Stem Cell-Derived Therapies for Tissue Repair and Regeneration

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Abstract- Stem cell-based regenerative medicine holds immense promise for addressing organ shortages, chronic diseases, and tissue regeneration. Stem cell research has evolved significantly since Maximow's discovery of hematopoiesis in 1902, culminating in transformative breakthroughs such as the development of induced pluripotent stem cells (iPSCs) by Yamanaka in 2006 and the application of mesenchymal stem cells (MSCs) in COVID-19 treatment in 2020-2021. This article explores the historical milestones, clinical applications, emerging technologies, and future prospects of stem cell research. From the transplantation of cardiac and blood vessel cells for cardiac regeneration to the development of neuronal tissue engineering through electrical stimulation, the potential of stem cell-based therapies in treating various animal diseases, including heart failure, spinal cord injury, and neurodegenerative diseases, is elucidated. Additionally, the role of MSCs in improving local microenvironments for stress urinary incontinence treatment and managing inflammatory diseases through their immunomodulatory properties is examined. This comprehensive review highlights the transformative impact of stem cell research on regenerative medicine and underscores the need for continued innovation in addressing the challenges and limitations of stem cell-based therapies.

Keywords: Regenerative Medicine, Tissue Repair, Stem Cell Therapy, Organ Transplantation, COVID 19.

INTRODUCTION

The history of medical research is rich, beginning with the landmark work of Maximow in 1902, who discovered hemopoiesis, and Mathe in 1958, who performed the first bone marrow transplant utilizing stem cells. The area has advanced over the years through important discoveries made by McCulloch & Till, Evans & Kaufman, and Thomson. Yamanaka's creation of induced pluripotent stem cells (iPSCs) in 2006 was a game-changer for regenerative medicine. Mesenchymal stem cells (MSCs) were used in COVID-19 treatment in 2020–2021, which is a significant advancement in stem cell research that began with Atala's isolation of stem cells from amniotic fluid and continued with other ground-breaking discoveries.

A stem cell is a type of tissue cell that, in healthy conditions, reproduces to create new, functioning tissue cells and maintains its own population without decreasing in size or function. The daughters' attainment of their functional stage may or may not require additional differentiation and/or maturation [1]. The stem cells can be categorized according to where they are found. For instance, adult stem cells are found in an adult, embryonic stem cells are found in an embryo, and cord blood stem cells are found in the umbilical cord. Each of these three types of stem cells has its own name. Additionally, stem cells are categorized according to the features of their differentiation; totipotent, pluripotent, multipotent, oligopotent, and unipotent stem cells, for instance, are the five main types of stem cells. A stem cell line is characterized as a multipotent, clonal, self-renewing cell population that may produce multiple differentiated cell types. It is mainly identified based on its potency, origin, and lineage development [2]. The fields of regenerative medicine and stem cell biology are still in their infancy. On the other hand, stem cells have garnered a lot of attention lately, maybe as a result of their potential for treatment of many illnesses [3]. The field of regenerative medicine focuses on developing novel treatments to replace or rejuvenate the body's aging, damaged, or missing cells in order to restore function. Collaborative work in the fields of stem cell biology, genetics, bioengineering, materials science, non-mammalian and human development, and tissue engineering are helping to achieve this aim. Currently, the field's focus is on comprehending human reparative processes that are already in place as

well as investigating the potential for tissue regeneration [4]. If clinical obstacles can be addressed, especially with regard to their potential tumorigenicity, regenerative medicine, which is predicated on the transplantation of tissue native cells (such as myocytes, chondrocytes, etc.) or stem cells capable of differentiating into somatic cells, has enormous potential. This was demonstrated in a case study on a child who had fetal neural stem cells (SC) implanted to cure a neurological disorder; sadly, the transplanted neural stem cells later caused the child to develop a multifocal glioneuronal tumour.

In the past 20 years, numerous studies have been published in this field. The ability of cells to divide, multiply, and contribute functionally to the regenerative processes is necessary for the regeneration of injured tissue or organs. Heart failure, atherosclerosis, osteoarticular disorders, diabetes, and liver illnesses are a few potential middle-term therapeutic uses [5].

The cornerstone of stem cell-based regenerative medicine is the Replacement, Regeneration, and Rejuvenation paradigm, which provides several approaches to tissue repair. In regeneration, progenitor cells are engrafted to grow and differentiate in vivo, reconstituting functioning tissues, whereas replacement therapy includes transplanting cellular-based products to restore tissue function. Conversely, rejuvenation comprises natural tissue recycling mechanisms that substitute younger cells for older ones in order to increase tissue survival and stress tolerance. The historical turning points, medicinal applications, evolving technology, and potential applications of stem cell research are all covered in this article. It is detailed how stem cell-based therapies may be used to cure a variety of animal conditions, including heart failure, spinal cord injuries, and neurodegenerative illnesses [6].

