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Original Article

Revisiting Immune Tolerance: The Role of Hematopoietic Stem Cells in Organ Transplantation

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Abstract - *Transplantation of the organ is the conclusive mode of treatment for end-stage organ failure, but the graft survival is not long-term due to immune-mediated rejection and complications of lifelong immunosuppressive therapy. Recent progress in transplantation immunology has brought the possibility of Hematopoietic Stem Cells (HSCs) into the limelight to ensure immune tolerance and increased graft survival. HSCs have a distinct biological property, such as self-renewal and multilineage differentiation, and they can be used to reconstitute hematopoietic and immune systems. Transplanting donor-derived HSCs into recipients can result in the development of mixed hematopoietic chimerism, i.e., the co-existence of donor and recipient immune cells. This immunological condition is favorable to donor antigen tolerance in both central and peripheral ways, including the deletion of alloreactive T cells, generating regulatory T cells, and altering the operation of antigen-presenting cells. The preclinical and clinical experiments showed that combined organ and hematopoietic stem cell transplantation could make it possible to have a stable graft survival without or with a minimal amount of immunosuppressive treatment. Although these results are encouraging, challenges such as graft-versus-host disease, toxicity of conditioning regimen, and the inconsistency of chimerism stability are still notable obstacles. This review will discuss the biological properties of HSCs, the immunology of transplant rejection, and how HSCs facilitate immune tolerance. Also, the present therapeutic approaches, clinical evidence, and future of the therapy of stem cell-based tolerance in organ transplantation are discussed.*

Keywords - *Hematopoietic Stem Cells; Immune Tolerance; Mixed Chimerism; Organ Transplantation; Transplant Immunology.*

1. Introduction

Organ transplantation is an intervention therapy that saves the lives of patients with end-stage organ failure. Although surgical procedures and immunosuppressive therapy have made great advances, the long-term graft survival is still limited due to the immune-related rejection and the adverse effects of chronic immunosuppression (Grinyo 2013; Li, Ding, and Cai 2026).

Calcineurin inhibitors, corticosteroids, and anti-proliferative agents are all examples of immunosuppressive drugs that have made a substantial contribution to improving short-term graft survival. Nevertheless, the long-term effects of these drugs are enormous, including nephrotoxicity, metabolic disorders, risk of increased infection and malignancy (Kalluri 2012) (Miller 2002). Thus, the maintenance of protective immune responses and simultaneous development of Donor-Specific Immune Tolerance (DSIO) is one of the primary goals of transplantation research.

Immune tolerance is a condition where the recipient's immune system specifically tolerates the transplanted organ, and it is still able to generate immune responses to pathogenic substances. One of the approaches put forward to attain this objective is induction of hematopoietic chimerism by hematopoietic stem cell transplantation, which has proved to be a promising option (Yolcu, Shirwan, and Askenasy 2017)(Sykes 2007).

Hematopoietic stem cells are hematopoietic progenitor cells that have the capacity to produce all blood and immune cell lineages during the lifetime. The donor HSCs infused into a conditioned recipient have been able to engraft in the bone marrow and produce donor-derived immune cells.

The presence of the donor and recipient hematopoietic cells results in a condition referred to as mixed hematopoietic chimerism that has been found to induce immunological tolerance against the transplanted tissues (Greb 2024; Ruffinatto et al. 2024).

Initial experimental models showed that transplantation of donor hematopoietic cells had the ability to induce tolerance to organ grafts through the eradication of donor-reactive immunity (Sykes 2009). Further studies have affirmed that mixed chimerism induces central and peripheral tolerance via deletion of alloreactive T cells in the thymus and regulatory immunity, respectively.

The recent clinical trials of combined kidney and hematopoietic stem cell transplantation have shown the possibility of attaining immunosuppression-free graft survival in some patients (Ohm et al. 2025; Robinson et al. 2018). The findings have created a lot of attention in the use of stem cell-based tolerance strategies as a revolutionary solution in the field of transplantation medicine.

