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Role of MHC antigens and Immunoregulation in Graft Survival in autoimmunity

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CHAPTER 8

Role of MHC Antigens and Immunoregulation in Graft Survival

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This manuscript is dedicated to late Prof. R.V.S. Yadav of Postgraduate Institute of Medical Sciences, Chandigarh, India and the founding Editor of the Indian Journal of Transplantation

Abstract

Using a syngeneic islet transplantation model system we have showed that in autoimmune type 1 diabetes transplanted islets are destroyed by the host immune system unless the transplanted islets lack class I major histocompatibility complex (MHC) molecules. Alternatively, immunomodulation of the host by induction of regulatory T cells prevented the destruction of autologous islet graft. We conclude that these approaches will allow successful transplantation of autologous islets derived from the host by stem cell or other technology without immunosuppression to reverse autoimmune type1 diabetes.

In many autoimmune diseases autologous tissues or cells are targeted for destruction by the immune system of the host. Replacing these tissues or cells by transplantation leads to recurrence of disease even when autologous tissues or cells are used. This is because the host immune system is primed against the autologous transplant. With the likely availability of compatible cells or tissues for transplantation from the host by stem cell or other technologies, this poses a serious limitation for treating autoimmune conditions. To address this problem we used the NOD mouse model of autoimmune type 1 diabetes (1) to explore ways to preserve

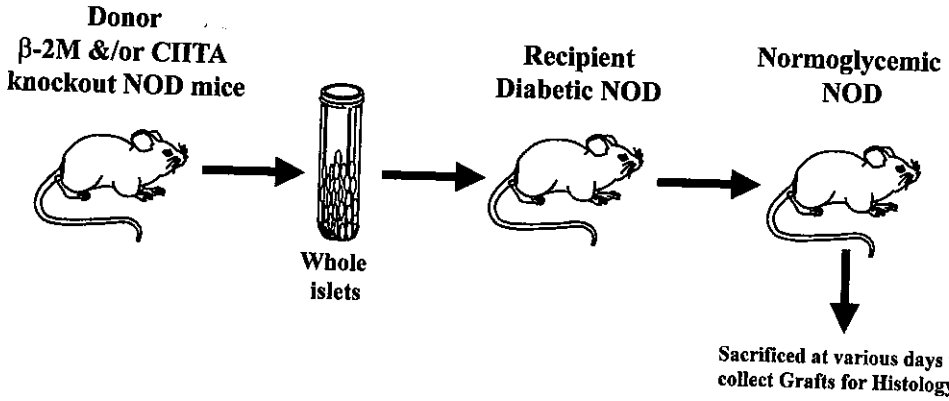
the histocompatible transplants without chronic immunosuppression. Our approach has been to:

- Block the effector mechanism in the host by modification of donor tissue
- Induce immunoregulatory cells in the host to down regulate the autoimmunity

Role of donor MHC molecules in prevention of autologous islet transplants in diabetic NOD mice

In type1 diabetes, cytotoxic T cells (CTL) are primarily responsible for the destruction of insulin producing islet b cells in the pancreas (1). Class I major histocompatibility complex (MHC) molecules are involved in the presentation of the islet antigens to the cytotoxic T cells. Syngeneic islets transplanted into diabetic NOD recipients are subject to autoimmune recurrence of injury, identical to pathways responsible for b-cell destruction in spontaneous disease. To explore the role of the MHC molecules in this process we used a model of syngeneic donor islet transplantation. Islets isolated from young donor mice were transplanted under the kidney capsule of female hyperglycaemic NOD mice (Fig 1). We transplanted islets from donor NOD mice that lacked class I, class II or both class I and class II molecules. We also explored the role of class III MHC molecules using similar approach (2).