These treatments include the development of neural tissue engineering through electrical stimulation as well as the transplanting of heart and blood vessel cells for cardiac regeneration. Despite these developments, there are still challenges facing the field of regenerative medicine, including ethical dilemmas, regulatory impediments, immunological rejection, and unknown long-term outcomes. Stem cell-based therapies, however, show much promise for treating chronic diseases, organ shortages, and tissue regeneration in addition to symptomatic care. This has led to a fresh round of innovative medical research [7].

There are studies that also examines the potential immunomodulatory effects of mesenchymal stem cells (MSCs) in the management of inflammatory diseases and in improving local microenvironments for the treatment of stress urinary incontinence.

TABLE.1: Significant Milestones in the field of Stem Cell Biology

YEAR	SIGNIFICANT ENDEVOUR
1902	ALEXANDER M. MAXIMOW discovered haematopoiesis [8].
1958	GEORGE MATHE performed bone marrow transplant the first therapy using stem cell [9].
1963	ERNEST Mc CULLOCH & JAMES TILL found self-renewing property in bone marrow cells of mice from transplanted cells [10].
1981	MARTIN EVANS AND MATHEW KAUFMAN first isolated and cultured ESCs from which later leads to formation of the model organisms [11].
1988	JAMES THOMSON had isolated human embryonic stem cell for the first time [12].
2005	SCIENTISTS in Kingston university had purported they had found another type of stem cell [13].
	HWANG WOO-SUK claimed that he been created several HESCs from unfertilised oocytes [14].
2006	SHINYA YAMANAKA and his team had been successfully converted fibroblast into pluripotent stem cells [15].
	SCIENTISTS at Newcastle university created first artificial liver cells using cord blood stem cell [16].
2007	Dr ANTHONY ATALA and his team claimed that they have been isolated a new type of stem cell from amniotic fluid [17].
2008	CLINICIANS FROM REGENERATIVE SCIENCE had published study of cartilage regeneration in human knee by using the adult MSCs [18].
2009	AUSTRALIAN SCIENTIST found a way to improve chemotherapy of mouse muscle stem cells [13].
2010	GERON OF MENLO PARK had treated spinal injury by derived hESCs [19].
2013	SHOUKHRAT MITALIPOV has been produced hESCs from felt cells by therapeutic cloning [20].
2014	CHARLES VACANTI and HARUKO OBOKATA discovered that any cell can be potentially rewound to a pre-embryonic state [21].
	DIETER EGLI independently produce hESCs from adult cells resulting demonstrating it can be turned into beta cells which produced insulin [22].

2015	CRISPR-cas9 technology has been involved in hESCs gene editing [23].
2017	Report on iPSCs-derived retinal cells for macular degeneration treatment [24].
2020-2021	Clinically MSCs are applied for COVID - 19 treatment [25].
2022-PRESENT	Clinical trials for Parkinson's disease (PD) treatment involving the transplantation of dopaminergic neurons derived from PSCs, aiming to replace damaged cells are currently underway [26].

