Evaluating organ regeneration through stem cells

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Abstract: Over the past three decades, the number of patients on organ transplant waitlists has surged sixfold, while organ transplants currently meet only about 10% of global demand. This critical shortage has prompted a search for alternative solutions, leading to intensified research in the field of organ regeneration using the patient's own stem cells. Stem cell-based regeneration not only offers a reduced risk of immune rejection but also eliminates the reliance on donor organs. This review delves into the current landscape of stem cell research and its applications in organ regeneration, highlighting significant advancements across various stem cell types. Additionally, it addresses the scientific and ethical challenges that accompany these innovative approaches.

Introduction

Driven by an aging population and a rise in chronic diseases, the global burden of organ failure has increased dramatically. Despite the advancements in surgical techniques and immunosuppressive therapy, organ transplants are only able to meet 10% of the global clinical needs. According to the International Transplant Registry, demand has grown exponentially while donor availability has largely remained.

Moreover, even when organs are available, patients face major challenges like immune rejection. The human immune system protects them from harmful pathogens like viruses and bacteria. Sometimes, when a person receives an organ, the immune system recognizes it as 'non-self' and it triggers an immune response. To avoid this, Recipients require taking immunosuppressants, which carry serious side effects and do not guarantee long-term transplant success.

The persistent shortage and immune rejection crisis have intensified research and have made stem cell-based organ regeneration a highly promising alternative. Stem cells (including embryonic, pluripotent, and adult stem cells) possess a unique capability for self-renewal and make different specialised cells. They can not only help replace damaged tissues but also generate entire organs specifically tailored to fit the patient's body. Such advances reduce the risk of immune rejection and the need for the waiting list. So is it truly possible to engineer whole organs from one's own stem cells, which is safe, ethical, and clinically effective?

Methodology

This review synthesizes findings from peer-reviewed journals, government publications, and institutional reports published till 2025. Articles were selected based on relevance to the use of stem cells, organ regeneration, and the latest development in experimental medicine using databases such as National Library of Medicine, Springer Open, PubMed Central, Nature, National Center for Biotechnology Information, and University of California, San Francisco

To understand how and why organ regeneration is possible through stem cells, it is essential to first explore what stem cells are, how they can be directed to develop specific tissues, and the mysteries that surround them. There are many different types of stem cells, and they all trace back to a single stem cell- the zygote. It is a totipotent stem cell that is capable of forming all cell types. As it divides, cells with different levels of potency are achieved.

The different possible levels of potency:

- **Totipotent**: Capable of forming any cell type in the body, including extra-embryonic tissues.
- **Pluripotent:** Able to differentiate into any cell type, with the exception of extra-embryonic tissues
- **Multipotent:** Limited to forming a selection of cell types associated with a specific tissue or organ.
- **Oligopotent:** Restricted to producing a few closely related cell types.
- **Unipotent**: Capable of generating a single cell type while retaining the ability to self-renew

Types of stem cells-

1. **Embryonic stem cells-** They are pluripotent cells that are extracted from the inner mass of the blastocyst (an early embryo stage). They are capable of differentiating into any type of cell. Embryonic stem cells have been the foundation of regenerative medicine. ECGs have been applied in regenerating organ-specific tissues such as hepatocytes for liver repair and cardiomyocytes for the heart.
2. **Adult stem cells-** They are multi-potent cells found in various organs for maintenance and repair. For example, some are tissue-specific and reside inside organs like the liver, intestine, and brain. Another type of adult stem cell is hematopoietic stem cells and mesenchymal stem cells, which are both found in the bone marrow. Hematopoietic stem cells are responsible for generating blood and immune cells, whereas mesenchymal stem cells can differentiate into bones, cartilage, and fat.
3. **Induced Pluripotent Stem cells-** They are generated by reprogramming adult somatic cells back into the pluripotent state via genetic reprogramming, thus bypassing the ethical concerns associated with the use of embryonic cells. iPSCs have been used to create organoids and functional tissues such as kidney nephron-like structures and pancreatic β-cells. However, they face challenges like the low efficiency of cell derivation.

Application of stem cells

The understanding of stem cells has revolutionized medicine, providing new opportunities for treating various diseases and injuries.

- **Liver regeneration using iPSCs-** In a 2023 study, researchers used iPSCs and differentiated them into hepatocyte-like cells (HLCs) capable of restoring liver function. The process began with reprogramming patients' adult cells into iPSCs. They were then kept for over 21 days in culture until they expressed liver-specific genes (like albumin and CYP450) and matured. The formed HLCs were then seeded onto decellularized liver scaffolds or infused into damaged liver tissue. (Zhang et al., 2023)
- **Autoimmune diseases-** Autoimmune diseases occur when the immune system mistakenly attacks the body's own cells. In many clinical trials from 2018 to 2025, researchers have tested different types of cell-based approaches, one of which is mesenchymal stromal/stem cells (MSC). MSCs can migrate to the inflamed tissue. They can orchestrate local and systemic innate and adaptive immune responses through the

release of various mediators, including immunosuppressive molecules, growth factors, exosomes, chemokines, complement components, and various metabolites. Through this mechanism, MSCs reduce inflammation, promote tissue repair, and help restore immune tolerance. (Thompson et al., 2021)

