Penile Transplantation – The Science of Rejection and Erection

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Penile transplantation has been successfully used in two cases to treat penile tissue loss.

It is unknown how the different tissues comprising the penis will undergo tissue rejection.

It is unknown how rejection and immunosuppression therapy will affect tissue function.

For vascularized composite allotransplant (VCA) grafts, skin can commonly be surveilled to monitor tissue rejection (Banff Classification).
Background – Penile Transplant Models

Lack of animal models – Four reports using rats, all heterotopic transplants, one report using Beagles, which was an orthotopic transplant.

Rat models have used either omental wraps or anastomosed branches of the femoral artery with the corpus spongiosum to retrograde perfuse the transplanted graft. Technically challenging anastomoses and precludes the ability to evaluate urethral tissues or erectile function.

Canine study evaluated 10 orthotopic penile transplantations in half-brother Beagles treated with immunosuppression. Animals were able to spontaneously void after 10 days and there were no signs of acute rejection when tissues were collected at 14 days post-operatively. Erectile function was not assessed.
Goals

To develop better models of penile transplantation and rejection

To use those models to better understand how the tissues of penis reject and how rejection and immunosuppression affect tissue function
Rat Heterotopic Allotransplantation Model

2009 APS Sonmez et al.
Grafts rejected by POD 7
Leukocyte infiltration of the urethra and nervous tissue
Apoptosis of urethral tissues

TUNEL Staining

24 Hour Post-Transplant

72 Hour Post-Transplant
Rodent model conclusions

Difference in rejection rates between tissue types

Time consuming and technically challenging

Need for an easier, high volume model
Mixed Lymphocyte Reaction (MLR)

Established 30 years ago to study immune cell activation and screen compatibility between donor and recipients for solid organ transplantation.

In vitro experiment performed by mixing peripheral blood mononuclear cells (PBMCs) of the donor with PBMCs of the recipient. Measure cell proliferation, cytokine production, subpopulations, etc... as markers of activation.

2014 Tissue Antigens Lindemann et al.
Ex-vivo Organotypic Mixed Lymphocyte Reaction

Control

Autograft

Allograft

Allograft + Immunosuppression
Real-Time Fluorescent Imaging

SNARF  Activated Caspase-3/7  Labeled PBMCs  Merge
Ex-vivo MLR allotransplant has increased apoptosis

- Autotransplant
  - Day 1
  - Day 7

- Allotransplant
  - Day 1
  - Day 7
Tacrolimus reduces tissue apoptosis in ex-vivo MLR
Ex-vivo MLR allograft immune cell activation

7 Days
Penile tissue components have different immunogenicity
Human urethra also undergoes rejection
Human ex-vivo MLR to test erectile function
Ex-Vivo MLR – validation of the model
Ex-Vivo MLR – validation of the model
Rejection impairs erectile physiology

EFS – Electrical Field Stimulation
Rejection affects tissue morphology and is prevented by CsA Immunosuppression
Rejection affects tissue morphology and is prevented by CsA Immunosuppression
Although it prevents rejection, cyclosporine A also impairs erectile physiology.

EFS – Electrical Field Stimulation
FK506 does not impair erectile physiology

2016 EurUrol Sopko et al.
Conclusions

Penile rejection in the setting of transplantation is complex – many different tissue types, which have different immunogenicity

Animal models are very limited given anatomical correlation, size, and ethical concerns using large animals

Ex-vivo MLR can be used to model penile tissue rejection including sub-tissue types

Tissue rejection and CsA treatment impairs erectile physiology

FK506 may be more suitable for immunosuppression