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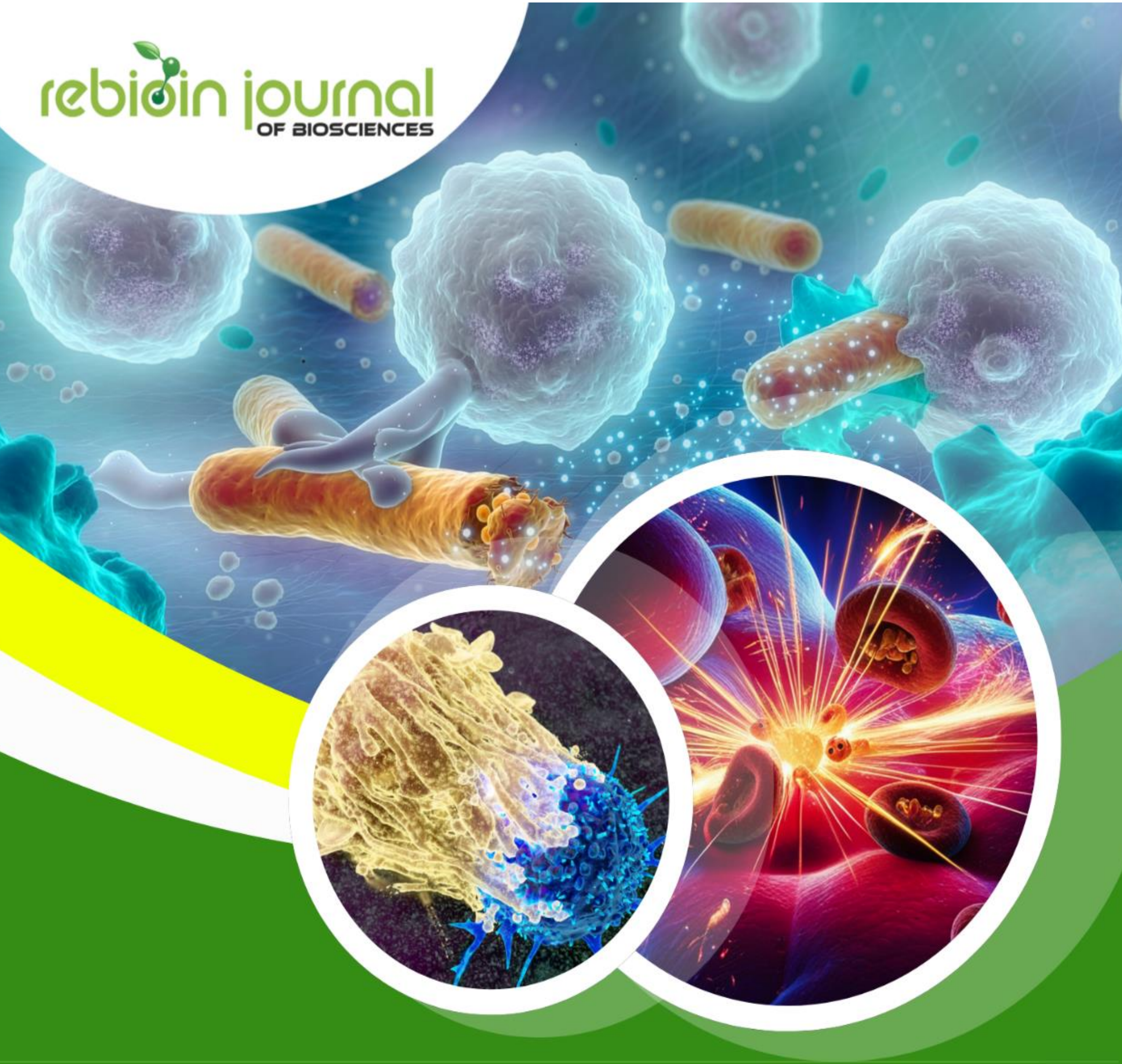

