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Classification of Immune Mediated Tissue Injury

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- Type I: Anaphylactic Type
  - Allergen binding to mass cell to cause degranulation
  - Prototype disorders
    - Allergic rhinitis
    - Asthma
    - Anaphylaxis (insect venom)
  - Immune mechanism
    - IgE-Mast cell binding
    - Vascular permeability
    - Eosinophils
  - Clinical
    - Result of exposure to environmental allergens in genetically susceptible individuals
    - Genetics not clearly defined, but association exists
    - Atopy: genetic predisposition for developing IgE responses to many antigens
    - Local or systemic symptoms
    - Most common form - allergic rhinitis
      - Certain types of asthma
      - Atopic dermatitis (eczema)
      - GI food allergies
    - Allergens: pollens, molds, house dust mites, animal dander
  - Pathophysiology
    - Antigen presented by APC to Th cell --> IL-4 activation of B cell
    - IgE antibodies secreted by B cell
    - IgE antibodies bind to Fc receptors on mast cells
    - Antigen binds to IgE on mast cells
    - Degranulation of mast cell releases cytokines
      - IL-4,5,6 stimulates B cells
      - IL-3,4 stimulates GM-CSF, TNF-α, IL-8/0, inflammatory cell activation
    - Mediators have variety of effects
      - Increase vascular permeability
      - Constrict airways
      - Cell infiltration
      - Asthma, eczema, hay fever
      - Feedback effects on immune system
  - Effects of mediators
    - Histamine --> vascular permeability, vasodilation of post-capillary venule, smooth muscle contraction
    - Chemotactic factors
    - Cytokines
    - Lipid mediators
      - Arachidonic acid metabolites: LTC4,D4,E4 --> smooth muscle contraction; prostaglandins --> vasodilation
      - PAF - platelet activating factor
      - Acetylated glycerol ether phophocholine --> activates phagocytic cells, smooth muscle contraction
  - Eosinophils
    - Normal levels: 2 to 3% of total WBCs
    - Type 1 response: up to 10%

        - Secretory products
            - NADPH oxidase derived oxidants
            - Prostaglandins and leukotrienes (LTC4)
            - Major basic protein: cytotoxic
            - Cytokines
            - Others
    - Symptoms depends on tgt organ
        - Skin
            - Gross: swelling, wheal and flare
                - Early: preformed mediators
                - Late: synthesized mediators
            - LM: edema, eosinophils
            - EM: edema, endothelial cell gaps
        - Mucous and serous glands: increased secretion
        - Bronchial and GI smooth muscle contraction
    - Threapeutics
        - Avoid antigen
        - Mediator antagonists
            - Anti-histamines: receptor antagonist
            - Leukotriene inhibitors: lipase inhibitors, receptor antagonists
            - Fxnl: sympathetic stimulatants (EPI)
        - Inhibit mast cell degranulation: cromolyn
        - Non-specific anti-inflammatory agents: corticosteroids
        - Immunotherapy: "allergy shots"
    - Diagnosis
        - Skin tests: swell, wheal, flare (w/in mins) --> Type I hypersensitivity
        - RAST: bead w/ Ag + pt's serum + antihuman IgE --> if fluorescent --> allergic
        - RIST: bead + anti-human IgE + serum --> how much IgE
- Type II, Cytotoxic type
    - Involves binding of IgG to tgt cell and cytotoxic action/complement activation
    - Prototype disorders
        - Hemolytic rxns
        - Goodpastures syndrome
        - Myasthenia gravis
        - Grave's disease (hyperthyroidism)
    - Immune Mechanisms
        - IgG
        - Complement
        - Phagocytic cells
        - ADCC
    - Pathophysiology
        - Binding of antibody w/ cell membrane or tissue antigens
        - RBC membrane antigens - hemolytic anemias
            - Mother is Rh-
            - First baby is Rh+
            - Mother develops anti-Rh+ IgG
            - 2nd child is Rh+
            - IgG crosses placenta
            - Binds to RBC of fetus --> hemolysis
            - Treat by blocking sensitization of mother anti-D Ig w/in 72 hrs of first birth
        - Platelet antigens - thrombocytopenia cell membrane - petechiae
        - Basement membrane - goodpasture's syndrome (kidney, lung)
    - Mechanisms
        - Opsonin dependent phagocytosis