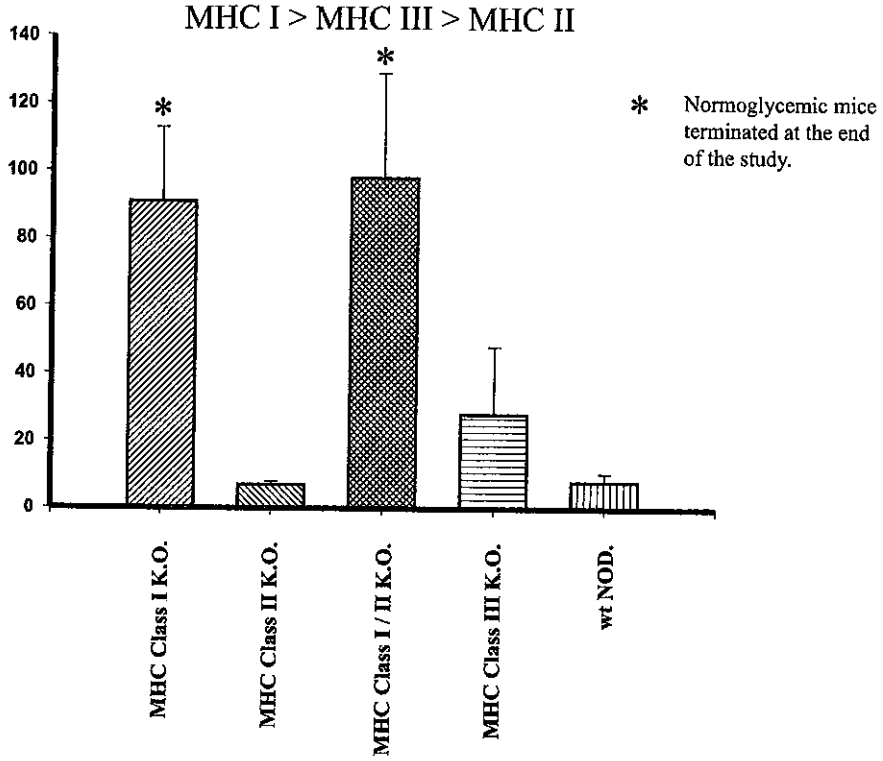
Figure. 1 : Transplantation of MHC knockout islet grafts in diabetic NOD mice.



As shown in Fig. 2, islets from NOD mice that lack class I MHC survive indefinitely, (3) while islets from class II MHC knockout (K.O.) NOD mice were rapidly destroyed (4) upon transplantation in the diabetic NOD mice. For these studies, class I MHC null islets from NOD mice lacking beta-2 microglobulin (b_2M) (3) were used. These studies confirmed that the absence of target expression in the presence of primed $CD8^+$ T cells conveys protection to

the islets isolated from class I MHC deficient NOD mice.

Figure. 2 : Role of MHC in islet Graft Survival in diabetic NOD mice.

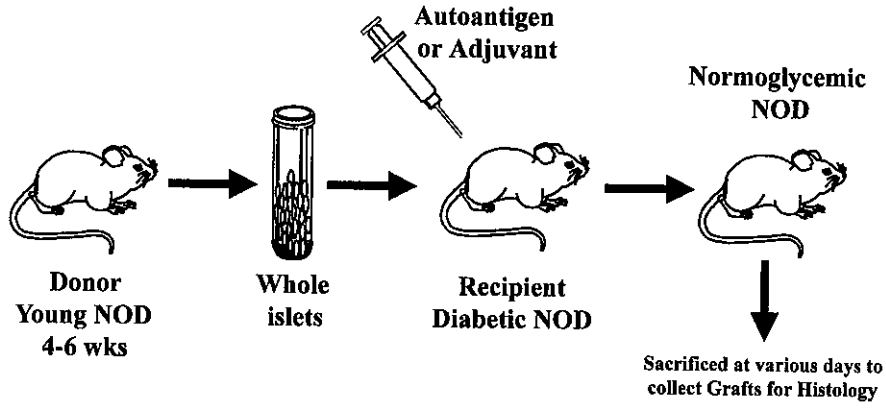


Down regulation of class II MHC was achieved by using class II transactivator gene (CIITA) transcription factor knockout NOD mice (5). CIITA is critical for the expression of class II molecules (5). As shown Fig 2 islets from class II MHC null NOD mice were rapidly destroyed in the diabetic NOD recipient. However, the presence or absence of MHC class II molecules on the passenger leukocytes and antigen-presenting cells (APC) in the islet grafts had no effect on islet survival (4). Islets from NOD mice that lacked both class I and class II molecules survive indefinitely, (4) but those that carry different class III molecules have a delayed destruction (2). The class III MHC molecules also played a role (2) as the islets from class I and class II MHC null mice that carry allo-class III MHC were also destroyed in the diabetic NOD environment, although at a much slower rate than wild type NOD islets; thus, MHC class I molecules play a key role in transplanted islet destruction.

