Induction of Long Term Graft Survival by Aberrant T cell Activation and Dynamic Maintenance of Donor Specific Tolerance

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Purpose and methods : Although the immunosuppressive activity of FTY720 is known to be exerted by sequestration of effector T cells, the intensification of regulatory T cell activity by FTY720 is also suggested. Here, we evaluated the synergistic effects of lymphocyte sequestration and aberrant T cell activation regarding graft survival and the capacity of regulatory T cells using allogeneic skin graft model. And we also investigated the nature of the maintenance of donor-specific tolerance.

Results : In-vitro allogeneic T cell responses were attenuated by the addition of either FTY720 or anti-CD154 mAb (MR1) in dose-dependent manner. In minor histocompatibility mismatch model (DBA/2 to Balb/c), either FTY720 or MR1 administration prolonged skin graft survival significantly but failed to induce long term graft survival. On the other hand, combination treatment of both agents induced the indefinite graft survival. The synergistic effect of combination treatment was also effective in MHC mismatch skin graft (C57BL/6 to Balb/c), although the single agent treatment showed limited benefits on the graft survival. FoxP3 expressing regulatory T cells are more frequent in FTY720 treated recipients than in non-treated recipients and regulatory T cells from FTY720 treated or FTY720+ MR1 treated recipients exert more profound regulatory activity in in-vitro allogeneic T cell proliferation. Also, the achievement of long term graft survival by combination treatment is maintained, not statically, but by active regulation. When the second graft from same strain of first donor was performed on recipients that showed long-term graft survival, the second graft survived without specific treatment. On the other hand, the recipients having first graft more than 100 days rejected promptly not only the second graft from different strain but also rejected the first graft. The $CD4^{+}CD25^{+}$ T cells from recipients showing rejection after second graft exerted weaker regulatory activity against antigens from first graft strain compared to T cells from recipients having healthy second graft in in-vitro allogeneic immune responses.

Conclusion : The combination of lymphocyte sequestration and aberrant T cell activation is a powerful tool for induction of long-term graft survival, and the maintenance of donor-specific tolerance is an active, not static, process.