TRANSFORMING HEALTHCARE: CURRENT ADVANCEMENTS AND POTENTIAL APPLICATIONS OF STEM-CELL TREATMENT

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Transforming healthcare: current advancements and potential applications of stem-cell treatment

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Abstract

Stem Cell Therapy - The Next Generation of Regenerative Medicine Stem cell therapy is a rapidly developing area of advanced medicine. Part of this development has been the discovery of the unique properties of stem cells which allow them to self-renew and differentiate into a wide variety of specialized cell types. These features of stem cells are the foundation for and contribute to their important role in regenerative medicine, offering tremendous possibilities for repairing and regenerating damaged tissues and treating diseases that previously could not be treated.Foundational concepts regarding stem cell biology were established during the late nineteenth and early twentieth centuries, as scientists such as Boveri, Häcker, Maximow and Cohnheim performed pioneering work in embryology and established the principles of stem cell biology. Milestones in the field of stem cell therapy include the discovery of embryonic stem cells in 1981 and the development of the induced pluripotent stem cell in 2007, which allowed for expanded therapeutic applications and lessened the ethical concerns associated with obtaining embryonic stem cells.While stem cell-based therapies offer great promise, the clinical translation of these therapies is limited by many obstacles, including immune rejection of transplanted stem cells, the potential for tumor generation from transplanted stemcells and the need for precise control of the destiny and function of stem cells. Recent advances in biotechnology, such as the use of exosomes for drug delivery, the use of single cell RNA sequencing, and the use of CRISPR-Cas9 gene editing technology, have improved the accuracy with which stem cells can be managed and have expedited the development of stem cell therapies that will take place clinically. Stem cell therapies for regenerative medicine are subject to regulatory oversight by multiple agencies to ensure patient safety, efficacy, and the proper use of stem cell therapies for treating patients.

1. Introduction

Stem cell therapy is an exciting new direction in medicine that utilizes the unique and extraordinary power of stem cells to develop novel treatments for a wide range of diseases. Stem cells are important to the field of regenerative medicine because they have the ability to develop into many different types of cells and can replicate themselves indefinitely. The ability of stem cells to repair and regenerate tissues is incredibly exciting and has the potential to change the way we treat diseases[1,2].An essential part of stem cell research began in the late nineteenth and early twentieth centuries with the works of Boveri, Häcker, Maximow, and Cohnheim and the development of embryology[3].Beginning in 1986, these pioneers established a basis for understanding the basic principles of stem cells as well as understanding how they function during development and repair of tissues. Their original insights are the basis for a current wave of investigations into stem cells which continue to expand our understanding of their biological importance[3,4].The first important milestones in stem cells were the finding of embryonic stem cells (ESCs), by Kaufman and Evans in 1981[5,6,7],and the discovery of induced pluripotent stem cells (iPSCs), by Thomson in 2007[8]. There is great promise and potential for stem cell therapy; however, there are significant clinical translation challenges (e.g.; immunological rejection, tumorigenesis, and very specific approaches to manipulating stem cell behaviour in order to maximize the potential of stem cells for therapeutic outcomes)[9]. These challenges represent significant barriers that must be thoroughly examined and that require innovative solutions[1,10,11,12]. With the rapid development of biotechnological tools, particularly through exosome therapeutics, single-cell RNA sequencing (scRNA-seq), and the CRISPR-Cas9 system as a new genetic engineering approach (CRISPR)[13,14,15], precision genome modification has been made realizable; enabling the creation of genetically altered organisms and applications across a spectrum of areas from biosciences to the pharmaceutical industry[16,17]. New treatments for people with no other way to manage their medical condition -this is the focus of regenerative medicine. There have been many different types of research studies on stem cells over the last several years due to the positive results seen in pre-clinic trials. The development of these types of therapies is regulated based on the guidelines and requirements established by the appropriate regulatory bodies, and include drug approval through the development, manufacturing and distribution of regenerative medicines.[18]. There are four main sources of stem cells for the purposes of tissue engineering and cellular therapies. These primary sources of stem cells either come from embryonic and fetal sources (with the major locations of the embryo/fetus being placenta with the chorion and amnion, umbilical cord (commonly referred to as Wharton's jelly), or specific tissue types found within the adult: blood, skin, skeletal muscle, adipose tissue, and bone marrow. The other major category consists of somatic cells, which have been genetically reprogrammed so they are different than they were originally, the most common form of genetically reprogrammed somatic cell are induced pluripotent stem cells (iPSCs)[19].

