Analysis of Acute Skin Rejection in Non-Human Primate Models of Face and Hand Allotransplantation

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INTRODUCTION: The incidence of acute rejection (AR) of the skin within the first year after hand or face transplantation is approximately 85% and up to 56% of patients experience multiple episodes[1]. Significant immunosuppression is required to prevent allograft loss, and recent studies suggest that repeated AR episodes can lead to VCA dysfunction and loss[2]. The mechanisms underlying variability in AR presentation remain poorly defined however.

MATERIALS AND METHODS:
8 cynomolgus monkeys received either an orthotopic hand (n=2) or heterotopic face VCA (n=6) from MHC-mismatched donors following induction with anti-thymocyte globulin. Post-operatively, triple immunosuppression – tacrolimus, mycophenolate mofetil, methylprednisolone – was maintained for up to 120 days before bone marrow transplantation (BMT) was performed. Protocol biopsies of VCA skin were performed at 30-day intervals for histopathology and flow cytometric analysis of resident skin leukocyte populations; VCA-resident cells were differentiated by H38 status (mouse antihuman HLA class I monoclonal antibody that cross reacts with cynomolgus monkeys) for donor or recipient derivation. Clinical AR was treated with steroids and further biopsies were taken for histologic confirmation; corresponding anti-donor responses were evaluated by mixed lymphocyte reaction (MLR) and allo-antibody formation.

RESULTS:
Up to three episodes of AR (from POD 14, Banff I to II) developed while recipient animals were maintained on triple immunosuppression. Corresponding flow cytometric analyses demonstrate > 80% of skin-resident T lymphocytes (CD4+, CD8+) within VCA dermis were of recipient origin, suggesting rapid immigration of various lineages into the VCA. These observations coincided with the first episode of AR in fully mismatched recipients but haplomatched animals remained rejection-free. All but one episode of AR were successfully treated. No allo-antibodies were detected and anti-donor responses by MLR were comparable to that against third-party. Following BMT, mixed chimerism was detected and enabled immunosuppression withdrawal. However, this was transient and once lost, clinical AR developed and nearly 100% of both dermal and epidermal lymphocytes were recipient-derived.

CONCLUSION:
We report a clinically-relevant model for studying AR in VCA. Our results suggest that further understanding of the relative importance of MHC differences in transplant pairs may lead to differences in outcomes for VCA recipients maintained under standard immunosuppression. Immunosuppression-free tolerance of non-hematopoietic antigens in composite tissues can be achieved, but require additional strategies to achieve stable, rather than transient mixed chimerism following BMT.

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