are promising cells derived from the inner cell mass of blastocysts that have the potential to give rise to any human cell type; they are great genetic contributors in the study of developmental biology as well as regenerative medicine (Biswas and Hutchins, 2007). Recent research concentrates on their potential to treat various diseases and injuries and to produce limited cells for tissue repair. A breakthrough discovery in the field of ESCs was made by Takahashi and Yamanaka, (2006) known as the induced pluripotent SCs (iPSCs) with better ethical consequences.

Adult (Somatic) SCs

Adult or somatic SCs are a type of cell that can alter or differentiate into any type of specialized cell to repair and rebuild tissue in all regions of your body. They have been isolated from a wide variety of tissues, including bone marrow, fat tissue and within the brain their role is supposed to be one of maintaining homeostasis and preventing tissue dysfunction (Collins et al., 2013). Some studies in recent years have emphasized their application for various therapeutic purposes such as degenerative disorders and traumas. Research by Li et al. 2023 ensures the future treatment of diseases like spinal cord injuries. Since it was able to establish that adult SCs can differentiate into neural tissues. Study the somatic SCs and their contribution to heart healing and regeneration to further develop cardiovascular protocols of treatment. Mizumaki et al. (2023) studied the basis of the differentiation of adult stems into therapeutic lineages to advance their application. A superficial look at some of the more typical sources of SCs has been presented in Table 1.

Induced pluripotent SCs

The next revolution in regenerative medicine is foreseen to be Induced Pluripotent SCs (IPCs), reprogramming somatic cells to a more pluripotent state much like embryonic SCs (Fig1). When induced pluripotent SCs were identified, many of the ethical issues related to embryonic SCs were bridged and hence made much therapeutic benefit from that research study (Takahashi & Yamanaka, 2006).

EMBRYONIC STEM CELL SOURCES

Embryo development

The inner cell mass in the early stages of development is a valuable source of embryonic SCs for studying the diversity of mechanisms involved in cell differentiation and specialization. Due to this intense level of pluripotency, ESCs are remarkably solely capable of becoming any type of naturally occurring cell in the human body. This characteristic is perfect for medical research purposes, as embryonic SCs could potentially replace or repair damaged tissues (Reynolds et al., 2009).

The study by Alvarez et al. (2012) identified methods for the improvement of the derivation process of functional cell type from ES cells and hence overcoming significant challenges for their use in therapies. Such studies do point out

Table1. Brief overview of common types of SCs, their source and potency in our body

Type of Stem Cell	Source	Potency	Examples
Embryonic SCs	Embryos (blastocysts)	Pluripotent	Derived from early-stage embryos, can give rise to many cell types
Adult (Somatic) SCs	Adult tissues (bone marrow, adipose tissue, etc.)	Multipotent	Found in specific tissues, can differentiate into a limited range of cell types
Induced Pluripotent SCs (iPSCs)	Adult cells (e.g., skin cells) reprogrammed to behave like embryonic SCs	Pluripotent	Generated by reprogramming adult cells, can differentiate into many cell types
Fetal SCs	Fetal tissue	Pluripotent	Found in developing fetuses, can differentiate into many cell types

the importance of embryo development in taping the therapeutic potential of SCs.

Ethical Considerations

The ethical conflicts with the use of SCs for scientific research and medical treatment are extremely complex and serious. It has immense promise in the repair of damaged tissues, including a wide range of diseased or injured conditions and organs. However, its usage possesses moral implications that require consideration (Lo & Parham, 2009). One of the questions being asked concerns their origin. The application of human embryo-derived SCs presents controversy due to ethical issues in killing embryos. Adult SCs, present in many types of tissues, pose fewer ethical issues. Recent technology in iPSCs that can reprogram an adult cell into a state without the need for embryos resolves the ethical issues brought about by earlier technologies that required the destruction of embryos (Pera & Trounson, 2004).

ADULT STEM CELL SOURCES

Bone Marrow

Bone marrow serves as a reservoir of SCs that participate in the production of multiple types of blood cells. In particular, Hematopoietic SCs (HSCs) within the marrow possess the ability to self-renew and differentiate into erythrocytes, leukocytes and thrombocytes, all of which are crucial to maintaining the balance of circulatory functions. Due to the presence of this regenerative quality, bone marrow is looked upon as an attractive treatment prospect for developing remedies related to the treatment of blood abnormalities via stem cell transplantation and biotechnology research (Fig 2) by applying regenerative medicine (Dawn & Bolli, 2005).

