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Transplantation Self Study

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- Basics
  - Transplantation performed to replace non-functioning vital organ
  - Risk include (not limited to) rejection and immunosuppressants-->infection
- ABO Matching
  - Mismatching leads to endothelial damage by ABO antibodies
  - Subsequent widespread thrombosis and graft loss
  - O cannot accept A, B, AB
  - A cannot accept B, AB; B cannot accept A, AB
  - AB an accept everything
  - Hyperacute rejection
    - w/in hours
    - Antibody mediated
    - Marked by expanded inflammatory infiltrate composed of mononuclear lymphocytes
  - Acute and chronic rejection mediated by T cells
- MHC Rejection
  - T cell mediated
  - HLA molecules in MHC most important
  - Syngeneic grafts (same donor/recipient) never rejected
  - If HLA antigens not identical, T cells will react against foreign HLA molecules
  - Matching
    - HLA-identical siblings optimal
    - Post-transplant immunosuppression required for all transplant pairs except identical twins
  - MHC antigens
    - Self proteins loaded into HLA peptide groove
    - Even when HLA antigens identical, differences in self-peptides from donor organ can facilitate immune response
  - Matching
    - MHC matching sufficient but minor histocompatibility antigens not matched
    - T cells clones recognizing allogenic MHC molecules are abundant
    - Better matching results in lower likelihood of rejection and better response to immunosuppressants
    - T cells for minor antigens less abundant and well controlled immunosuppressants
- Immunosuppression
  - Increases risk of infection
  - NSAIDs
    - Reduce inflammation by inhibiting enzymes
    - Aspirin, ibuprofen, acetaminophen, naproxen
  - Corticosteroids
    - Prednisone
    - Inhibit antigen driven T cell differentiation by inhibiting expression of genes
    - Lead to apoptosis of activated T cells
    - Suppress action of inflammatory cells reducing both PG and LT synthesis and inhibiting emigration of leukocytes from blood vessels
    - SE: fluid retention, weight gain, diabetes, bone mineral loss, thinning of skin
  - Anti-metabolic drugs
    - Azathioprine, cyclophosphamide, mycophenolate
    - Act by killing all dividing cells
    - Nucleoside analogs that inhibit nucleotide synthesis or by alkylating DNA

        - Act by killing T cells and B cells undergoing antigen driven differentiation
        - SE: bone marrow stem cells, skin, hair follicles, epithelial cells in intestine, fetus
    - Immunosuppressive drugs
        - Prevent signaling that is important to antigen-dependent T and B cell differentiation
        - Bind to cytoplasmic proteins that prevent signal transduction from T cell or Ig receptor via calcineurin (cyclosporin A and tacrolimus) or inhibit protein translation and progress through cell cycle (rapamycin)
        - Cyclosporin A/tacrolimus lead to reduced expression of cytokines
        - Rapamycin leads to T cell apoptosis
        - Agents are very effective inhibitors of antigen-driven immune responses
    - Combo of drugs usually used
        - Using smaller doses but multiple groups inhibition is improved but w/ less side effects
        - General immunosuppression still exists
- Matching
    - Type for MHC expressed on leukocytes using antibodies
        - Antibodies for a single allele difficult to obtain
        - Many alleles cannot be typed w/ antibodies, esp. class II genes
    - Type for MHC genes by PCR and sequencing
        - Finds all potential differences
        - Expensive and time consuming
        - Method of choice if time not major issue
    - Mixed Lymphocyte Rxn
        - MLR is co-culture from two individuals
        - Detects ability of T cells to recognize allogenic differences of WBC from another individual
        - T cells divide after recognition
        - Cell division can be measured by uptake of tritiated thymidine from culture media into cells
        - Negative control is potential graft recipients rxn to his/her own lymphocytes
        - Test is recipients lymphocytes reacting to donor's x-irradiated lymphocytes
        - Differences in class II are key differences that result in thymidine uptake
        - Sensitive measure of immunological recognition
        - Availability of suitable reagents is not an issue
        - Takes about a week and is expensive
- Bone Marrow Transplantation: Graft-versus-host disease also occurs
    - Hematopoietic stem cell transplantation: effective after transplantation b/c stem cells go to bone marrow and reconstitute all components of bone marrow
    - GHVD caused by mature T cells that contaminate bone marrow or stem cell preparation
        - Donor T cells recognize allogenic MHC molecules of host or minor HC antigens
        - Initiate inflammatory immune response against host tissue
        - Syngeneic > Genotypic-identical sibling > Other family member > Matched unrelated donor
            - The probability that any two unrelated persons will match is extremely low
            - Broad application of this technique is made feasible by large volunteer registries
    - Conditioning regimens
        - Bone marrow transplant recipients undergo chemo/radiation to reduce GVHD chance
            - Tumor burden w/ cytotoxic drugs
            - Immunosuppress recipient to prevent rejection of bone marrow transplant
    - Complications of transplant
        - Toxicity from conditioning regiment: short and long term effects
        - Graft rejection
        - GVHD
            - Acute
                - Usu. Develops w/in first 100 d of transplant
                - Primary tgts are skin, liver, intestines
            - Chronic

- Clinically represents autoimmune disease
- Skin (scleroderma), dry eyes, mouth and vagina (sicca like syndrome), liver, GI, lungs, fasciitis, serositis