Immunoregulatory cells prevent destruction of transplantation autologous islets in diabetic NOD mice

In autoimmunity, the primary cause of the destruction of autologous or transplanted autologous tissue or cells is the recognition of auto antigens by the host immune system in the context of self MHC molecules. We have reported that immunoregulatory T cells induced by immunization of pre-diabetic young NOD mice with mycobacterial preparations such as complete Freunds' adjuvant (CFA) or Bacillus Calmette-Guerin (BCG) (6, 7) or with islet auto antigen, such as insulin, (8) prevented the destruction of islet cells in the host. As shown in Fig 3, we investigated the induction of immunoregulatory T cells in modulating syngeneic islet transplantation in fully diabetic NOD mice.

Figure. 3 : Transplantation of NOD islets in autoantigen or adjuvant immunized diabetic NOD mice.

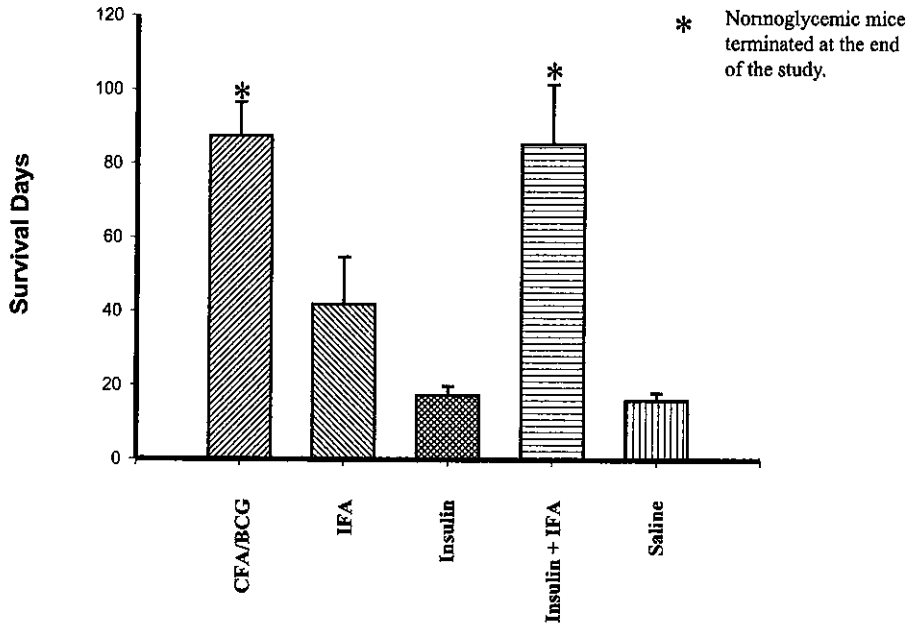


Diabetic NOD mice were treated with CFA, BCG or insulin three days prior to the transplantation of autologous islets from pre-diabetic young NOD mice. As shown in Fig. 4, this pretreatment prevented the autoimmune attack of the donor syngeneic islets by the host immune system. The protection is mediated by the induction of regulatory T cells (9) and/or the deletion of auto reactive T cells (10). The protective role of the regulatory T cells was further confirmed by the recurrence of disease following their elimination by cyclophosphamide (11). We also found novel $CD4^+CD8^+$ $CD25^+$ regulatory T cells in CFA immunized NOD mice (12). The use of microbial agents for immunomodulation has potential to expand the regulatory approaches discussed above (13, 14).

Treatment of NOD mice with insulin induce regulatory T cells and we identified $CD4^+CD25^+$ T cells in the insulin B9-23 peptide immunized NOD mice (15). In Fig 4 we have shown

significant protection of syngeneic islet graft in insulin immunized diabetic NOD mice (8). These results can be explained by an induction of insulin-specific regulatory cells that prevent the destruction of transplanted syngeneic islet cells from the infiltrating host auto reactive T cells.

Figure. 4 : Modulation of Islet Graft Survival by Immunoregulation in diabetic NOD mice.



We postulate that these approaches will be useful for the replacement of damaged tissue or cells in autoimmune diseases without chronic immunosuppression.

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