https://ijmsweb.com

Indian Journal of Medical Sciences

Review Article

Stem cells: Current applications and future prospects

Dhanvin Richie Gupta[1], Sakshya Singh[1]

[1]Department of Biotechnology, Delhi Technological University, Delhi, India.

ABSTRACT

Stem cells are non-specialized cells that can differentiate into many kinds of cells. They have been an important part of research since their discovery due to their immense potential for treating many incurable diseases through various kinds of related therapies or procedures. Stem cell technology and research are developing rapidly every year. This paper summarizes the latest developments in stem cell research while also commenting about its future potential and the ethical concerns related to it.

Keywords: Stem cells, Regenerative medicine, Tissue engineering, Mitochondria, Cell differentiation

INTRODUCTION

Stem cells are immature non-specialized cells that can differentiate into multiple different types of cells depending on their potency and origin.[1]

Potency

A zygote cell is totipotent and can develop into any of the three germ layers (mesoderm, ectoderm, and endoderm) and form the placenta. The zygote develops into the blastocyst, where the inner cell mass (later, the embryo) contains pluripotent stem cells (PSCs) which can differentiate into any of the three germ layers but not any extraembryonic structure (placenta). The trophectoderm of the blastocyst develops into the placenta, which contains PSCs.[2] PSCs differentiate into multipotent stem cells which can differentiate into any cell of a specific lineage but converts into an oligopotent stem cell after differentiating. For example, a multipotent hematopoietic stem cell (HSC) differentiates into an oligopotent myeloid stem cell. An oligopotent stem cell can differentiate into multiple different cell types of a single lineage and an unipotent stem cell divides repeatedly into the same type of cell.[3]

Origin

Stem cells obtained from human embryos are embryonic stem (ES) cells and those obtained from developed organs and tissues are called adult stem cells. Adult stem cells are mostly used by the body to repair and replace damaged tissue. Furthermore, cells that are harvested from the umbilical cord after childbirth are called cord blood stem cells, stem cells found in amniotic fluid are called amniotic fluid stem cells, and stem cells obtained from the placenta are called placental stem cells. Cord blood stem cells are used to treat children with blood cancers.[4] Placental stem cells are a great source of fetal mesenchymal stem cells (MSCs).[2]

All stem cells are surrounded by a special environment inside the body called the niche. When the niche is changed due to some external stress such as injury or transplantation into a different environment, stem cells show the property of plasticity. This means they can differentiate into a wider variety of cells required by their new surroundings. For instance, skin sweat gland stem cells, when transplanted into mammary fat pads, can form milk-producing glandular structures. Inside the body, along with nearby stem cells replenishing a vacancy, committed progeny can also dedifferentiate and assume the same role.[5]

In addition, it is possible to convert adult stem cells into PSCs, called induced PSCs (iPSCs).[6] They can be used as an alternative to ES cells.[7]

SOME CURRENT APPLICATIONS OF STEM CELLS

Stem cells are being used in a wide variety of ways ranging from developing artificial organs for research and transplantation to even mitochondrial therapy. Some of these developments are–

***Corresponding author:** Dhanvin Richie Gupta, Department of Biotechnology, Delhi Technological University, Delhi, India. dhanvinrichie@gmail.com

Received: 14 August 2023 **Accepted:** 07 September 2023 **EPub Ahead of Print:** 16 November 2023 **Published:** 07 February 2024 **DOI:** 10.25259/IJMS_178_2023

HSC transplantation

Healthy HSCs can be transplanted into patients suffering from various types of bone marrow or blood disorders such as leukemia, lymphoma, and tumors to replace the dysfunctional bone marrow cells. The transfer can be autologous (cells originating from the patient), allogeneic (cells originating from a different person), or syngeneic (cells originating from identical twins).[8] Bone marrow transplants have a long history and have become a standard medical procedure.[9]

HSC therapy (HSCT)

HSCT has been used to treat multiple sclerosis in clinical trials. Multiple sclerosis is an autoimmune disease targeting the central nervous system. The traditional approach for the treatment of multiple sclerosis is disease-modifying therapy (DMT). DMT targets the immune system by modulating it, alternating the immune cell trafficking, or reducing the immune cell population. However, it requires long-term administration and can have serious side effects. The clinical trials of HSCT have produced better results than DMT.[10]

Placental stem cell therapy

Placental stem cells have shown promising results and potential in healing and curing diseases in various parts of the body such as Alzheimer's, liver diseases, pancreatic diseases, myocardial infarction, muscle dystrophy, lung fibrosis, and large lytic lesions in bones. They also have applications in tissue engineering.[2]

