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Review article

Advancements and challenges in stem cell transplantation for regenerative medicine

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Abbreviations: A1AD, (Alpha-1 Antitrypsin Deficiency); AdSCs, (Adult Stem Cells); ADSCs, (Adipose-Derived Stem Cells); ALCAM, (Activated Leukocyte Cell Adhesion Molecule); ALI, (Acute Lung Injuries); AML, (Acute Myeloid Leukemia); AR, (Acute Reaction); ARMD, (Age-Related Macular Degeneration); ASD, (Autism Spectrum Disorder); ASIA, (American Spinal Injury Association); AT-MSCs, (Adipose Tissue-Derived MSCs); Atoh1, (Atonal Homolog 1); BMDMSCs, (Bone Marrow-Derived MSCs); BMDMNCs, (Mononuclear Cells from Bone Marrow); BMP, (Bone Morphogenetic Protein); CA, (Cardiac Adipose); CD, (Crohn's Disease); cDE, (Definitive Endodermal Progenitors); CFU-F, (Colony-Forming Unit); CLL, (chronic lymphocytic leukemia); cMYC, (Cellular Myelocytomatosis); COPD, (Chronic Obstructive Pulmonary Disease); COX-1, (Cyclo-oxygenase-1); cPB, (Pancreatic β-Cells); cPF, (Foregut-Like Progenitors); CR, (Chronic Reaction); CYP2C9, (Cytochrome p450 2C9); CYP3A4, (Cytochrome P450 3A4); CYP450, (Cytochrome P450); DC1, (DC type 1); DCs, (Dendritic Cells); DE, (Definitive Endoderm); DMD, (Duchenne Muscular Dystrophy); DPCs, (Dermal Papillary Cells); DPSCs, (Dental Pulp Stem Cells); EC, (Embryonic Cancer Cells); ECM, (Extracellular Matrix); EOMES, (Recombinant Eomesodermin); EPSCs, (Epithelial Progenitor Stem Cells); ESCs, (Embryonic Stem Cells); FGF, (Fibroblast Growth Factor); FGF2, (Fibroblast Growth Factor 2); FOXG1, (Forkhead Box G1); GABA, (Gamma-Aminobutyric Acid); GABAergic, (Γ-Aminobutyric Acid-Secreting); GAG, (Glycosaminoglycan); GATA3, (Recombinant GATA Binding Protein 3); GCK, (Glucokinase); GFAP, (Glial Fibrillary Acidic Protein); GFP, (Green Fluorescent Protein); GLUT2, (Glucose Transporter Type 2); GVHD, (Graft-Versus-Host Disease); hES, (Human Embryonic Stem Cell Line); hESCs, (Human Embryonic Stem Cells); HGF, (Hepatocyte Growth Factor); HLA, (Human Leukocyte Antigen); HSCT, (Hematopoietic Stem Cell Transplantation); ICM, (Inner Cell Mass); IDO, (Indoleamine-Pyrrole 2,3-Dioxygenase); IESCs, (Inner Ear Stem Cells); iGABA-INs, (Induced Γ-Aminobutyric Acid-Secreting Interneurons); IFN-γ, (Interferon-Gamma); IL-10, (Interleukin-10); IL-4, (Interleukin-4); INs, (Interneurons); INS1, (Insulin 1); IPCs, (Intestinal Progenitor Cells); iPSCs, (Induced Pluripotent Stem Cells); iTSCs, (Induced Trophoblast Stem Cells); KO, (Knock-Out); LM, (Leishmania Major); LPSCs, (Limbal Progenitor Stem Cells); LY411575, (Γ-Secretase Inhibitor); MABs, (Mesoangioblasts); MHC, (Major Histocompatibility Complex); MS, (Multiple Sclerosis); MSCs, (Mesenchymal Stem Cells); Mφ, (Macrophages); NEC, (Necrotizing Enterocolitis); NHL, (Non-Hodgkin Lymphoma); NK, (Natural Killer); NO, (Nitric Oxide); NPCs, (Neuronal Progenitor Cells); OCT4, (Octamer-Binding Transcription Factor); PCs, (Pacemaker Cells); PDGF, (Placental-Derived Growth Factor); PD-L1, (Programmed Cell Death 1 Ligand 1); PDX1, (Pancreatic and Duodenal Homeobox 1); PEG, (Polyethylene Glycol); PGE2, (Prostaglandin E2); PL-MSCs, (Placenta-Derived Mesenchymal Stem Cells); PPCs, (Pancreatic Progenitor Cells); PXR, (Pregnane X Receptor); RGCs, (Retinal Ganglion Cells); RPE, (Retinal Pigment Epithelium); SAN, (Sinoatrial Node); SCIs, (Spinal Cord Injuries); SIS, (Small Intestinal Submucosa); SKPs, (Skin-Derived Precursors); SOX2, (SRY-Box Containing Gene 2); SSCs, (Spermatogonial Stem Cells); T2DM, (Type 2 Diabetes); TFAP2C, (Transcription Factor AP-2 Gamma); TGF-β, (Transforming Growth Factor-beta); TGF-β1, (Transforming Growth Factor-B1); TNF-α, (Tumor Necrosis Factor-Alpha); TR, (Transplantation Rejection Reaction); TSPSCs, (Tissue-Specific Progenitor Stem Cells); VSMCs, (Vascular Smooth Muscle Cells); WT, (Wild-Type).

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ABSTRACT

Stem cell transplantation has emerged as a promising avenue in regenerative medicine, potentially facilitating tissue repair in degenerative diseases and injuries. This review comprehensively examines recent developments and challenges in stem cell transplantation. It explores the identification and isolation of various stem cell types, including embryonic, induced pluripotent, and adult stem cells derived from multiple sources. Additionally, the review highlights the tissue-specific applications of these stem cells, focusing on bone and cartilage regeneration, treatment of neurological disorders, and management of hematological conditions. Future advancements and effective resolution of current challenges will be crucial in fully realizing the potential of stem cell transplantation in regenerative medicine. With responsible and ethical practices, the field can potentially transform disease and injury treatment, ultimately improving the quality of life for countless individuals.

1. Introduction

Regenerative medicine aims to restore tissues and organs in patients with severe injuries or chronic conditions where natural regenerative processes are inadequate. Stem cells offer a promising solution to the shortage of donated tissues and organs, especially for aging populations, due to their ability for continuous cell division and differentiation to potentially repair tissue abnormalities from congenital disabilities, diseases, and age-related degeneration [1]. Stem cells are vital for the body's tissues and organs, contributing to disease progression, development, and tissue repair. They are categorized by their differentiation potential: Unipotent Stem Cells (single cell type), Multipotent Stem Cells (multiple cell types within a specific tissue or organ system), Pluripotent Stem Cells (broader differentiation capabilities), and Totipotent Stem Cells (highest differentiation potential and versatility) [2]. Fig. 1 highlights the unique characteristics of various types of stem cells, emphasizing that the zygote is the only totipotent stem cell in the human body. Regardless of their developmental stage—whether embryonic, extraembryonic, fetal, or adult—the distinctive properties of these cells depend on the interplay of pluripotency-associated factors. The upregulation of these critical factors can initiate a transformative process, resulting in the generation of iPSCs [3].

Stem cell transplantation methods include autologous, allogenic, and syngeneic approaches to facilitate tissue regeneration and enhance immune responses. Human leukocyte antigen (HLA) tissue typing is used to mitigate host-versus-graft rejections during

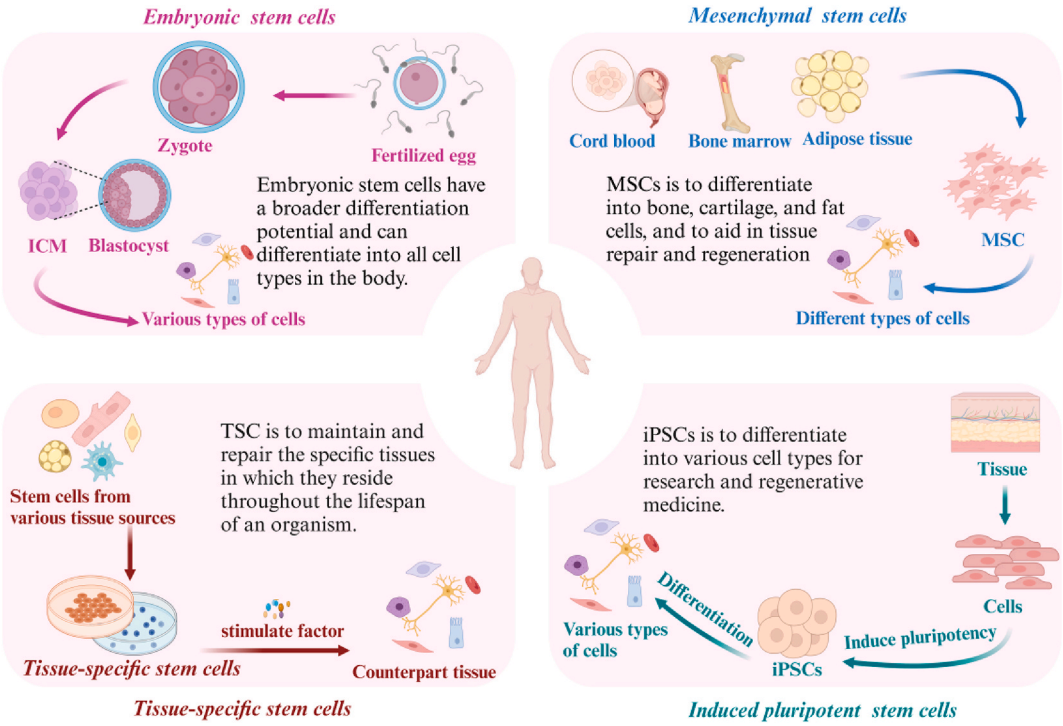

Fig. 1. Revolutionizing Regenerative Medicine: Explore the potential of six key classes of stem cells—Embryonic Stem Cells (ESCs), Tissue-Specific Stem Cells (TSCs), Mesenchymal Stem Cells (MSCs), and Induced Pluripotent Stem Cells (iPSCs). Uncover their myriad promises for advancing regenerative medicine and therapeutic interventions in various diseases.

transplantation, and immunosuppressants are often recommended to further reduce the risk of rejection [4]. Modern stem cell regenerative medicine integrates tissue engineering principles, utilizing cell transplantation, material science, and microengineering to create organoids. These organoids have the potential to regenerate impaired tissues and organs, restoring their normal physiological function [5]. Optimal scaffolds in regenerative medicine must meet specific criteria to ensure effectiveness and safety in tissue engineering applications. The abundance of stem cells in a tissue transplant is crucial for determining regenerative outcomes, as a higher quantity of stem cells positively correlates with an increased potential for successful tissue regeneration and repair [6]. The ex vivo expansion of transplantable stem cells is imperative in situations requiring a larger quantity of cells to ensure a successful regenerative outcome [7]. Successful tissue regeneration relies on transplanted stem cells' survival, proliferation, and differentiation within the target tissue. Integration into the host's circulatory system is also crucial, ensuring a sufficient supply of nutrients and signaling molecules that contribute to successful regeneration of damaged or diseased tissue [8]. This review examines the various types of stem cells and their unique properties, transplantation methods, and the integration of tissue engineering principles, emphasizing the critical factors that influence successful regenerative outcomes.