Recent studies on the bone marrow microenvironment and its interactions with stem cell activity have enhanced our knowledge about how SCs are regulated (Morrison & Scadden, 2014). Current studies view the manipulation of bone marrow-derived SCs in treating neurological diseases, cardiac problems and autoimmune disorders (Vagnozzi et al., 2020). Tapping the potential of the produced SCs underlines their critical value for developing treatment modalities in a host of disease conditions.

Adipose Tissue

Adipose, more commonly referred to as fat tissue, is considered a rich source of mesenchymal SCs (MSCs) with very good prospects in the field of regenerative medicine (Fraser et al., 2008). These MSCs are capable of differentiating into several cell types, including but not limited to adipocytes, osteocytes and chondrocytes. Ease of accessibility by minimally invasive procedures like liposuction makes the ADSCs practical for therapeutic uses (Kim et al., 2021). Li et al., (2023) on the other hand, discussed the neuroprotective role of ADSCs in neurodegenerative disorders besides discussing their immune-modulatory role, proving their importance in immune-related diseases.

INDUCED PLURIPOTENT STEM CELL GENERATION

Methods of cell reprogramming have shifted production in generating induced pluripotent SCs (IPSCs) and have developed into a valuable resource in the research of regenerative medicine and pathobiology. Recent innovations in this field include new techniques, improvements in efficacy and safety and scalability (Warren et al., 2010). One interesting avenue of reprogramming involves the use of synthetic mRNA to transiently express the reprogramming factors without affecting the DNA itself, hence limiting the chance of genetic complications (Warren et al., 2010). Further development of safer strategies involved the use of episomal vectors and non-integrating viral vectors such as the Sendai virus. Small compounds, including modifier compounds aimed at inhibitors, also contribute to better reprogramming (Hou et al., 2013).

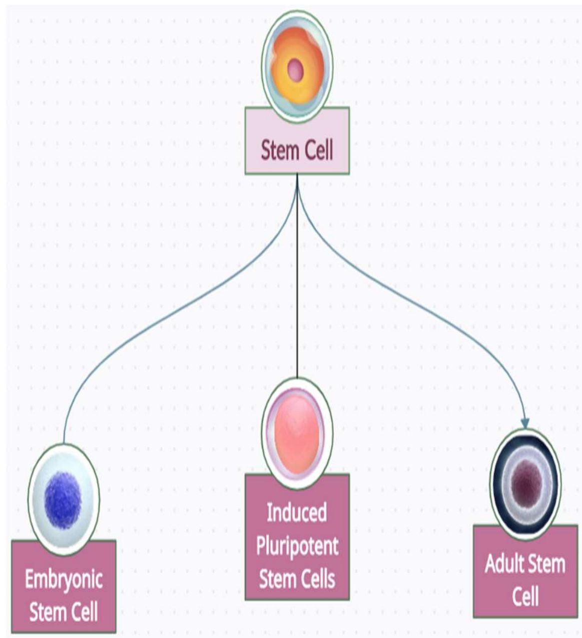

Fig 1. Types of Stem Cell

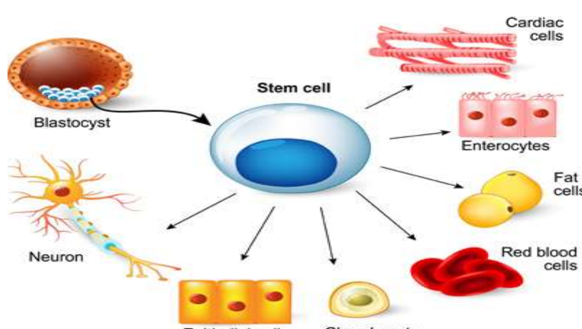

Fig 2. Resources of SCs in human body

TECHNIQUES IN STEM CELL ISOLATION AND CULTURE

Cell sorting technologies

One of the major applications regarding cell sorting in stem cell research is the correct gathering and culture of specific subsets of cells (Zhu & Murthy, 2013). Methods in use include techniques such as fluorescence-activated cell sorting (FACS) and magnetic-activated cell sorting (MACS) to isolate/purify the desired SCs, based on particular surface markers or other features, classifying the population of interest as a measured study for later use (Fraser et al., 2008). Modern cell-sorting techniques have immensely improved in efficacy and precision for isolating SCs. Advanced techniques include microfluidic devices and state-of-the-art flow cytometry systems, improving throughput and reducing the risk of sample contamination (Marzano et al., 2020). Such methods are relevant in the isolation of rare populations of SCs, which have great value in regenerative medicine and therapeutic purposes. These methods of cell sorting thus form an important approach in the isolation and culture of SCs and further support the development of regenerative medicine and research (Kamei, 2013).