STEM CELLS IN REGENERATIVE MEDICINE

Medical Research (RM) is often seen as a cutting-edge field of study, however, the concept of constructing artificial organs is not entirely new. In 1938, the author of "The Culture of New Organs" (by Alexis Carrell, who was awarded the Nobel Prize for his research on vascular anastomosis) published a book with the co-author of the same title, Charles Lindbergh. Lindbergh, who was the first person to fly over the Atlantic solo, was perplexed as to why his brother-in-law, who had a fatal heart condition, could not have it surgically repaired. Despite not being a medical professional, Lindbergh eventually collaborated with Carrell at the Rockefeller Institute of Medical Research in the 1930s to develop an artificial perforation pump, which enabled the perfusion of organs outside of the body during surgery; their work laid the foundation for the artificial heart. Recovering body parts is a common occurrence in nature; for example, an amputated limb can be regenerated by a salamander in a matter of days [27]. When a fingertip has been amputated in a young child, there is an extraordinary ability for the finger to regenerate if given the opportunity and if the injury can be treated with a non-invasive technique [28]. In ancient times, the potential for human regeneration was well-known, as evidenced by the legend of Prometheus, whose liver was consumed by an eagle in one day and regenerated itself in a single night [29]. Although modern medicine has achieved a number of successes in this area, such as the use of antibiotics, anaesthesia, and sterilization, there are still a number of pathologies that cannot be cured by preserving the organs, but necessitate resection of lesions, autologous tissue repair, or even the use of allografts for replacement [6]. Short bowel syndrome is a difficult condition for gastroenterologists to treat, as it necessitates a combination of medical, nutrition, surgical and psychosocial therapies. Treatment should be tailored to the patient's age, residual gastrointestinal anatomy, nutritional baseline and general health, as well as to the associated complications [30]. Augmented cystoplasty may be necessary for individuals with high-pressure or inadequately compliant bladders. This procedure involves the use of a portion of the small intestine to repair the bladder. As gastrointestinal tissues absorb solutes rather than releasing them, a repaired bladder is often subject to complications such as an increase in mucous production, infection, metabolic disorders, urinary tract disorders, perforation, and even cancer [31]. When it comes to organ replacements, 1954 was the first time a human was replaced with a kidney, but it was between identical twins so it didn't cause rejection. Later on, cell transplantation was also done – an immunocompromised patient got their brother's bone marrow. Initially, transplants were only used for research because of the bad immunological reactions, but with the introduction of ciclosporin in the 1980s, transplantation became a life-saving treatment because it could drastically reduce the risk of rejection. Nowadays, transplantation has a lot of side effects, which is one of the two biggest issues when it comes to organ transplants. The other is the lack of donors – they can't keep up with the ever-growing demand for organs. As the population ages, more and more people will need transplants to replace organs that have become diseased due to age-related diseases [32]. Social Security, or OASDI, as it is formally known, is chronically underfunded (as measured by the actuarial balance). OASDI's reserves, held on deposit with the Federal Reserve, will run out in 2033, even though there isn't any money there. Surpluses built up after the 1983 Amendments expired in 2010. The "reserves" have since been poured into other government programs and liabilities. In addition to the economic and social implications of these issues, the prevalence of chronic diseases, such as invalidating conditions, is impacting a relatively small portion of working-age citizens. For example, in 1941, the average number of workers per retired person in the United States was 41; however, today, the number of workers per retiree is only three [33]. So, medicine is facing a lot of challenges that need to be solved and medical treatments need to be changed. Regenerating damaged tissue is called "the fourth R" and it could totally change modern medicine and give us a new way to treat things instead of just treating symptoms [34].

Strategies for regenerative medicine:

The scope of Stem Cell Based Regenerative Medicine is defined by the Convergent Repair Triad of Replacement, Regeneration, and Genuinely Rejuvenated Parts. The R3 paradigm of therapeutic repair emphasizes that these approaches overlap in practice, while intrinsic distinctions conceptualize the field of regenerative medicine. From transplantation of pre-existing parts ('replacement') to the creation of new components ('regeneration') to induction of regenerative self-renewing parts ('rejuvenation'). The scope of Stem Cell Based Regen" rati'e Medicine is defined by the Convergent Repair Triad of Replacement, Regeneration, and Genuinely Rejuvenated Parts. The R3 paradigm of therapeutic repair emphasizes that. These approaches overlap in practice, while intrinsic distinctions conceptualize the field of regenerative medicine. From transplantation of pre-existing parts ('replacement') to the creation of new components ('regeneration') to induction of regenerative self-renewing parts ('rejuvenation') [6].

Replacement:

Replacement strategy is the transplantation of a cellular-based product that restores homeostasis to the recipient by continuing the tissue function of the donor [17]. The field of surgery pioneered replacement with the development of solid organ transplants. If the heart had been damaged beyond the capacity to palliate the disease, then the only option was to replace the diseased tissue by a functioning donor heart. Cell-based replacement is used in addition to solid organ transplants to replace circulating blood to increase the oxygen carrying capacity and treat life threatening blood loss or anaemia. Replacement strategy "recombin" the "used parts" of cells, tissues or organs to restore physiologic function. One major limitation of replacement strategy is the lack of adequate donors and the challenge of matching immunological criteria to ensure a safe and successful transplantation [35].

Regeneration:

Regenerative Strategy is the practice of engrafting progenitors that are required to grow and differentiate in vivo in order to maintain the homeostasis of the recipient in a de novo manner through the stem cell-based transplant. Advancements in haematology led to the development of regenerative strategies by identifying bone marrow derived stem cells that, upon harvest, could be implanted in small quantities in the peripheral blood, thereby engrafting and reconstituting the functional bone marrow through the continuous generation of the entire hematoencephalic system. The success of this approach was largely due to the presence of the host bone marrow, which provided a protective barrier to sustain the long-lived progenitor stem cells. This strategy "restores" function by "renewing" the pool of functionally functioning progenitors, allowing for differentiation as required from exogenously derived stem cells. Efforts are currently being made to identify tissue-specific nonhematopoietic stem cells that are capable of re-establishing lost function through ectopically transplantation into a broad range of malignant tissues, including diabetes, ischaemic heart disease and degenerative neurodegenerative diseases [36].