2. ESCs in regenerative medicine

In 1998, James Thomson successfully isolated human embryonic stem cells (hESCs) for the first time. These cells exhibit pluripotency, allowing them to differentiate into over 200 distinct cell types, and hold significant potential for treating a wide range of diseases [9]. The pluripotent status of ESCs is regulated by the dynamic functionality of specific transcription factors, including OCT4, SOX2, NANOG, and others, collectively known as pluripotency factors. In ESCs, the two alleles of OCT4 remain distinct and are preserved in a pluripotent state. These alleles undergo homologous pairing during embryogenesis and transdifferentiation processes [10]. ESCs function as a crucial regulatory switch for lineage commitment, rendering them an ideal model for regenerative therapies. This review section investigates treatment using ESC transplantation and transdifferentiation into various cell types (Fig. 2), with promising outcomes noted in individuals with spinal cord injuries (SCIs), resulting in enhanced body control, balance, sensory perception, and limb mobility [11].

Transplanted stem cells target injury sites, as seen in age-related macular degeneration (ARMD), which results from retinal pigment epithelium (RPE) degeneration in the macula. Genomic integration of the COCO gene directs ESCs toward cone cell differentiation while simultaneously suppressing the Transforming Growth Factor-beta (TGF-β), Bone Morphogenetic Protein (BMP), and Wnt signaling pathways. Transplantation of these cone cells into the eye restores individuals affected by ARMD, forming a sheet-like

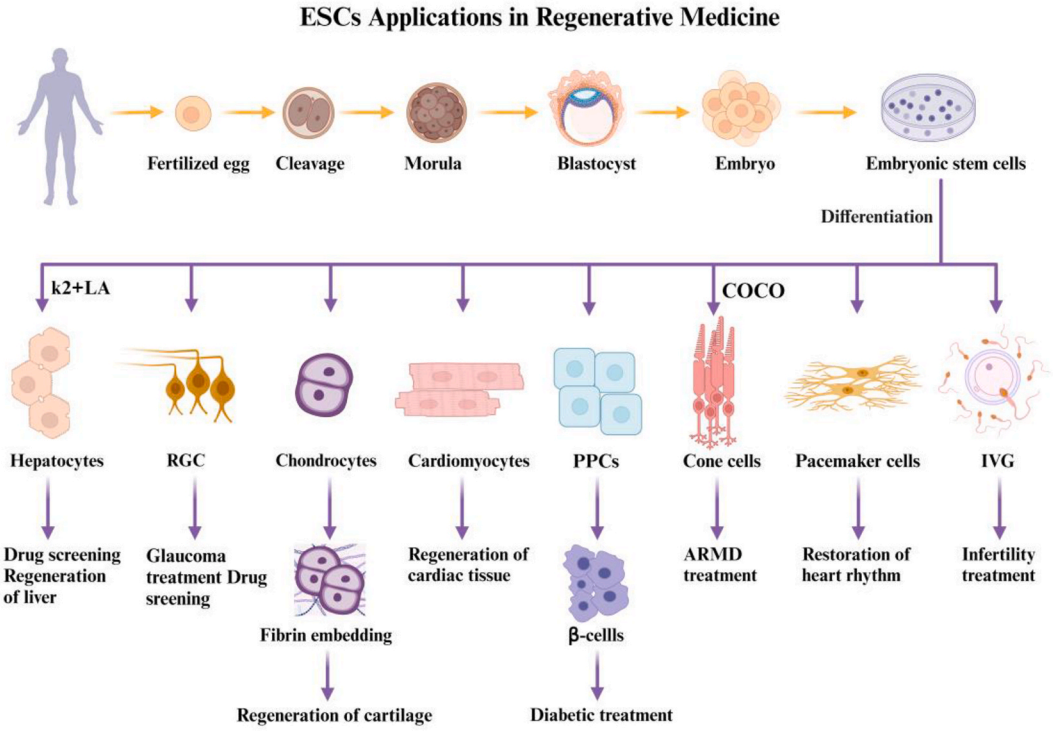

Fig. 2. ESCs, originating from the inner cell mass (ICM) of gastrula-stage embryos, are key players in advancing regenerative medicine. Their remarkable versatility allows them to differentiate into over 200 cell types across all three primary germ layers. With precise culture conditions, ESCs can be guided to form specialized cells like hepatocytes, retinal ganglion cells, chondrocytes, pancreatic progenitors, cone cells, cardiomyocytes, pacemaker cells, eggs, and sperm cells. These diverse cell types are crucial in tissue regeneration and targeted disease treatment, providing tailored interventions for specific tissues.

structure within the host [12]. The challenge in age-related macular degeneration (ARMD) therapeutics involves establishing connections among retinal ganglion cells (RGCs), cone cells, and the retinal pigment epithelium (RPE). A breakthrough by Donald Z. Jacks' group at Johns Hopkins University involves using CRISPR-Cas9-m-Cherry reporter ESCs to generate RGCs. CRISPR-Cas9 facilitates the insertion of m-Cherry into the BRN3B gene, which is specific to RGCs. Forskolin enhances the production of RGCs, and scaffolds coax RGCs into axonal differentiation. This refinement offers potential vision restoration in glaucoma and ARMD patients [12].

Globally, and particularly in India, cardiovascular issues contribute significantly to mortality rates. Immediate restoration of heart function is critical for biomedical therapies targeting these conditions. Cardiac tissue regeneration can be achieved through the transplantation of cardiomyocytes, cardiovascular progenitors derived from ESCs, and mononuclear cells from bone marrow (BMDMNCs). Notably, cardiomyocytes and progenitor cells demonstrate superior healing capacity compared to BMDMNCs. Mature cardiomyocytes, in particular, effectively address heart arrhythmias, establish electromagnetic coupling with heart functions, and provide mechanical and electrical restoration without the risk of tumorigenesis [13].

Similar to the differentiation of cardiomyocytes, liver stem cells derived from ESCs can be converted into Cytochrome P450 (CYP450) hepatocytes. These specialized cells play a central role in chemically modifying and breaking down harmful xenobiotic drugs. The limited accessibility and heterogeneity of fully functional hepatocytes pose a significant obstacle in evaluating drug safety. Stimulating ESCs with ex vivo Vitamin K12 and lithocholic acid activates the pregnane X receptor (PXR), Cytochrome P450 3A4 (CYP3A4), and Cytochrome P450 2C9 (CYP2C9). This prompts the differentiation of ESCs into hepatocytes that closely mimic primary hepatocytes, serving as a reliable resource for drug screenings and predicting clinical outcomes [14]. Hepatic cells can be generated from ESCs through various methods, including chemical approaches, serum-free differentiation, and genetic transformation [15]. Hepatocytes derived from ESCs are a resilient resource for treating liver injuries and facilitating high-throughput drug screening [16]. Transplanting biomaterial-encapsulated pancreatic progenitor-derived hESCs, expressing CD24, CD49, and CD133, leads to differentiation into β-cells. This process mitigates glycemic and obesity effects induced by a high-fat diet in mice.

Adding antidiabetic drugs to the transdifferentiation regimen enhances ESC transition into β-cells. Theoretically, this approach holds the potential for a permanent cure for Type 2 diabetes (T2DM) [16]. ESCs can directly differentiate into insulin-secreting β-cells, identified by markers such as Glucose Transporter Type 2 (GLUT2), Insulin 1 (INS1), Glucokinase (GCK), and Pancreatic and Duodenal Homeobox 1 (PDX1). PDX1-mediated epigenetic reprogramming facilitates this differentiation process [17]. Stem cell transplantation offers an alternative for treating osteoarthritis, a global health issue. Chondrocytes derived from hESCs, implanted in a fibrin gel, successfully repair damaged cartilage within 12 weeks. Transplanted chondrocytes show positive outcomes in mouse knee joints, expressing markers like SRY-box containing gene 2 (SOX9) and collagen II for over 12 weeks, highlighting their clinical potential for cartilage lesion treatment [18]. ESCs hold promise as a biological pacemaker by differentiating into sinoatrial node (SAN) pacemaker cells. Cultivating ESCs in inert biomaterial under specific conditions or introducing the TBox3 gene ex vivo can generate pacemaker-like cells expressing Activated Leukocyte Cell Adhesion Molecule (ALCAM). Transplanting these cells may restore pacemaker functions in diseased hearts [12].

These studies highlighted that the discovery of hESCs 1998 revolutionized regenerative medicine, offering a versatile platform for cellular differentiation. Controlled by pluripotency factors like OCT4, SOX2, and NANOG, hESCs show promise for treating conditions such as SCIs, ARMD, and cardiovascular diseases through transplantation and transdifferentiation. For instance, transplantation of hESC-derived cone cells restores vision in ARMD, while hESC-generated cardiomyocytes and hepatocytes aid in heart and liver regeneration, respectively. Moreover, hESC-derived pancreatic progenitors hold potential for curing T2DM, and other applications include cartilage repair in osteoarthritis and the development of biological pacemakers using ESC-derived pacemaker cells, demonstrating the broad therapeutic utility of hESCs.

3. PSCs technology advancements

iPSC technology, pioneered in 2006 by scientists like Takahashi and Yamanaka, involves reprogramming skin fibroblasts with key factors (Klf4, Oct 3/4, Sox2, and c-Myc) to resemble ESCs. iPSCs closely mimic ESCs in transcriptome profiling, epigenetic marks, and functional capabilities, representing a significant advancement in stem cell research [19]. Recent advancements in iPSC technology enable the direct transformation of skin cells into kidney organoids, closely resembling natural kidney tissue. Concerns about retrovirus usage have been addressed, allowing for the generation of iPSCs from adult cells through ESCs transition or direct transdifferentiation. The applications of iPSCs in regenerative medicine are emphasized. Notably, the ex vivo generation of functional nephron-containing kidney organoids in humans, resembling first-trimester fetal kidneys, has been achieved. These organoids serve as valuable models for drug screening, disease study, and potential transplantation. However, creating fully functional kidneys remains a complex challenge with current scientific technologies [20]. Transplanting neuronal progenitor cells (NPCs) derived from iPSCs in preclinical studies has shown promise in slowing the progression of ARMD. In rats, this therapeutic intervention facilitates the generation of 5–6 layers of photoreceptor nuclei, thereby enhancing the restoration of visual acuity [21]. The different strategies involving iPSCs for retinal regeneration, including their application in ARMD, have been comprehensively reviewed in other publications [22]. A distinctive experimental approach has successfully achieved nuclear reprogramming in both wild-type (WT) mice and OCT4 knock-out (KO) fibroblasts. This method involves the temporary activation of recombinant eomesodermin (EOMES), transcription factor AP-2 gamma (TFAP2C), recombinant GATA binding protein 3 (GATA3), and optionally, Cellular Myelocytomatosis (cMYC), which induces the differentiation of induced Trophoblast Stem Cells (iTSCs). These iTSCs closely mirror blastocyst-derived TSCs regarding H3K7ac, DNA methylation, nucleosome deposition of H2A.X, and other epigenetic markers. The chimeric differentiation of iTSCs is precisely guided to generate placental tissue and hemorrhagic lineages, bypassing the pluripotent phase. This advancement opens up

new possibilities for generating fully functional placental tissue for human use in a more logistically and rephrased manner [23].

Pluripotent stem cells (PSCs) technology faces several challenges. There's a potential risk of tumorigenicity after transplantation, and achieving consistent and efficient differentiation into desired cell types remains difficult. PSC-derived cells may also face immune rejection when transplanted into patients. Large-scale production of PSCs and their derivatives is complex and costly, compounded by ethical issues and regulatory hurdles associated with embryonic stem cells. Ensuring long-term genetic stability during culture and differentiation is challenging, as is ensuring proper integration and functionality of differentiated cells in host tissue. Developing standardized protocols for PSC culture, differentiation, and transplantation is necessary but difficult. Additionally, rigorous preclinical and clinical testing is required to ensure safety and efficacy. Finally, the high cost of PSC research and therapeutic applications limits accessibility and widespread adoption [24].