2. Recent developments in the study of stem cells

In recent years, the amount of knowledge surrounding stem cell biology has significantly increased because of many new advancements in the field of stem-cell research[20]. One of the advances includes new strategies to improve our ability to assess stemcell fates. Furthermore, researchers have shown that several important signaling pathways as well as several key transcription factors can regulate the differentiation of stem cells[21,22]. The Notch signaling pathway is an essential cell communication systemrequired for normal growth, function and other physiological processes[23]. Several studies show how important the Notch Pathway is for determining cellular fate, differentiating between cell renewal (i.e., cells continue to divide) and cell differentiation (i.e., become specialized stem cells). Examples include embryonic stem cells (ESCs)[24], pluripotent stem cells (PSCs)[25], hematopoietic stem cells (HSCs)[26], neural stem cells (NSCs)[27], intestinal stem cells (ISCs)[28], etc. Other examples of pathways include PI3k/AKT[29] and TGF-β[30]. Stem cells and their role in developmental processes and stem cell derived from embryonic stem cells are all regulated by an NF-κB transcription factor (NF-κB)[31]. These will increase the ability to manipulate stem cells for specific therapeutic uses and create unprecedented opportunities for intervention through targeted cells[32]. Recently, the nuances involved in lineage determination and subsequent differentiation of cells have been studied in the area of embryonic stem cell development. Researchers have determined the regulatory networks that regulate the process of differentiation of distinct cell types from stem cells, providing insight into how molecular events lead to cell fate[33,34].

In addition to these exciting advances, scientists have found new information regarding the epigenomic changes that happen to cells during their reprogramming process, allowing us to better understand how somatic cells Became Pluripotent[35].For example, several studies have shown that during iPSC formation, gene expression and the identity of these newly formed cells will largely be determined by changes in the patterns of DNA methylation that occur after they have been reprogrammed[36].Modification of histones by acetylation and methylation is important to gene regulation and chromatin structure, but also plays a major role in reprogramming capabilities. Understanding how different types of epigenetic pathways are used will further clarify how complex the pluripotent induction and cellular reprogramming processes are.

The development of new technologies has helped to improve iPSC-derived technologies for drug discovery, disease modeling, and personalized regenerative medicine. A second major development in stem cell research has been the area of tissue regeneration[37].

Table 1.

S.no.	Conditions	Stem cell type	Application	Conclusion	Reference
1.	**Cell differentiation ,reprogramming and regeneration**	Wharton's jelly-MSCs (WJMSCs)	To examine the influence of nanostructures on the WJMSCs differentiating into motor neuron lineage following exposure to sonic hedgehog and retinoic acid.	WJMSCs are a good source of stem cells that can generate and repair motor neurons.	38

