Immune Rejection in Transplantation: Identifying the Optimal Strategy for Long-Term Graft Survival

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Content

1.Abstract

Although promising therapeutic potency in a wide range of diseases, stem cell transplantation still faces formidable immune rejection challenges. Strategies to overcome immune rejection will be reviewed, including pharmacological strategies involving the use of new immunosuppressants, genetic engineering for immune evasion and tolerance of stem cells, and biomaterials-based physical shielding from immune attack. A comparative analysis of all these methods outlines the advantages and disadvantages, pinpointing localized immune tolerance as the superior strategy in graft survival and reducing systemic side effects. It thus places strong demands on developing personalized approaches matched to the condition of the patient to ensure optimal outcomes for transplantation.

2.Introduction

2.1 Stem cell advances and limitations

In the new era of stem cell development, a wide range of potentials of SCs were discovered making a clinical contribution to treating and regulate hundreds of diseases and disorders. In neurological disorders, Alzheimer's disease is one example of neurological diseases that were regulated using NSCs for ex vivo delivery of protease genes as a treatment for AD [1]. In addition to implications of cancer stem cells in types of cancer such as the blood, breast, central nervous system, pancreas, skin, head and neck, colon, and prostate [2]. In addition to many other diseases such as leukemia and T1D.

It is obvious that stem cell therapy is essential in treating and regulating various diseases, however, immune rejection is one barrier against stem cell transplantation and, therefore, it is necessary to find and justify the reason behind it to conduct an applicable solution for it. But before discussing the cause of immune rejection or its mechanism, transplantation methods should be mentioned first as it plays a crucial role in the process of immune rejection.

2.2 Immune rejection: digging deeper

There are two ways to transplant solid organs, Autologous and Allogeneic, or self and non-self-transplantation, respectively. As normal, immune cells oversee preventing foreign cells' entrance to the body as they can pose a danger on it. So that in Autologous method, immune system does not express any action towards the transplanted cells as they carry the same genes that express receptors immune cells can identify. On the other hand, non-self-transplantation causes the cell-identifying immune cells, T and B cells, to activate attack protocol towards the foreign cells. So, it can be induced that Allogeneic transplantation is the only method that can be

exposed to immune rejection. But to fully understand how to treat, or avoid, immune rejection, deeper details in the process must be investigated.

MHC, or Major Histocompatibility complex, is the protein family where antigens, the protein in charge of recognizing other cells in the process of cell recognition, are relevant to transplantation belong to. MHC I, II, and III are the types of MHC molecules. MHC I contain peptides of some pathogens so that they are responsible for the defense against infectious disease. Recognition of peptide–MHC class I molecules on a cell result in CD8+ T cell killing of that cell. MHC class II molecules are expressed only on specialized antigen-presenting cells, such as dendritic cells, macrophages and B cells; presentation of non-self-antigen on MHC class II molecules leads to activation of CD4+ T helper cells. Both MHC class I, II are relevant to the allorecognition, immune rejection. [3]

2.3 Approaches

There have been many approaches to avoid immune rejection in many fields such as pharmacology, cell biology and genetic engineering, and others. So, as there are many methods used to reach one approach, it is necessary to put priorities to use the best method in each patient's condition.

3.Literature review

Recent studies investigated several ways of avoiding immune recognition including immunosuppression drugs, HLA-matching, genetic engineered B cells, and using HSCT to produce new immune system components beside immunosuppression drugs. These methods showed a noticeable effectiveness in avoiding rejection. However, there was a lack of knowledge of the priorities on which each method should be arranged according to its effectiveness on recipients.

3.1 Novel Immunosuppressive Agents

Immunosuppressive agents are a primary method in avoiding immune responses against grafting, transplanted, SC, tissue, or solid organ like kidney or liver. And here are some examples of new immunosuppressive drugs.

Belatacept

Belatacept is a fusion protein, and an immunosuppressive drug used in post-kidney transplantation, which binds the cytotoxic T lymphocyte antigen-4 (CTLA-4) to the Fc portion of human IgG-1. It blocks T cells activation by binding to CD80/86 to inhibit them from binding to CD 28 that is necessary to activate T cells. It is also used to inhibit CD80/CD86 and PDL-

1/PDL-2 to get the same target. The drug was approved by the Food and Drug Administration in 2011 for rejection prophylaxis in adult organ transplantation as it showed an impressive result in a study on the 666 patients who underwent kidney transplantation where the rate of death or graft loss was 43% less in the Belatacept group than in cyclosporine-A group, another immunosuppressive drug. [4,5].