Autologous limbal stem cells (holoclar) transplantation

Autologous limbal cell culture contains stem cells (holoclones) that can be used to treat patients with loss of corneal epithelium.[11] Burns to the eye may lead to loss of vision by destroying the limbus or causing limbal stem cell deficiency.[12] Holoclar has been formally approved in Europe for moderate to severe limbal stem cell deficiency in adults.[13]

Development toward artificial organ engineering

When stem cells are cultured in a 3D environment, in permissive growth conditions without any external input, they multiply and differentiate into structures like their origin. These structures mimic organs, including providing the niche for stem cells, and are called "organoids." Organoids show a level of organization that is not replicable with current technology, but they show heterogeneity in size, shape, cell composition, etc., from culture to culture. These organoids are used for various studies.[14]

Hollow organ engineering

Stem cells show promising results in the engineering of hollow organs such as trachea and vagina. There is a case report showing the successful use of autologous stem cells for the successful production of trachea.[15] Stem cells can be used to engineer new trachea for patients suffering due to mustard gas.[16] The use of appropriate scaffold along with MSCs can form the basis for developing artificial vagina for treating many diseases which are ignored or have non-effective treatments.[17]

Anti-aging effects

The aging process is characterized by molecular mechanisms, including DNA damage, telomere shortening, loss of proteostasis, mitochondrial dysfunction, and stem cell exhaustion.[18] Adipose-derived stem cells promote mitophagy and increase mitochondrial production while also reducing reactive oxygen species, eventually changing the cell metabolism to resemble youthful cells. The pathways related to the metabolism of nucleotides and those associated with mitochondria are enriched as well.[19]

Minimizing mitochondrial injury

Mitochondrial dysfunction plays an important role in the pathogenesis of many seemingly unrelated diseases such as neurodegenerative disorders, cardiac diseases, sepsis, cancer, diabetes, and fluoroquinolone-associated disability.[20] MSCs accelerate mitochondrial recovery, promote mitophagy, and induce the transfer of healthy mitochondria in cells suffering from mitochondrial damage or dysfunction.[21]

Treatment of diabetes

Multiple types of stem cells have been used to treat diabetes in clinical trials.[22] Diabetes mellitus can be caused by lifestyle choices and genetic inheritance (type 2 diabetes), autoimmune causes (type 1 diabetes), or even hormonal changes due to pregnancy (gestational diabetes).[23] Typical treatment of diabetes includes injection of insulin, but it poses an issue due to high insulin costs and the temporary nature of the treatment.[24] Stem cells can solve this problem by directly healing the pancreatic cells. In addition, diabetes-related injuries such as non-healing wounds are being treated using stem cells.[25]

Disease modeling and study of differentiation

Since their development, iPSCs have been used by scientists in a variety of ways for studying the pathogenesis of diseases, for inventing novel ways of iPSC formation, for studying the inheritance of genetic diseases, for studying neurodegenerative diseases, etc.[7]

Cell-free therapy

Cell-derived membrane-bound vesicles and extracellular vesicles (EVs) from stem cells such as exosomes have been shown to have effects such as neuroprotection, neuroregeneration, neural development, and improvement in neural function. The use of EVs reduces the risks and limitations of cell-based therapy, being non-invasive, crossing blood–brain barrier, and being non-tumorous.[26]

Wound healing

Stem cells promote cell proliferation and cell differentiation at the wound site, help in the control of immune response, and contain antibacterial properties due to the secretion of antimicrobial factors. The use of autologous stem cells removes the possibility of immune rejection.[27]

Treatment of burn wounds

Stem cells show better potential and results in treating burn wounds than currently available methods. Using stem cells by direct injection, tissue-engineered grafts or exosome treatment shows promising results in burn wound healing.[28]

Significance in research

Stem cells are being used to study diseases such as congenital heart disease, and neurodevelopmental defects and for the study of the effects of the environment on cell and tissue development.[29]

CURRENT LIMITATIONS

Many factors are currently holding back stem cell research, causing its slow development.