2.	**Alzheimer disease**	Corpus cerebrospinal fluid produced from iPSC (CNSC-SE)	5 µg/g CNSC-SE that was produced using iPSC or r/iPSC until 12 weeks was the overall dosage given.	The CNSC-SE can be created from human iPSCs and can be used for neurogenesis and dendritic morphogenesis.	39
3.	**Parkinsons disease**	ADMSCs	The 4 categories of study subjects were as follows: control group, sham group, treatment cell group and lesion group. The treatment cell group received an intravascular injection of MSCs (adipose derived; ADR).	ADMSs could also be used to treat patients with Parkinson's disease by increasing the number of TH+ neurons.	40
4.	**Cardiovascular diseases**	iPSC-derived cardiomyocyte (iPSC-CM)	Administered dosages to the treatment cell group were between 2 x 10^5 and 4 x 10^8 cells. The follow-up was done from 1 week after treatment to 12 weeks after treatment.	The methodology of iPSC-CM therapy can safely enhance heart functioning for individuals having an infarction.	41
5.	**Orthopedic conditions**	Autologous-ADMSC	There were three categories of thirty cases,	ADMSC therapy can be safely used as well to prevent	42

			two of which received a single injection or two injections of 100x106 ADMSCs (one injection at the beginning and one injection at six months later), and the third category was the control group.	the occurrence of these disease processes.	
6.	**Hematological condition**	Allogeneic stem-cell transplantation (allo-SCT)	Among 104 patients who received an allogeneic stem cell transplantation (allo-SCT),	In addition, patients receiving Allo-SCT have shown significant benefits.	43
7.	**Diabetes**	UC-MSCs	73 received three serial infusions of umbilical cord mesenchymal stem cells (UC-MSCs), at 4-week intervals. All patients were monitored for 48 weeks after their last dose.	Using umbilical cord mesenchymal stem cells is a viable method for decreasing time to onset of type II diabetes; mesenchymal stem cell-derived exosomes have demonstrated anticancer activity.	44
8.	**Cancer**	MSC-exosomes	Four different cell cultures were used including ACHN, LNCaP, 5637	mesenchymal stem cell-derived exosomes have demonstrated anticancer	45

			and PC3, and are accepted as genuine models of hormone-sensitive prostate tumor derived from kidney and bladder tissues. The cell lines received multiple dosages of exosomes from mesenchymal stem cells.	activity.	
9.	**Autoimmune diseases**	MSCs	Functional, normal mice, known as the 'negative' mice, were infected with 48 hr of intravenous injection of either Lactobacillus delbrueckii (D-MSC), rhamnosus (R-MSC) group (Naïve MSC). The functional group consisted primarily of Lupus mice (Lupus MS), which received intravenous	administration of mesenchymal stem cells with Lactobacillus strains may mitigate symptoms consistent with lupus.	46

			injections of D MSC or R-MSC after receiving MS from D and R from MS for 48 hours post.		
10.	**Covid-19**	hUCMSCs	Subjects from both groups that received Human umbilical cord mesenchymal stem cells (hUC-MSC) therapy over a period of three months were assessed in order to identify both positive and negative effects of hUC-MSC therapy.	umbilical cord mesenchymal stem cells were indicated to potentially be an initial success and overall safety for patients with COVID-19.	47

3. Stem-cell treatment in particular medical domains

Stem cell-based regenerative medicine has examined its vast potential to provide numerous innovative treatment options for challenges throughout a wide variety of different medical specialties[48].Patients may undergo harvesting of their own stem cells (also known as autologous stemcells), which are cultured or expanded in the laboratory and then re-injected into the same patient. Autologous stem cells can be classified into two main categories: modified autologous or unmodified autologous (expanded). Similarly, allogeneic (donor-derived) stem cells can also be classified as modified or unmodified expanded, and are derived from healthy donors[49]. Autologous stem cell acquisition is straightforward and will not generate an immunological response after infusion. Allogeneic stem cell sources offer multiple advantages, such as the ability of selecting a donor from different sources, have minimal chances of initiating an immune response and are immediately available. In addition, allogeneic MSC's are immunogenic therefore capable of generating an immunological response and have the potential to be remembered by the immune system under certain situations[50,51,52].

