CHAPTER 4

CELLULAR IMMUNOTOLERANCE IN THE TRANSPLANT

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Abstract: In humans, a state of operational tolerance has been observed in some recipients who anecdotally or experimentally abandoned their immunosuppressive treatment. Besides, advances in the understanding of the immune response and the continuous appearance of new biological molecules have boosted the growing interest in transferring the knowledge concerning immune tolerance from experimental models to clinical transplantation. Most of the strategies for inducing tolerance target the T-lymphocytes, especially T CD4+ since they play a central role in the regulation of the immune response. However, an effective tolerogenic treatment must also take into account the role of alloantibody producing B-lymphocytes, which have been shown to play a fundamental role in chronic rejection phenomena. There are multiple regulation and silencing mechanisms that operate both during lymphocyte ontogeny in the bone marrow and thymus (central tolerance) and in the periphery (peripheral tolerance). These regulatory mechanisms include the destruction of APCs by cytotoxic lymphocytes, suppressive cytokines, and activation-induced cell death, among others. However, the mechanism that in recent years has come to be attributed the greatest role has been the active suppression of the response by T-lymphocytes themselves. These lymphocytes are named as regulatory T cells that include Tregs CD4+CD25+, Tr1 cells and Th3. The great therapeutic potential of regulatory lymphocyte populations for the control of allogeneic rejection is evident and several clinical trials in humans have been started to be implemented using populations of both Tregs and Tr1 cells for the prevention of allogeneic reactions.
INTRODUCTION

The main objective of organ transplantation is to achieve long-term acceptance of the allograft with minimal or indeed without pharmacological immunosuppression. This is what is known as tolerance to the allograft or allotolerance. Ideally, this allotolerance should exist in the context of an immune system that has properly functioning antitumor and allergic responses and reactions to microorganisms, etc. In human transplantation, a state of tolerance has been observed in some recipients who anecdotally or experimentally abandoned their immunosuppressive treatment, mainly in the case of liver transplants. In recent years, there has been great progress in our understanding of the multiple mechanisms involved in the achievement of allotolerance, and this has led to the development of strategies for inducing tolerance.1 While these strategies have been found to be successful in murine experimental models, they have seemed less effective in clinical trials with humans. So far, most therapeutic approaches target T-lymphocytes. However, an effective tolerogenic treatment must also take into account the role of B-lymphocytes in alloantibody production as well as components of the innate immune system. It should be noted that the divisions between innate and acquired, as well as cellular and humoral, responses are artificial and merely serve to help us understand the system, while in an individual they are all perfectly connected and regulated. In this chapter the most important evidence to date in this field will be reviewed.

EFFECTOR ALLOIMMUNE RESPONSE

Allorecognition

In order to intervene in the mechanisms involved in the development of immunological allotolerance, it is necessary first to understand the basis of the immune response that is responsible for allogeneic rejection.2 In general, this rejection occurs as a consequence of the uncontrolled activation of the immune system.

The vascular endothelium of the allograft is the boundary at which the immunocompetent cells of the host first come into contact with those of the donor. One of the earliest assaults which occur during the event of graft rejection is endothelial activation. This is accompanied by the expression of many surface molecules and the secretion of cytokines and chemokines which go on to directly regulate the inflammatory process. Essentially, the vascular endothelium of vascularised allografts is able to influence the rejection mediated by alloreactive T-lymphocytes of the host through two main mechanisms. Firstly, the endothelium plays a central role in the regulation of the extravasation of effector T-lymphocytes to the parenchyma of the graft. Secondly, endothelial cells participate directly in the activation of alloreactive T-lymphocytes by presenting alloantigens and supplying costimulation signals.3

The role of the innate immune system in allogeneic rejection has been clearly demonstrated in recent years. The transplant in itself means an injury that induces the activation of several innate immune response signals. In this way, according to the danger theory proposed by Polly Matzinger, soluble mediators of the innate response perpetuate the inflammatory state and promote the development of the acquired response. The activation of the complement cascade, apart from its involvement in the pathogenicity of humoral lesions, is able to modulate the alloreactive T-cell response, probably by acting on the dendritic cells. In addition, Toll-like receptors (TLR) have recently been shown to be