Transplants and Grafts

Promoting Long-term Graft Survival in Composite Tissue Allotransplantation

Composite tissue allotransplantation (CTA) another term for vascularized composite allotransplantation, is the transplantation of multiple tissue types as a functional unit, such as a hand/limb, face, or abdominal wall. One of the major hurdles to widespread use of CTA for severe injuries is the need for prolonged immunosuppression to prevent graft rejection. Extended immunosuppression can lead to many negative side effects including kidney or liver failure. Alternative strategies to suppress immune rejection would reduce prolonged immunosuppression and improve outcomes following CTA.

To this end, investigators at the University of Pittsburgh (Pittsburgh, PA) and Wake Forest Institute for Regenerative Medicine (Winston-Salem, NC) developed a controlled release drug delivery system consisting of microparticles (MPs) that slowly release agents involved in the recruitment (Recruitment-MPs) or expansion (Expansion-MPs) of regulatory T cells (Tregs). Tregs down regulate local immune responses but are found in relatively low numbers throughout the body.

By engineering MPs which release the Treg-attracting protein, CCL22, Tregs can be recruited to the transplanted allograft site to suppress graft rejection. The Recruitment-MPs have been found to prolong graft survival over 200 days when administered in a rodent model of hind limb transplantation; untreated graft recipients rejected the implanted tissue within 2-3 weeks after immunosuppression cessation.

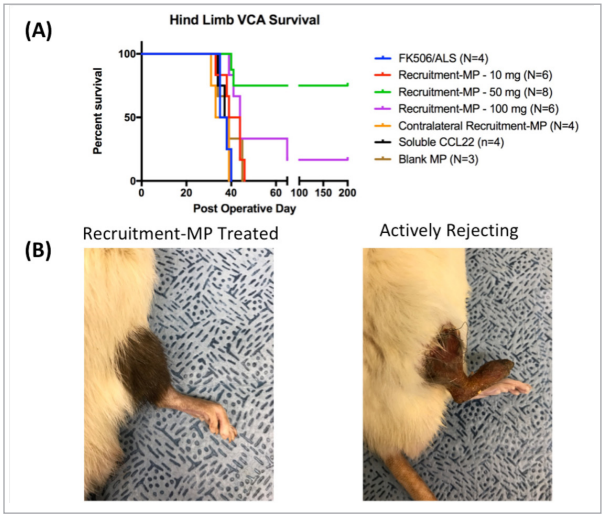

FIGURE 7-40: A) Treatment with 50mg of Recruitment-MP is able to prolong allograft survival to at least 200 days in 6/8 animals. This result is statistically significant $p<0.05$ when compared to all controls. B) Animals receiving a hind limb transplant were monitored daily and scored on a five-point rejection scale. Limbs displaying a progressive stage 3 rejection were considered "rejected." (Figure used with permission from the authors).

Additionally, the investigators developed Expansion-MPs, which release factors known to promote naive T cell maturation into Treg. When administered in a rodent hind limb transplant model, Expansion-MPs releasing the proteins IL-2 and TGF-beta, and the drug rapamycin, were shown to delay rejection more than 300 days (Figure 1).

Treatment with both Expansion-MPs and Recruitment-MPs led to decreased inflammation, increased numbers of Tregs in the lymph nodes, and Tregs with superior donor specific suppression of T effector cells compared to controls.

Minimizing the use of harsh immunosuppressive agents through the use of Recruitment- and Expansion-MPs will help enable the widespread use of CTA for severely injured Service members while enhancing quality of life and improving health outcomes for CTA recipients.

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