Belimumab

Belimumab is a B lymphocyte stimulant (BLyS) inhibitor. BlyS plays a crucial role in proliferating B cells, as a result, it causes apoptosis, decreases in circulation of B cell clones, and blocks the conversion of B cells to plasma in the immune response. However, it has several disadvantages including: the increased risk of infections because of injection of Belimumab and other immunosuppressant that targets the B lymphocyte, Psychiatric influences such as anxiety or depression, and the inability to inject living vaccines to patients receiving Belimumab [5].

Siplizumab

It is an antibody that acts against CD2, which is responsible for the adhesion of T cells to APC through the interaction with LFA-3 ligand. Binding between CD2 and LFA-3 ligand is essential in T cells activation. Siplizumab has shown promising effects in preventing acute kidney allograft rejection and treating acute graft host-host-disease [5].

3.3 Engineering of SC derived islets

It is a new method discovered in 2022 by Dario Gerace, Quan Zhou, and others. This method depends on genetically engineered SCs islets to be immune-evasive and immune tolerizing cells. It is divided into two pathways: Genetic Engineering for Immune Evasion and Localized Immune Tolerance.

Genetic Engineering for Immune Evasion

In this pathway, SC-islets is modified to over express Programmed death ligand- 1, which is responsible for interaction with the PD-1 receptor on immune cells, specifically T cells, to block their activation. So, it was used to help SC evade the immune response against transplanting it.

In addition, the SC-islets were also modified to express long-chain fusion of HLA-E, which stops the activity of the natural killer (NK) cells. To increase the efficiency of this method, both the methods in this pathway were combined to be more effective in evading immune rejection.

Localized Immune Tolerance

In this pathway, scientists engineered SC-islets to secrete 3 main cytokines to employ immune-tolerizing strategy, the cytokines are:

1- Interleukin-10 (IL-10): this cytokine can suppress various immune responses by downregulating inflammatory cytokine production and inhibiting the activation of immune cells.

2- Transforming Growth Factor-beta (TGF-β): TGF-β induces the differentiation and function of T cells which is important in immune responses against grafted SCs or organs.

3- Modified IL-2 (IL-2 mutein): this cytokine promotes the expansion of (Tregs) or regulatory T cells, which tolerate the foreign cells instead of destroying it by activating effector T cells.

This method is so powerful as it doesn't evade immune rejection effectively only, but also help to treat T1D as it is caused by and autoimmune disease as it has successfully reversed diabetes and were able to resist immune rejection much longer than cells engineered with immune evasion mechanisms alone [6].

3.4 Biomaterials for blocking immune recognition.

Biomaterials have been used to physically separate donor cells from the host immune system, most notably in mouse models of type 1 diabetes mellitus. The Edmonton protocol for treatment for type I diabetes uses allogeneic cells rather than the technically complicated procedure of trans planting the whole pancreas. Islets of Langerhans isolated from donor pancreases are embolized into the hepatic portal circulation under immune system suppression with tacrolimus and sirolimus, and with initial treatment using daclizumab (which neutralizes the interleukin 2 receptor on T cells) [8,9]. Currently, 44% of patients are treated with the Edmonton protocol and its derivatives are insulin-independent three years after transplantation.

Researchers are now developing biomaterials-based methods to achieve similar clinical outcomes with less immunosuppression. Encapsulation of islets in hydrogels to restrict contact between donor islets and the host immune system was first attempted in the early 1980s [7]. The pore size of the hydrogel was large enough to allow diffusion of small molecules and signaling proteins, including insulin, but small enough to block passage of antibodies, complement, host antigen-presenting cells (which could collect antigen) or T cells (which could kill encapsulated host cells by cytolytic mechanisms).

In principle, encapsulation should reduce the need for immunosuppressive drugs after transplantation of allogeneic or even xenogeneic islets. In one study, an encapsulation approach restored normoglycemia for more than one year in mice with autoimmune diabetes that were transplanted with xenogeneic adult porcine islets together with CTLA4-Ig and anti-CD154 (CD40 ligand).