Some of these factors are as follows – problems in culturing most stem cells,[30] conventional 2D culturing techniques being expensive and inefficient for culturing stem cells, difficulty in mimicking the stem cell niche, loss of capacity to differentiate during culturing, lack of standardized 3D culturing techniques, lack of proper scale up techniques, etc.[31]

PSCs may result in the formation of teratoma (benign tumors, containing tissues of all germ layers) when injected into the body.[32]

Cultures studying placental stem cells all result in a mixture of different types of cells; it is challenging to get specialized cells in high purity in a sustainable way.[2]

Furthermore, the introduction of stem cells into the body can result in an immune response.[33]

Therefore, better and more efficient therapies need to be developed.

FUTURE PROSPECTS

Stem cells in gene editing

By combining stem cell technology with gene editing methods like CRISPR-Cas9, new opportunities for treating hereditary disorders and fixing genetic flaws are made possible. Gene-edited stem cells may be used to treat genetic diseases and lessen the chance of damaging mutations being passed onto future generations.

Stem cells for autoimmune illnesses

The immune deficiencies suffered due to AIDS can be treated using stem cells.[34] They control the immune system and encourage tissue regeneration, holding potential for treating autoimmune illnesses. Future studies will concentrate on creating secure and efficient stem cell treatments for diseases such as type 1 diabetes, rheumatoid arthritis, and multiple sclerosis.

Regenerative medicine

In the field of regenerative medicine, damaged or diseased tissues and organs can be repaired or replaced with healthy cells derived from stem cells. This could revolutionize the treatment of conditions such as heart disease, Parkinson's, spinal cord injuries, and more.

Personalized medicine

With the advent of iPSCs, it is now possible to derive stem cells from a patient's cells, creating an unlimited source of personalized cells for therapeutic use. IPSCs can be genetically matched to the patient, significantly reducing the risk of immune rejection, and enabling tailored treatments for various medical conditions.

Tissue engineering

Organoids can be used for drug testing, disease modeling, and personalized medicine, paving the way for more precise and efficient treatments.

Artificial organs and body parts

In the not-so-distant future, we might witness the creation of fully functional artificial organs and body parts using stem cells. This could potentially alleviate the organ shortage for transplants and provide customized solutions for patients in need.

ETHICAL AND MORAL CONCERNS

The distinction between labeling human ES cells as embryos or specialized body tissue significantly impacts their ethical

acceptability.[35] This distinction influences individuals' opinions, with some valuing embryos' protection and others attributing little moral status to early embryos.

At present, three potential sources for stem cells exist: Adult stem cells from donors, ES cells from fragmented preimplantation embryos, and embryonic stem cells from aborted fetuses (EG cells) from aborted fetuses.

Harvesting stem cells from naturally aborted fetuses raises fewer moral issues but faces practical challenges due to the difficulty of isolating functional EG cells from spontaneously aborted tissue. Approximately 60% of spontaneous abortions result from fetal anomalies, with chromosomal abnormalities identified in 20%.[36]

The use of ES or EG cells obtained from elective abortions raises specific moral questions for those opposing abortion or the destruction of early embryonic life. This dilemma leads to concerns of complicity with perceived wrongdoing, particularly in religious contexts like Roman Catholicism.

Comparing a somatic cell's potential to be cloned to an embryo's potential development reveals that the former may have more developmental potential. Embryonic disk cells, the source of stem cells, naturally contribute to human development. However, separated from the embryo, these cells cannot form essential structures for further development, distinguishing them as pluripotent rather than totipotent.

Advanced technology might potentially render these cells totipotent, as demonstrated in a 1993 Canadian study using genetically altered embryos and mouse stem cells to grow and populate an entire organism.[37]

THE INDIAN PERSPECTIVE

HSCs harvested from cord blood are being used to treat over 80 diseases including leukemia, bone marrow failure syndrome, phagocyte disorders, and leukodystrophy disorders.[38] Lifecell stores and preserves cord blood to treat many disorders the baby might be suffering from.[39] Bone marrow-derived stem cells are being used for treating knee osteoarthritis, diabetic foot, and ischemia by companies such as Stempeutics.[40] Peripheral blood stem cells are being used for the treatment of Lyme disease.[41] The Institute for Stem Cell Science and Regenerative Medicine, Department of Biotechnology, and Government of India manages several excellent research facilities focused on stem cell research and development, with the aim to become the leading institute for stem cell research and application in India.[42] The raising of clinical researchers is needed to bridge the gap between clinicians and scientists.[43]

CONCLUSION

The use of human stem cells for research is already the subject of widespread public discussion. While the future of stem cell research holds great promise, it is imperative to address the challenges and ethical considerations that come with such groundbreaking advancements. The journey of stem cell research has only just begun, and the possibilities are boundless.

