



An Overview on Transplantation Tolerance

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Abstract

Organ transplantation has become a common practice in modern medicine. With advancements in surgical techniques and immunosuppressive drugs, transplantation has increased, providing patients with a new lease of life. However, transplantation is not without its challenges. The immune system of recipients recognizes transplanted organs as foreign, triggering an immune response that can lead to graft rejection. This process is mediated by various immune cells and molecules, including T cells, B cells, antibodies, cytokines, and complement proteins. To prevent graft rejection, patients receive immunosuppressive drugs, which can increase the risk of infection and cancer. Therefore, there is a need for alternative strategies to induce transplantation tolerance, which refers to the state of immune unresponsiveness towards the transplanted organ. Transplantation tolerance can eliminate or reduce the need for immunosuppressive drugs and improve the long-term outcomes of transplantation. In this article, we will review the current understanding of transplantation tolerance and the strategies that are being developed to achieve it.

Keywords: Organ transplantation; Immunosuppressive; Destruction

Introduction

Mechanisms of allograft rejection

Before discussing transplantation tolerance, it is important to understand the mechanisms of transplant rejection. Transplant rejection can occur through two main pathways: direct and indirect allorecognition. Direct allorecognition occurs when recipient T cells recognize donor MHC molecules presented on the surface of donor cells or donor APCs (antigen-presenting cells) in the context of self-MHC molecules [1]. This recognition leads to the activation of recipient T cells, which can then migrate to the transplanted organ and cause tissue damage through various effector mechanisms, such as cytotoxicity, cytokine release, and recruitment of inflammatory cells. Indirect allorecognition, on the other hand, occurs when recipient APCs take up donor antigens from the transplanted organ and present them to recipient T cells in the context of self-MHC molecules. This recognition also leads to the activation of recipient T cells and the subsequent destruction of the transplanted organ [2].

Strategies for allograft acceptance

To achieve transplantation tolerance, several strategies are being developed that aim to modify the immune system of recipients or the transplantation process itself. These strategies can be broadly classified into two categories: central and peripheral tolerance induction [3].

Central tolerance induction

Central tolerance induction aims to eliminate or suppress the donor-reactive T cells in the thymus, where T cells develop and undergo selection. This can be achieved by several methods, including:

- **Thymic transplantation:** Thymic transplantation involves the transplantation of the thymus gland from the donor into the recipient before or at the time of solid organ transplantation. This allows the recipient to develop a new population of T cells that are tolerant to the donor antigens. However, thymic transplantation is technically challenging and has limited clinical application [4].

- **Hematopoietic stem cell transplantation (HSCT):** HSCT in-

volves the transplantation of hematopoietic stem cells from the donor into the recipient, which can differentiate into all blood cells, including T cells. If the donor cells engraft in the recipient's bone marrow and generate a new immune system, the recipient may become tolerant to the donor antigens [5]. HSCT is currently used to treat certain blood disorders and cancers, but its application in solid organ transplantation is limited due to the risk of graft-versus-host disease (GVHD), a condition in which the donor immune cells attack the recipient's tissues [6].

- **Chimerism induction:** Chimerism induction involves the administration of non-myeloablative (low-dose) conditioning regimens, followed by the infusion of donor bone marrow or peripheral blood stem cells. This results in the presence of both recipient and donor immune cells in the recipient's body, leading to the development of mixed chimerism, in which the recipient's immune system becomes tolerant to the donor antigens. Chimerism induction has been successful in inducing transplantation tolerance in animal models and some clinical trials [7].

Peripheral tolerance induction

Peripheral tolerance induction aims to suppress or redirect the donor-reactive T cells in the periphery, where they encounter the transplanted organ. This can be achieved by several methods, including:

- **Costimulation blockade:** Costimulation blockade involves the administration of antibodies that block the interaction between costimulatory molecules on T cells and APCs, thereby inhibiting T cell activation. This approach has been successful in preventing rejection in animal models and some clinical trials, but its efficacy in inducing

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transplantation tolerance remains to be established [8].

- Treg cell therapy: Treg cells are a subset of CD4+ T cells that have immune-suppressive properties and play a role in maintaining peripheral tolerance. Treg cell therapy involves the isolation and expansion of Treg cells from the recipient or donor, followed by their infusion into the recipient before or after solid organ transplantation. This approach has shown promise in inducing transplantation tolerance in preclinical studies and some clinical trials [9].
- Gene editing: Gene editing technologies, such as CRISPR/Cas9 [10]

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is one of the first retrospective comparison studies that evaluated the outcomes of heart transplantation using organs preserved and transported using the system compared with SCS. Although the group showed longer total allograft ischemic time, patients using required fewer units of blood product for perioperative transfusion and had similar early-term survival compared with SCS. Although a multicenter trial is warranted to further validate findings described in this study, accepting organs from a more remote location may be a safe and practical strategy to expand the donor pool by using advanced technologies, such as the system.

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