A more sophisticated device, which contained hydrogel-encapsulated islets within polymer film membranes, prevented rejection of xenogeneic rat islets and restored normoglycemia in pigs with chemically induced diabetes for more than two months with no chemical or biomolecular suppression of the immune system. In those experiments, the eventual loss of glycemic control may have been due to growth of the recipient animal but not of the donor islet mass, which suggests that the duration of graft function could have been extended [5].

Methodology

In this paper, prospective cohort is followed as it aims to find the differences between several methods or drugs that overcome the stem cell rejection and indicate the long-term effects of each method or drug and finally determine the most efficient ones.

The data is collected in the secondary way as the paper focuses on data collected from other resources instead of conducting the data entire the research itself. In addition, to collect data about the recent ways or methods to avoid immune rejection, hundreds of experiments were done to test each method's efficiency in the labs.

Results

After discussing several methods of avoiding immune rejection either by pharmacology, genetic engineering, biomaterials, and others, we concluded all the methods in one table, **as shown below**, to analyze the advantages and disadvantages of each method and conduct the most, but not the best as there is no perfect cure or drug for avoiding immune rejection, suitable and safe method among all of them.

Method	Types	Pros	cons
pharmacology	Belatacept	- Blocks T cell activation, reducing rejection risk in kidney transplants. - Binds more strongly to CD80/86 than abatacept, improving efficacy. - Reduces the need for calcineurin inhibitors (which can be toxic). - Protects against chronic allograft nephropathy and maintains better GFR (glomerular filtration rate). - Does not require dose adjustments in kidney or liver failure. - Can be used both in induction and maintenance therapy after transplantation.	- Associated with a higher risk of acute rejection and post-transplant lymphoproliferative disease (PTLD). - Higher rates of EBV (Epstein-Barr virus) reactivation. - Requires intravenous administration, which may be less convenient. -Needs frequent dosing initially after transplant.
	Belimumab	- Targets and inhibits B-lymphocyte stimulator (BLyS), reducing B cell activation and proliferation. - Shown to reduce the risk of developing donor-specific antibodies (DSAs), which can. - Does not increase the risk of infection significantly compared to placebo. lead to graft dysfunction. - Used for patients with systemic lupus erythematosus and being explored for use in solid organ transplantation.	- Can cause hypersensitivity and infusion reactions, including anaphylaxis. - Associated with psychiatric side effects like anxiety and depression. - Increases the risk of severe infections when combined with other B cell-targeting therapies. due to higher infection risks. - Not recommended with live vaccines, cyclophosphamide, or anti-CD20 therapies
	Siplizumab	- Blocks CD2 antigen, preventing T cell adhesion and activation, which helps reduce rejection. - Has shown beneficial effects in preventing acute renal allograft rejection and treating graft-versus-host disease (GVHD). - Demonstrated potential as an induction agent for renal transplant patients. - Has an acceptable safety profile based on clinical studies.	- Clinical data are still limited, so further research is needed to fully understand its long-term benefits and risks. - Effectiveness and safety in broader clinical applications are not as well established as with more commonly used agent
Biomaterials	For blocking immune recognition	- Reduced Immunosuppression: Encapsulation of donor islets in hydrogels can potentially reduce or eliminate the need for systemic immunosuppressive drugs, lowering the risk of related side effects. - Selective Permeability: The hydrogels are designed with pore sizes that allow small molecules like insulin to pass through while blocking larger immune system components. (e.g., T cells, antibodies, and antigen-presenting cells), reducing the likelihood of immune-mediated rejection. - Improved Islet Survival: In mouse models, encapsulation has successfully prolonged the survival and function of donor islets, even with xenogeneic transplants (e.g., porcine islets). - Long-Term Function: Some studies demonstrated normoglycemia for over a year in autoimmune diabetic mice, with protection from immune rejection.	- Limited Longevity: Encapsulation devices can lose effectiveness over time, as seen in experiments where glycemic control was lost, potentially due to factors like recipient growth without corresponding growth of the islet mass. - Incomplete Immune Protection: While encapsulation prevents direct immune cell contact, it may not entirely block immune system recognition or response, especially over long periods. - Size Limitations: The encapsulation material may limit the amount of islet tissue that can be effectively transplanted, which may impact long-term function. - Complexity of Materials: Developing effective biomaterials that balance diffusion, immune protection, and biocompatibility can be technically challenging.
Engineering of SC derived islets	Genetic Engineering for Immune Evasion	- Reduced Immune Rejection: By overexpressing PD-L1 and HLA-E, this method directly inhibits the immune system's ability to attack the transplanted stem cell-derived islets, reducing the risk of rejection. - T-Cell Inactivation: PD-L1 blocks the activation of T cells, which are crucial players in immune rejection, effectively suppressing the body's immune response against the transplant.	- Limited Longevity: Despite the immune evasion, the transplanted cells can still be rejected over time, as seen in xenotransplantation models, where the cells were rejected within 10 days. - Species-Specific Issues: The effectiveness of PD-L1 and HLA-E can vary across species, making it challenging to translate results from animal models to humans, as interactions like PD-L1/PD-1 may differ. - Partial Protection: While immune evasion provides some protection, it may not be enough to fully prevent