Rejuvenation:

Tissue recycling is a natural process that allows cells to be replaced as they age with younger, more resilient cells that are better equipped to tolerate stress and support tissue survival. Daughters are derived from the cell cycle that is reactivated in mature cell types under (physiologically) pathological stress. In a regenerative strategy, tissue is "renewed" from the stem cells that are present in the body. By "renewing" the tissue structure, the stem cells are "recycled" for proactive tissue regeneration. Rejuvenation ensures that the body produces the renewable tissue that is needed for long term stress tolerance. However, most tissues can only partially regenerate themselves. A biological or pharmacological treatment is likely to stimulate an adaptive response and support adequate biogenesis for functional tissue in acute and progressive disease. An inherent repair strategy might not be sufficient in the case of massive acute injury such as a myocardial (heart) infarction [37].

Application of MSCs in regenerative medicines in animal models

Cell based therapy can be used in treatment for different animal diseases. The self-renewal and the ability to differentiate multi lineage of stem cells can be very beneficial in the regenerative medicines it can treat the diseases which conventional medicines can't cure. Embryonic stem cells, adult stem cells are used in the regenerative medicines. Not only that embryo

derived stem cells which reprogrammed from adult stem cells which is named pluripotent stem cells. In clinical trials biomaterials which are the biocompatible and biodegradable materials used to reduce cell loss and long-term in vitro retention of stem cells, is used in drug and cell delivery system, tissue engineering and regenerative medicines.

Heart failure

MSCs are one of the effective agents used to treat cardiovascular regenerative therapy. Bone marrow derived mesenchymal stem cells transplantation used and it helps in the functions in non-ischemic cardiomyopathy, and this study conducted in the rabbit by. another study, discovered that the transplantation done in the ovine model of heart failure by cord blood stem cells, improved the right ventricular mass, systolic right heart function and diastolic right heart function this leads to the improvement of the heart function. MScs are really effective for cell transplantation, includes vascular endothelial cells, and provide anti apoptotic and angiogenic mediators. Disorders with vascular deficit, umbilical cord blood mesenchymal stem cells (UCBMSCs) are used as a therapeutic element. Both small and large animals used as models which have both advantages and disadvantages.

Advantages of small animal models include their ease of handling, lower maintenance costs, and shorter lifespan, making them convenient for research. Additionally, in small animals, ischemia-reperfusion induced arrhythmias are infrequent and easily reversible if they occur, making them suitable for specific studies. Small animal models can also be perfect for producing transgenic strains due to their genetic manipulability. However, small animal models cannot be used effectively in chronic studies, and their phylogenetics differ from humans, impacting the generalizability of findings. Moreover, their reaction to pharmaceuticals may not always accurately reflect human responses. On the other hand, larger animal models are ideal for chronic studies and demonstrate responses to techniques similar to humans. They also have a closer resemblance to the human heart, which can be advantageous in cardiac research. Nevertheless, larger animal models come with drawbacks such as longer lifespans, higher costs, and limitations in producing transgenic strains, which can affect the feasibility and scope of certain research projects [38].

IHD

Ischemic heart diseases (IHD) are one of the most dangerous cardiovascular diseases. This causes by the death of myocytes. Stem cells treatments are most beneficial for IHD. The loss of cardiomyocytes leads to IHD and by using stem cell transplantation can cure and produces cardiomyocytes. Xenogeneic stem cells, allogenic stem cells, autologous stem cells are the types of stem cells used in the treatment for IHD. MSCs are another type of stem cells which uses in the treatment of IHD. Using MSCs injection in the necrotic tissue can cause high cell proliferation and this can reduce the chance of apoptosis this would be beneficial as a treatment method. Some of the cons using the EMSCs in the treatment for cardiovascular diseases is that it causes formation of teratoma in rodent models and face some legal issues for the use of EMSCs. Stem cells are most commonly used in tissue engineering rather than other types of cells. Especially MSCs are used in the tissue engineering fields [39].

