IMMUNOBIOLOGY OF TRANSPLANTATION

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Immunobiology of Transplantation

- Overview
  - Transplantation: A complex immunologic process
  - Contributions
    - Innate Immunity
    - Adaptive immunity
      - T Cells
      - B Cells
      - HLA
  - Consequences of Transplantation
    - Rejection
      - Cellular
      - Antibody mediated
    - Graft loss
    - Tolerance
Immunobiology of Transplantation: Innate Immunity

• Inflammatory response
  • Recovery of organs and subsequent transplant induces an inflammatory response
  • Innate immunity contributes substantially to the early response in transplantation

• Ischemia reperfusion
  • Toll Like Receptors (TLR)
  • Damage associated molecular patterns (DAMPS)
  • Injury vs. upregulation of adaptive immunity

• Complement
  • Injury vs. upregulation of innate immunity
  • Chronic injury
Immunobiology of Transplantation: Ischemia Reperfusion Injury

• TLR
  • Pattern recognition receptors on immune and non-immune cells
  • Recognize LPS and DAMP’s
  • TLR are expressed in renal tissue such as renal tubules (TLR2/TLR4)
  • Activation of TLR leads to activation of apoptotic pathways and increased cytokine and chemokine release.
Immunobiology of Transplantation: Ischemia Reperfusion Injury

• I/R injury
  • Recovery of organs and reperfusion results in ischemia reperfusion injury
  • This results in increased expression of TLR and their cognate antigens DAMPs
  • Activation of this cascade leads to greater cascade of tissue injury.
Immunobiology of Transplantation: Ischemia Reperfusion Injury

- What is amplified by this process?
  - Immune cell migration
  - Immune cell activation
  - Tissue death
    - Direct
    - Indirect
Immunobiology of Transplantation: The role of complement

- Complement
  - A system of protein recognition molecules, enzymes, and effector products that provides innate defense against pathogens
- Three pathways
  - Classical
  - Lectin
  - Alternative
- Peripheral versus Intravascular complement components
Immunobiology of Transplantation: The role of complement

- Complement
  - Activation of complement pathways affects transplanted organs via multiple mechanisms
  - Ischemia reperfusion
    - Lectin pathway
    - Alternative pathway
  - Peripheral activation of complement
  - Direct tissue injury and release of inflammatory/chemotactic products
Immunobiology of Transplantation: The role of complement

- Complement
  - Activation of complement pathways affects transplanted organs via multiple mechanisms
  - Upregulation of innate immunity
  - Complement components acting on antigen presenting cells and on T-cells
    - 1. APC effectiveness - costimulatory molecules
    - 2. T cell survival
  - Complement’s diagnostic role (see later)
Immunobiology of Transplantation: Adaptive Immunity

- Adaptive Immunity
  - T cells
  - B cells
  - HLA
- Most well studied immunologic component of biology of transplantation
- FYI
  - Most therapies to promote clinical success of transplantation are focused on adaptive immunity
    - Immunosuppression
    - Tolerance induction
Immunobiology of Transplantation: T-Cells

- T-Cells
  - Thymus derived lymphocytes
  - Development of these cells is not driven by alloimmunity but rather protection against pathogens
  - However the nature of T-cell development requires interaction with other human cells (HLA)
    - This results in 10% of the entire T-cell repertoire being allospecific
Immunobiology of Transplantation: T-Cells

- The vast repertoire of T-cells directed for allospecificity represent a critical issue in the inflammatory response against transplanted organs.
- Activation of these T-cells results in the generally negative consequences following transplantation (if untreated):
  - Acute cellular rejection
  - Graft loss
- Mechanisms of activation i.e. allo-recognition:
  - Direct
  - Indirect
Immunobiology of Transplantation: T-cells and the TCR

• TCR
  • Activation of the TCR and interaction between the TCR, MHC, and co-stimulation molecules are critical for T-cell activation and the subsequent response to transplanted organs
  • Incomplete/ineffective activation
    • Leads to cell death, anergy, and tolerance.
Immunobiology of Transplantation: B-cells

- B-cells
  - Early on in transplantation, contribution of B-cells was not well recognized
  - B-cell contributions to transplant biology (just some)
    - Hyperacute rejection
      - The Crossmatch
    - Antibody mediated rejection
    - Graft fibrosis and chronic graft injury
    - Sensitization
    - IVIG
  - B-cell activation:
    - T-cell mediated
    - B memory cell
Immunobiology of Transplantation: B-cells

- **B-cells**
  - ABO incompatibility
    - Liver transplantation vs. Kidney transplantation
  - Hyperacute rejection
    - Nearly immediate rejection mediated by pre-formed antibodies to donor HLA molecules
    - IgG-Donor specific antibody
    - Type I versus Type II-Terasaki
  - Antibody mediated rejection
    - Late effect of antibodies against donor HLA
  - Sources
    - Pre-formed
    - De Novo
Immunobiology of Transplantation: B-cells and chronic graft injury

• What causes grafts to fail long-term?
  • Graft fibrosis and chronic injury
    • Kidney-IFTA-interstitial fibrosis and tubular atrophy
    • Liver-vanishing bile duct syndrome
    • Lung-bronchiolitis obliterans syndrome
    • Heart-chronic coronary artery changes
  • Contributors
    • Infection-CMV, BK
    • Antibody mediated damage is likely the prime causal agent in chronic graft injury
  • Sensitization is a process by which antibody forms in patients as exposure to alloantigens increases
    • Pregnancy
    • Transplant
    • Transfusion
    • Sensitization leads to alloantibody (IgG against HLA) production and subsequent antibody mediated graft injury => chronic graft injury and graft loss
Immunobiology of Transplantation: B-cells and the Crossmatch

- Terasaki-antibodies against HLA are detrimental to graft outcome
  - Crossmatch
    - CDC crossmatch
      - Indirect vs. direct
    - Flow crossmatch
    - Virtual crossmatch
  - Class I versus Class II
  - Which organs?
    - Heart, Liver, Lung, Pancreas, Kidney, Intestine.
Immunobiology of Transplantation

HLA

- MHC
  - Set of genes encoding 6 major antigens or HLA’s
    - A, B, C(w) class I
    - DP, DQ, DR class II
  - Incredible diversity among humans
  - Allospecificity of T-cells is driven by differences in HLA
  - Is tissue typing and crossmatching necessary?
    - Kidney
    - Liver
    - Heart
    - Lung
  - Are all HLA equally important?
    - HLA A, B, DR
      - Graft outcomes with and without matching
    - HLA DQ
Immunobiology of Transplantation Outcomes or putting it all together

• Transplant occurs across different MHC in humans, i.e. allogeneic

• Transplanted organs need to be procured resulting in ischemia-reperfusion injury.

• I/R injury induces direct innate immune mediated organ damage as well as priming the adaptive immune system

• Adaptive immunity namely T-Cells and B-Cells become activated via direct and indirect allo-recognition.

• Activated T-cells mediate tissue injury-ACR. Activated B-cells form antibody-AMR

• Immune injury is a primary contributor to early and then late graft loss
• Occasionally though a different outcome can occur.
Immunobiology of Transplantation

Tolerance

• The “Holy Grail” of transplantation
  • Clinical data for its existence
    • Non-compliant patients who don’t lose grafts
    • BMT+solid organ transplant recipients off immunosuppression
  • Types
    • Central versus peripheral
  • Mechanisms
    • Central regulation
    • Anergy
    • Apoptosis
    • Suppression
  • Regulatory cells
    • T and B cells can be regulatory cells
      • TCR and T-reg cells
Questions?