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CD4-specific monoclonal antibody can prolong cardiac allograft survival without T-cell depletion

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Current immunosuppressive regimens for clinical transplantation are immunologically non-specific, are associated with acute and chronic toxic side-effects [1] and are unable to prevent chronic graft loss in a significant proportion of patients. Additionally, new and increasingly powerful drugs are being introduced to induce non-specific immunosuppression, and therefore this is likely to be followed by an increase in related complications such as the induction of cancers. Hence, there is a need for an alternative approach.

It has been shown that long-term survival of murine cardiac grafts can be induced by the monoclonal antibody YIS 191 that depletes $CD4^+$T cells in vivo [2]. In this study, we have investigated the ability of a non-depleting antibody to produce better graft survival.

Key words: Immunosuppression – Monoclonal antibodies – YTS 191

Materials and methods

C3H/He mice were treated with 2 doses of either 25 μg of YTS 191 [3] (IgG2b) or 200 μg of KT6 [4] (IgG2a) intravenously (i. v.) on consecutive days, and lymph node single cell suspensions were assessed for the proportion of $CD4^+$T cells present by flow cytometry. Adult C3H/He mice received heterotopic C57BL/10 heart transplants representing a H-2 and multiple minor antigen mismatch and were treated either with 25 μg of YIS 191 or increasing doses, from 25 to 200 μg, of KT6 i. v. on the day prior to and at the end of the transplant operation.

Results

Cellular depletion of $CD4^+$ cells after treatment with YTS 191 was maximal by 3 days, when the animals were 87% depleted of $CD4^+$ cells relative to naive mice. No depletion occurred in animals treated with KT6 even at doses of 400 μg. In vivo, a 25-μg dose of depleting antibody YTS 191 given the day before and at the time of heart transplantation prolongs graft median survival time (mst) beyond 100 days. Grafts transplanted in animals receiving this same dose (2×25 μg) of KT6 were minimally prolonged ($n = 5$, mst 11.5 days) compared with untreated controls ($n = 6$, mst 8 days), but increasing doses of KT6 were progressively more immunosuppressive. When 2×200 μg of KT6 were used, marked prolongation of graft survival was obtained ($n = 9$, mst 58 days; versus controls $P = 0.0018$) and long-term survival in one-third.

Discussion

Perioperative treatment with the $CD4^+$T-cell-depleting monoclonal antibody YTS 191 has been shown to induce immunosuppression and long-term graft survival in this transplant model. In humans, attempts to induce immunosuppression and tolerance by cellular depletion may be complicated by toxicity from cell lysis and a prolonged period of non-specific immunosuppression. A regimen involving only non-depleting CD4-specific antibody to induce immunosuppression and tolerance might avoid these complications and additionally should not be associated with the sequelae of T-cell activation as seen with T-cell receptor antibodies such as OKT3. Towards this aim we have shown that a simple non-depleting regimen targeting only the $CD4^+$ subset of T-cells can be profoundly immunosuppressive and induce the long-term survival of vascularised grafts in a murine model.

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