686-392 General Pathology
“Immunopathology”

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Content

- Immune cells
- Cytokines
- Major histocompatibility complex
- Hypersensitivity reactions
- Graft rejection
- Immune tolerance
- Autoimmune diseases
- Amyloidosis
Immune system

- Innate immunity
- Adaptive immunity

- Humoral immunity
- Cellular immunity
Blood cells

1 Neutrophil
2 Lymphocyte
3 Monocyte
4 Eosinophil
5 Basophil
T-lymphocyte

- 60-70% of lymphocytes in peripheral blood
- TCR:CD3 complex
- CD28 (binds costimulatory molecules CD80 or CD86 on APC)
- CD4+ cell (MHC II)
  - Th1: IL-2, IFN-γ (cell-mediated immunity)
  - Th2: IL-4, IL-5, IL-13 (B-cell activation)
- CD8+ cell (MHC I)
- CD4:CD8 ~ 2:1
B-lymphocyte

- 10-20% of lymphocytes in peripheral blood
- CD19, CD20
- MHC II, FcR, CD21 (receptor for complement, EBV)
- Differentiation to plasma cell and produce IgG, IgA, IgE (requires help from CD4+ T-cell)
Macrophage

- Antigen-presenting cell
- MHC class II
- Secrete IL-1, TNF-α

Dendritic cell
Natural killer cell

- 10-15% of lymphocytes in peripheral blood
- TCR-, CD3-
- Innate immune system
- Destroy virus, some tumor cells
- CD16, CD56
  - CD16 is FcR for IgG (ADCC)
- Produce IFN-γ (recruit T lymphocytes)
Immune response

(a) Antigen

APC (dendritic cell)

Co-stimulatory signal

$\rightarrow$

$T_H$ activation

Effectors + Memory $T_H$ cells

(b) Antigen

CD40:CD40L

B cell

Cytokines

$\rightarrow$

$T_H$ cell

(c)

$T_C$ cell

Altered self cell

$\rightarrow$

Memory $T_C$ cell

CTL

Killing

Lysis

Memory B cell

Plasma cell
Cytokines

- Mediate innate immunity: IL-1, TNF-α, IL-6, type 1 IFN
- Regulate lymphocyte proliferation and differentiation: IL-2, IL-4, IL-5, IL-12, IL-15
  - IL-10, TGF-β down regulate immune response
- Activate inflammatory cells (mostly produced from T cells): IFN-γ, TNF-α, TNF-β, migration inhibition factor
- Affect leukocyte movements (chemotaxis): IL-8, eotaxin, macrophage inflammatory protein-1α
- Stimulate hematopoiesis: colony-stimulating factors, IL-3, IL-7 (affect growth of lymphocyte progenitor cells)
Major Histocompatibility Complex

- MHC class I: HLA-A, HLA-B, HLA-C
  - Presence on all nucleated cells and platelets
- MHC class II: HLA-DP, HLA-DQ, HLA-DR
  - Presence on APC, B cell
- MHC class III: C2, C3, Bf
Major Histocompatibility Complex

- Organ transplantation
- Induction of immune response
- Regulation of immune response
- Disease association
  - HLA-B27 – ankylosing spondylitis
  - HLA-DR4 – rheumatoid arthritis
  - HLA-B12, B51, Cw7 – recurrence aphthous stomatitis
  - HLA-B5, B12, B27 – Behçet’s syndrome
Immediate (Type I) hypersensitivity

Antigen --- IgE --- IgE Fc receptor

Signals for activation of phospholipase A2

Signals for degranulation

Degranulation

Granule contents
- Histamine
- Proteases
- Chemotactic factors (ECF, NCF)

Secreted cytokines
Arachidonic acid
Leukotrienes
Prostaglandin

PAF

Primary mediators

Secondary mediators

Nucleus

Membrane phospholipids

Smooth muscle spasm

Edema

Leukocyte infiltration

Mucus secretion

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Arachidonic acid metabolites

Cell membrane phospholipids
- Phospholipases
  - Steroids inhibit

Arachidonic acid pathway:
- 5-Lipoxygenase
  - 5-HETE
  - LTB₄ (chemotaxis)
  - Vasoconstriction
  - Bronchospasm
  - Increased permeability
- 12-Lipoxygenase
  - LTC₄
  - LTD₄
  - LTE₄
  - Lipoxin A₄
  - Lipoxin B₄
  - Vasodilation
  - Inhibit neutrophil chemotaxis
  - Stimulate monocyte adhesion