2. Biology of Hematopoietic Stem Cells

Hematopoietic Stem Cells (HSCs) are uncommon multipotent precursors that form the blood and immune cells throughout life. Such cells have two characteristic features: the self-renewing property and the ability to develop into all the hematopoietic lineages (Szilvassy 2003)(Hawley, Ramezani, and Hawley 2006).

The HSCs are found mostly in specialized microenvironments called the bone marrow niches, and their survival and differentiation are modulated by interacting with stromal cells, extracellular matrix components, and cytokines (Kwon et al. 2024). In the niches, HSCs are mostly dormant but can quickly divide and turn into other cell types when physiological needs arise.

In the process of hematopoiesis, the HSCs develop into multipotent progenitors that in turn develop into lineage-restricted progenitors and fully developed blood cells such as erythrocytes, platelets, granulocytes, monocytes, and lymphocytes. This is immunosurveillance and tissue homeostasis by the hematopoietic system through this hierarchical process.

HSCs are identified by the use of specialized surface markers like CD34, CD90, and c-Kit that enable them to be identified and isolated in order to be used in clinical transplantation (Shevyrev et al. 2023). These cells may be sourced in various ways, and some of the ways in which these cells may be sourced are bone marrow, mobilized peripheral blood, and umbilical cord blood. The mobilized peripheral blood stem cells are highly employed in medical practice owing to their high output and simplicity in collection.

With regard to transplantation, HSCs are the only ones that can be used to rebuild the immune system of the recipient after transplantation. Donor-derived HSCs are able to engraft the recipient bone marrow and produce immune cells that are able to recognize both donor and recipient antigens, thus leading to immune tolerance (Czechowicz and Weissman 2011).

Mixed hematopoietic chimerism occurs when the donor and recipient hematopoietic cells coexist in the host. In this condition, T cells in the thymus are exposed to donor and recipient antigens in the selection phase, leading to the deletion of the highly alloreactive clones and their replacement by central tolerance (Zuber and Sykes 2017). Besides the effect of central tolerance, peripheral immune control also helped in the maintenance of tolerance. Tregs (regulatory T cells) are vital in regulating immune response towards donor antigens and preventing graft rejection (Camirand and Riella 2017). Such cells also generate anti-inflammatory cytokines like interleukin-10 and transforming growth factor-B that suppress the effector T-cell response.

The capacity of HSCs to reconstruct the immune system and, at the same time, induce immunotolerance has rendered them a central point of interest in the research of transplantation immunology. It is very important to learn the biological characteristics of these cells in order to make useful therapies that will produce tolerance.

3. Immunological Basis of Transplant Rejection

Transplant rejection is a condition in which the recipient's immune system perceives the transplanted organ as foreign, and therefore, it retaliates by mounting an immune response against the antigens of the donor. Human Leukocyte Antigen (HLA) molecules are the main factors that determine the compatibility of a transplant; they are also central in antigen presentation and immune recognition (A et al. 2011).

The disparities between the donor and recipient HLA molecules activate the recipient T cells via the pathways, which are collectively referred to as allorecognition. Under the direct pathway, the recipient T cells can identify intact donor HLA molecules as expressed by donor antigen-presenting cells. Indirect pathway– In the indirect pathway, recipient antigen-presenting cells process and present donor antigens to T cells (Siu et al. 2018).

Transplant rejection has been characterized into three large categories, namely, hyperacute, acute, and chronic rejection. Hyperacute rejection is the onset of rejection in a few minutes to hours following transplantation and is precipitated by already existing antibodies against donor antigens. The effect of these antibodies is the activation of the complement cascade, resulting in the rapid destruction of graft vasculature.

Acute rejection normally occurs within the span of weeks or months after transplantation and is a combination of cellular and humoral immune reactions. Cytotoxic T

lymphocytes directly correlate with the direct attack of graft cells and the stimulation of B cells to produce donor-specific antibodies by helper T cells.

Progressive fibrosis, vascular constriction, and graft failure are the main features of chronic rejection. It is still ranked among the most common causes of chronic graft failure, even with the progress in immunosuppressive treatment (Hassanein and Augustine 2020).