Culture media and conditions

The medium and conditions are so crucial because, upon isolation, the process needs appropriate conditions for the proliferation of the SCs and the attainment of their general activities with minimal differentiation. Recent studies have shown the importance of optimizing culture conditions to improve the yield of SCs and their therapeutic potential (Costa et al., 2021). Employment of culture systems such as hydrogels and scaffolds has shown promise by better mimicking the microenvironment. Temporal modification of culture conditions can be achieved using release systems, thereby enhancing certain cell lineage differentiation processes (Li et al, 2023).

MICROENVIRONMENT INFLUENCE ON STEM CELL BEHAVIOR

It is considered to be the most important parameter controlling stem cell behavior which is commonly referred to as the stem cell niche. The local microenvironment, therefore, may include a range of physical, chemical and biological properties that are all fate determinants of a stem cell. Specifically, the mechanical properties of the microenvironment, such as stiffness and topography, bear strongly on the stem cell destiny vs. self-renewal. For instance, there is evidence that mechanical signals emanating from the microenvironment instruct the fate of mesenchymal SCs into specific lineages (Engler et al., 2006). Growth factors and cytokines are forms of chemical messengers that regulate SCs. They assist in regulating events such as growth, specialization and motility of the cells. Signaling molecules present in the environment influence how SCs make their "life choices" (Lutolf et al., 2009). Besides that, adhesion molecules and communication routes spur interactions between other cells within the niche that further regulate stem cell activity.

MECHANISMS OF STEM CELL DIFFERENTIATION

Signaling pathways

The process of the development of SCs is determined by complex signaling systems. In such a process, cell fate is determined. Wnt, Notch and Hedgehog have interconnected pathways as they influence developmental choices by regulating gene expression. Among the three pathways, during embryonic development, the Wnt signaling pathway plays an extremely important role that practically governs how SCs choose their fate (Nusse & Clevers, 2017).

Extracellular matrix interactions (ECM)

The development process of SCs is structured by the extracellular matrix. Such a relationship provides an important environmental clue. Upon interaction with the ECM, specific elements like fibronectin and collagen could initiate some signal-transmitting ways, such as Wnt and Notch, thus influencing the fate of SCs (Bonnans et al., 2014). The interaction of the cell with the ECM is a complex process that influences cell adhesion, migration, and communication. A family of integrins serves as cell surface receptors that mediate cell-ECM interactions, resulting in signaling within the cell (Juliano, 2002). The ECM includes many diverse components, which include collagen, fibronectin, and laminin that provide structural support and biochemical cues that direct cellular activities.

STEM CELL FATE DECISIONS

Wnt signaling

Wnt signaling now plays a central role in understanding how infants develop inside their mothers, how our body maintains health and how we become diseased. There are generally two types of Wnt pathways, those that tell whether genes are on or off, determining the type of cell we have and the proliferative rate (Piccin and Morshead, 2011). A new study implicates Wnt signaling in cancer, in brain disorders that make people forget things, and in how our bodies fight off infections. In its failure, Wnt signaling is associated with tumorigenesis in cancer (Zhao et al., 2021). In other words, disorders like Alzheimer's perturb this Wnt signaling, which would affect how well our brain cells communicate with one another. (Peri et al., 2023).

Hedgehog signaling

The Hedgehog signaling system (Hh) is essential in the development of various embryos, tissue homeostasis, and the pathogenesis of many diseases. It emanates when proteins, within which one is Sonic Hedgehog (Shh), are produced to initiate this pathway, which enables cells to act through a succession of steps. The Patched (ptch) protein present in the outer layer or membrane of the cell releases another protein termed Smoothened. This allows the activity of Smo to take place and initiate the activation of Gli transcription factors, which in turn regulate gene activity (Briscoe & Thérond, 2013). Research found that this route is critical for cancer, brain cell formation, and stem cell survival. When this route is not effectively managed, it can cause a wide range of health issues, making it critical for illness treatment (Ruiz i Altaba et al., 2007).