Cyclooxygenase pathway:
- Prostaglandin G₂
  - Prostaglandin H₂
- Prostaglandin E₂ (PGD₂, PGE₂, PGF₂α)
  - Vasodilation
  - Potentiate edema
- Aspirin, indomethacin inhibit

Leukotriene A₄ (LTA₄)
- Leukotriene C₄ (LTC₄)
- Leukotriene D₄ (LTD₄)
- Leukotriene E₄ (LTE₄)

Prostacyclin, PGI₂
- Vasodilation
- Inhibits plt aggregation

Thromboxane A₂ (TXA₂)
- Thrombosis
- Promotes plt aggregation
Acute laryngeal edema caused by anaphylactic reaction to penicillin
Antibody-mediated (Type II) hypersensitivity

A. Opsonization and phagocytosis

1. Opsonized cell
2. Fc receptor
3. C3b receptor
4. Phagocyte
5. Phagocytosed cell
6. Complement activation
7. C3b
8. Phagocytosis

- Target cell + Ab
- Target cell + Complement
- Membrane attack complex
- Osmotic lysis
- C5-9
- C1423
- C3b
- Opsonization
- Fc receptor
- Macrophage
- Phagocytosis
Complement activation

**CLASSIC PATHWAY**

- Antigen-antibody (IgG or IgM) complex
- C1
- C4+C2
- C1 Activated C1

**Classic pathway**

- C3 convertase: C4b2a
- C3b
- C1
- Activated C1

**Alternative pathway**

- Microbial surfaces, Polysaccharides
- Mannose binding lectin
- Factor B, Factor D
- C3Bb

- Alternative pathway C3 convertase stabilized by properdin

**CLASSIC PATHWAY**

- C4b2a3b
- C5 convertase: C4b2a3b
- C5a
- C6 C7 C8 C9

**ALTERNATIVE PATHWAY**

- C5b
- C5-9
- Also generated via plasmin or lysosomal proteases
The membrane attack complex:

Intact *E. coli*

After incubation with complement
Antibody-mediated (Type II) hypersensitivity

B. Complement- and Fc receptor-mediated inflammation

- Fc receptor
- Complement activation
- Complement by-products (C5a, C3a)
- Neutrophil enzymes, reactive oxygen intermediates
- Inflammation and tissue injury

C. Antibody-mediated cellular dysfunction

- Antibody against TSH receptor
- Thyroid epithelial cell
- Thyroid hormones
- Antibody stimulates receptor without hormone

- Nerve ending
- Acetylcholine (ACh)
- Antibody to ACh receptor
- Antibody inhibits binding of neurotransmitter to receptor

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Goodpasture’s syndrome: this is the even linear pattern of immunofluorescence with antibody to IgG (autoantibody) which is directed against the entire glomerular basement membrane (linear pattern).

From: www-medlib.med.utah.edu/WebPath/

From: Robbins and Cotran Pathologic basis of disease. 7th ed.

sompid/immunopath50
Immune complex-mediated (Type III) hypersensitivity

**NEUTROPHIL AGGREGATION**
- Complement activation
- Platelet aggregation
- Activation of Hageman factor
- Chemotactic factors
- Anaphylatoxin generation
- Microthrombi formation
- Release of vasoactive amines
- Ischemia

**VASODILATATION AND EDEMA**
- Release of lysosomal enzymes and free radicals

**NECROSIS**

**PHASE I**
- Antigen in circulation
- Immune Complex Formation

**PHASE II**
- Immune Complex Deposition
- Antigen-antibody complex
- Plasma cell
- Free antibody

**PHASE III**
- Immune Complex-Mediated Inflammation
- Inflammatory cell
- Cytokines
- Neutrophil
- Complement
- Neutrophil lysosomal enzymes

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Hageman factor (XII)

Plasmin, Kallikrein → Collagen, basement membrane, activated plt

Prekallikerein activator (XIIa)

Prekallikrein → XIa

Kallikrein

Kininogen → Kinin

Vasodilation, Pain
Vasc. Permeability

Kininogen → Kallikrein

Kininogen

Kallikrein

Vasodilation, Pain
Vasc. Permeability

Acute inflammation

PARs

C3 → C3a

Fibrin split products

Vasc. Permeability, Chemotactic
Immune complex vasculitis

Vasculitis with fibrinoid necrosis
Cell-mediated (Type IV) hypersensitivity

- Delayed type hypersensitivity
  - Granulomatous inflammation
  - Type I DM, multiple sclerosis
  - Contact dermatitis
Delayed hypersensitivity in the skin

- Perivascular infiltration by T cells and mononuclear phagocytes
- Anti-CD4 antibodies
Formation of granuloma in cell-mediated (type IV) hypersensitivity

From: www-medlib.med.utah.edu/WebPath.html
Contact dermatitis: pre-sensitized lymphocytes led to this inflammatory reaction a couple of days after contact with the offending plant material (poison oak and poison ivy).