4. Ethical and regulatory considerations in stem cell research

The use of ESCs entails the destruction of human embryos, prompting substantial ethical concerns, particularly among individuals who attribute the beginning of life to conception. Ensuring informed consent for embryo donation, often sourced from surplus embryos generated during in vitro fertilization (IVF), presents another ethical issue, as donors must fully comprehend the potential uses of their embryos in research [25]. Additionally, there are concerns about the potential exploitation of donors, particularly women, for the eggs required to create embryos [26]. In contrast, iPSCs sidestep many of these ethical dilemmas as they do not necessitate embryos or oocytes. Acquiring somatic cells through a skin biopsy is relatively noninvasive, presenting fewer risks to donors compared to egg donation. The President's Council on Bioethics has deemed iPSCs "ethically unproblematic and acceptable for use in humans," suggesting that neither the donation of materials to derive iPSCs nor their proceture raises significant ethical concerns. Nevertheless, ethical considerations persist regarding the potential misuse of iPSCs in human cloning or germline modification [27]. Stem cell research encounters varied regulations across countries, posing challenges for international collaboration. Some nations impose stringent restrictions on embryonic stem cell research, while others adopt more permissive policies [28]. Recent changes in international regulations offer insight into how different regions navigate stem cell research's ethical and scientific complexities. For example, certain countries have revised their guidelines to accommodate emerging technologies and discoveries in this field [29]. Researchers face the challenge of navigating complex regulatory environments to ensure compliance with ethical standards and legal requirements, which includes obtaining approvals from ethical review boards and adhering to regulatory guidelines. Given the importance of maintaining public trust, transparent regulatory practices and effective communication aboutstem cell research's ethical implications and benefits are essential. Addressing these ethical considerations and regulatory challenges can provide a more comprehensive overview of the stem cell research landscape, enhancing the manuscript's depth and contributing to a nuanced understanding of this evolving field [30].

4.1. Induced GABAergic interneurons (iGABA-INs) for neurodegenerative disorders

Neurodegenerative disorders, such as intractable epilepsies and Alzheimer's disease, have the potential to induce degeneration of the cerebrum, affecting both excitatory and inhibitory signaling within the brain. Within the cerebral cortex and hippocampus, the essential function of γ-aminobutyric acid-secreting (GABAergic) interneurons (INs) is to provide inhibitory signals. The gradual reduction of these neurons is intimately associated with the progressive process of neurodegeneration [31]. Through the genomic integration of key genes (Ascl1, Foxg1, Dlx 5, Lhx6) into both mouse and human fibroblasts, there is potential to convert these adult cells into GABAergic interneurons, referred to as iGABA-INs. These cells exhibit similarities to telencephalic interneurons, releasing GABA and capable of providing inhibition to host granule neurons. This innovative approach shows promise in addressing the loss of GABAergic interneurons in the context of neurodegeneration [32]. The transplantation of iGABA-INs into a developing embryo presents a promising method for treating both acquired and genetic seizures. The transplanted cells exhibit dispersion and maturation, ultimately establishing functional neuronal circuits and serving as local interneurons. This approach holds the potential to provide a curative solution for seizures, addressing both genetically-induced and acquired forms of the condition through a standardized and logistical framework [33]. Inhibiting TGF-β and BMP signaling with Dorsomorphin and SB-431542 facilitates the transformation of human iPSCs into cortical spheroids. These formations consist of peripheral and cortical neurons, accompanied by neighboring astrocytes. Their transcription profiles and electrophysiological features closely mirror those observed in developing fetal brain tissue and fully developed neurons. This method offers a systematic and practical approach to induce the formation of cortical spheroids, replicating key aspects of natural brain development [34].

4.2. 3D organoid cultures for Autism spectrum disorder (ASD) and schizophrenia

The complex biology, unclear etiology, and challenges in genetic reprogramming that hinder the understanding of ASD and schizophrenia have been addressed through 3D organoid cultures derived from the iPSCs of ASD patients. These brain organoids, which resemble the fetal brain, exhibit conditions similar to those in ASD patients, including increased inhibitory GABAergic neurons and imbalanced neuronal connections. The elevated expression of the Forkhead Box G1 (FOXG1) gene in organoids indicates its potential role in ASD development [35].

4.3. Lung organoids for studying lung diseases

Degeneration of organs, such as the lungs in conditions like tuberculosis, fibrosis, and cancer, can be studied using organoid cultures. Directing iPSCs into inert biomaterial under specific conditions can generate lung organoids composed of epithelial and mesenchymal cells. These miniature lung organoids, resembling large airways and alveoli tissues, serve as valuable tools for studying lung development and screening drugs for conditions like tuberculosis and cancer [36].

4.4. Efficient iPSC generation with CRISPR-Cas9

A CRISPR-Cas9 system-based episomal reprogramming approach condenses the traditional multistep process for iPSCs into a single step, yielding cells resembling ESCs in under two weeks. This accelerated method mitigates risks of genetic alterations and unwanted epigenetic changes, offering a more personalized and efficient approach for individuals with conditions like retinal degradation and severe immunodeficiency. Correcting genetic mutations in key genes such as OCT4 and DNMT3B enhances the precision of iPSCs generation [37].

4.5. iPSCs in HIV-1 and AIDS treatment

iPSCs expressing antiCCR5-RNA and possessing the ability to differentiate into HIV-1 resistant macrophages hold significant potential for the treatment of AIDS [38]. The development of methods to derive iPSCs has significantly advanced stem cell research and has the potential to transform various medical fields, including cancer immunotherapy. iPSCs can proliferate indefinitely and differentiate into nearly any specialized cell type. Precise multigene engineering at the iPSC stage enables the creation of master cell lines after clonal selection and promotes differentiation into natural killer (NK) cells and T-cells. This advancement opens new avenues for providing off-the-shelf cytotoxic lymphocytes with direct antigen targeting to treat patients with relapsed or refractory cancer [39]. This approach represents a promising application of iPSCs in immunotherapy, offering hope for combating HIV-1 infection.

4.6. Alpha-1 antitrypsin deficiency (A1AD) and iPSCs

Alpha-1 antitrypsin deficiency (A1AD), a significant contributor to lung and liver conditions such as liver cirrhosis and chronic

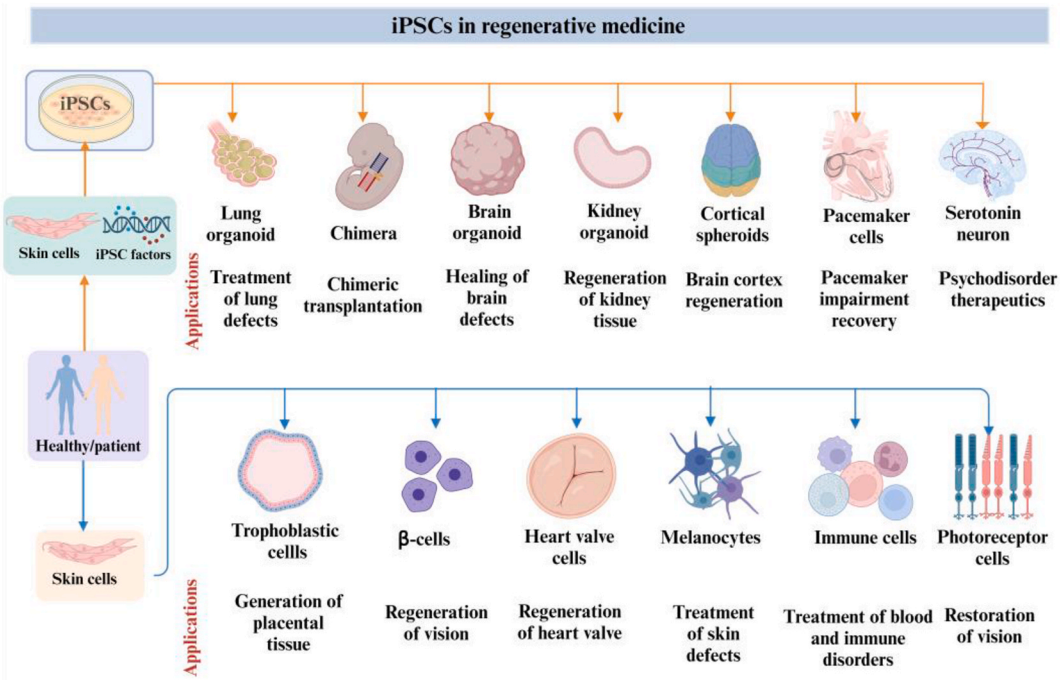

Fig. 3. The function of iPSCs, a groundbreaking technology derived from adult sources like skin fibroblasts, is transforming regenerative medicine. Reprogramming adult cells into an ESC-like state opens new avenues for therapeutic applications. Under tissue-specific conditions, iPSCs can differentiate into various cell types, including trophoblasts, heart valve cells, photoreceptor cells, immune cells, and melanocytes. When integrated with extracellular matrix (ECM) complexation, iPSCs can generate tissue organoids for organs such as the lung, kidney, and brain. Comparable to ESCs, iPSCs exhibit the capacity to differentiate and give rise to cell lineages representing all three embryonic germ layers, providing versatile potential for diverse applications in regenerative medicine.

obstructive pulmonary disease (COPD), involves the breakdown of lung connective tissue by neutrophil elastase. Leveraging patient-specific iPSCs derived from lung and liver cells provides a valuable platform for investigating the pathophysiology of A1AD. iPSCs originating from COPD patients exhibit drug sensitivity, indicating an increased susceptibility to drug-induced effects. Since A1AD often results from a single base pair mutation, correcting this genetic anomaly in hepatic iPSCs holds the potential for effectively addressing the deficiency. This comprehensive approach offers insights into the mechanisms underlying A1AD-related lung and liver diseases and presents a potential avenue for targeted therapeutic interventions [40].

4.7. Therapeutic potential of iPSC-Derived neurons and cells

Manipulating Wnt signaling in iPSCs allows for in vitro differentiation into serotonin-like neurons. These iPSC-derived neurons mimic serotonin neurons, exhibiting specific electrophysiological properties, expressing hydroxylase two as a developmental marker, and releasing serotonin. Predominantly localizing to the rhombomere 2–3 segment of the rostral raphe nucleus, these neurons hold therapeutic potential for transplantation in conditions such as schizophrenia, bipolar disorder, and other neuropathological disorders associated with serotonin neuron dysfunction [41]. Reprogramming ventricular myocytes using iPSC technology generates cells resembling pacemaker cells (PCs) in morphology and functionality. Transplanting these iPSC-derived PCs into large animals enhances rhythmic heart functions, showcasing their therapeutic potential. Understanding the transformation process and identifying optimal transplantation sites is crucial for validating iPSC-derived pacemaker cells' reliability and robust performance in therapeutic applications [42]. In a stepwise process, skin cells are directly reprogrammed into pancreatic β-cells, bypassing the pluripotent stages. This approach involves converting cells into foregut-like progenitors (cPF) and definitive endodermal progenitors (cDE), which eventually develop into pancreatic β-cells (cPB). On the first reprogramming day, pluripotency factors (OCT4, SOX2, KLF4) and hairpin RNA targeting p53 are utilized. Growth factors (EGF, bFGF) and chemical supplements (CHIR, Par, NECA, NaB, and RG) are added by day seven. After two weeks, additional factors (Activin-A, CHIR, NECA, NaB, and RG) induce the formation of definitive endoderm (DE) and cPF. Transplanting cPB into diabetic mice demonstrates glucose-stimulated insulin secretion, indicating potential for personalized treatment of Type 1 and Type 2 diabetes [43].