Stem cell in spinal cord repair

Using stem cells for treatment in the spinal cord injury become new invention recently, and this become improving the neuroprotection and neuroregeneration of damaged tissues. Undifferentiated neural stem cells and iPSC have the ability to adapt the damaged environment and it produce lesion produced secretome. MSCs found in the bone marrow, adipose tissue, Wharton's jelly, dental pulp, skin and peripheral blood and MSCs are very much beneficial role in the treatment for spinal cord injury. Secretome is also used for the regenerative medicines. Secretome contains EV (extracellular vesicles) they participate in the cell-to-cell communications and EV contains nucleic acids such as mRNA, microRNA and tRNA which contains signals that is useful for the therapeutic effects. Intravenous administration of stem cell derived EV has the ability to reduce neuronal apoptosis, microglia activation and neuroinflammation. MSCs are likely to produce secretome in vitro that are used therapeutically, undifferentiated transplanted NSCs or iPSCs are able to adapt to the injured environment and produce the composition of a given lesion-induced secretome. Developing and studying about the stem

cell in the spinal cord injury can be very beneficial for the future and can study further more to understand the positive and negative sides of this therapeutic methods [40].

MSCs in Covid 19 treatment

MSCs are type of stem cells can be used in multi treatments in human diseases also treatment for Covid 19. After the Covid 19 some of them developed a disease called Acute Respiratory Distress Syndrome (ARDS). Not everyone developed into those condition and it's a serious damage to the lungs. Clinical trials states that MSCs are safe to use as treatment for lungs diseases. There is lots of similarities between human lung MSCs and bone marrow MScs. Having a high rate in survival and being more efficient than other stem cells it's a best element for treating post Covid 19 lung disease. In the future the further understanding and study of MSCs can be great regenerate medicine and treatment for systematic diseases [41].

Wound healing and Neurodegenerative disease treatment in animal models

MSCs can be used for most common conditions such as wound healing. Cytokines and growth factors provide best result for wound healing which highly present in MSCs which is derived from dental tissues [42].

Having multiple therapeutic uses MSCs can be used in the treatment for Alzheimer, Parkinson and other neurodegenerative diseases. For treating Parkinson disease in a rat animal model iPS cells are used through this the dopamine neurons function properly. BMSCs have the ability to decreases the amyloid deposition in the brain which can be beneficial for the Alzheimer treatment [38].

Clinical Cardiac Regeneration applications

Plasticity refers to the ability of stem cells to change into immature cell types outside of their original lineage as a result of microenvironmental signals. For instance, HSCs that are transplanted into (the murine) the myocardium may be able to change into cardiac (cardiomyocytes) and blood vessel (blood vessels) cells, resulting in improved cardiac function and survival [43]. It has been proposed that bone marrow cells may be capable of extensive cardiomyocyte regeneration via trans differentiation post-infarct. However, in bone marrow-derived cells are being utilized in clinical studies, the identity, longevity, and fate of such cells in infarrhythmiated myocardium has yet to be studied in detail. In this study, various approaches were employed to induce acute cardiac injury and to transport transgenically labelled bone marrow cells into the myocardium that had been injured. It was demonstrated that unfractionated bone marrow cells, as well as a purified subset of haem apheresis-derived stem and progenitor cells, were effectively engrafted within the myocardium following infraction. However, the engraftment was only transient and haematopoietic in nature. On the other hand, bone marrow-derived cardiac exudates were observed at a low incidence outside the myocardium and were exclusively derived through cell fusion [44]. It looks like the science behind stem cell therapy is a lot more complicated than we thought it would be. It's been suggested that stem cells release ligands that help with angiogenesis, stop cardiomyocytes dying, increase the number of cardiomyocytes in the body, and even recruit local cardiac stem cells. But basically, everyone agrees that stem cell therapy can help improve blood flow and contractile function in the heart that's been hurt [43].

APPLICATION OF REGENERATIVE MEDICINE

Electrical stimulation within a conductous scaffold may be beneficial in promoting stem cell differentiation toward a neuron phenotype. To enhance stem cell based regenerative therapies it is important to use conductous scaffolds with suitable stiffnesses to control the amount and delivery of ES. Biodegradable, electroconductous substrates with varying stiffnesses are manufactured from Chitosan Grafted-Polyaniline Co-polymer (CS-GPPAN). Human mesenchymal stem cells (hMSC) cultured on conductous scaffolds exhibit a morphological alteration with significant filoplastic elongation post-electrical stimulation, along with an increase in neuron markers and a decrease in glial markers (Glial Fibrillary Acute Protein (GFAP), and Glial Fibrillary Acid (Vimentin)) expression after ES. In comparison to stiff conductous scaffolds or non-conductous CS scaffold, soft conductous CS-GPPAN scaffolds promote an increase in MIC2 (Microtubule-Associated Protein 2) and NF-H (Neurofilament) expression post-ES. Additionally, the increase in intracellular Ca2+ (Ca2+) during spontaneously

induced Ca2+ transient cells (Ca2). Based on these results, the use of a soft conductive substrate with ES is an exciting new approach for improving the results of neuronal tissue engineering [45].