From: www-medlib.med.utah.edu/WebPath.html
Graft rejection

**DIRECT PATHWAY**
- Antigen-presenting cell in the graft
  - Class I MHC molecule
  - Class II MHC molecule

  - CD8
  - CD4

  - CD8+ CTLs
    - Increased vascular permeability and endothelial injury with thrombosis

  - CD8
    - Damage
      - RENAL TUBULE

**INDIRECT PATHWAY**
- Graft cells
- Recipient’s antigen-presenting cell

  - CD4
  - CD8

  - CD4+ helper T cells
    - Increased MHC
    - IFN-γ

  - CD4
  - Plasma cell
    - Antibodies
    - Endothelial injury

  - B lymphocyte
    - Graft antigen

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Hyperacute rejection of renal allograft: Preformed antibodies in the recipient's blood have attacked the endothelium in this transplanted kidney, leading to thrombosis with consequent widespread infarction of the renal cortex (note the characteristic pale appearance). The renal pelvis shows hemorrhagic infarction.

From: Robbins and Cotran Pathologic basis of disease. 7th ed.
Acute rejection of renal allograft: The cortex is thickened and pale tan due to an intense infiltrate of predominantly mononuclear cells. Compare with the previous image. The mononuclear inflammatory infiltrate on the right of the image represents acute cellular rejection. The thrombosed vessel and consequent infarction with typical coagulative necrosis are manifestations of acute humoral rejection.
Chronic rejection of renal allograft: The kidney is shrunken with a greyish irregular surface, indicating scarring. This is due predominantly to chronic vascular injury, resulting in atrophy and fibrosis of the renal parenchyma.

From: Robbins and Cotran Pathologic basis of disease. 7th ed.
Acute vascular rejection in heart transplant. The inflammatory reaction consists mostly of lymphocytes and is seen mainly around small arteries, a vasculitis.
By immunofluorescence, antibody to IgG is seen highlighting the vascular walls in this heart with acute vascular rejection.
Chronic vascular rejection in renal transplant: a renal biopsy shows marked interstitial fibrosis.

From: www-medlib.med.utah.edu/WebPath.html
The renal arteries with chronic vascular rejection are markedly thickened and fibrotic.
Acute cellular rejection in heart transplant: T-lymphocytes are identified by immunoperoxidase staining with antibody to CD3.
GVHD: Besides the icterus in this skin there is a fine scaling rash in this patient following bone marrow transplantation with a 5 out of 6 antigen match. An example of GHVD in which donor lymphocytes attack host tissues.
GVHD: There is vacuolization and dissolution of epidermal cells along the basal layer, along with lymphocytes. At the arrow is a rounded pink apoptotic body.
GVHD: marked cholestasis in the liver, seen here as large collections of yellow-green bile pigment in the bile canaliculi.

From: www-medlib.med.utah.edu/WebPath.html
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GVHD: there are yellow-brown collections of bile in the canaliculi, as well as chronic inflammatory cells within the liver parenchyma.
# Autoimmune disease

<table>
<thead>
<tr>
<th>Organ-Specific</th>
<th>Systemic</th>
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</thead>
<tbody>
<tr>
<td>Hashimoto thyroiditis</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Autoimmune atrophic gastritis of pernicious anemia</td>
<td>Sjögren syndrome</td>
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<td>Multiple sclerosis</td>
<td>Reiter syndrome</td>
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<tr>
<td>Autoimmune orchitis</td>
<td>Inflammatory myopathies*</td>
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<tr>
<td>Goodpasture syndrome</td>
<td>Systemic sclerosis (scleroderma)*</td>
</tr>
<tr>
<td>Autoimmune thrombocytopenia</td>
<td>Polyarteritis nodosa*</td>
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<tr>
<td>Insulin-dependent diabetes mellitus</td>
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<tr>
<td>Myasthenia gravis</td>
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<tr>
<td>Graves disease</td>
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<td>Primary biliary cirrhosis*</td>
<td></td>
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<tr>
<td>Autoimmune (chronic active) hepatitis*</td>
<td></td>
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<tr>
<td>Ulcerative colitis*</td>
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</tbody>
</table>

*The evidence supporting an autoimmune basis of these disorders is not strong.

