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TRANSPLANTATION

Successful adoptive transfer of tolerance in miniature pigs

Understanding the mechanism by which tolerance is induced is essential to developing new approaches to induce tolerance in clinical transplantation. A new study reports the successful induction of tolerance of allogeneic kidneys in miniature pigs by the adoptive transfer of cells and tolerated kidney grafts from long-term tolerant (LTT) animals that were major histocompatibility complex (MHC) matched to the naive donor kidney. "To our knowledge this is the first successful demonstration of adoptive transfer of tolerance in large animals," says researcher Kazuhiko Yamada.

Previous studies suggested that regulatory mechanisms have an essential role in the induction and maintenance of tolerance, but provided only indirect evidence of the role of regulatory cells in this process. To evaluate the involvement of regulatory mechanisms in tolerance, Yamada and colleagues used a model of adoptive transfer to investigate whether cells from tolerant animals could induce tolerance of class I MHC-mismatched kidney grafts in naive recipients.

The researchers performed their studies in Massachusetts General Hospital miniature swine. "These are unique inbred animals that enable us to study transplantation immunology on a genetically defined MHC background," explains Yamada. "We have previously demonstrated that a 12 day course of high-dose ciclosporin uniformly induces tolerance of class I MHC-mismatched kidney allografts in this model." Allograft recipients (SLA^{dd}) received 1.5 Gy whole body irradiation and class I-mismatched (SLA^{gg}) kidneys from naive pigs with or without cotransplanted kidneys and/or adoptively transferred peripheral blood mononuclear cells (PBMCs) from LTT SLA^{dd} recipients of SLA^{gg} grafts. The LTT donors had received 12 days of ciclosporin and were demonstrated to be unresponsive to donor MHC.

Yamada and colleagues found that the infusion of PBMCs alone from LTT animals was insufficient to prolong graft survival in naive allograft recipients. To increase the number and potency of T regulatory (T_{REG}) cells, LTT animals were given a donor-specific transfusion (DST) of donor-matched, nonirradiated whole blood, 8 days before PBMCs or kidneys were donated to adoptive transfer recipients. Adoptive transfer of DST-primed donor PBMCs or kidneys did not reliably induce tolerance in the recipient; however, co-transfer of PBMCs and kidneys from DST-primed animals showed markedly prolonged survival of the naive renal grafts in two of three animals (>150 days).

To translate these findings to clinically applicable protocols, the researchers are now assessing the immunogenic characteristics of the tolerated kidney grafts. "Defining the tolerogenic mechanisms of the graft infiltrating T_{REG} and renal parenchymal cells might enable us to use these cells for the induction of tolerance of naive kidneys without co-transplantation of LTT kidneys," concludes Yamada.

Susan J. Allison

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