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Mhc Class I Sharing Influences the Fate of the Epidermal Component of Vascularized Composite Allografts in Mixed Chimerism Based Tolerance Protocols in Miniature Swine.

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PURPOSE: While skin remains one of the most difficult tissues for induction of transplant tolerance, the precise mechanisms that govern skin tolerance/rejection remain poorly understood. Skin-containing vascularized composite allograft (VCA) transplants, including face, hand, lower extremity and abdominal wall transplants, have emerged as a treatment option in patients with severe tissue loss. The induction of robust VCA transplant tolerance, including tolerance of the skin component, would obviate the need for chronic immunosuppression and allow broader application of this reconstructive modality. Disparate results with regards to skin tolerance have been observed in two related large animal experiments in our laboratory using MGH miniature swine. Long-term tolerance to VCAs (>600 days), including the skin component, has been achieved across a single haplotype MHC-mismatch barrier using a mixed chimerism-based protocol. However, when a similar protocol was used across a full MHC-mismatched combination, the outcome was tolerance to all components of VCAs except the skin epidermis. This result suggested that sharing of MHC at class I and/or class II may be required for stable skin tolerance in a mixed chimerism model.

METHODS: Using a non-myeloablative protocol (CD3 T-cell depletion, 100 cGy total body irradiation and 45 days of cyclosporine) with hematopoietic stem cell transplantation (HSCT), mixed chimeras were generated across either a MHC Class I (n=2) or a MHC Class II mismatch (n=2). VCAs consisting of primarily vascularized fasciocutaneous flaps were transplanted at the time of HSCT. VCA outcomes were monitored by clinical inspection and histology and peripheral blood chimerism was assessed in multiple cell lineages using flow cytometry. In vitro immune responsiveness was assessed using mixed lymphocyte reaction (MLR) and cell-mediated lymphocytotoxicity (CML) assays.

RESULTS: Regardless of the MHC mismatching, all animals displayed high-level chimerism at all time points in lymphoid (50–70%), myeloid (40–80%) and granulocyte (40–80%) lineages. MHC Class II-mismatched chimeras remained tolerant of VCAs, without significant histological or clinical features of rejection at any time-point. In contrast, both MHC Class I-mismatched animals experienced acute rejection crises of the epidermal component of the VCAs following tapering of immunosuppression, with one of these animals mounting recurrent rejection episodes. Histological visualization confirmed that rejection was confined to skin epidermis. In vitro assays in all animals demonstrated donor-specific non-responsiveness at all points, including after rejection crises, suggesting that the epidermal rejection in the MHC class I-mismatched animals was a local effect.

CONCLUSIONS: The identification of MHC Class I sharing as a determinant of skin tolerance may have important immunological as well as clinical implications. These data suggest that local regulation of immune tolerance is critical in long-term acceptance of all components of the VCA, and that sharing of MHC class I may be necessary for establishing and maintaining tolerance of epidermal tissue. In the clinic, MHC matching of recipient and donor has not been taken into consideration in VCA transplants under cover of conventional immunosuppression. But with the goal of developing tolerance-inducing approaches in the future, these results suggest that sharing of class I antigens could have a beneficial effect in mixed-chimerism-based clinical tolerance protocols.