PSCs hold significant potential for pharmaceutical companies, clinical research institutions, drug industries, and clinical research laboratories in developing therapeutics. However, this potential is often underestimated. Despite their promise, safety concerns may limit their use in transplantation endeavors (Fig. 3) [44]. Transplanting human iPSCs into mouse gastrula results in their colonization and differentiation into the three germ layers, indicating clinical developmental success. Overcoming the species barrier between

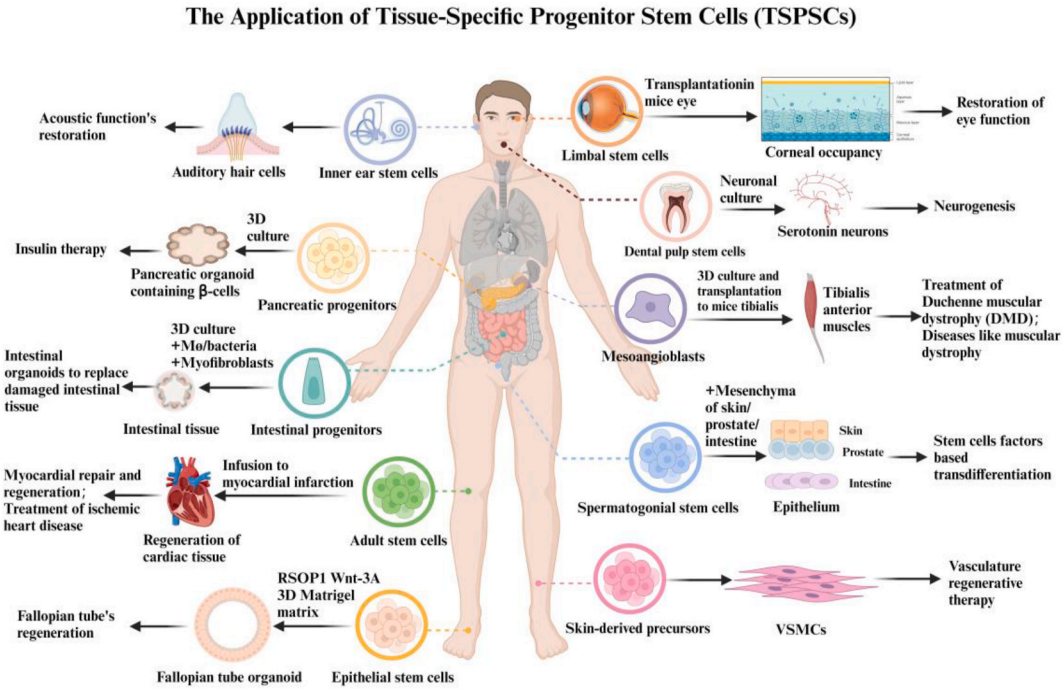

Fig. 4. Utilizing TSCs in Regenerative Medicine: TSCs showcase differentiation potential into various cell types within specific tissues. For instance, inner ear stem cells can transform into auditory hair cells, and dental pulp stem cells can differentiate into serotonin-producing cells. When cultured in biomaterials in a 3D environment, TSCs form tissue organoids, such as pancreatic and intestinal organoids. Transplanting TSCs presents the regenerative potential for repairing target tissues; for example, mesoangioblasts regenerate tibialis muscles, and AdSCs contribute to cardiac tissue regeneration. Growth and transformation factors secreted by TSCs influence neighboring cells, prompting their conversion into different cell types. In specific instances, coculturing SSCs with mesenchyme leads to the transformation of MSCs into epithelial cells.

humans and mice highlights the importance of precise timing and reprogramming regimes. This breakthrough paves the way for generating human organs in closely related primates, offering potential embryo-level treatments for genetic diseases. The approach holds significant implications for medical research and therapeutics [45].

5. Therapeutic potential of specific TSC

TSCs are vital for sustaining tissue homeostasis through continuous cell division. Unlike ESCs, TSCs preserve stem cell plasticity but have a restricted differentiation capacity into specific cell types within a tissue. It is crucial to highlight that the quantity of TSCs in a tissue is relatively limited compared to the overall cell population, presenting challenges in harvesting and in vitro manipulation [46], exploring the therapeutic applications of TSCs on a large scale presents challenges due to their limited numbers. The human body harbors various TSCs, making it impractical to delve into detailed therapeutic applications for all of them in this section. In the following section, we will concentrate on particular types of TSCs, such as pancreatic progenitor cells (PPCs), dental pulp stem cells (DPSCs), inner ear stem cells (IESCs), intestinal progenitor cells (IPCs), limbal progenitor stem cells (LPSCs), epithelial progenitor stem cells (EPSCs), mesoangioblasts (MABs), spermatogonial stem cells (SSCs), skin-derived precursors (SKPs), and adipose-derived stem cells (ADSCs). These cells promise diverse therapeutic applications across various medical fields (Fig. 4).

For instance, during embryogenesis, PPCs give rise to insulin-producing β-cells, and the differentiation of PPCs into β-cells is negatively regulated by insulin [47]. For their development, PPCs rely on active fibroblast growth factor (FGF) and Notch signaling. Their growth is more robust within a community of cells than in single-cell populations, emphasizing the functional significance of the niche effect in processes such as self-renewal and transdifferentiation. In a 3D scaffold culture system, PPCs derived from mouse embryos can organize into hollow organoid spheres. These organoids subsequently undergo differentiation, forming clusters of insulin-producing β-cells, holding promise for therapeutic applications in diabetes and other related conditions [48].

However, several challenges hinder their clinical application. Limited availability and scalability of TSCs, risks of immune rejection, and ensuring consistent differentiation and integration in host tissues are major hurdles. Additionally, maintaining genetic stability during cell culture, addressing ethical concerns, and the high cost of research and development present significant obstacles. Overcoming these challenges is crucial to fully realize the therapeutic potential of TSCs [49].

5.1. Neurogenic differentiation of DPSCs and their therapeutic applications

DPSCs, crucial for dental health, are extractable from various dental tissues, including deciduous teeth, dental follicles, apical papillae, and periodontal ligaments. These cells emerge as promising candidates for regenerative medicine, holding the potential to address a variety of diseases. Additionally, DPSCs may be explored for their capacity to contribute to restoring neurogenic functions in dental tissues [50].

Cultivating DPSCs in a specific neuronal culture medium induces their differentiation into various neurons, but they lack some essential channels for spontaneous action potential generation. Nonetheless, these early-stage neural stem cells hold therapeutic potential for neurodental issues [51]. A study found that transplanting human neuronal stem cells into the hippocampus of mice with cyclophosphamide-induced cognitive decline restored cognitive abilities within one month. The engrafted cells differentiated into astroglial and neuronal lineages, alleviating neuroinflammation and restoring microglial functions. Preemptive transplantation before chemotherapy positively impacted specific hippocampal neurons, reducing spine and dendritic cell density. These findings suggest that brain stem cell transplants may help restore cognitive functions affected by chemobrain [52].

Inhibiting the Notch signaling pathway in inner ear progenitors with a γ-secretase inhibitor (LY411575) activates Atoh1, prompting differentiation into cochlear hair cells. Transplanting these in vitro-generated hair cells has shown promise in restoring acoustic functions in mice, suggesting potential applications in treating deafness [53].

Hair cell generation can also be accomplished by overexpressing Atoh1 and β-catenin in Lgr5+ cells in vivo. This alternative approach offers another means of producing new hair cells and holds promise for regenerative therapies in the auditory system [54].

5.2. Biomaterial-based 3D scaffolds for intestinal tissue regeneration

The intestinal region of the digestive system contains unique stem cells that give rise to specific tissues, playing a crucial role in regenerating intestinal tissue and maintaining digestive system health and functionality [55]. Dysregulation of common stem cell signaling pathways, including Notch, BMP, TGF-β, and Wnt, in intestinal tissue can contribute to developing various diseases. The proper function of these pathways is crucial for maintaining the health and balance of intestinal tissue [56]. Encouraging tissue-specific progenitors in the intestine involves utilizing immune cells, connective tissue cells, and probiotic bacteria in non-reactive biomaterial 3D scaffolds. This approach shows potential in differentiating progenitors and forming crypt-villi structures. Implanting these structures in dogs has improved intestinal mucosa regeneration, suggesting therapeutic benefits for tissue loss in diverse conditions [57]. In vitro culture, intestinal stem cells often differentiate into various cell types. However, the introduction of specific factors like valproic acid and CHIR-99021 can inhibit this process, creating an unlimited source of stem cells with potential for regenerative applications. This method holds promise for maintaining a stable population of intestinal stem cells for therapeutic use [58].

5.3. Limbal stem cells in corneal regeneration and mesoangioblasts in muscle tissue engineering

Limbal stem cells, characterized by the presence of ABCB5 and situated in the basal limbal epithelium, play a crucial role in both regenerating and preserving corneals [59]. The survival and functional integrity of limbal stem cells heavily rely on the critical role played by ABCB5, which acts as a safeguard against apoptotic cell death, ensuring their proper functioning [60]. The deficit of limbal stem cells causes the replacement of corneal epithelium with non-functional conjunctival tissue, ultimately resulting in compromised vision. Causes of this deficiency include factors such as burns, inflammation, and genetic abnormalities [61]. Transplanting human corneal stem cells into mice has showcased their capacity to regenerate and form a fully functional human cornea. The blood-eye barrier phenomenon may facilitate this regeneration. This technology can potentially treat eye diseases where corneal tissue regeneration is crucial for restoring vision [62].

The field of tissue engineering technology exhibits potential in tackling muscle degenerative diseases such as Duchenne muscular dystrophy (DMD), which has the potential to result in significant muscle impairment.The approach involves encapsulating MABs from mice or humans, genetically modified to produce placental-derived growth factor (PDGF), and then encapsulated within a polyethylene glycol (PEG) fibrinogen hydrogel. These encapsulated MABs are transplanted beneath the skin in the area of an ablated tibialis anterior muscle, forming artificial muscles that function similarly to normal tibialis anterior muscles. PDGF can draw in diverse cell types to the transplant location, supporting the transdifferentiation of mesoangioblasts into muscle fibrils. This approach exhibits promising applications in tissue regeneration for muscle-related diseases [63]. Researchers have thoroughly examined the therapeutic potential of MABs in the regeneration of skeletal muscle, investigating their ability to achieve varied therapeutic outcomes [64].

5.4. Transdifferentiation potential of SSCs in regenerative medicine

Male germline stem cells, commonly known as SSCs, play a vital role in generating the spermatogenic lineage through their interactions with mesenchymal and epithelial cells, creating a niche effect that influences other cells.During in vivo transplantation experiments, the co-transplantation of SSCs with prostate, skin, and uterine mesenchyme leads to the differentiation of SSCs into the epithelial cells specific to each respective tissue. The recently developed tissues display the physical and physiological traits of the prostate and skin. At the same time, in the uterus, they showcase the physical attributes specific to this tissue. They also express tissue-specific markers [65].