Brain Organoids are 3D structures derived from Human Pluripotent Stem Cells (HPSCs) which reflect the early organization of the brain. Brain organoids contain a variety of cell types similar to those of the human brain, such as neurons, glia, and more. Human Brain Organoids offer a unique opportunity to model characteristics of the human brain that are not adequately represented in conventional cell culture and animal models. Brain Organoids provide a more precise representation of the human brain's development and functioning, making them an appropriate model for neurodegenerative diseases. Brain Organoids derived from patient cells have enabled the study of diseases at various stages of development and improved understanding of the mechanisms of disease. Multi-Brain Regional Associeties (MBRAs) allow for the exploration of interactions between different brain regions while obtaining a higher degree of consistency in Molecular and Functional characterization. Despite their promising features, the usefulness of Brain Organoids is limited by a number of unresolved constraints, such as Cellular Stress, Hypoxia, Necrosis, Limited Maturation, and Circuit Formation [46].

Corneal Endothelial Disease (CED) is a major contributing factor to the occurrence of Corneal Blindness. The conventional approach to treat this condition is to transplant the affected cornea using a donor cornea from a deceased individual. However, the global shortage of donor graft material has necessitated the development of new therapeutic approaches. One promising approach is a stem cell approach to regenerative medicine. This approach is based on the concept of induced pluripotency (iPSC). iPSCs have the capability to regenerate themselves, can be obtained from adult somatric cells, and are capable of distinguishing between all cell types, including Corneal Endothelial Cells (CEC) [47].

Stress urinary tract (SUI) treatments are ideal non-invasive treatments for SUI. MSC (mesenchymal stem cells) treatment is a novel modality but there is little research in the area of gynecologic pelvic floor and no effective method to induce endogenous MSC homing for SUI improvement. In this study, we developed an injectable self-healing hygienic hydrogel from the β-chitel family which is composed of the amino group of QC (quaternized beta-chitin) and the aldehyde group (oxidized dextran) between dynamic Schiff base linkages. This hygienic hygienic c vaginal hydrogel carries bFGF and sDF-1a, and can be administered non-invasively into the vaginal forelimb of mice in the early stages of treatment. In the late stages, it slowly releases factors and promotes in vivo homing of MSc's, which improves local microenvironment, increases collagen deposition, repairs tissue surrounding urethra, and ultimately improves SUI [48].

The role of MSCs in regulating inflammatory processes has been the focus of much research in recent years. MSCs are currently being studied for their therapeutic potential in a variety of degenerative and inflammatory diseases including Crohn's disease, graft-vs-host disease, diabetes nephropathy, organ fibrosis and more. The mechanisms behind MSCs' therapeutic actions are complex, but in general they are thought to allow damaged tissues to create a balance of inflammatory and regenerative mediators in the face of vigorous inflammation.Over the past few years, studies have shown that MSCs, when exposed to an environment of inflammation, can orchestrate local as well as systemic innate and adaptive immunological responses by releasing various mediators including immunosuppressants, growth factors and exosomes and chemokines as well as complement components and metabolites. It is interesting to note that nonviable MSc's can also have therapeutic benefits, with apoptotic MSc's demonstrating immunosuppressive function in vivo. The immunomodulatory capacity of MSCs is not constitutive, but rather is mediated by inflammatory cytokines. Therefore, the net outcome of MSC activation may vary depending on the level and types of inflammation of the tissues inside the body [49].

EMERGING TECHNOLOGIES

In regenerative medicine, the most pressing challenge is to identify a reliable stem cell source that has the capacity to differentiate into a variety of cell types and can be used to reconstruct the three-dimensional functional tissue of an organ that has been damaged. Even if PSCs are available that can differentiate into all cell types of a given organ, the subsequent challenge will be to use these cells to restore the tissue's three-dimensional structure. Stem cells used as therapeutics must replicate the organogenesis

