Allopeptides and the alloimmune response ☆

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Abstract

The inherent ability of the host immune system to distinguish between self- and non-self forms the basis of allorecognition. T lymphocytes constitute the most important effector arm of allorecognition. Here we describe the fundamentals of direct and indirect pathways by which allopeptides are presented to effector T cells. The nature of allopeptides presented along with tolerogenic strategies like altered peptide ligands and intra- or extra-thymic allopeptide inoculation are discussed. In addition, we speculate on the potential of regulatory T cells to modulate alloimmune responses.
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1. Introduction

Allorecognition refers to the phenomenon by which the recipient immune system reacts with donor antigens that are considered to be "non-self". T cells constitute the principal effector arm of allorecognition. In contrast, there exists a "tolerogenic" arm of regulatory T cells that suppresses the alloimmune response and facilitates tolerance. Nevertheless, the most common natural consequence following transplantation is allograft rejection. This suggests that the alloreactive T cells have a survival advantage following transplantation and are able to predominate. In this review, we discuss the nature of allopeptides recognized by T cells along with the different pathways of allorecognition. In addition, we speculate on the potential role of regulatory T cells in suppressing alloreactive T cells and achieving allograft tolerance.

2. Cellular basis of allopeptide recognition

The main targets of the recipient immune response against the allograft are the donor major (MHC) histocompatibility antigens present on the allogeneic tissue. The recognition of mismatched donor histocompatibility antigens is the primary event that ultimately leads to allograft rejection [1–3]. Allorecognition occurs through two unique but not mutually exclusive pathways: called direct and indirect pathways of antigen presentation. Direct pathway involves recognition of intact donor MHC molecules on the donor cells, usually the antigen presenting cells (APC). Both $CD8^+$ and $CD4^+$ T cells can directly recognize donor MHC class I and class II, respectively. The indirect pathway, in contrast, involves presentation of processed donor antigens by recipient APC to recipient T cells (Fig. 1). Again, both $CD4^+$ and $CD8^+$ T cells can mediate indirect allorecognition.

2.1. Direct allorecognition

Direct pathway involves presentation of intact donor antigens to the recipient T cells. This may seem to contradict the classic self-MHC restriction property of T cells
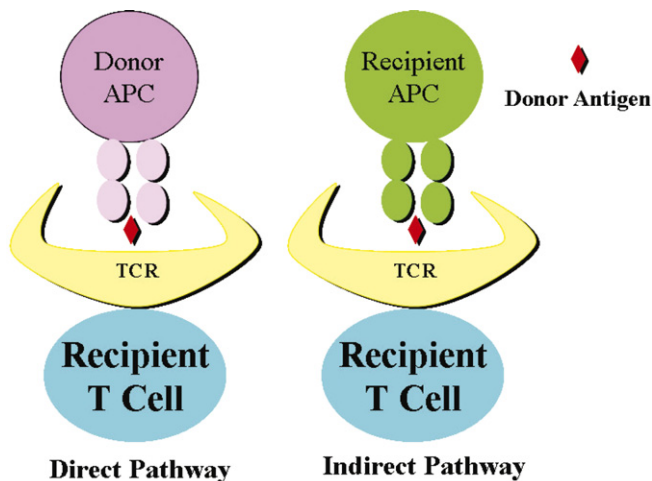
Fig. 1. Direct and indirect allorecognition.

since the peptide being recognized is presented in a non-self MHC. Two models have been proposed to explain this discrepancy [2].

The first, called the "high determinant density" model, proposes that the direct alloreactive T cells recognize amino acid polymorphisms on the MHC molecules of the donor cells and the nature of peptide in the MHC groove is not important. Therefore, all the donor cells of any given MHC act as ligands for the direct alloreactive T cells, thereby creating a very high ligand density. Consequently, the affinity of the alloreactive T cell receptors required to generate an optimal alloimmune response can be significantly lower compared to that required for self-MHC peptide complex [4].

The "multiple binary complex" model proposes that the alloreactive T cells recognize specific peptides in the donor MHC grooves. These peptides are derived from the same normal cellular proteins that are present even in the recipient. However, the differences in the allo-MHC groove causes different set of peptides to be presented from homologous proteins. These peptides can be recognized by the recipient T cells. Therefore, even a single MHC mismatch between the donor and the recipient would be able to stimulate a large number of alloreactive T cells by providing a completely different set of peptides. It is now known that the TCR contact surfaces of many MHC alleles may be similar, thereby providing a degeneracy effect with regards to MHC-restriction and allowing the recipient T cells to cross-react with donor MHC. In another version of this model, any particular cell surface MHC protein is complexed with a naturally arising peptide from the intracellular proteolytic machinery, forming a heterogeneous population of binary complexes. Such a multitude of MHC-peptide complexes could be recognized by many different T cell clones in the recipient [5,6].

It is hypothesized that the allograft brings with it "passenger" APC that are able to stimulate recipient T cells directly. There have been several classical studies to support the concept of passenger APC. Lafferty et al. demonstrated that cultured thyroid tissue has prolonged survival due to the loss of passenger APC [7]. Another important set of experiments revealed that depleted passenger APC survive permanently in allogeneic recipients [8]. Importantly, the recipients of the re-transplanted kidneys rapidly rejected the allografts when injected with donor APC [9]. These reports also indicate that the allospecific T cells reactive through the direct pathway need to be primed by the donor passenger APC. If this is not achieved while the passenger APC are present, the direct alloreactive T cells cannot mediate rejection. More conclusive evidence of the direct pathway in allograft rejection came from studies from Pietra et al. [10]. They demonstrated that lymphocyte deficient, SCID or RAG1$^{-/-}$, mice when reconstituted with CD4$^+$ T cells rejected MHC class I but not MHC class II deficient cardiac allografts. Furthermore, RAG1$^{-/-}$ mice that were also MHC class II deficient rejected cardiac allografts when reconstituted with CD4$^+$ T cells. This indicated that CD4$^+$ T cells alone, directly activated by donor MHC class II bearing APC, could mediate rejection. Another interesting observation that emerges from the above studies is that the direct pathway may be of decreasing importance with time after transplantation as the passenger APC are lost.

2.2. Indirect allorecognition

The indirect pathway of allorecognition is more representative of how the immune system typically recognizes an antigen. Here, the T cells recognize the donor antigens that have been processed and presented in the context of self-MHC on the recipient APC. Using monoclonal antibodies directed against specific MHC-peptide complexes, it was demonstrated that MHC-derived peptides could be presented in the context of other (recipient) MHC molecules. One of the first such monoclonal antibodies developed was the Y-Ae [11,12]. This antibody reacts to a peptide derived from the H2-Eα chain presented in the context of H2-A^b. This antibody brightly stained dendritic cells (DC) and B cells from murine strains co-expressing H2-A^b and H2-E but not from those expressing either of these alone. When H2-E bearing DCs were injected into the H2-A^b recipients, a significant proportion of recipient DCs in the draining lymph nodes became reactive with the Y-Ae antibody. These studies clearly show that MHC molecules can be processed and presented by self- or by allogeneic MHC.

Seminal studies done by Fangmann et al. demonstrated that immunization with peptides corresponding to the MHC class I molecules could accelerate rejection of renal allografts in rats [13,14]. Furthermore, CD4$^+$ T cells from recipient mice could specifically proliferate in presence of these peptides and recipient APC. Conclusive evidence for the indirect pathway of allorecognition in organ rejection came from the reports of Auchincloss et al. [15]. They demonstrated that MHC class I deficient mice could reject skin grafts from MHC class II deficient donor mice. The