Acknowledgment

We thank Dr. Richie Gupta for overall guidance during the preparation of this manuscript.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Zakrzewski W, Dobrzyński M, Szymonowicz M, Rybak Z. Stem cells: Past, present, and future. Stem Cell Res Ther 2019;10:68.
2. Oliveira MS, Barreto-Filho JB. Placental-derived stem cells: Culture, differentiation and challenges. World J Stem Cells 2015;7:769-75.
3. Alison MR, Poulsom R, Forbes S, Wright NA. An introduction to stem cells. J Pathol 2002;197:419-23.
4. Cafasso J. Stem cell research: Uses, types and examples; 2017. Available from: https://www.healthline.com [Last accessed on 2023 Sep 01].
5. Gola A, Fuchs E. Environmental control of lineage plasticity and stem cell memory. Curr Opin Cell Biol 2021;69:88-95.
6. Ye L, Swingen C, Zhang J. Induced pluripotent stem cells and their potential for basic and clinical sciences. Curr Cardiol Rev 2013;9:63-72.
7. Singh VK, Kalsan M, Kumar N, Saini A, Chandra R. Induced pluripotent stem cells: Applications in regenerative medicine, disease modeling, and drug discovery. Front Cell Dev Biol 2015;3:2.
8. Khaddour K, Hana CK, Mewawalla P. Hematopoietic stem cell transplantation. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.