5.5. Advancements and challenges in satellite cell research for muscle regeneration

In 1961, the satellite cell was initially identified through electron microscopic examination of skeletal muscle, revealing a cell between the muscle fiber's plasma membrane and the basement membrane. Recent research has firmly established the satellite cell as the primary cellular source for muscle regeneration, capable of self-renewing and functioning as a bona fide skeletal muscle stem cell (MuSC). As we commemorate the satellite cell's 50th anniversary, we seize this opportunity to delve into the current advancements and uncertainties within the MuSC field [64].

In this review, we discuss lies on the present state of satellite cell research through the lens of stem cell biology. We emphasize recent studies demonstrating the crucial role of satellite cells in maintaining the stem cell pool and repairing differentiated muscle tissue. Furthermore, we examine the shared properties between satellite cells and other stem cell populations alongside the mechanisms governing satellite cell functions [66].

6. Therapeutic applications of AdSCs in treating diabetic retinopathy

6.1. Mechanisms of AdSCs in vascular regeneration

Diabetic retinopathy, affecting over 100 million people globally, is marked by progressive retinal vascular loss and vision impairment. Mouse experiments show that intravitreal injections of adipose-derived stem cells (AdSCs) can restore the microvascular capillary bed. AdSCs from healthy donors produce higher levels of vasoprotective factors than those from diabetic mice, improving vascularization. However, therapeutic use of AdSCs for diabetic retinopathy requires further standardization, including precise cell dosage quantification and comprehensive efficacy evaluation across diverse populations [67].

6.2. Applications of AdSCs in tissue regeneration

In addition to AdSCs, various stem cell types show significant therapeutic potential for treating eye disorders in regenerative medicine. These applications have been extensively reviewed by other researchers [68]. The fallopian tubes, crucial for egg fertilization, often face inflammation and scarring, leading to infertility and ectopic pregnancies. They are also linked to the onset of ovarian cancer. Historically, studying ovarian cancer has been challenging due to limited tools. Recent advancements in 3D organoid cultures of fallopian tube epithelial cells, which preserve tissue-specific characteristics through active Wnt and Notch signaling, offer a promising method for cancer screening and investigating the origins and causes of ovarian cancer [69].

CA-derived stem cells, akin to fallopian tube stem cells, differentiate into cardiovascular tissues and contribute to heart tissue regeneration and improved cardiac function when infused into the ischemic myocardium of mice. They exhibit greater differentiation and heart regeneration potential than AdSCs from other sources, making them strong candidates for regenerative medicine in treating

myocardial ischemia [70].

SKPs, progenitor cells of dermal papilla, hair, and hair sheath, exhibit the remarkable ability to generate tissues derived from mesoderm and ectoderm. These tissues include diverse cell types such as neurons, Schwann cells, adipocytes, chondrocytes, and vascular smooth muscle cells (VSMCs). VSMCs are essential for wound healing and angiogenesis [71]. Previous studies indicate that VSMCs can be generated from human foreskin progenitor SKPs, highlighting the potential of SKP-derived VSMCs in regenerative medicine. These cells show promise for treating conditions related to tissue repair and vascular health [72].

7. Tissue-specific stem cell applications

7.1. Characteristics of mesenchymal stem cells (MSCs)

MSCs are multipotent stem cells that differentiate into mesoderm-derived tissues, including tendons, bone, cartilage, ligaments, muscles, and neurons. They are characterized by expressing CD73, CD90, and CD105, while lacking CD11b, CD14, CD19, CD34, CD45, CD79a, and HLA-DR markers. Further information on MSCs can be found in previous reviews on the topic [73]. A comprehensive understanding of MSCs in regenerative medicine can be achieved by evaluating outcomes from ongoing clinical trials at various stages of completion. Detailed information on these applications is available in existing reviews [74]. In this review section, we spotlight the latest and representative applications of MSCs, as depicted in Fig. 5.

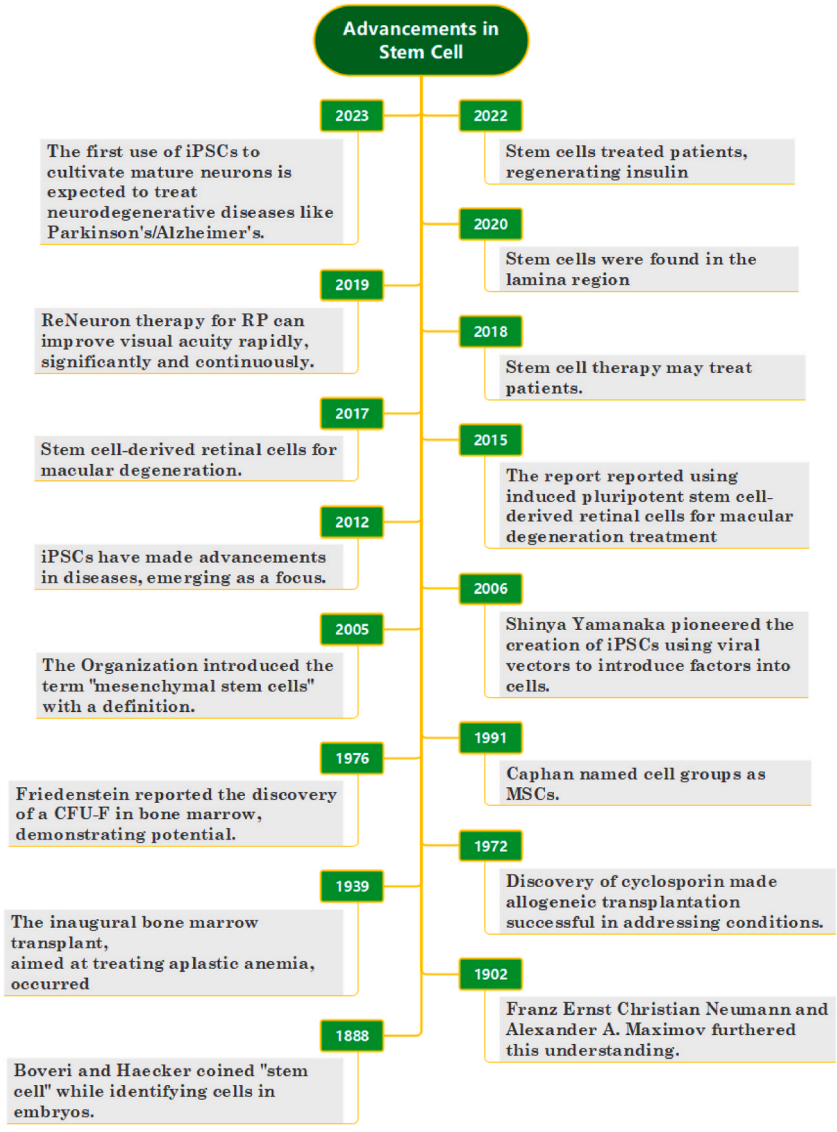

Fig. 5. A Chronological journey through key milestones in stem cell discovery, development, and applications.

It is essential to note that the anatomical and physiological characteristics of both the donor and recipient significantly influence therapeutic outcomes. For instance, bone marrow-derived MSCs (BMDMSCs) from baboons exhibit morphological and phenotypical features similar to bladder stem cells, making them suitable for bladder tissue regeneration. These BMDMSCs, expressing CD105 and CD73 while lacking CD34 and CD45, were further enhanced with a Green Fluorescent Protein (GFP) reporter. When transplanted onto small intestinal submucosa (SIS) scaffolds, they substantially healed degenerated bladder tissue within ten weeks. This underscores the importance of characterizing donor MSCs using specific markers, such as CD, to achieve superior regenerative outcomes [75].

7.2. Innovations in MSC-based liver regeneration

MSCs also hold promise in regenerating liver tissue and treating conditions like liver cirrhosis, as extensively discussed in various sources and reviews [76].The regenerative applications of MSCs involve two main strategies: direct transplantation and ex vivo transdifferentiation followed by transplantation. However, using retroviral delivery systems in ex vivo transdifferentiation poses a risk of oncogenic effects. To mitigate this risk, nonviral methods like NanoScript technology have been developed. NanoScript employs gold nanoparticles coupled with modified transcription factors to target specific regulatory regions within the genome, efficiently directing the differentiation of MSCs into various cell lineages. For example, NanoScript-MRF, which incorporates myogenic regulatory factors, can direct the transformation of adipose tissue-derived MSCs into muscle cells. This innovative approach minimizes oncogenic risks while enhancing the precision of cell fate determination [77]. MSCs, due to their multipotency, hold promise for producing stable tissue constructs via 3D organoid culture. However, uneven MSC dispersion can impede cell proliferation, limiting their therapeutic potential. To address this, a two-step culture system can be used to achieve a more homogeneous MSC distribution within biomaterial scaffolds. For example, fetal MSCs can initially be cultivated in a rotating bioreactor before transitioning to static culture, resulting in more equitable MSC dispersal within ECM components. This approach aims to enhance the effectiveness of MSC-based therapies by optimizing the spatial arrangement of cells within tissue constructs [78].

7.3. Applications of MSCs in dental and orthopedic regeneration

Dental caries, periodontal disease, and tooth injuries can significantly impact an individual's health. In such cases, tooth bioengineering emerges as a promising solution. By precisely guiding epithelial-MSCs with dental stem cells within a synthetic polymer, it is possible to create fully developed teeth units. These units, which include fully developed teeth and oral tissues, hold potential applications in regenerative therapeutics [79]. Both humans and animals are susceptible to orthopedic injuries affecting structures such as bones, joints, tendons, muscles, and cartilage. While the body's innate healing abilities are typically sufficient for minor injuries, severe trauma and conditions like tumor regression can hinder the regenerative capacity of bone-forming stem cells. However, the in vitro chondrogenic, osteogenic, and adaptogenic potential of MSCs underscores their therapeutic promise in treating orthopedic injuries [80]. Transplanting lineage-induced MSCs into biomaterial scaffolds at damaged bone sites promotes tissue regeneration. Noticeable enhancements in bone tissue are seen within four weeks post-transplantation, with gradual integration over 32 weeks leading to a fully healed bone structure [81].

Osteoblasts, the cells responsible for bone formation, exhibit a less prominent actin cytoskeleton than adipocytes and MSCs. Treating MSCs with cytochalasin-D triggers the reorganization and transport of G-actin, transforming these cells into osteogenic cells and promoting bone formation. Additionally, injecting cytochalasin-D into the tibia of mice enhances bone formation within one week. Research on bone formation in mice, dogs, and humans shows fundamental similarities, making insights from animal studies valuable for human regenerative applications. For example, injecting MSCs into the femur head of a dog with Legg-Calve-Perthes disease results in rapid bone healing and reduced pain [82].

7.4. MSC therapy for muscle repair and heart regeneration

Muscle atrophy and muscle spasms affect canines, other animals, and individuals in athletic activities. In such cases, the direct injection of adipose tissue-derived MSCs into the site of a tear in the semitendinosus muscle of dogs has been shown to promote faster healing than traditional therapies [83]. The treatment for heart muscle damage and regeneration is more complex than for skeletal muscles due to the need for precise coordination between neurons and muscles. Researchers have found that inducing MSCs into an alginate gel enhances cell retention duration, allowing them to release tissue-repairing factors systematically. When these encapsulated cells are transplanted into the hearts of mice, they reduce scar size and promote vascularization, restoring heart functions. Additionally, encapsulated MSCs are protected from the transplant site's inflammatory immune responses and mechanical pressures. This encapsulation technique enables the cells to sense and respond to the host tissue's microenvironment effectively [84].