Regenerative medicine is the field of medicine that deals with repairing, restoring, or regenerating tissue and organ function by utilizing the unique properties associated with stem cell biology[53].Within this umbrella term, there are many different approaches and ways to take advantage of the vast potential that exists with stem cells for use in medicine. While stem cells can self-renew (create copies of themselves) and be differentiated (transformed) into many different cell types, stem cells also have the potential to be used as therapeutics for treating a variety of diseases and injuries[54].

This new area of research has great potential to develop individualized cancer treatment options. Researchers are looking at how using the distinct characteristics of stem cells will lead to new ways of managing and possibly curing cancer. This research signals a dramatic change in the way that oncologists will think about treating cancer, but also provides hope for innovative therapies and new breakthroughs in cancer treatment[55,56].Cancer treatments that use stem cells are proving to be more effective each day. Stem cells are capable of not only finding and attacking the main tumor as well as metastatic tumors but can also serve as bee hives to deliver new types of drugs through modification. In studies with small animals, stem cells with different cytotoxic chemicals attached consistently produced smaller tumors and increased the likelihood of survival[57,58].To reduce side effects and enhance the effectiveness of medicine (primary medicine), the use of stem cells to carry viruses and/or nanoparticles has led to new ways that stem cells can be used. For example, stem cells are a possible treatment alternative for Immunotherapy," a way of destroying the cancerous cells using the patient's immune system. In addition, stem cells could provide treatment options for Anticancer Drug Screening, Regenerative Medicine, and Cancer Stem Cell Targeted Treatment on many different types of cancer such as osteosarcoma, lung cancer, and breast cancer[59].

Advanced regenerative strategies in orthopedics encompass osteonecrosis of the hip joint (advanced), intervertebral herniations,osteoporosis,targeted injuries to joints,restoration of cartilage,and repair of bone utilizing stem cells and tissue engineering methods through these same methods[60,61].Recent research has also uncovered several novel techniques including the development of MSC, the use of PRP injections, and the development of a biocompatible scaffold with the addition of growth factor[62].These are the new methods of treating MPC and demonstrate positive results for optimizing cartilage repair/bone regeneration[63,64].

Innovations within cardiology include using stem-cell therapy and bioengineered cardiac patches to repair damaged and/or regenerate heart tissue due to heart problems like an MI[65]. Much of the current work being conducted in industry and academia is being conducted using different types of Stem Cells (iPSCs and Cardiac Progenitor Cells) to regenerate damaged cardiac muscle; thus, restore cardiac function. Similarly, work is being conducted on bioengineered cardiac patches using scaffolds and the same type of biocompatible materials used in reconstructive surgery to create patches that are designed to function as real heart tissue[66].

Currently, the regenerative medicine area of research in dermatology is an area of rapidly evolving scientific study with respect to stem cell use in skin[67].The stem cells in the skin have great potential to lead to new treatment options for many different types of dermatological disorders and injuries[68].The ability of these stem cells to regenerate is also expected to have significant future benefits for improving wound healing, treating burns, and treating skin diseases like psoriasis and vitiligo[69,70].The use of stem cells in cosmetic dermatology for anti-aging and skin quality improvement are both examples of their wide-ranging clinical uses[71].

There has been great interest in the role of stem cells in the rejuvenation of the retina and cornea, particularly in the treatment of macular degeneration[72].Recent publications, including "Investigative Ophthalmology and Visual Science" and "British Journal of Ophthalmology," have explored advances in the use of stem cells for regenerating the eye[73,74].The use of stem cell therapies to replace retinal cells and repair corneal disease offers exciting possibilities for treating a number of vision-related disorders[75].

Stem cell use in the fields of cancer treatment, regenerative medicine, and treatment for disease has become an ever-expanding field of exploration and innovation[76]. Stem cells are being explored for their use in cancer treatment, as well as their potential ability to reprogram cells and modify the immune systemto help fight tumors[77].Because stem cells have potential for use as an immunomodulator, there is great interest in using them in the area of biomedical research for the treatment of autoimmune diseases and graft-versus-host disease (GVHD) and for improving transplant outcomes[78].The ability of stem cells to significantly change how immune cells function presents tremendous opportunities for new therapies[79].

