UNIT 2
Acute and Chronic Inflammation

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Lecturer
Assigned Reading

• Chapter 2, “Acute and Chronic Inflammation” in Robbins’ Basic Pathology, Sixth Edition, pages 25 - 46
Introduction

• Injurious stimuli cause a protective vascular connective tissue reaction called “inflammation”
  – Dilute
  – Destroy
  – Isolate
  – Initiate repair

• Acute and chronic forms
Acute inflammation

- Immediate and early response to tissue injury (physical, chemical, microbiologic, etc.)
  - Vasodilation
  - Vascular leakage and edema
  - Leukocyte emigration (mostly PMNs)
Vasodilation

• Brief arteriolar vasoconstriction followed by vasodilation
  – Accounts for warmth and redness
  – Opens microvascular beds
  – Increased intravascular pressure causes an early transudate (protein-poor filtrate of plasma) into interstitium (vascular permeability still not increased yet)
Vascular leakage

- Vascular permeability (leakiness) commences
  - Transudate gives way to exudate (protein-rich)
  - Increases interstitial osmotic pressure contributing to edema (water and ions)
Vascular leakage

- Five mechanisms known to cause vascular leakiness
  - Histamines, bradykinins, leukotrienes cause an early, brief (15 – 30 min.) immediate transient response in the form of endothelial cell contraction that widens intercellular gaps of venules (not arterioles, capillaries)
Vascular leakage

– Cytokine mediators (TNF, IL-1) induce *endothelial cell junction retraction* through cytoskeleton reorganization (4 – 6 hrs post injury, lasting 24 hrs or more)

– Severe injuries may cause immediate *direct endothelial cell damage* (necrosis, detachment) making them leaky until they are repaired (*immediate sustained response*), or may cause delayed damage as in thermal or UV injury,
Vascular leakage

– (cont’d) or some bacterial toxins (*delayed prolonged leakage*)

– Marginating and endothelial cell-adherent leukocytes may pile-up and damage the endothelium through activation and release of toxic oxygen radicals and proteolytic enzymes (*leukocyte-dependent endothelial cell injury*) making the vessel leaky
Vascular leakage

- Certain mediators (VEGF) may cause increased transcytosis via intracellular vesicles which travel from the luminal to basement membrane surface of the endothelial cell.

• All or any combination of these events may occur in response to a given stimulus.
Leukocyte cellular events

• Leukocytes leave the vasculature routinely through the following sequence of events:
  – Margination and rolling
  – Adhesion and transmigration
  – Chemotaxis and activation
• They are then free to participate in:
  – Phagocytosis and degranulation
  – Leukocyte-induced tissue injury
Margination and Rolling

• With increased vascular permeability, fluid leaves the vessel causing leukocytes to settle-out of the central flow column and “marginate” along the endothelial surface
• Endothelial cells and leukocytes have complementary surface adhesion molecules which briefly stick and release causing the leukocyte to roll along the endothelium like a tumbleweed until it eventually comes to a stop as mutual adhesion reaches a peak
Margination and Rolling

• Early rolling adhesion mediated by selectin family:
  – E-selectin (endothelium), P-selectin (platelets, endothelium), L-selectin (leukocytes) bind other surface molecules (i.e., CD34, Sialyl-Lewis X-modified GP) that are upregulated on endothelium by cytokines (TNF, IL-1) at injury sites
Adhesion

• Rolling comes to a stop and adhesion results
• Other sets of adhesion molecules participate:
  – Endothelial: ICAM-1, VCAM-1
  – Leukocyte: LFA-1, Mac-1, VLA-4
  (ICAM-1 binds LFA-1/Mac-1, VCAM-1 binds VLA-4)
• Ordinarily down-regulated or in an inactive conformation, but inflammation alters this
Transmigration (diapedesis)

- Occurs after firm adhesion within the systemic venules and pulmonary capillaries via PECAM-1 (CD31)
- Must then cross basement membrane
  - Collagenases
  - Integrins
Transmigration (diapedesis)

- Early in inflammatory response mostly PMNs, but as cytokine and chemotactic signals change with progression of inflammatory response, alteration of endothelial cell adhesion molecule expression activates other populations of leukocytes to adhere (monocytes, lymphocytes, etc).
Chemotaxis

- Leukocytes follow chemical gradient to site of injury (chemotaxis)
  - Soluble bacterial products
  - Complement components (C5a)
  - Cytokines (chemokine family e.g., IL-8)
  - LTB₄ (AA metabolite)
- Chemotactic agents bind surface receptors inducing calcium mobilization and assembly of cytoskeletal contractile elements
Chemotaxis and Activation

• **Leukocytes:**
  – extend pseudopods with overlying surface adhesion molecules (integrins) that bind ECM during chemotaxis
  – undergo activation:
    • Prepare AA metabolites from phospholipids
    • Prepare for degranulation and release of lysosomal enzymes (oxidative burst)
    • Regulate leukocyte adhesion molecule affinity as needed
Phagocytosis and Degranulation

• Once at site of injury, leukocytes:
  – Recognize and attach
  – Engulf (form phagocytic vacuole)
  – Kill (degrade)
Recognition and Binding