7.5. GAG-coated DPCs for hair regeneration in alopecia

Alopecia, characterized by hair loss due to factors such as aging, disease, and medication, can significantly impact individuals emotionally and psychologically. Current treatments, including hair transplantation and medications, are often expensive and struggle to generate new hair follicles. Dermal papillary cells (DPCs), specialized mesenchymal stem cells found in hair follicles, play a crucial role in hair follicle morphogenesis and cycling [85]. Researchers have developed a layer-by-layer Glycosaminoglycan (GAG) coating for DPCs. This coating consists of an outer layer of gelatin, a middle layer containing fibroblast growth factor 2 (FGF2) within alginate, and an innermost layer of gelatin. The GAG coating creates a tissue microenvironment for DPCs, providing resilience against

immunological and mechanical challenges and facilitating new hair follicle growth. Transplantation of GAG-coated DPCs has yielded remarkable outcomes, resulting in abundant hair growth and maturation of hair follicles. The GAG coating acts as an extracellular matrix (ECM), enhancing the intrinsic therapeutic capacity of DPCs in treating alopecia [86].

8. Advancements in stem cell types and sources

In 1888, German zoologists Theodor Heinrich Boveri and Valentin Haecker coined the term "stem cell" while identifying cells in embryos with the capacity to differentiate into specialized cells, marking the inception of regenerative medicine. In 1902, Franz Ernst Christian Neumann and Alexander A. Maximov further advanced this understanding by describing hematopoietic progenitor cells [5]. The inaugural bone marrow transplant, aimed at treating aplastic anemia, occurred in 1939. However, it wasn't until the discovery of cyclosporin, an immunosuppressive drug, in 1972 that allogeneic transplantation became successful in treating conditions such as aplastic anemia and acute myeloid leukemia [87], the initial treatment of allogeneic hematopoietic stem cell transplantation (HSCT) by E. Donnall Thomas, Dr. George Mathe, and others had limited success due to its experimental and exclusive nature [88]. In 1976, Friedenstein reported the discovery of fusiform fibroblast colony-forming units (CFU–F) in bone marrow, demonstrating high self-renewal and differentiation potential [89]. These cells could facilitate hematopoietic cell cloning, suggesting they might be stromal cell precursors. Mesenchymal stem cells (MSCs), originally identified in bone marrow, represent a type of pluripotent cell widely distributed throughout the human body. As early as 1867, Cohnheim in Germany speculated about the existence of non-hematopoietic stem cells in bone marrow through experiments. In 1991, Caplan named these cell groups, which exhibited consistent adhesion ability, high in vitro expansion, and multi-differentiation capabilities, as MSCs [90].

In 2005, the International Society for Cellular Therapy defined "mesenchymal stem cells." Embryonic stem cell research dates back to the 1970s when studies on teratomas revealed embryonic carcinoma (EC) cells capable of self-renewal and differentiation into various cell types in vitro. Mouse embryonic stem cells were established in 1981, and later, Professor Thomson from the University of Wisconsin developed the human embryonic stem cell line (hES) based on the primate embryonic stem cell line [91]. Because of their unique properties, ESCs have been extensively studied and hold significant potential for regenerative medicine and cell therapy. They offer hope for treating many incurable diseases [5]. Some individuals, based on religious and moral beliefs, consider embryos to be human beings with inherent rights. They argue that extracting the inner cell mass from a blastocyst to derive an embryonic stem cell line is equivalent to taking a life [92].

In 2006, scientist Shinya Yamanaka pioneered the creation of iPSCs by reprogramming differentiated somatic cells using viral vectors and four transcription factors. This process transformed the cells into a type resembling embryonic stem cells, known as iPSCs. iPSCs have emerged as a significant focus of research in the stem cell industry, showing promising advancements in treating cardiovascular diseases, nervous system diseases, and eye diseases. Yamanaka's groundbreaking work earned him the Nobel Prize in Physiology or Medicine in 2012. Importantly, the use of iPSCs avoids moral and ethical controversies associated with other stem cell sources [93]. The groundbreaking utilization of induced pluripotent stem cell-derived retinal cells has been reported as a potential treatment for macular degeneration [94]. A significant stride has been made with the exploration of autologous-induced stem cell-derived retinal cells, particularly in treating macular degeneration [95].

Stem cell therapy is now considered a promising avenue for treating spinal cord injuries, demonstrating significant potential advancements in regenerative medicine [96]. ReNeuron's retinal progenitor cell therapy emerges as a beacon of hope for retinitis pigmentosa (RP) treatment, showcasing the potential for rapid, substantial, and continuous improvement in visual acuity [97]. Notably, stem cells with the capability to preserve vision have been identified in the optic nerve lamina region, further expanding our understanding of the potential applications of stem cell therapies [98]. Scientists are poised to leverage retinal pigment epithelial stem cells as a prospective treatment for human blindness, marking a significant stride toward addressing visual impairments [99]. In a remarkable development, stem cells have demonstrated successful treatment outcomes for patients with type 1 diabetes, exhibiting the regeneration of stable insulin levels within a 90-day timeframe [100].

The groundbreaking cultivation of highly mature neurons using iPSCs marks a significant leap forward in the potential treatment of neurodegenerative diseases, including Parkinson's and Alzheimer's disease. This innovative approach holds promise for addressing the complex challenges associated with these debilitating conditions, paving the way for novel therapeutic interventions and advancements in regenerative medicine [101].

Our historical review has revealed the evolution and significant advancements of stem cells from discovery to application. The above researches acknowledge that Stem cell research began in 1888 with Boveri and Haecker's identification of cells that could differentiate into specialized types, laying the foundation for regenerative medicine. Key milestones include the description of hematopoietic progenitor cells by Neumann and Maximov in 1902, the first bone marrow transplant in 1939, and the use of cyclosporin in 1972 for successful allogeneic transplantation. Friedenstein's identification of mesenchymal stem cells (MSCs) in 1976, their formal definition in 2005, and the establishment of embryonic stem cell (ESC) lines in the 1970s were significant advances. Shinya Yamanaka's creation of iPSCs in 2006 revolutionized the field, earning him a Nobel Prize in 2012. Recent advancements show promising treatments for macular degeneration, retinitis pigmentosa, type 1 diabetes, and neurodegenerative diseases, marking a new era in regenerative medicine. By examining research methods and outcomes across different periods, we have witnessed crucial progress from early isolation and cultivation of various stem cell types to the artificial induction of stem cells. Numerous studies on directed differentiation of stem cells are poised to enhance therapeutic efficacy and accelerate clinical translation. These efforts are pivotal in advancing the medical applications of stem cell therapy, offering new possibilities for treating a broader range of diseases.

9. Immunomodulatory properties of MSCs

As previously highlighted, MSCs can alter immune responses through various mechanisms, including suppressing T cells and facilitating a shift in macrophages from an M1 to M2 phenotype [102]. Therefore, there is a growing exploration of these cells as a promising therapeutic strategy for addressing immune-mediated disorders such as graft-versus-host disease (GVHD), multiple sclerosis (MS), and Crohn's disease (CD) [103]. The therapeutic effectiveness of MSCs has been validated for treating acute lung injuries (ALI) and musculoskeletal diseases. After systemic injection, MSCs migrate to injury sites and exert therapeutic effects through mechanisms such as immunomodulation and angiogenesis [104].

MSCs mediate immunomodulation through direct cell-to-cell contact and trophic factor secretion. They can alter cytokine release profiles of immune cells, such as dendritic cells (DCs), T cells, and natural killer (NK) cells, fostering an anti-inflammatory or tolerant phenotype (Fig. 6). Specifically, MSCs reduce tumor necrosis factor-alpha (TNF-α) secretion by mature DC type 1 (DC1), increase interleukin-10 (IL-10) secretion by DC2, decrease interferon-gamma (IFN-γ) release by Th1 cells, and boost interleukin-4 (IL-4) secretion by Th2 cells. The precise mechanisms of MSC-mediated immunomodulation remain incompletely understood [105]. Moreover, MSCs increase the frequency of regulatory T cells (Tregs) while decreasing the production of IFN-γ by NK cells [106]. This process involves a variety of soluble factors, including transforming growth factor-β1 (TGF-β1), prostaglandin E2 (PGE2), hepatocyte growth factor (HGF), indoleamine-pyrrole 2,3-dioxygenase (IDO), nitric oxide (NO), and interleukin-10 (IL-10) [107]. PGE2, a lipid mediator, is crucial for T-cell suppression by MSCs. It is produced from arachidonic acid through the actions of constitutive cyclooxygenase-1 (COX-1) or inducible COX-2, commonly found in human MSCs [107]. Indoleamine-pyrrole 2,3 IDO is another soluble factor released by MSCs that breaks down tryptophan, essential for T lymphocyte effector functions. This leads to immunosuppression at injury sites following MSC transplantation. MSCs do not constitutively express IDO, but they can be induced to express it in response to IFN-γ, though not by TNF-α [108]. Undrud et al. propose that IDO could impede T cell proliferation and the activation of effector T cells. Additionally, it may trigger apoptosis in NK cells [109]. According to other reports, molecules such as programmed cell death 1 ligand 1 (PD-L1) and FasL may also contribute to the immunoregulation induced by human MSCs, including Placenta-Derived Mesenchymal Stem Cells (PL-MSCs) [62].

A research indicates that human T-effector cells exhibit elevated expression of PD receptors when co-cultured with MSCs in vitro. This suggests that the PD-1/B7–H1 axis may play a role in the inhibitory effect of MSCs on effector T cells [110]. Research indicates that human T-effector cells exhibit elevated expression of PD receptors when co-cultured with MSCs in vitro. This suggests that the PD-1/B7–H1 axis may play a role in the inhibitory effect of MSCs on effector T cells [111]. TGF-β and IL-10 are pivotal in the suppressive activities of Tregs and are essential for maintaining immune homeostasis [112]. The significance of TGF-β as an immune regulator in T cell function is highlighted by the similarities observed in TGF-β1 knockout mice and mice with T cell-specific TGF-β receptor II knockout. Both models exhibit severe multiorgan autoimmunity, leading to premature death, underscoring TGF-β′s crucial role in maintaining immune tolerance and preventing autoimmune diseases [113]. Genomic and proteomic analyses have revealed that MSCs express and secrete high levels of HGF. Studies have demonstrated that HGF plays a potent role in MSC-induced immunomodulation. Monocytes treated with HGF remain undifferentiated and can shift Th cells from a Th1 to a Th2 phenotype. This shift modulates the immune response, as Th1 cells are associated with pro-inflammatory responses, whereas Th2 cells are involved in anti-inflammatory and regulatory responses. Thus, HGF is critical in promoting an immunomodulatory environment through its effects on immune cell differentiation and function [114]. In vivo, studies demonstrate that MSCs can alleviate early ALI by leveraging the paracrine action of HGF. HGF prompts the conversion of mature DCs into regulatory DCs in rodent models, resulting in diminished inflammation. This underscores the pivotal role of HGF in the immunomodulatory effects of MSCs during lung injury. Some research investigates enhancing endogenous HGF secretion as a potential therapeutic approach for inflammatory lung diseases. Increasing HGF

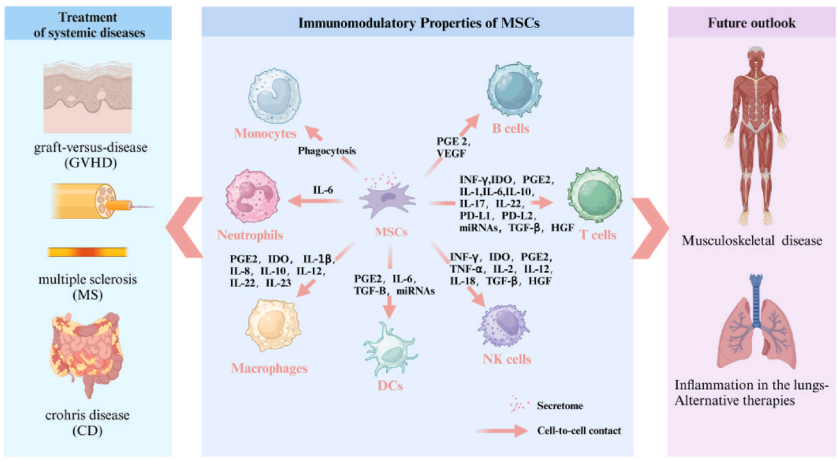

Fig. 6. MSCs can influence the cytokine release profiles of immune cells, such as dendritic cells, T cells, and NK cells, promoting an anti-inflammatory or tolerant phenotype.

levels may offer partial relief for individuals with such conditions, highlighting the therapeutic promise of HGF in immunomodulation and tissue repair [114]. The study elucidates the immunomodulatory properties of MSCs, which carry therapeutic potential for disorders such as GVHD, MS, and CD. MSCs migrate to injury sites, contributing to immunomodulation and angiogenesis, critical for conditions like acute lung injuries and musculoskeletal diseases. Key factors such as TGF-β, PGE2, HGF, and IDO play pivotal roles in bolstering regulatory T cells while suppressing effector T cells and NK cells, thereby upholding immune homeostasis and fostering tissue repair.

