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The Role of Donor Class I Major Histocompatibility Complex Peptides in the Induction of Allograft Tolerance

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INTRATHYMIC injection of donor antigens combined with immunosuppressive regiments that allow for temporary down regulation of the immune system can result in the induction of tolerance to allografts. We have recently demonstrated that cardiac allograft rejection in a rat strain combination incompatible for an isolated class I major histocompatibility complex (MHC) molecule (RT1.A^a) involves the recognition of this antigen as peptides presented by recipient MHC molecules (indirect pathway). Three synthetic peptides, corresponding to the α-helices of the α1 and α2 domains of the donor class I RT1.A^a molecule, served as T and B cell epitopes for graft rejection. In this study, we sought to determine whether the peptides that served as efficient T cell epitopes during graft rejection can induce transplantation tolerance when presented to the recipient immune system as a consequence of intrathymic injection.

MATERIALS AND METHODS

Synthetic Peptides

Three synthetic peptides corresponding to specific region of the RT1.A^a molecule were used in this study. Peptides 1 (17 amino acids) and 2 (12 amino acids) correspond to the helix of the α-1 domain while P3 (11 amino acids) is derived from the helix of the α-2 domain of the RT1.A^a molecule. These peptides were synthesized and purified by reverse-phase HPLC in the Core Chemical Facilities of the Molecular Biology Institute of the University of California at Los Angeles.

Tolerance Induction

Varying doses of peptides were injected intrathymically into PVG.1U rats in 100 μL phosphate buffered saline 7 days before transplantation. At the completion of the immunization procedure, each rat received 1 mL of anti-lymphocyte serum intraperitoneally (Accurate Chemical and Scientific Corporation, Westbury, NY). Injections into the thymus of PBS alone or unrelated peptide served as negative controls.

RESULTS AND DISCUSSION

Alloimmunity involves recognition by T cell receptor of donor MHC antigens as intact molecules (direct recognition) or as peptides presented by recipient MHC molecules (indirect recognition). The relative contribution of these 2 pathways to graft rejection remains to be fully elucidated. In this study we tested whether intrathymic presentation of synthetic peptides representative of donor class I RT1.A^a molecules can influence the survival of cardiac allografts. Intrathymic administration of a mixture of 3 peptides at 150 μg/peptide/animal resulted in prolonged survival of PVG.R8 heart allografts (median survival time (MST) = 163 d; n = 7). The effect of peptides on graft survival was dose-dependent as administration of smaller amounts (50 μg/peptide) had a more moderate effect on prolonging graft survival (MST = 22 d; n = 6). Individual peptides were less efficient in inducing tolerance. There was a direct relationship between the potency of peptides to serve as a T cell epitope during graft rejection and their ability to induce intrathymic tolerance. We have previously demonstrated that P2 is the most efficient epitope for recognition by T cells activated by allografts.[1] Forty-two percent of graft recipients administered P2 alone accepted their grafts for longer than 72 days, compared to 20% of recipients given P1 or P3, peptides that serve as weak epitopes.[1] Peptide-induced tolerance was donor-specific as long-term graft survivors rejected third party LEW hearts with no adverse effect on the survival of the original PVG.R8 hearts. These observations are consistent with data obtained from a series of studies demonstrating that intrathymic injection of foreign antigens can result in antigen-specific tolerance.[2–4]

The induction of allograft tolerance with class I peptides clearly demonstrates that the indirect recognition pathway plays a critical role in the immune responses to allografts. Additionally, the prevention of graft rejection by class I peptides indicates that the indirect recognition pathway can down-regulate allograft reactions invoked by the direct recognition pathway. The ability of class I peptides to

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modulate graft survival may have the potential in selected settings to provide an effective therapeutic approach to prevent rejection and induce transplantation tolerance.

REFERENCES

1. Shirwan H, Leamer M, Makowka L, et al: Transplantation 59:401, 1995

2. Sayegh MH, Perico N, Imberti O, et al: Transplantation 56:461, 1993

3. Sayegh MH, Perico N, Gallon L, et al: Transplantation 58:125, 1994

4. Knechtle SJ, Wang J, Jiao S, et al: Transplantation 57:990, 1994