- Opsonized by serum complement, immunoglobulin (C3b, Fc portion of IgG)
- Corresponding receptors on leukocytes (FcR, CR1, 2, 3) leads to binding
Phagocytosis and Degranulation

• Triggers an oxidative burst (next slide) engulfment and formation of vacuole which fuses with lysosomal granule membrane (phagolysosome)
• Granules discharge within phagolysosome and extracellularly (degranulation)
Oxidative burst

- Reactive oxygen species formed through oxidative burst that includes:
  - Increased oxygen consumption
  - Glycogenolysis
  - Increased glucose oxidation
  - Formation of superoxide ion

- $2O_2 + \text{NADPH} \rightarrow 2O_2^{-\text{rad}} + \text{NADP}^+ + H^+$
  - (NADPH oxidase)

- $O_2 + 2H^+ \rightarrow H_2O_2$ (dismutase)
Reactive oxygen species

- Hydrogen peroxide alone insufficient
- MPO (azurophilic granules) converts hydrogen peroxide to HOCl⁻ (in presence of Cl⁻), an oxidant/antimicrobial agent
- Therefore, PMNs can kill by halogenation, or lipid/protein peroxidation
Degradation and Clean-up

- Reactive end-products only active within phagolysosome
- Hydrogen peroxide broken down to water and oxygen by catalase
- Dead microorganisms degraded by lysosomal acid hydrolases
Leukocyte granules

- Other antimicrobials in leukocyte granules:
  - Bactericidal permeability increasing protein (BPI)
  - Lysozyme
  - Lactoferrin
  - Defensins (punch holes in membranes)
Leukocyte-induced tissue injury

• Destructive enzymes may enter extracellular space in event of:
  – Premature degranulation
  – Frustrated phagocytosis (large, flat)
  – Membranolytic substances (urate crystals)
  – Persistent leukocyte activation (RA, emphysema)
Defects of leukocyte function

- Defects of adhesion:
  - LFA-1 and Mac-1 subunit defects lead to impaired adhesion (LAD-1)
  - Absence of sialyl-Lewis X, and defect in E- and P-selectin sugar epitopes (LAD-2)

- Defects of chemotaxis/phagocytosis:
  - Microtubule assembly defect leads to impaired locomotion and lysosomal degranulation (Chediak-Higashi Syndrome)
Defects of leukocyte function

• Defects of microbicidal activity:
  – Deficiency of NADPH oxidase that generates superoxide, therefore no oxygen-dependent killing mechanism (chronic granulomatous disease)
Chemical mediators

• Plasma-derived:
  – Complement, kinins, coagulation factors
  – Many in “pro-form” requiring activation (enzymatic cleavage)

• Cell-derived:
  – Preformed, sequestered and released (mast cell histamine)
  – Synthesized as needed (prostaglandin)
Chemical mediators

- May or may not utilize a specific cell surface receptor for activity
- May also signal target cells to release other effector molecules that either amplify or inhibit initial response (regulation)
- Are tightly regulated:
  - Quickly decay (AA metabolites), are inactivated enzymatically (kininase), or are scavenged (antioxidants)
Specific mediators

• Vasoactive amines
  – Histamine: vasodilation and venular endothelial cell contraction, junctional widening; released by mast cells, basophils, platelets in response to injury (trauma, heat), immune reactions (IgE-mast cell FcR), anaphylatoxins (C3a, C5a fragments), cytokines (IL-1, IL-8), neuropeptides, leukocyte-derived histamine-releasing peptides
Specific mediators

- Serotonin: vasodilatory effects similar to those of histamine; platelet dense-body granules; release triggered by platelet aggregation

- Plasma proteases
  - Clotting system
  - Complement
  - Kinins
Clotting cascade

- Cascade of plasma proteases
  - Hageman factor (factor XII)
  - Collagen, basement membrane, activated platelets converts XII to XIIa (active form)
  - Ultimately converts soluble fibrinogen to insoluble fibrin clot
  - Factor XIIa simultaneously activates the “brakes” through the fibrinolytic system to prevent continuous clot propagation
Kinin system

• Leads to formation of bradykinin from cleavage of precursor (HMWK)
  – Vascular permeability
  – Arteriolar dilation
  – Non-vascular smooth muscle contraction (e.g., bronchial smooth muscle)
  – Causes pain
  – Rapidly inactivated (kininases)
Complement system

- Components C1-C9 present in inactive form
  - Activated via classic (C1) or alternative (C3) pathways to generate MAC (C5 – C9) that punch holes in microbe membranes
  - In acute inflammation
    - Vasodilation, vascular permeability, mast cell degranulation (C3a, C5a)
    - Leukocyte chemotaxin, increases integrin avidity (C5a)
    - As an opsonin, increases phagocytosis (C3b, C3bi)
Specific Mediators

• Arachidonic acid metabolites (eicosanoids)
  - Prostaglandins and thromboxane: via cyclooxygenase pathway; cause vasodilation and prolong edema; but also protective (gastric mucosa); COX blocked by aspirin and NSAIDS
Specific Mediators