9.1. Immunomodulation and allogeneic transplantation

The antigen-antibody immune response is characterized by an initial exposure that inhibits further reaction, leading to immune tolerance upon subsequent encounters. This immunotolerance is primarily observed in transplantation and autoimmune diseases [115]. Graft-versus-host disease (GVHD) occurs when the body mounts a typical immune response against the graft following transplantation, resulting in inactivation or destruction of the graft tissue. The pathogenesis of GVHD is primarily attributed to the body's specific immune response to the graft tissue. Besides T cells, other humoral immune reactions are also involved [116]. GVHD can manifest at various time points post-transplantation, typically developing 3–4 weeks after the removal of the donor organ [117].

9.2. Immunomodulatory potential of MSCs in treating infectious diseases

During infections, immune cells release inflammatory cytokines that attract MSCs to the site of inflammation. MSCs then modulate inflammatory responses, making them valuable candidates for treating infectious diseases in regenerative medicine. In a coculture experiment involving macrophages (Mφ) and adipose-derived MSCs from mice susceptible and resistant to Leishmania major (LM) infection, it was observed that adipose-derived MSCs educated macrophages against LM infection. This education resulted in the differential induction of M1 and M2 macrophage phenotypes, suggesting that adipose-derived MSCs could potentially serve as a therapeutic agent for leishmanial therapy. This highlights the immunomodulatory capacity of MSCs and potential role in shaping immune responses during infectious diseases [118].

9.3. Graft rejection

Transplant rejection stems from graft-host tissue interactions, leading to acute (AR) and chronic reactions (CR). AR involves a nonspecific immune response due to heightened antigen presentation by the graft and recipient's hyperactive response to donor cells post-transplantation. Conversely, CR signifies a prolonged, recurring specific immune reaction between graft and donor tissue, typically appearing 3–5 years after transplantation [119]. The main mechanisms of TR are (1) Repeated stimulation of graft antigen, that is, T cells, B cells, etc., are constantly recognized and killed by allogeneic lymphocytes so that they produce tolerance; (2) The recipient's innate immune response is overactive, mainly due to the high titer of specific antibodies produced by the donor B cells, so that the recipient T cells produce immune responses to their tissues and organ antigens; (3) The recipient B cells have a gene mutation and cannot produce enough antibodies to neutralize the graft antigen so that the graft antigen-specific immune response can persist; (4) Allogeneic lymphocytes and tissue fragments were present in the grafts. In addition, microbial contamination in the graft may cause CR induction [120].

In addition to DAMPs (damage-associated molecular patterns), grafts that encounter alloantigens (foreign molecules) activate the host's immune system, provoking an intensified immune response and inflicting further damage to the graft. The diversity in major histocompatibility complex (MHC) genes plays a critical role in facilitating the recognition of foreign "non-self" components by host or donor immune cells during allogeneic and xenogeneic organ transplantation. Recognition of these "non-self" antigens initiates immune signaling between the donor and host, subsequently eliciting adaptive memory immunity and innate trained immunity against the graft. This presents a significant challenge to the long-term survival of the graft [121].

9.4. The allograft

In the contemporary scientific landscape, there is a renewed focus on understanding the shifts in immune cell activity induced by effector molecules released by Mesenchymal Stem Cells (MSCs). Recent studies have unveiled the intricate mechanisms MSCs modulate immune responses, offering crucial insights into their therapeutic applications across diverse diseases. MSCs emit a broad spectrum of bioactive molecules, encompassing cytokines, chemokines, growth factors, and extracellular vesicles, which exert immunomodulatory influences on different subsets of immune cells [78]. Research indicates that factors derived from MSCs can profoundly influence the function and behavior of various immune cell types, including T cells, B cells, dendritic cells, macrophages, and natural killer cells. For instance, molecules such as transforming growth factor-beta (TGF-β), prostaglandin E2 (PGE2), hepatocyte growth factor (HGF), indoleamine 2,3-dioxygenase (IDO), and interleukin-10 (IL-10) secreted by MSCs have been shown to enhance the expansion and activity of regulatory T cells (Tregs) while simultaneously suppressing the activation and proliferation of effector T cells. Additionally, MSCs demonstrate the capacity to bias macrophage polarization towards an anti-inflammatory M2 phenotype, thereby mitigating excessive inflammation and tissue damage [122].

Understanding the specific alterations in immune cell behavior induced by MSC effector molecules is crucial for optimizing MSC-based therapies and developing targeted immunomodulatory strategies. While mesenchymal stem cells hold promise as a treatment approach for attenuating solid organ transplant rejection, significant hurdles have hindered their clinical implementation in humans.

Mesenchymal stem cell-derived extracellular vesicles have emerged as a potential solution to overcome these challenges, although their clinical investigation remains constrained. Significantly, a recent study documented the effective treatment of graft rejection and inflammation in two patients who underwent bowel transplants using MSC-derived extracellular vesicles [78].

These studies represent a foundational advancement in developing more effective treatment strategies for immune-mediated disorders like graft-versus-host disease (GVHD), autoimmune conditions, and inflammatory diseases. Furthermore, gaining insight into the mechanisms through which MSCs modulate the immune system holds great potential for creating innovative immunotherapeutic approaches and personalized medicine customized to the unique characteristics of individual patients (Fig. 7).

10. Advancements in delivery and tissue integration

Tissue Engineering, a branch of biomedical engineering, focuses on restoring, maintaining, enhancing, or replacing biological tissues. It integrates cells, engineering principles, material technologies, and precise biochemical and physicochemical factors manipulation. Rooted in biomaterial science, It encompasses the incorporation of scaffolds, cells, and biologically active substances to construct functional tissues. The ultimate goal is to build structures capable of repairing, preserving, or enhancing damaged tissues and organs [123]. Tissue engineering consists of three vital components: 1) Reparative cells producing functional matrices, 2) Transplantation-ready scaffolds, and 3) Bioreactive molecules guiding tissue generation. These elements can be used independently or synergistically to facilitate organ and tissue regeneration [124]. Scaffolds in tissue engineering typically comprise biodegradable polymers, ECM components, and growth factors. They provide a structural framework for cells to inhabit, gradually allowing them to develop into three-dimensional tissues [125]. The extracellular matrix (ECM) is synthesized and released by clusters of cells. It acts as a vital nexus for various signaling molecules and offers structural support to the cells residing in the tissue [126]. Consequently, cells receive signals from diverse sources within their immediate surroundings. These signals have the potential to initiate a series of events that ultimately dictate the fate of the cell [127]. Researchers have successfully utilized these processes to repair damaged tissues or create entirely new ones. This achievement involves examining how individual cells respond to signals, interact with their environment, and organize themselves into functional tissues and organisms [128]. However, only a limited array of tissue engineering products sees active clinical use. This disparity between theory and practice highlights the imperative for advancements in delivery techniques to enhance the efficacy and safety of stem cell based therapies across diverse diseases. Confronting these challenges is pivotal for unleashing the full potential of stem cell technology in tissue engineering [129].

In tissue engineering, specific growth factors play a crucial role beyond the extracellular matrix. These growth factors are essential for tissue regeneration and repair, as they influence various cellular processes [130]. Recombinant growth factors have garnered significant attention in regenerative medicine due to their potential to enhance tissue healing in preclinical studies. However, their clinical success remains uncertain. Challenges in translating growth factors to clinical use include their short half-life, rapid dispersion from the delivery site, and concerns about cost-effectiveness [131]. Prospective regenerative therapy solutions focused on growth

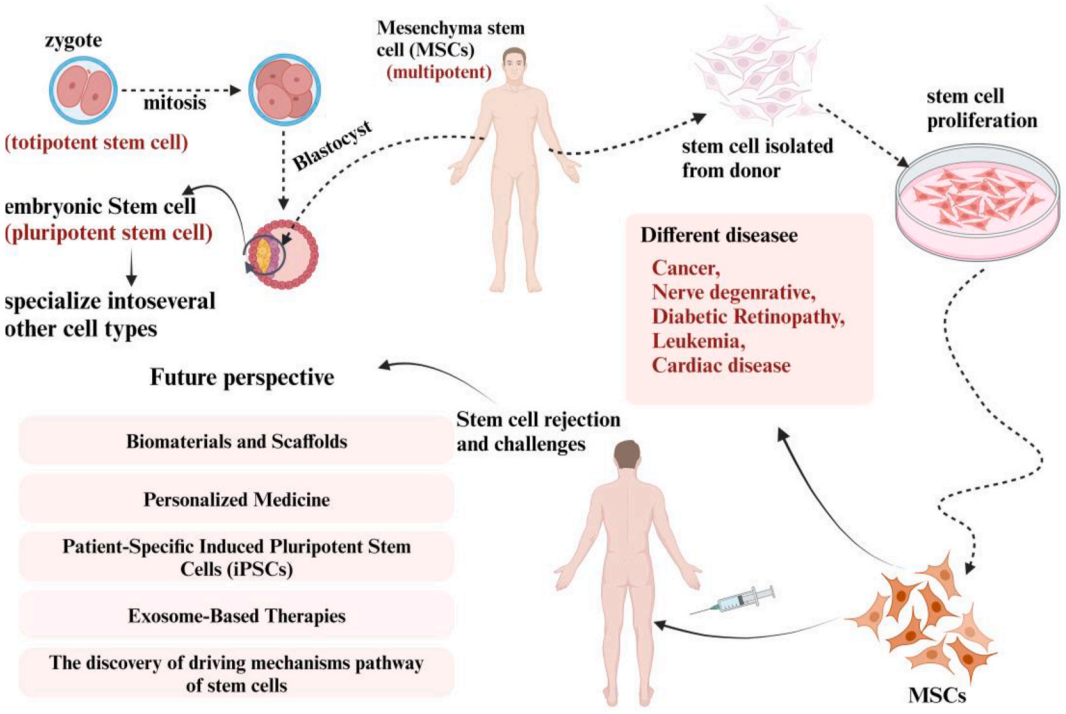

Fig. 7. Complications arising from MSCs Therapies: This figure illustrates the various challenges and complications associated with MSCs therapies.

factors could benefit from a more holistic approach to tissue regeneration, acknowledging the crucial role of the immune system in the regenerative process. Future efforts might explore combining growth factors with immunomodulators or developing multifunctional fusion proteins that promote morphogenesis and modulate the immune system. Furthermore, various delivery systems aim to enhance the controlled release and stability of growth factors at the delivery site [132].