Conventional immunosuppressive treatments attempt to suppress T-cell activation and growth. Although such therapies are efficient in the elimination of acute rejection, they fail in the production of donor-specific tolerance. Because of that, transplant patients have to undergo immunosuppression throughout their lives, and this process is fraught with such threats as infection and malignancy (Kamila Szumilas et al. 2023).

Immunotherapy approaches to induce immune tolerance are intended to circumvent these shortcomings by selectively targeting the inhibition of immune responses to donor antigens without affecting the immunity against pathogenic infections. Among the possible solutions, one is the institution of hematopoietic chimerism via transplantation of donor hematopoietic stem cells (Luo, Miller, and Shea 2016).

Research has shown that chimerism changes immune recognition signaling and enhances control mechanisms that reduce graft rejection. These include regulatory T cells, tolerogenic dendritic cells, and immunosuppressive cytokines, which play a role in promoting long-term graft acceptance (Kumar 2025).

4. Role of HSCs in Organ Transplantation

Hematopoietic stem cells have become a potential therapy in inducing immune tolerance in the transplantation of organs. Contrary to the traditional immunosuppressive treatments, which suppress the immune system in a general manner, the HSC-based based therapies are designed to reprogram the immune system to tolerate the donor tissues specifically.

The main idea of this strategy is hematopoietic chimerism. Upon transplantation to a recipient with the use of donor HSCs after conditioning therapy, they have the ability to engraft within the bone marrow and produce donor-derived immune cells. A mixture of donor and recipient immune cells leads to a condition referred to as mixed hematopoietic chimerism (Hayashi et al. 2002).

It has been proven through experimental studies that mixed chimerism can induce tolerance to transplanted organs through the induction of central and peripheral immune regulation. The T cells developed so far go through selection in the thymus, where both the donor and recipient antigens are present, thereby deleting the highly alloreactive clones.

Graft acceptance is also caused by peripheral tolerance mechanisms. Regulatory T cells are a type of T cell that interferes with the immune system's response against tissues of donors and are important in tolerance maintenance (Kumar 2025). Moreover, the dendritic cells of the donor might favor tolerogenic antigen presentation and prevent the activation of the effector T cells.

A number of experimental models have shown that mixed chimerism is effective in inducing organ graft tolerance. Animal model studies demonstrated that donor bone marrow cell transplantation was able to cause tolerance to kidney grafts without long-term immunosuppression (Murakami, Cosimi, and Kawai 2009).

Mixed chimerism has also been applied in clinical transplantation. One of the landmark studies has demonstrated that kidney transplant patients who received the infusion of donor hematopoietic stem cells were able to have stable graft function without the chronic use of immunosuppressive therapy. The second clinical trial showed that a combination of kidney transplant and hematopoietic stem cell transplantation was able to cause sustained chimerism and immune tolerance in recipients with HLA mismatch (Wilson et al. 2026).

Further research has indicated that even short-term chimerism can be adequate to cause long-term tolerance by regulatory means (Lowsky and Strober 2022). According to these findings, tolerance induction can be achieved by permanent donor cell engraftment in some cases. There are also a number of benefits to stem cell-based methods when compared to the conventional immunosuppressive treatments. They comprise the possibility to eradicate life-long immunosuppression, lessen the development of chronic rejection, and sustain immune reaction against infections.

HSC biology has demonstrated new opportunities in the utilization of HSC-based tolerance strategies as a result of the advancements in stem cell biology. Recent studies have been done on the application of induced pluripotent stem cell-derived hematopoietic progenitors to immune regulation in transplantation (Biermann and Reya 2021).

Moreover, the promotion of cells and other immunomodulatory cell groups has also been explored to augment the engraftment of stem cells and diminish the chance of graft-versus-host disease. Taken together, these results illustrate the potential of hematopoietic stem cell transplantation as a way of transforming the prospects of immune tolerance and enhancing the outcome after organ transplantation.

5. HSC-Based Strategies in Transplantation

A number of strategies have been designed aimed at exploiting the immunomodulatory capabilities of the hematopoietic stem cell in transplantation.