From: Robbins and Cotran Pathologic basis of disease. 7th ed.
Mechanisms of autoimmune diseases
Systemic lupus erythematosus (SLE)

• Causes: unknown
  – Genetic predisposition
  – Exogenous factors: drug (procainamide, hydralazine, isoniazid, D-penicillamine), UV, hormone (estrogen)
• Failure to maintain self tolerance with activation of B cell
• Tissue damage caused by immune complex (type 3 hypersensitivity) and antibody-mediated injury (type 2 hypersensitivity)
**SLE:** malar/butterfly rash over the face, the rashes are made worse by sun exposure.
LE cell test: the pink blobs are denatured nuclei (here are two). One is seen being phagocytozed in the center by a PMN. This test is not nearly as sensitive as the ANA which has supplanted the LE cell test. Therefore, NEVER order an LE cell test.
ANA test: homogenous or diffuse, rim or peripheral, speckled, and nucleolar pattern.
ANA test: double stranded DNA. These little Crithidia organisms have a small kinetoplast between the nucleus and the flagella which glows bright green under immunofluorescence microscopy, and is indicative of anti-native DNA antibody that is very specific for SLE.
Skin biopsy: the region of rash reveals liquefactive necrosis of the basal layer at the dermal-epidermal junction along with dermal chronic inflammatory cell infiltrates (often perivascular) and extravasation of red blood cells (purpura) leading to the visible rash.
Skin biopsy: the region of rash reveals liquefactive necrosis of the basal layer at the dermal-epidermal junction along with edema.

Immunofluorescence: IgG deposits along the dermal-epidermal junction.
Immunofluorescence of skin with antibody to IgG shows a band-like deposition of immune complexes that is bright green at the dermal epidermal junction in this skin biopsy taken from an area with a visible rash. With SLE such deposition can be found in skin uninvolved by a rash, whereas with DLE the immune complexes are found only in involved skin.

From: www-medlib.med.utah.edu/WebPath.html
sompid/immunopath50
SLE: Vasculitis with chronic inflammatory cells

From: www.medlib.med.utah.edu/WebPath.html
sompid/immunopath50
SLE: shown here is Libman Sacks endocarditis in which there are many flat, reddish-tan vegetations spreading over the mitral valve and chordae.
Lupus nephritis in SLE: a glomerulus with thickened pink capillary loops, the so-called “wire loops”. The surrounding renal tubules are unremarkable.
A granular pattern of immunofluorescence in the glomerulus with antibody to IgG, indicative of deposition of immune complexes in the basement membranes of the glomerular capillary loops (lumpy-bumpy pattern).

From: www-medlib.med.utah.edu/WebPath.html
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Granular pattern of immunofluorescence in the glomerulus with antibody to C1q complement, which is more specific for SLE

From: www-medlib.med.utah.edu/WebPath.html
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**SLE**: the thickened basement membrane (arrow) that results from immune complex deposition in the glomerular capillary loop is prominent in this electron micrograph.

From: www-medlib.med.utah.edu/WebPath.html

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Rheumatoid arthritis

- Autoimmune disease
- A chronic systemic inflammatory disorder that may affect many tissues and organs, but principally attacks the joints, producing a nonsuppurative proliferative and inflammatory synovitis that often progresses to destruction of the articular cartilage and ankylosis of the joints.
Immunopathogenesis of rheumatoid arthritis

- Antigen (? microbe)
- MHC Class II (genetic susceptibility)
- CD4+ T cells
- Cytokines
- B-cell activation
- Formation of rheumatoid factor
- Immune complex formation and deposition
- Joint injury
- Fibroblasts
- Chondrocytes
- Synovial cells
- Release of collagenase, stromelysin, elastase, PGE\(_2\), and other enzymes
- Proliferation
- Expression of adhesion molecules
- Accumulation of inflammatory cells
- Pannus formation; destruction of bone, cartilage; fibrosis; ankylosis
• Associated with MHC Class II
• HLA-DR4 (risk 4-6 times)
• Rheumatoid factor (RF) – most IgM
• Autoantibody to Fc portion of IgG
• Positive 60-90% of RA, SLE, SS
Rheumatoid arthritis
Sjögren syndrome