APPLICATIONS OF SCS IN REGENERATIVE MEDICINE

SCs potentially hold great promise in regenerative medicine, having the capacity to repair or replace tissues and organs that have been damaged.

Wound healing

These are activities that accelerate wound healing and tissue regeneration, hence the reason why SCs are effective in skin treatments and cosmetic surgery (Wu et al., 2021). They are very crucial for wound healing because they promote the regeneration and repair of tissues. Besides, MSCs possess anti-inflammatory properties which speed up wound healing and diminish scars. Also, embryonic SCs (ESCs) aid in tissue repair by transforming into other types of cells (Wu et al., 2021).

Cardiovascular regeneration

SCs have a vast potential for treating cardiac-related ailments. This is because studies by Sanganalmath & Bolli, 2013 indicate that they help to repair damaged cardiac tissues. The SCs can differentiate into cardiac cells; hence, this will enable the heart to mend and function effectively. This discovery is very hopeful for treating cardiac illness as both animal and human trials have evidenced. SCs have great potential in resolving cardiac diseases and developing new ways of treatments. It has also been documented in research that they possess the ability to differentiate into heart cells, thereby restoring heart tissue and recovering heart function after a heart attack (Kreke *et al.,* 2012).

CHALLENGES AND FUTURE PERSPECTIVES

Embryonic SCs are a source of ethical problems in stem cell research, including but not limited to killing embryos and their potential abuse (Iyer, 2021). Informed consent, the privacy of patients and equal dissemination of access to new medications are also other concerns (Thomson *et al.,* 1998; Lo & Parham, 2009). Applications of medical studies on stem cell therapies offer hope for many diseases. Up to now, promising results have been seen in the treatment of heart disease and neurological disorders. This illustrates one of the many ways in which SCs hold the key to changing treatment options for diseases and opening up new and exciting medicinal possibilities (Maumus *et al.,* 2020).

FUTURE DIRECTIONS AND EMERGING TECHNOLOGIES

CRISPR-Cas9 and gene editing

Gene editing, therefore, has a bright future ahead as scientists still improve and work out the kinks in the CRISPR-Cas9 technology. Recently, innovations have been made possible in the use of CRISPR for diagnostic tests such as DETECTR and SHERLOCK, improving the accuracy and flexibility of genetic modifications (Janik et al., 2020). Researchers are also studying CRISPR-Cas systems for uses other than protecting bacteria. This includes two new classes of the CRISPR-Cas12 and Cas13 types that further extend the gene-editing toolbox. However ethical discussions about gene modification in future generations are paramount, so it is important to continue discussing it and setting guidelines (Iyer, 2021).

3D bioprinting in regenerative medicine

The point is that the development of regenerative medicine goes within a bundle with the progress of 3D bioprinting. New research proposes using bioinks made from decellularized extracellular matrices to ensure cell viability and better cytocompatibility of the structures being printed (Yang et al., 2023). Furthermore, the integration of the 3D bioprinting technique with microfluidics can easily allow for the formation of complex networks of blood arteries inside the printed tissues, which is one of the huge challenges in tissue engineering (Gungor-Ozkerim et al., 2018). Currently, research is ongoing to combine bioprinting with iPSCs for the fabrication of personalized functional tissues for regeneration (Yang et al., 2023).

CONCLUSION

Thus, SCs have tremendous potential in regenerative medicine, which may, in the long run create new potentials to human health's problem-solving. These versatile cells can be transformed into specific kinds of cells so as to replace and repair damaged tissues and organs. Studies describe that SCs can be utilized in treatment protocols, that regenerative medicine is an approach whereby SCs can be used in the treatment of diseases concerning the heart, difficulties arising in cases of the brain and nerves, and an injury to the spinal cord. Several studies indeed have shown convincing evidence that SCs can regenerate or repair human body tissues. Takahashi & Yamanaka (2006), also presented a breakthrough in showing how adult cells could be reprogrammed into specialized SCs now called iPSCs, which may open up new avenues for the treatment of diseases based on specific individuals. In addition, Xia et al. (2018) represented the study results of embryonic SCs showing their ability to mend injured tissues.

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