gov/books/NBK536951 [Last accessed on 2023 May 06].
9. Mayo Clinic Staff. Bone marrow transplant; 2022. Available from: https://www.mayoclinic.org/tests-procedures/bone-marrow-transplant/about/pac-20384854 [Last accessed on 2023 Sep 01].
10. Atkins H. Stem cell transplantation to treat multiple sclerosis. JAMA 2019;321:153-5.
11. Trounson A, McDonald C. Stem cell therapies in clinical trials: Progress and challenges. Cell Stem Cell 2015;17:11-22.
12. Rama P, Matuska S, Paganoni G, Spinelli A, De Luca M, Pellegrini G. Limbal stem-cell therapy and long-term corneal regeneration. N Engl J Med 2010;363:147-55.
13. Benstetter M. First stem-cell therapy recommended for approval in EU. Netherlands: European Medicines Agency; 2014. Available from: https://www.ema.europa.eu/en/news/first-stem-cell-therapy-recommended-approval-eu [Last accessed on 2023 Sep 01].
14. Brassard JA, Lutolf MP. Engineering stem cell self-organization to build better organoids. Cell Stem Cell 2019;24:860-76.
15. Elliott MJ, De Coppi P, Speggiorin S, Roebuck D, Butler CR, Samuel E, *et al*. Stem-cell-based, tissue engineered tracheal replacement in a child: A 2-year follow-up study. Lancet 2012;380:994-1000.
16. Khazraee SP, Marashi SM, Kaviani M, Azarpira N. Stem cell-based therapies and tissue engineering of trachea as promising therapeutic methods in mustard gas exposed patients. Int J Organ Transplant Med 2018;9:145-54.
17. Henckes NAC, Faleiro D, Chuang LC, Cirne-Lima EO. Scaffold strategies combined with mesenchymal stem cells in vaginal construction: A review. Cell Regen 2021;10:26.
18. Mc Auley MT, Guimera AM, Hodgson D, Mcdonald N, Mooney KM, Morgan AE, *et al*. Modelling the molecular mechanisms of aging. Biosci Rep 2017;37:BSR20160177.
19. Lv M, Zhang S, Jiang B, Cao S, Dong Y, Cao L, *et al*. Adipose-derived stem cells regulate metabolic homeostasis and delay aging by promoting mitophagy. FASEB J 2021;35:e21709.
20. Lowes DA, Wallace C, Murphy MP, Webster NR, Galley HF. The mitochondria targeted antioxidant MitoQ protects against fluoroquinolone-induced oxidative stress and mitochondrial membrane damage in human achilles tendon cells. Free Radic Res 2009;43:323-8.
21. Zhao L, Hu C, Zhang P, Jiang H, Chen J. Mesenchymal stem cell therapy targeting mitochondrial dysfunction in acute kidney injury. J Transl Med 2019;17:142.
22. Päth G, Perakakis N, Mantzoros CS, Seufert J. Stem cells in the treatment of diabetes mellitus - Focus on mesenchymal stem cells. Metabolism 2019;90:1-15.
23. NIDDK. Symptoms and causes of diabetes. United States: NIDDK; 2016. Available from: https://www.nih.gov [Last accessed on 2023 Sep 01].
24. WebMD Editorial Contributors. Understanding diabetes--diagnosis and treatment; 2021. Available from: https://www.webmd.com [Last accessed on 2023 Sep 01].
25. Lopes L, Setia O, Aurshina A, Liu S, Hu H, Isaji T, *et al*. Stem cell therapy for diabetic foot ulcers: A review of preclinical and clinical research. Stem Cell Res Ther 2018;9:188.
26. Nasiry D, Khalatbary AR. Stem cell-derived extracellular vesicle-based therapy for nerve injury: A review of the molecular mechanisms. World Neurosurg X 2023;19:100201.
27. Ayavoo T, Murugesan K, Gnanasekaran A. Roles and mechanisms of stem cell in wound healing. Stem Cell Investig 2021;8:4.
28. Abdul Kareem N, Aijaz A, Jeschke MG. Stem cell therapy for burns: Story so far. Biologics 2021;15:379-97.
29. Artinger KB, Watanabe M. Introduction to "Stem Cells" special issue. Birth Defects Res 2022;114:921-5.
30. Choumerianou DM, Dimitriou H, Kalmanti M. Stem cells: Promises versus limitations. Tissue Eng Part B Rev 2008;14:53-60.
31. McKee C, Chaudhry GR. Advances and challenges in stem cell culture. Colloids Surf B Biointerfaces 2017;159:62-77.
32. Amariglio N, Hirshberg A, Scheithauer BW, Cohen Y, Loewenthal R, Trakhtenbrot L, *et al*. Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient. PLoS Med 2009;6:e1000029.
33. Miller KK, Schrepfer S. Stem cell transplant immunology. In: Ieda M, Zimmermann WH, editors. Cardiac regeneration: Cardiac and vascular biology. Vol. 4. Cham: Springer; 2017.
34. Chapman AR, Frankel, MS, Garfinkel MS. Stem cell research and applications monitoring the frontiers of biomedical research. United States: American Association for the Advancement of Science; 1999. Available from: https://www.aaas.org/sites/default/files/content_files/Stem%20Cell%20Research%20and%20Applications%20Report.pdf [Last accessed on 2023 Sep 01].
35. In testimony before the senate appropriations subcommittee on labor, health and human services, education, and related agencies, John Gearhart discussed in general how his laboratory collected tissue from therapeutic abortions. Testimony on stem cell research; 1998. Available from: https://www.c-span.org/video/?116037-1/embryonic-stem-cell-research [Last accessed on 2023 Sep 01].
36. Boué J, Bou A, Lazar P. Retrospective and prospective epidemiological studies of 1500 karyotyped spontaneous human abortions. Teratology 1975;12:11-26.
37. Nagy A, Rossant J, Nagy R, Abramow-Newerly W, Roder JC. Derivation of completely cell culture-derived mice from early-passage embryonic stem cells. Proc Natl Acad Sci U S A 1993;90:8424-8.
38. Diseases treated with stem cells and its potential applications. Available from: https://www.cordlifeindia.com [Last accessed on 2023 Sep 01].
39. Your baby is born with the power of stem cells! Available from: https://products.lifecell.in/EMI-Agency-Apr2023-ggl-smart?gclid=EAIaIQobChMIgJ3bv4mRgQMV7ieDAx1PdAMQEAAYAyAAEgJkKfD_BwE [Last accessed on 2023 Sep 01].
40. Helping lifesavers save lives. Available from: https://www.stempeutics.com/ [Last accessed on 2023 Sep 01].
41. Stembrella. Our head doctor @ Stembrella. Dr Ashish Verma has been a pioneer in the area of stem-cell propagation in India since the early 2000s; 2023. Available from: https://www.facebook.com/573210309721788/photos/our-head-doctor-stembrelladr-ashish-verma-has-been-a-pioneer-in-the-area-of-stem/601308750245277/ [Last accessed on 2018 Sep 01].
42. About us (n.d). Available from: https://instem.res.in/about-us [Last accessed on 2023 Sep 01].
43. Kandhari R. Good and bad stem cell research: How India's scientists view providers of unproven stem cell treatments. SSM Qual Res Health 2023;3:100278.

How to cite this article: Gupta DR, Singh S. Stem cells: Current applications and future prospects. Indian J Med Sci. 2024;76:2-6. doi: 10.25259/IJMS_178_2023