One of them is nonmyeloablative conditioning regimens, which permit the engraftment of donor stem cells with minimal toxicity (Slavin et al. 1998). These regimes usually encompass low-dose radiation or chemotherapy with immunosuppressive medicines.

Other technologies that have also been investigated are the use of donor stem cell infusion after organ transplantation as a way to induce immune tolerance. It has been revealed that infusion of donor HSC can induce donor-specific hyporesponsiveness and increase graft survival (Annamalai et al. 2023). Other elements of certain tolerance-inducing protocols are facilitating cells. These cells increase the engraftment of the stem cell and minimize the chances of graft-versus-disease (Leventhal et al. 2012).

Mesenchymal stem cells are also examined with regard to immunomodulatory properties. These cells have the ability to suppress the activation of T-cells and induce regulatory immune responses, which favor the induction of tolerance. The current innovations of gene editing tools have facilitated the production of genetically engineered stem cells capable of producing molecules that facilitate immune regulation.

These approaches promise safety and effectiveness of stem cell-based therapy in transplantation.

6. Clinical Evidence and Trials

In the last twenty years, there have been a number of clinical trials that have tried to utilize hematopoietic stem cells to induce immune tolerance in organ transplantation.

The rejection of donor hematopoietic stem cell transplantation was proven to be the first using the case of kidney transplant recipients, who were able to have a normal graft function without immunosuppression with long-term use (Hotta, Hirose, and Kawai 2022). These results were subsequently confirmed by other studies that found that durable mixed chimerism was possible in carefully selected patients [9].

In a different study, patients who received combined kidney and hematopoietic stem cell transplantation had stable graft survival and less immunosuppressive needs in the long-term follow-up (M 2026). Other researchers have also shown that temporary chimerism can be adequate in creating long-term tolerance by means of immune regulation mechanisms. The above clinical results indicate the possibility of stem cell-based tolerance induction and its potential to replace lifelong immunosuppression therapy.

7. Challenges and Risks

Although the results of HSC-based tolerance approaches are promising, there are still a number of difficulties in their implementation. Among the issues is the graft-versus-host disease, whereby transplant tissues are attacked by the immune cells of the donor. This complication may involve various organs and could be lethal.

One more difficulty is the toxicity of conditioning regimens needed to ensure the stem cell engraftment (Li et al. 2026). Even the low-intensity regimens may result in complications, including infection, cytopenia, and organ toxicity. Some patients also find it hard to achieve stable hematopoietic chimerism.

Donor cells can either fail to engraft or deteriorate with time. Also, transplantation of organs and stem cells together demands specific infrastructure and collaboration between the transplantation teams. The challenge of these issues will be critical to the implementation of stem cell-based tolerance strategies into clinical practice.

8. Conclusion

Hematopoietic stem cells are a promising instrument for precipitating immune tolerance in organ transplantation. Mixed hematopoietic chimerism can be used to improve the acceptance of transplanted tissues by the recipient immune system through the actions of the donor stem cells.

Clinical and experimental studies have shown that stem cell-based therapies have the capacity to induce long-term graft survival and minimize immunosuppressive therapy. Despite these problems, more progress in stem cell biology and transplantation immunology will probably enhance the safety and efficacy of these methods. The use of immunomodulatory effects of hematopoietic stem cells could eventually revolutionize the field of transplantation medicine, making it possible to achieve long-lasting immune tolerance and better patient outcomes.

Future Perspectives

The new direction of research in transplantation immunology will be the enhancement of the safety and the effectiveness of stem cell-based tolerance regimens. With the emerging advances in gene editing technologies, cellular therapies, and regenerative medicine, it is potentially possible to create engineered stem cells that can be used to improve immune regulation.

A combination of complementary therapies, like regulatory T cell therapy and mesenchymal stem cell therapy, can also improve the tolerance induction. These approaches will require large multicenter clinical trials to prove their long-term safety and effectiveness.

Author's Contribution

Syed Zain conceptualized the study, did a literature survey, wrote and edited the manuscript.

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Conflict of Interest

There is no potential conflict of interest to declare.

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