        - Complement dependent Ab lysis
        - Ab-dependent cell cytotoxicity
        - Examples
            - Goodpasture's: antigen is basement membrane of kidney and lung
            - Dermatitis herpetiformis: basement membrane reticulin
            - Bullous pemphigoid: epidermis basement membrane
            - Pemphigus vulgaris: epidermis keratinocyte membrane
        - N'phil, frustrated phagocytosis, extracellular enzyme release
    - Goodpasture's
        - Hemoptysis, pulmonary infiltrates, renal failure, anemia
        - Pathology
            - Circulating anti-GBM antibodies
            - LM: n'phils, hemorrhage
            - Immunofluoresence: Ig and complement deposition; linear
                - Linear antigen deposition --> Ab + complement deposition --> linear secondary anti-human Ab to IgG or complement contain fluorescent marker
            - EM: no electron dense deposits
        - Antibody binds to GBM --> complement --> C3b deposition + C3a/C5a --> PMN recruitment --> proteastes + ROS --> tissue injury
        - Lung: hemorrhage, hemoptysis, alveolar infiltrates
        - Kidney: proteinuria, hematuria, renal failure
    - Antibody binding to cell receptor (Type V rxns)
        - Grave's disease: IgG binds to TSH-R and stimulates cell to make T3/T4
        - Myasthenia Gravis: Ab to Ach-R at synapse blocks neuromuscular transmission --> muscle weakness
- Type III, Immune Complex Disease
    - Antibody binds to antigen and deposits on tissues
    - Protoype disorders
        - Post-strep glomerulonephritis
        - Vasculitis: polyarteritis nodosa
    - Immune mechanisms
        - Ab-Ag rxns
        - Complement
        - Neutrophils
        - Fibrin, hemorrhage
    - Pathophysiology
        - Ag-Ab complex deposits in tissues
        - Complement activation via IgG/IgM --> C5a
        - Monocyte/mphage activation --> cytokines
        - N'phil influx
        - Phagocytosis of immune complexes
        - Release of ROS and lysosomal enzymes
        - Tissue Injury (firbrinoid necrosis, hemorrhage, n'phils, Ab+complement deposition
        - LM: n'phils, hemorrhage, edema
        - EM: electron dense deposits
        - Granular immunofluorescene
    - Systemic Immune Complex Disease
        - Foreign antigen injected IV
        - Immune response w/ Ab prod (IgM, IgG)
        - Circulating immune complexes formed
        - Tissue deposition w/ complement fixation
        - Arteritis/glomeurolonephritis (w/ proteinuria)
    - Clinical
        - Depends on tgt organ and/or site of immune complex deposition

        - Synovium - RA
        - Kidney - glomerulus
            - Post-strep glomerulonephritis --> granular immunofluoresence
            - Systemic lupus erythematousus
        - Blood vessel walls - vasculitis
            - Polyarteritis nodosa
            - Early transplant rejection
        - Lung - hypersensitivity pneumonitis
    - Diagnosis
        - Skin tests for Type III rxns
        - Takes several hours to mainfest b/c requires complement fixation
    - Treatment
        - Elimination of antigen - tranfusion rxns, hypersensitivity lung rxns to foreign antigens, certain drug rxns
        - Corticosteroid and immunosuppressive therapy (cytoxan, cyclosporin, anti-TNFs)
        - Plasmapheresis - filtration of plasma antibodies
- Type IV, Cell-Mediated (Delayed) Hypersensitivity
    - Antigen binding to T cells causes m'phage activation and release of inflammatory mediators
    - Prototype Disorders
        - Poison Ivy, epidermal
            - Eczema
            - Infiltration of lymphocytes and later macrophages, edema
            - 1st contact sensitizes --> creation of T memory cells
            - 2nd contact --> T memory cells --> Th cells --> mphage activation --> dermatitis
        - Tuberculosis
            - Local hardening and swelling +/- fever
            - Infiltration of lymphocytes, monocytes and mphages
            - Intradermal injection used diagnostically, tuberculin, mycobacterial and leishmainial antigens
        - Granulomatous
            - 4 wk rxn time
            - Hardening in skin or lung
            - Granuloma containing epithelioid cells, giant cells, mphages; fibrosis +/- necrosis
            - Persistent Ag or Ag-Ab complexes in mphages or non-immunological
        - Cytotoxic T-Cells
    - Immune Mechanisms
        - T-lymphocytes
        - Monocytes/macrophages
    - Sensitization phase
        - Hapten enters and is taken up by Langerhans' cells in skin
        - Migrates to lymph node
        - Germinal center forms --> T cells proliferate
    - Contact hypersensitivity
        - Hapten enters and is carried to circulation
        - Binds to langerhans cel
        - CD8, Th1 cells activated
        - Macrophage activated
    - Granulomatous Inflammatory Rxns
        - APC-Th1 interaction --> IL-2 --> T cell proliferation
        - IL-3,6, IFN-γ, TNF --> mphage activation --> epithelioid cell --> TNF causes fusion to make giant cell
        - Mphages and lymphocytes surround antigen-antibody complexes to prevent spread
    - Skin Test takes 48-72 hours
- T-Cell Mediated Cytotoxicity

- Mechanisms
  - CD8+ T cell
  - Antigen expressed w/ class I MHC
  - IL-2 clonal expansion
  - Cytotoxic effector cell recognizes Ag+class I MHC
- Initiates programmed cell death
  - Perforins/cytolysins
  - Proteolytic enzymes: granzymes
  - FAS-induced apoptosis: CD8+ T cell:FAS ligand
  - Cytokines: IFNγ, TNFα/β