		- Natural Killer (NK) Cell Suppression: The expression of HLA-E inhibits NK cells, adding another layer of protection for the transplanted cells. - Increased Efficiency: Combining PD-L1 and HLA-E expression provides a more comprehensive immune evasion strategy, making it more effective than using one method alone. - No Need for Systemic Immunosuppression: By genetically modifying the cells to avoid drugs, reducing the associated risks of infections and long-term toxicity. immune detection, this method minimizes the need for systemic immunosuppressive	immune responses, especially in more complex immune environments like xenotransplantation. - Complexity of Genetic Modifications: The process of genetically modifying cells to express PD-L1 and HLA-E is technically complex, increasing production costs and making it less accessible for widespread clinical use. - Risk of Immune Suppression: Overexpression of PD-L1 may lead to over-suppression of the immune system, potentially allowing cancerous cells to evade immune surveillance or increasing the risk of infections.
	Localized Immune Tolerance	Long-Term Graft Survival: By secreting immune-modulatory cytokines (IL-10, TGF-β, and IL-2 mutein), this method promotes longer-term survival of transplanted cells by actively suppressing immune attacks. - Localized Effect: The immune tolerance is localized to the transplant site, reducing the need for systemic immunosuppression and minimizing the risk of broader immune suppression. - Expansion of Regulatory T Cells (Tregs): The secretion of IL-2 mutein selectively promotes Treg expansion, helping to maintain immune tolerance and prevent graft rejection. - Reduced Inflammation: IL-10 and TGF-β help downregulate inflammatory responses, creating a favorable environment for the transplant to thrive without immune interference. - Dual Benefit for Autoimmune Diseases: This method not only protects the graft but also addresses underlying autoimmune issues (like in type 1 diabetes) by modulating the immune system. - Minimal Systemic Side Effects: Since the immune tolerance is localized, there's less risk of systemic immune suppression, reducing the chance of opportunistic infections or cancer.	- Risk of Chronic Immunosuppression: The continuous secretion of immune-modulatory cytokines may result in chronic local immunosuppression, potentially allowing infections or abnormal cells to persist near the graft. - Cytokine Imbalance: Excessive levels of IL-10, TGF-β, or IL-2 mutein could lead to over-suppression of the immune system locally, potentially causing undesired effects on surrounding tissue. - Limited Duration: While more durable than immune evasion alone, the effectiveness may diminish over time, especially as cytokine production could decline or immune tolerance mechanisms wear off. - Complex Engineering and Delivery: The process of engineering cells to secrete multiple cytokines in precise amounts is technically challenging and increases production complexity. - Potential for Off-Target Effects: Although the approach is localized, there's still a risk that the cytokines could diffuse beyond the target area, affecting other parts of the immune system and potentially leading to unintended immune suppression elsewhere. - Unclear Long-Term Outcomes: The long-term impact of sustained cytokine production and Treg expansion on overall immune function, especially in a human clinical setting, is not fully understood.

Conclusion

To sum up, stem cells are widely used for many pharmacological purposes making them essential in the treatment of several diseases. However, biologists suffer from after-transplantation complications. One major protein in recognition is MHC as discussed previously, so scientists study this protein group to create a treatment for the rejection. Three main methods for avoiding complications: pharmacology, Biomaterials, and genetic engineering.

The paper aims to make a comparison between all of them to find the most suitable one for each specific patient's need. Finally, the results showed that localized immune tolerance is the most effective and advantageous method among the other ones, making it the best choice for most patients.

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