- **Regenerating corneal tissue-** Corneal cell therapy uses special stem cells to fix damaged parts of the cornea. Limbal epithelial stem cells (LESCs) are used to repair the surface layer, and corneal stromal stem cells (CSSCs) help rebuild the thick collagen layer, allowing the cornea to become clear again. Pluripotent stem cells can also be turned into cornea-like cells. The stem cells are transplanted by joining them with pre-existing corneal tissue. They then start to multiply, turning into specific corneal cells that are needed. Scientists often put these stem cells on a scaffold, which acts as a support. (Gonzalez et al., 2020)
- **Vascular Grafts-** One of the major concerns in cardiovascular surgery is poor grafts. The graft can get blocked or fail over time. To solve this, scientists developed vascular grafts that were flexible, strong, and shaped like normal vessels using biomaterials. (Gui et al., 2011)
- **Cardiac tissue repair-** Human pluripotent stem cells have been used to treat myocardial infarction. They support cardiac repair, reduce scar formation, and protect heart muscles. They also modulate inflammation by releasing signals to grow new blood vessels. (Menasché et al., 2018)
- **Pancreatic beta cell regeneration-** Researchers grow β-cells from human pluripotent stem cells and then inject them into the patient. The cells are often placed in a semipermeable encapsulation device to protect them from the immune system. Once the cells are implanted, the progenitor cells mature in the body to release insulin. (Pagliuca et al., 2014)
- **Lung alveolar repair-** In research done in 2022, scientists took alveolar type 2 cells and injected them into the lungs of patients. The AT2 cells started dividing, and some of them changed into AT1 cells to replace the damaged ones. The stem cells were guided by nearby cells (like endothelial cells, fibroblasts, and immune cells) through the release of chemical signals. (Shiraishi et al., 2022)
- **Treatment for some cancers-** Stem cell transplants are most often used to treat people with cancers that affect blood cells, such as leukaemia, lymphoma, multiple myeloma, and myelodysplastic syndromes. Doctors first collect healthy blood-forming stem cells from the patient or the donor. These cells are usually collected from the bloodstream using an apheresis machine, bone marrow, or umbilical cord. Before the transplant, the patient undergoes chemotherapy to destroy the cancerous blood cells. The collected

stem cells are infused into the patient through a vein. Once inside, the stem cells can grow, restoring the patient's immune system and blood. In some cases, the donor's white blood cells can attack remaining cancer cells.

- **Cartilage repair-** Mesenchymal stem cells (MSCs) and induced pluripotent stem cells are used to repair damaged cartilage because they can be turned into chondrocytes (cells that make cartilage). MSCs are taken from tissue like bone marrow, fat, and umbilical cord. They release substances, like growth factors and anti-inflammatories, that help cartilage grow and heal. Scientists use techniques like 3D bioprinting, organoids, and cell sheets to create an environment that helps these cells grow. Clinical studies using MSCs either use injections or scaffolds like AMIC® and CARTISTEM®. They have shown they can improve cartilage repair, reduce pain, and help patients move better. However, getting enough cells and keeping them safe are difficult. (Gomes et al., 2022)
- **Spinal Cord Repair-** In a 2023 study, scientists explored how neural stem cells can help repair damaged spinal cord tissue when they are combined with a special material called conductive hydrogel scaffold. The NSCs were placed inside the conductive hydrogen gel and then implanted into the spinal cord injury site. The cells grew, forming new nerve connections and reducing tissue damage. (Liu et al., 2023)
- **Organoids for drug testing-** In pharmaceutical development, organoids serve as an advanced platform for high-throughput screening. Their 3D structure enables a more accurate simulation than flat cell cultures, helping scientists study how any drug behaves in your body. This allows researchers to test many drug candidates quickly and get reliable data. Organoids also help identify organ-specific toxicity before moving to animal or human trials. This increases the overall success rate of drug development before clinical trials. (Yin et al., 2024)

Current challenges in Stem cell-based organ regeneration

1. Pluripotent stem cells like embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) can divide quickly, leading to a risk of tumor formation (teratoma) if undifferentiated cells are implanted. (Takahashi & Yamanaka, 2016)
2. Identifying the most suitable type of stem cells for specific clinical situations is complex due to the heterogeneity of stem cells, which complicates standardization. (Wong et al., 2022).
3. It is difficult to produce and maintain a large quantity of clinically graded stem cells consistently. (Ribas et al., 2019)

4. Precise control over how stem cells differentiate into the desired cell types proves to be a significant challenge. (Shi et al., 2017)
5. Current processes for stem cell generation and organ fabrication are complex and costly, complicating efforts for widespread clinical application. (Mason & Dunnill, 2020)
6. Organoids and lab-grown tissue lack a proper blood vessel network, and without vascularization, larger constructs can die due to a lack of nutrients. (Takebe et al., 2017)
7. Using a patient's own iPSCs can lower the risk of immune rejection, but there are still challenges with how the immune system responds to the engineered tissues(De Almeida et al., 2014)
8. The use of embryonic stem cells (ESCs) raises ethical questions, particularly regarding the source of these cells.(Lo & Parham, 2009)
9. The long-term implications of using stem cells, particularly iPSCs, are currently unknown. (Trounson & DeWitt, 2016)
10. iPSCs necessitate strict regulations and guidelines to ensure their safety for clinical use. (Fox et al., 2021)

Conclusions

The field of stem cell-based organ regeneration is advancing at an extraordinary pace, bringing us closer to the goal of creating fully functioning, patient-specific organs. Scientists have already built technology to ethically isolate stem cells, reprogram them into specific tissue types, and manipulate bioscaffolds that create the extracellular environment needed for tissue development. Studies on liver organoids, cardiac repair, lung alveolar regeneration, β-cell development, cartilage repair, corneal tissue, and many more. These breakthrough signals a future where organ shortage won't determine the patient's future. Regenerative medicine will offer a safe, reliable, and personalised treatment. However, the next steps are critical and challenging due to the various issues like immune responses, vascularisation, tumor formation, complexcity of large-scale organs, and ethical considerations.

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