process during embryonic development, which is a temporary solution. This can be achieved through the use of 3D scaffolds that are prepared with organic or synthetic fibres or derived from de-cellulized normal organs [50]. Organ-derived scaffolds, which are composed of connective tissue fibres, may be used to regenerate human organs by reseeding them with stem cells. This technique has been successfully used to recover functional kidney fragments in mice. It is anticipated that the combination of scaffold technology and 3D printing will also allow for significant progress in the regeneration of human organs. Nevertheless, this remains a distant prospect, and early clinical trials have failed to replicate trachea using standard tissue-derived scaffolds. Cell delivery and dosage are also essential components of stem cell therapy [51]. Cells can be directly injected into the organs that have been damaged, injected into the arteries that supply the damaged tissue, or infused through the system. For instance, for the treatment of damaged heart tissue, cells can be directly injected through a catheter into the heart or infused into the coronary arteries. One way to enhance the therapeutic potential of existing stem cell therapies is to enhance the paracrine effects of stem cells. As mentioned above, stem cells are an abundant source of growth factors and cytokines and chemokines, as well as bioactive lipids. Stem cells may stimulate the growth of remaining stem cells, inhibit cell death and promote the neovascularization of damaged tissues, as well as activate local tissue-bound cells. Stems can be conditioned to secrete soluble parabolic factors more effectively by undergoing hypoxia treatment or by manipulating the expression of genes that code for anti-apoptotic (e.g., kit ligand), vascular endothelial (VET) growth factor, and fibroblast (fibroblast) growth factor 2 prior to infusion into patients [52].

RISK FACTORS

The long-term success of stem cell-based therapies is subject to a number of questions, including the ability of the transplanted cells to survive, engraft, proliferate, and regenerate [53]. The genomics and epigenetics of the in vitro cell lines used prior to the transplantation are essential for the survival and therapeutic benefit of the therapy. Stem cells have a wide capacity to replicate, however, the immune system's rejection of the donor cells after the transplantation is a major concern. Recent research has demonstrated that most donor cell death takes place within the first few hours to days of the transplantation, thus limiting the effectiveness and therapeutic value of the therapy (EMB). The immune compatibility status of ES cells in mice and humans has been traditionally classified as immune privileged. A recent study, however, used in vivo whole-animal and live cell-tracking techniques to show that ES cells in humans are rapidly rejected upon transplantation into immune-competent mice. Treatment of ES derived vascular progenitors with interferon (γ) to upregulate MHC (Class I) expression or ablation of NK (Class I) cells in vivo resulted in improved progenitors cell survival post-transplantation into a Syngeneic Murine Ischemic Hindlimb Model. This indicates that MHC dependent, NK cell mediated elimination is a key factor in graft survival. Given the potential for rejection, initial therapeutic trials using ES and iPS cells are likely to necessitate additional immunosuppression therapy (Ornal). However, immunosuppression also exposes the patient to the risk of infection and drug specific adverse reactions. Therefore, it is essential to elucidate the mechanisms that regulate donor graft tolerability by the host in order to advance the clinical use of stem cell-based therapies. In order to prevent immune rejection, an alternative strategy could be to use so-called 'gene editing'. This technique involves *ex vivo* manipulation of a stem cell genome to correct an underlying genetic defect before transplantation. Stem cell immunological markers could also be manipulated to elude the host immune system. Two recent studies provide alternative methods for 'gene editing' to address a genetic defect in an iPS cell derived from a patient with Huntington's disease (HGP). The cells from the patient with HGP had a dysmorphic nucleus and elevated progerin proteins, the cellular phenotype of which was particularly pronounced in mature differentiated cells [54]. The researchers used a zinc finger nuclease to correct a genetic defect in the iPS cells of a Parkinson's disease patient due to a mutation in an alpha-synuclein (synthesizing) gene. They were able to correct two distinct Lamin A (synuclein) mutations through the use of highly efficient helper dependent adenovirus vectors containing wild type sequences, which were then homologous to homologous to a Lamin A gene. The resulting genetic correction resulted in a reversal of the diseased cell phenotype after differentiation into

smooth muscle cells in the study. Furthermore, 'gene editing the use of embryonic stem cells (ES) has raised ethical and technical concerns in the past, which have restricted federal funding and hindered the advancement of this important research. As funding restrictions may be reintroduced in the near future, researchers are being less aggressive in their pursuit of ES cell technology, leading to a decrease in the number of young researchers entering the field. ES and iPS stem cells that are able to evade immune rejection may develop into oncogenic cells due to their unlimited replication capacity. To reduce the risk of these cells becoming oncogenic, ES or iPS cells must be directed to a mature cell type before transplantation. Generation of ES and ES cells containing an 'inducible 'kill-switch' may also inhibit uncontrolled growth of ES and/or derived cells(sb). Two ongoing human trials using ES cells have demonstrated that ES cells will not cause teratomas in animals, however, this has not been studied extensively. Enrolment of patients with ES cells will require close monitoring for this potentially fatal side effect [55].