- Dry eyes and dry mouth resulting from immune mediated lacrimal and salivary gland destruction (lymphocytic infiltration and fibrosis)
- 40% occur in isolation (primary form)
- 60% occur in association with other autoimmune diseases (secondary form)
Sjögren syndrome

- 75% of patients have RF
- 50-80% of patients have ANAs
  - Ribonucleoprotein antigens: SS-A and SS-B
- HLA-B8, HLA-DR3, DRW52 related with primary SS
- Commonly in older women, ages 50-60 y
- 40 times risk of developing lymphoid malignancies esp. NHL (marginal zone lymphoma)
Sjögren syndrome: the mononuclear inflammatory infiltrates, interstitial fibrosis, and acinar atrophy of a minor salivary gland in a biopsy of lip is typical for long-standing Sjögren syndrome.

From: Neville Damm Allen Bouquot. Oral & Maxillofacial Pathology, 2nd ed.
Systemic sclerosis

- Abnormal accumulation of fibrous tissue in the skin and multiple organs
- Excessive fibrosis triggered from abnormal immune responses and vascular damage
- Diffuse vs Limited scleroderma
- CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia)
  - Anticentromere antibody
A patient demonstrating the taut and shiny skin typical of sclerodactyly. The skin becomes inelastic and it is hard to move the fingers.

From: www-medlib.med.utah.edu/WebPath.html
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A higher magnification of the taut, shiny, inelastic skin with sclerodactyly. Note also the cheilosis at the corners of the mouth from riboflavin deficiency as a result of the malabsorption that can occur with scleroderma.
A, Normal skin. B, Skin biopsy from a patient with systemic sclerosis. Note the extensive deposition of dense collagen in the dermis with virtual absence of appendages (e.g. hair follicles) and foci of inflammation (arrow).
At low magnification, the collagen of the dermis is increased. Chronic inflammatory cells are sparse with systemic sclerosis, unlike SLE.
At high magnification, the dermis is expanded by dense collagenous fibrosis in a patient with systemic sclerosis. Immunofluorescence is not helpful with scleroderma.

From: www-medlib.med.utah.edu/WebPath.html
sompid/immunopath50
This trichrome stain of the stomach demonstrates intense blue staining in the submucosa from the collagen deposition. Such fibrosis can occur anywhere in the GI tract, but is most common in the lower esophagus, leading to the esophageal dysmotility with systemic sclerosis.
Renal disease suggests diffuse scleroderma in this patient with hyperplastic arteriolosclerosis and malignant hypertension (blood pressure 300/150 mm Hg)
Immunologic deficiency syndrome

• Primary immunodeficiencies – genetic
Immunologic deficiency syndrome

- Secondary immunodeficiencies – arise as complications of infections; malnutrition; aging; or side effects of immunosuppression, irradiation, or chemotherapy for cancer and other autoimmune diseases.
Amyloidosis

- Primary amyloidosis – association with some immunocyte dyscrasia, multiple myeloma
- Secondary amyloidosis – occurs as a complication of an underlying chronic inflammatory or tissue destructive process
- Hereditary or familial amyloidosis
Amyloidosis is characterized by slow deposition over years of increasing amounts of an amorphous proteinaceous material in one or more tissues. Seen here in the heart between the darker red myofibers are pale pink amyloid deposits.

From: www-medlib.med.utah.edu/WebPath.html
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With conge red stain and observed under polarized light, the amyloid has a characteristic “apple green’ birefringence as seen here in a deposit around an artery in the heart.
By electron micrograph, amyloid is composed of a “beta-pleated sheet” of fibrils, seen here as irregular grey material. When the amyloid protein is made up of immunoglobulin light chains, then it is “AL amyloid” and when it is derived from serum amyloid-associated protein, then it is “AA amyloid.” In terms of the effect upon the organs, “amyloid is amyloid”.

From: www-medlib.med.utah.edu/WebPath.html
sompid/immunopath50
This is the immunofluorescent appearance of the myocardium with antibody to lambda light chain. Thus, this is “AL amyloid”.

From: www-medlib.med.utah.edu/WebPath.html

sompid/immunopath50
References


- www-medlib.med.utah.edu/WebPath/TUTORIAL/TUTORIAL.html