The use of stem cells within the field of hematology involves a changing field of exploration and application within scientific and professional domains related to regenerative medicine and providing treatment for illnesses[80]. The purpose of research is to examine how to utilise their capacity to regenerate through primarily the use of HSCs, along with evaluating the use of HSCs in transplanting bone marrow and in providing immune cell therapies as a means of addressing various types of blood-related illnesses[81]. This expanding area holds great promise as an avenue for providing new therapies to individuals by demonstrating that stem cell utilization will change how diseases are treated within hematology and provide new methods to cure or provide biologically-tailored treatments for individuals with blood disorders will ultimately represent a significant change in disease management[82,83].

Research involving stem cells may help to treat diseases associated with the gastrointestinal systemlike Inflammatory Bowel Disease (IBD)[84,85].There are stem cell-based therapies being explored for different therapies including uses of stem cells to help heal injuries to the gastrointestinal tract, improve healing of ulcers, and alleviate symptoms associated with chronic conditions like Crohn's Disease and Ulcerative Colitis[86,87].

Research in dentistry is now centered around the new use of stem cells to regenerate the important parts of teeth; that is, enamel, dentin, and dental pulp[88].This type of research is changing the way we think about teeth and provide dental services. The goal is to provide high-quality treatment options for the most common dental problems such as cavities, gum disease, or trauma to the teeth[89]. By harnessing the regenerative potential of stem cells, scientists hope to find ways to induce the body's natural ability to regenerate and heal damaged or diseased dental tissue and, in doing so, fundamentally change oral health care[90,91].

4. Advancement in stem cell by using biotechnology

Advances in biotechnology, which focus on developing ways to use and work with stem cells, have greatly aided in the propagation of stem cell research through new and innovative technologies that have helped researchers better understand these versatile cells. The following paper explores a few biotechnological advancements made in stem cell research, including exosome-based treatments, single-cell RNA sequencing (scRNA-Seq), and the revolutionary gene-editing technology known as CRISPR/Cas9.

5. Future prospects

Stem cell therapy has the potential to significantly change many different aspects of medicine with the assistance of new technologies and the findings of ongoing research. One primary approach is to incorporate stem cell therapies into individualized approaches to delivering medicine (precision medicine). This represents a new chapter in the history of medicine where, based on a patient's genetic makeup, we will be able to deliver more customized care that will produce superior therapeutic outcomes, and fewer side effects. Due to advances in genomics (the study of genetic material) and the growing use of patient specific stem cells, this type of integration will continue to become more prevalent in our healthcare system. Future research will also need to investigate how to optimize immune modulation strategies related to stem cell therapies and will need to address issues such as immune rejection and graft-versus-host disease. Many creative methods, such as engineering stem cells and utilizing immunomodulatory molecules, are being researched with the intent of increasing compatibility of individuals receiving stem cell therapy.

6. Conclusion

A significant development in regenerative medicine is providing for self-renewal and differentiation ability of stem cells to allow for tissue repair and treatment of previously untreatable diseases as part of the therapy using stem cells.The ability to differentiate into multiple types and to self-renew provides the basis for their therapeutic benefits.Research has been accelerated through many important milestones related to the development of stemcells, including embryonic and induced pluripotent stem cells.Clinical application of stem cells is limited by numerous factors including immune rejection, tumor formation, and the ability to control the fate of stem cells.New technologies such as exosome therapies, single-cell RNA sequencing, and CRISPR/Cas9 technology will help improve the safety and efficacy of stem cell therapies. With the advances made in genomics and in patient-specific applications, stem cell therapy has the potential to revolutionize precision medicine by providing individualized therapies with greater effectiveness and fewer side effects. Future studies that focus on immune modulation and compatibility will be crucial to overcoming obstacles such as immune rejection and graft-vs-host disease.

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