LIMITATIONS

The potential of regenerative medicine is exciting; however, it also has its limitations. Ethical issues, intricate regulatory pathways, immune rejection, uncertain long-term results, and high development and implementation costs are some of the issues that must be addressed. Furthermore, the incorporation of regenerated tissue into biological systems and the replication of native tissue complexity remain challenges. It's hard for adult stem cells to grow in culture, and they don't have the same number of cells, which is something that's usually seen in vivo. Another concern that must be addressed prior to in vivo functional cell population administration is the type and number of progenitors delivered at the graft site and the risk of the formation of teratomas as a result of contamination of the graft site with residual undifferentiated European stem cells (ESCs). To mitigate this risk, it is proposed to reduce and highly purify the number of un-differentiated cells within the graft site to ensure that only the cells intended to replace diseased tissue are present. Cell surface markers can be used for flow-sorted protocols that are tested and proven to eliminate the number of undifferentiated cells, as well as for protocols that yield high yields of differentiated cells (Kim et al., 2023).Another concern that must be addressed before in vivo functional cell populations can be administered is the type and quantity of cells that are delivered at the graft site and the risk of the formation of teratomas as a result of contamination of the graft site with undifferentiated European stem cells (ESCs). To address this risk, it is proposed to reduce and highly purify the number of un-differentiated cells within the graft site to contain only the cells that are intended to replace the damaged tissue. Cell surface markers can be used for flow-sorted protocols that are tested and proven to eliminate the number of undifferentiated cells, as well as for protocols that yield high yields of differentiated cells [56].

FUTURE OF REGENERATIVE MEDICINE

Most of the research in this area is focused on enteric neuron types, but the research on enteric glia types is way behind. But more and more people are realizing that enteric glia cells are just as important as neurons when it comes to controlling lots of different bowel functions. Plus, a group of post-natal EGCs have really cool plasticity and can do a lot of different things, which makes them really important in regenerative medicine [57]. In this study, ADPECs (Adipose Stem Cells and Progenitor Cells) were isolated from human and animal tissues for the purpose of regenerative medical and therapeutic applications. However, there is limited knowledge of ADPECs in other species, particularly in cattle, where it is anticipated that ADPECs may improve the fat and meat composition of the animal. To investigate this, bovine ADPECs were isolated using cell surface marker. Specifically, ADPEC markers in human and experimental animals were identified, with the primary marker being CD26, and the secondary marker being CD54. Bovine fat stromal fraction cells were separated by flow cytometry prior to primary culture, and each fraction was evaluated for self-replenishment and adipogenesis potential. Four cell populations were identified, with CD26- ADPECs (PreAs) demonstrating slow proliferation and high adipogenesis capacity (ADPECs), particularly CD54+. In conclusion, it was possible to collect and characterise potential ADPECs, such as PreAs (CD26-ADPCCs), which are expected to be used in future in vitro abdominal fat assays (Shi et al., 2018). Currently, partial nephrectomies are the

preferred option for the treatment of cT1 a renal mass, however, indications are growing due to advances in anatomy and technology. Studies have indicated that advances in imaging techniques, such as cross-section imaging with 3D reconstruction, the use of Colour Doppler Intraoperative Ultrasound, and more recent studies using Contrast Enhanced Ultrasound, play an important role in certain patient populations. Indocyanine Green administration is widely used, however, novel fluorophore-guided imaging, including folate-targeting fluororescein molecules, is being explored to better identify tumor-papular margin. Augmented Reality is also being explored as an educational tool for patients and surgical trainees. Pre-operative and intraoperative imaging have been shown to be effective, however, the use of Near Infrared Guided Segmental and Sub-Segmental Vessel Clamping has not yet been demonstrated to significantly improve patient outcomes. Furthermore, studies on reconstructive techniques, and the replacement of reconstructive techniques with sealing agents, are also promising. Finally, the implementation of ERAS protocols has enabled patients to be discharged earlier without increasing complications and at a lower cost [58].

CONCLUSION

In conclusion, stem cell-based regenerative medicine stands at the forefront of medical innovation, offering promising solutions for organ shortages, chronic diseases, and tissue regeneration. Despite the challenges and limitations posed by ethical concerns, regulatory hurdles, and immune rejection, stem cell research has made significant strides over the years, propelled by landmark discoveries and transformative innovations. From historical milestones such as Maximow's discovery of hematopoiesis to recent breakthroughs like the application of MSCs in COVID-19 treatment, the trajectory of stem cell research reflects a relentless pursuit of medical advancement. Looking ahead, the future of regenerative medicine holds immense potential, with emerging technologies such as 3D scaffolds, gene editing, and novel imaging techniques offering new avenues for tissue repair and regeneration. By harnessing the power of stem cells and advancing our understanding of their therapeutic potential, we can pave the way for a future where personalized regenerative therapies offer hope and healing to patients worldwide.

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