In conclusion, stem cell technology in tissue engineering shows promise but faces challenges with delivery methods. Few products are in clinical use, indicating a need for better techniques. Tissue engineering uses cells, scaffolds, and growth factors to restore tissues. However, growth factors face issues like short half-life and high cost. Future strategies may combine growth factors with immunomodulators and develop advanced delivery systems for improved stability and effectiveness.

11. Challenges and safety concerns

Stem cell transplantation successfully treats blood system diseases, utilizing stem cells' self-renewal, multidirectional differentiation, and proliferation capabilities. This approach is particularly practical for hematological conditions such as acute myeloid leukemia (AML), non-Hodgkin lymphoma (NHL), and chronic lymphocytic leukemia (CLL). Despite positive outcomes in many patients, associated risk factors include donor rejection and the side effects of immunosuppressive drugs [133]. iPSCs and mesenchymal stem cells (MSCs) hold significant promise for regenerative medicine but present distinct challenges and safety concerns. iPSCs are celebrated for their pluripotent capabilities and ability to differentiate into various cell types; however, they pose risks such as potential tumorigenicity, epigenetic abnormalities, and uncertainty in their in vivo differentiation processes. Additionally, the reprogramming process of iPSCs can lead to genetic instability, raising concerns about their long-term safety [134].

Conversely, MSCs, while being multipotent and generally considered safer with lower tumorigenic risks, face their challenges. These include limited proliferation potential and a tendency for senescence. Furthermore, MSC populations' heterogeneity and their therapeutic efficacy variability can complicate their clinical application [135]. Both iPSCs and MSCs require rigorous validation, standardization, and stringent regulatory compliance to ensure their safety and effectiveness in clinical settings [63]. Cell therapies derived from iPSCs offer a promising avenue in regenerative medicine due to their expandability, immune compatibility, and pluripotent potential.

Many preclinical and clinical trials have explored the application of iPSC-based therapies for challenging diseases, such as muscular dystrophy. The unique syncytial nature of skeletal muscle allows stem/progenitor cells to integrate, forming new myonuclei and restoring the expression of genes affected by myopathies. This characteristic makes genome-editing techniques particularly attractive in these therapies. By combining genetic modification and iPSC lineage specification methodologies, it is possible to manufacture immune-compatible healthy iPSC-derived muscle cells that can reverse the progression of muscle diseases or facilitate tissue regeneration. Despite these advancements, developing iPSC-based therapies for muscle diseases and tissue regeneration remains largely confined to academic settings, with no successful clinical translation reported. Challenges such as the unknown differentiation process in vivo, potential tumorigenicity, and epigenetic abnormalities of transplanted cells hinder their clinical application [63]. The first isolation of human embryonic stem cells (hESCs), reported in the late 1990s, opened new possibilities in human developmental biology and regenerative medicine. Differentiating hESC lines into various precursor cells demonstrated their potential in treating several incurable diseases. Despite the promising nature of this field, it has faced significant ethical and experimental challenges [136].

This review part highlight the clinical trial studies involving hESCs, focusing on their advantages, limitations, and specific concerns. Some limitations of hESCs have been addressed, leading to ongoing clinical trials to improve their clinical applications, particularly in macular degeneration and neurodegenerative diseases. However, several critical issues regarding hESC-based therapy require further research and discussion [136]. Despite extensive studies to date, hESC-based therapies are not yet available for conventional clinical applications. More research and data are necessary to overcome clinical and ethical limitations. Once these limitations are fully resolved, hESCs may become superior to existing stem cell sources [136].

SCI impact patients physically, mentally, and financially. Secondary SCI involves inflammation, vascular damage, and permanent harm to the nervous system. Mesenchymal stem cells exhibit anti-inflammatory properties, support vascular regeneration, and release neuro-nutrients, offering promise for SCItherapy. Preclinical studies show MSCs enhancing sensory and motor function recovery in SCI animal models. Clinical trials report MSCs improving American Spinal Injury Association (ASIA) scores related to sensory and motor function in SCI patients. Challenges include potential MSCs tumorigenicity and ensuring MSCs survival in the hostile SCI microenvironment. Despite promising results, more research is needed to understand MSCs benefits and risks in SCI treatment [137]. In recent years, with the deepening of stem cell research, stem cell transplantation has been applied more and more in clinical practice, but there are still some challenges to overcome. The first is the safety issue, mainly including the risk of hematopoietic function and immune system disorders after transplantation. Stem cell transplantation is a safe and effective treatment.

However, there may still be problems, such as immune system disorders, low hematopoietic function, and even severe infections and death after transplantation [138]. Secondly, the safety of stem cells mainly includes two aspects: cell source and cell isolation. MSCs derived from cord blood or cord tissue are the primary stem cells used clinically. MSCs come from patients, have good hematopoietic and immune regulation functions, and can differentiate into diverse cell types. It is the most excellent source for treating leukemia and other blood-related diseases. MSCs are mainly derived from patients with good self-renewal and multidirectional differentiation ability. The cells formed after differentiation can proliferate, migrate to damaged tissues and organs, and play a role [139].

11.1. Current clinical trials and cost effectiveness

Current clinical trials investigating the therapeutic potential of mesenchymal stem/stromal cells (MSCs) span several medical

fields, including immunology, neurology, oncology, and regenerative medicine. These trials aim to evaluate the safety, efficacy, and optimal dosing regimens of MSC-based therapies for a variety of conditions, including autoimmune diseases like multiple sclerosis (MS) and Crohn's disease (CD), degenerative disorders such as osteoarthritis, and neurological conditions like stroke and spinal cord injury [140]. In immunology, ongoing trials are evaluating the use of MSCs for treating graft-versus-host disease (GVHD) following hematopoietic stem cell transplantation, as well as exploring their potential in modulating immune responses in conditions like rheumatoid arthritis and lupus. In neurology, MSC-based therapies are being investigated for their ability to promote neuroregeneration and functional recovery in stroke, traumatic brain injury, and neurodegenerative diseases such as Parkinson's and Alzheimer's disease [141].

In oncology, clinical trials explore the use of MSCs as delivery vehicles for targeted cancer therapies and their potential to enhance the efficacy of conventional treatments like chemotherapy and radiation therapy. Additionally, MSC-based immunotherapies are being studied for their ability to modulate the tumor microenvironment and enhance anti-tumor immune responses [142]. Moreover, ongoing research aims to optimize the manufacturing processes for MSC-based therapies to ensure consistent quality and scalability while minimizing costs. This includes developing standardized protocols for MSC isolation, expansion, and characterization, as well as exploring novel delivery methods and biomaterial scaffolds to enhance the therapeutic efficacy of MSCs [143].

Despite promising results from preclinical studies and early-phase clinical trials, several challenges persist in MSC-based therapy. These include the necessity for long-term safety and efficacy data, standardized criteria for patient selection and treatment monitoring, and regulatory approval pathways for MSC-based products. Addressing these challenges is essential for advancing the field and realizing the full therapeutic potential of MSC-based therapies [135]. In terms of cost-effectiveness, conducting economic evaluations of MSC-based therapies is crucial for assessing their potential impact on healthcare budgets and resource allocation. While initial treatment costs may be higher due to the complexity of MSC manufacturing and delivery, long-term cost savings may be achieved through reduced hospitalization rates, fewer disease complications, and improved patient outcomes. Therefore, understanding the economic implications of MSC-based therapies is essential for informing healthcare decision-making and ensuring their sustainable integration into clinical practice [144].

At a common willingness-to-pay (WTP) threshold of $50,000 per quality-adjusted life year (QALY), MSC therapy is deemed economically attractive if its unit cost does not exceed $16,748. However, this ceiling price can be increased to $101,450 if the therapy substantially reduces both in-hospital mortality and increases hospital discharge rates. Such economic evaluations offer valuable insights into the affordability and sustainability of MSC-based therapies, guiding decision-making processes in healthcare policy and practice [144]. Overall, ongoing clinical trials and economic evaluations are crucial in advancing our understanding of MSC-based therapies and determining their place in future clinical practice. By tackling key challenges and harnessing the latest scientific breakthroughs, MSC-based therapies hold the potential to revolutionize the treatment of various medical conditions and enhance patient outcomes globally [145].

In recent years, stem cell therapy has emerged as a highly promising and advanced field of scientific research, igniting significant expectations for the development of innovative treatment methods. This paper serves as a comprehensive review, focusing on the discovery of various types of stem cells and their potential therapeutic applications. It delves into the origins of stem cells, followed by the laboratory processes involved in controlled culturing and derivation. Essential procedures such as quality control and teratoma formation assays are highlighted to assess the properties of tested stem cells. Moreover, the methods of derivation and the use of culturing media are emphasized to establish optimal environmental conditions for controlled differentiation. Among the myriad applications of stem tissue, particular attention is drawn to the utilization of graphene scaffolds and the potential of extracellular vesicle-based therapies, given their remarkable versatility [146]. The review concludes by addressing the challenges that stem cell therapy must overcome to achieve global acceptance. With a wide array of possibilities, this cutting-edge therapy represents a pivotal moment in modern medicine, offering hope for previously untreatable diseases.

12. Future perspectives

The field of stem cell transplantation for regenerative medicine holds immense promise but also requires ongoing efforts to address existing challenges. Future research should prioritize optimizing stem cell sources, refining transplantation techniques, and comprehensively understanding the long-term effects of stem cell therapies. Collaborative endeavors among scientists, clinicians, and regulatory bodies are essential to fully realize the potential of stem cell-based regenerative medicine and translate these advancements into safe and effective clinical treatments.

13. Conclusion

Despite advancements, significant challenges persist in stem cell transplantation for regenerative medicine, including ethical issues, regulatory complexities, and safety concerns. Addressing these challenges requires collaboration among scientists, clinicians, ethicists, and regulators to balance scientific progress with ethical responsibility. Continued advancements and effective resolution of these challenges will play a crucial role in realizing the full potential of stem cell transplantation for regenerative medicine in the coming years. With responsible and ethical practices, the field can achieve transformative changes in disease and injury treatment, ultimately improving the quality of life for countless individuals. Additionally, the sustainability of stem cell sources and potential breakthroughs, such as developing universal donor stem cells and advancements in synthetic biology, could help alleviate current limitations. These challenges are anticipated to be progressively alleviated by the development of universal donor stem cells, advancements in synthetic biology, progress in large-scale cultivation techniques, and the application of precision medicine. In the

foreseeable future, with ongoing scientific and technological advancements, stem cell therapies are projected to become widely utilized in treating a broad spectrum of diseases, thereby significantly enhancing human health and quality of life.

Data availability

No data was used for the research described in the article.

CRediT authorship contribution statement

Lingxi Wei: Writing – review & editing, Writing – original draft. **Wenqi Yan:** Writing – review & editing, Writing – original draft. **Wahid Shah:** Writing – review & editing, Methodology, Conceptualization. **Zhengwei Zhang:** Writing – review & editing. **Minghe Wang:** Writing – review & editing. **Biao Liu:** Writing – review & editing. **Zhentong Xue:** Writing – review & editing. **Yixin Cao:** Conceptualization. **Xinyu Hou:** Writing – review & editing. **Kai Zhang:** Investigation. **Beibei Yan:** Writing – review & editing. **Xiaogang Wang:** Writing-review & editing, Methodology, Conceptulization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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