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REVIEW

# Cellular and molecular targeting for nanotherapeutics in transplantation tolerance

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**Abstract** The induction of donor-specific tolerance to transplanted cells and organs, while preserving immune function as a whole, remains a highly sought after and elusive strategy for overcoming transplant rejection. Tolerance necessitates modulating a diverse array of cell types that recognize and respond to alloantigens, including antigen presenting cells and T lymphocytes. Nanotherapeutic strategies that employ cellular and biomaterial engineering represent an emerging technology geared towards the goal of inducing transplant tolerance. Nanocarriers offer a platform for delivering antigens of interest to specific cell types in order to achieve tolerogenic antigen presentation. Furthermore, the technologies also provide an opportunity for local immunomodulation at the graft site. Nanocarriers delivering a combination of antigens and immunomodulating agents, such as rapamycin, provide a unique technology platform with the potential to enhance outcomes for the induction of transplant tolerance.


*Abbreviations:* Ag, antigen; LSEC, liver sinusoidal endothelial cell; LEC, lymphatic endothelial cell; CLR, C type lectin receptor; SR, scavenger receptor.

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## 1. Introduction

Cell and organ transplantation has become a standard procedure performed for the treatment of numerous end-organ damage conditions, including cardiac, hepatic, and end-stage renal failure. Donor tissue is normally derived from an allogeneic source, which initiates an adverse host immune response by the recipient immune system. With the advent of modern immunosuppressive drug therapies, substantial improvements have been made in allograft survival in the past 20 years, though these enhanced clinical outcomes are typically due to short-term graft survival [1]. Chronic graft rejection and dysfunction persist despite long-term immunosuppressive drugs, with only 47–61% of grafts surviving to the 10-year mark [1,2]. These life-long therapies are often harmful to the transplanted cells/organ and lead to non-specific suppression of the entire host immune system, resulting in patient susceptibility to infection and malignancies [3]. Further, patient quality of life is drastically impacted by long-term immunosuppression with side effects including headaches, gastrointestinal distress, hypertension, cataracts, hyperlipidemia, anemia, bone necrosis, renal damage, and arteriosclerosis [4].

The induction of antigen-specific tolerance to transplanted cells and organs to overcome immune-mediated rejection remains a primary objective. Tolerance implies that the host does not mount an immune response to the allogeneic graft, yet maintains full function for the remainder of the immune system. Tolerance necessitates modulating a diverse array of cell types that recognize and respond to alloantigens, including antigen presenting cells (APCs), T lymphocytes, and B lymphocytes. Targeting the alloreactive cells mediating rejection, as opposed to general immune suppression, is being enabled through advancements in nanotechnology. Nanotherapeutic approaches are being developed through cellular and biomaterial engineering for tissue and cell specific targeting within the body, delivery of immune-mediating factors (antibodies, cytokines, proteins), and synergy with current treatments. In this review we discuss the processes responsible for graft rejection and potential organ/cell targets for specifically modulating the immune response. We subsequently describe tolerogenic nanotherapeutic antigen carriers (Table 1) and discuss potential design considerations, including target cell subsets and mechanisms associated with tolerance.

## 2. Factors mediating transplant rejection

The process of transplant rejection is initiated by recognition of donor antigens in the graft by the recipient immune system. The majority of these alloantigens belong to a class of proteins called the major histocompatibility complex (MHC), or MHC Class I antigens, which are found on the surface of all nucleated cells. MHC molecules present peptides on the surface of cells to T lymphocytes to generate an immune response, whether this is activation towards a pathogen or suppression to maintain peripheral tolerance. MHC antigens are highly polymorphic: within any individual, there are 100- to 1000-fold more alloreactive T cells than T cells specific for other foreign antigens, creating a multitude of cell subsets contributing towards rejection [5,6]. Even among optimally MHC matched donor-recipient pairs, transplant rejection often occurs due to minor histocompatibility (H) antigens, such as proteins encoded on the male Y chromosome not recognized by females [7,8]. Hence, a multitude of donor antigens are responsible for transplant rejection, rendering tolerance induction historically difficult.

Recipient immune cells can respond to alloantigens presented by donor MHC molecules, termed *direct* allorecognition, or recipient MHC molecules, termed *indirect* allorecognition. Direct recognition typically occurs with the inadvertent and often unavoidable introduction of passenger leukocytes that accompany the cell or organ transplant, which prime T cells with direct donor specificity. This pathway plays a primary role in acute rejection immediately following transplantation. Conversely, alloantigens on transplanted tissues or organs can be processed and re-presented by recipient APCs in the context of recipient MHC molecules. Antigen from the graft is shed into