Innate and Adaptive Immune System

Immune Response

Tolerance
Main Concepts

- Innate immune activation at transplant (APC) stimulates adaptive immunity (T/B cells) which promotes alloreactivity over tolerance.
- Histocompatibility genes give rise to MHC:
  - MHC genes encode alloantigens known as HLAs (cell surface) {Class I and II}
  - MHC’s role is to present fragments of foreign antigens as complexes {Class II}
  - MHC are membrane associated and present to antigen-specific T Cells
- Deletion of alloreactive lymphocyte clones is a critical step in the development of long term liver transplant tolerance.


Immune Cells

- Innate (first line of defense, no memory, same response each time, non-specific)
  - Polys (PMNs, eos, baso)
  - Monocyte/Macrophage
  - NK (NKT)
  - DC
- Adaptive (effector, helper, memory; increased response every time, specific)
  - Lymphocytes
    - Cellular Immunity
      - CD4+ T helper (class II MHC)
      - CD8+ T cytotoxic (class I MHC)
    - Humoral Immunity
      - B cells
      - Plasma Cells
Inflammatory triggers of acute rejection of organ allografts

Types of Immune Response

- **Hyperacute** (preformed ABO Abs)
- **Acute** (T cell-mediated (TCMR); HLA Abs may add insult to injury)
- **Chronic**: fibrosis + vasculopathy – mix of TCMR/AMR
Hyperacute Rejection

Preformed antibodies exist if the graft is not ABO-matched; alloantibodies can be generated during previous blood transfusions, previous transplantation, or pregnancy.

Desensitization protocols work if needed (PP, IVIG, rituximab +/- splenectomy)

Early Direct pathway of Allorecognition

DIRECT (acute)

Donor APC

T helper cell 1

T helper memory cells

T helper effector cells

Donated organ cells

 alloantibodies

T cell

Donor APC

T helper cell 1

T helper effector cells

Cytoytic effector cells

Cytoytic memory cells

Interferon-γ

Perforins, apoptotic signals

B Cell

Eosinophil

IL-4

IL-5

IL-1, IL-12
Late Indirect Pathway of Allorecognition

Recipient APC

MHC I & II
CD40
CD40L
B7
CD28
ICAM
LFA-1

Recipient CD4 & CD8

Recipient T cells directly attack donor cells – acute rejection

Recipient T cells proliferate and generate long-term immune response to donor antigens – chronic rejection

Side by Side Comparison
De novo purine synthesis

IL-2 receptor (CD25)

Activated Calcineurin

NFAT

NFAT

IL-2 GENE PROMOTOR

Costimulatory Signals

Antigenic Signal

TCR

APC

IL-2

Calcineurin

Cell Cycle

G1

S

G2

M

De novo purine synthesis

Calcineurin

NFAT

P

IL-2 GENE PROMOTOR

Ca^{2+}

Activated Calcineurin

NFAT
Liver allograft antibody-mediated rejection and the role of the 'two-hit hypothesis'

- Immunological Tolerance: Absence of immune reactivity toward specific antigens but preservation of immunity against foreign antigens, in the absence of ongoing IS

- Operational tolerance: clinical circumstance in which graft function is stable without rejection in the absence of IS

- Prope (almost) tolerance: Minimal IS with stable graft function (“as little as possible without rejection”)

Tolerance
Regulatory T cells (Tregs)

- Naturally produced in the thymus and induced in the periphery to control effector responses to auto- and allo-antigens

- Require TCR interaction and IL-2 for proliferation

- Characteristically express:
  - High levels of CD25 (IL2 receptor)
  - Low CD127 (IL7 receptor)
  - FOXP3
  - TSDR (demethylated)
Why Consider IS Withdrawal in Liver vs. Other Organ Recipients?
Tolerance in LT

- In very select groups, can achieve tolerance in >50% with simple weaning
- Factors associated with IS withdrawal success
  - Late withdrawal in older recipients
  - Less inflammation and lower C4d on pre-withdrawal bx
- What can we learn?
  - Biopsies are important pre- and post-weaning
  - Do this late, but not too late when the impact of IS has already occurred
Algorithm for achieving tolerance after LT

4.1. Recipient selection

4.2. Donor selection

4.3. Induction therapy

4.4. Maintenance immunosuppression

Thanks