- Leukotrienes: via lipoxygenase pathway; are chemotaxins, vasoconstrictors, cause increased vascular permeability, and bronchospasm

- PAF (platelet activating factor)
  - Derived also from cell membrane phospholipid, causes vasodilation, increased vascular permeability, increases leukocyte adhesion (integrin conformation)
More specific mediators

- **Cytokines**
  - Protein cell products that act as a message to other cells, telling them how to behave.
  - IL-1, TNF-α and -β, IFN-γ are especially important in inflammation.
  - Increase endothelial cell adhesion molecule expression, activation and aggregation of PMNs, etc., etc., etc.
Specific mediators

• **Nitric Oxide**
  – short-acting soluble free-radical gas with many functions
  – Produced by endothelial cells, macrophages, causes:
    • Vascular smooth muscle relaxation and vasodilation
    • Kills microbes in activated macrophages
    • Counteracts platelet adhesion, aggregation, and degranulation
Specific mediators

• Lysosomal components
  – Leak from PMNs and macrophages after demise, attempts at phagocytosis, etc.
  – Acid proteases (only active within lysosomes).
  – Neutral proteases such as elastase and collagenase are destructive in ECM.
  – Counteracted by serum and ECM anti-proteases.
Possible outcomes of acute inflammation

• Complete resolution
  – Little tissue damage
  – Capable of regeneration

• Scarring (fibrosis)
  – In tissues unable to regenerate
  – Excessive fibrin deposition organized into fibrous tissue
Outcomes (cont’d)

• Abscess formation occurs with some bacterial or fungal infections
• Progression to chronic inflammation (next)
Chronic inflammation

- Lymphocyte, macrophage, plasma cell (mononuclear cell) infiltration
- Tissue destruction by inflammatory cells
- Attempts at repair with fibrosis and angiogenesis (new vessel formation)
- When acute phase cannot be resolved
  - Persistent injury or infection (ulcer, TB)
  - Prolonged toxic agent exposure (silica)
  - Autoimmune disease states (RA, SLE)
The Players (mononuclear phagocyte system)

• Macrophages
  – Scattered all over (microglia, Kupffer cells, sinus histiocytes, alveolar macrophages, etc.
  – Circulate as monocytes and reach site of injury within 24 – 48 hrs and transform
  – Become activated by T cell-derived cytokines, endotoxins, and other products of inflammation
The Players

- **T and B lymphocytes**
  - Antigen-activated (via macrophages and dendritic cells)
  - Release macrophage-activating cytokines (in turn, macrophages release lymphocyte-activating cytokines until inflammatory stimulus is removed)

- **Plasma cells**
  - Terminally differentiated B cells
The Players

- Produce antibodies

• Eosinophils
  - Found especially at sites of parasitic infection, or at allergic (IgE-mediated) sites
Granulomatous Inflammation

- Clusters of T cell-activated macrophages, which engulf and surround indigestible foreign bodies (mycobacteria, *H. capsulatum*, silica, suture material)
- Resemble squamous cells, therefore called “epithelioid” granulomas
Lymph Nodes and Lymphatics

- Lymphatics drain tissues
  - Flow increased in inflammation
  - Antigen to the lymph node
  - Toxins, infectious agents also to the node
    - Lymphadenitis, lymphangitis
    - Usually contained there, otherwise bacteremia ensues
    - Tissue-resident macrophages must then prevent overwhelming infection
Patterns of acute and chronic inflammation

• Serous
  – Watery, protein-poor effusion (e.g., blister)

• Fibrinous
  – Fibrin accumulation
  – Either entirely removed or becomes fibrotic

• Suppurative
  – Presence of pus (pyogenic staph spp.)
  – Often walled-off if persistent
Patterns (cont’d)

• Ulceration
  – Necrotic and eroded epithelial surface
  – Underlying acute and chronic inflammation
  – Trauma, toxins, vascular insufficiency
Systemic effects

• Fever
  – One of the easily recognized cytokine-mediated (esp. IL-1, IL-6, TNF) acute-phase reactions including
    • Anorexia
    • Skeletal muscle protein degradation
    • Hypotension

• Leukocytosis
  – Elevated white blood cell count
Systemic effects (cont’d)

– Bacterial infection (neutrophilia)
– Parasitic infection (eosinophilia)
– Viral infection (lymphocytosis)
Injury

Acute inflammation

Chronic inflammation

Resolution

Repair

Abscess
“Inflame” – to set fire.

Inflammation is “A dynamic response of vascularised tissue to injury.”

It is a protective response.

It serves to bring defense & healing mechanisms to the site of injury.
What is Inflammation?

- A reaction of a **living tissue** & its **micro-circulation** to a pathogenic insult.

- A defense mechanism for survival.
• Reaction of tissues to injury, characterized **clinically**
by: heat, swelling, redness, pain, and loss of function.

• **Pathologically** by: vasoconstriction followed by
  vasodilatation, stasis, hyperemia, accumulation of
  leukocytes, exudation of fluid, and deposition of fibrin.
How Does It Occur?

- The vascular & cellular responses of inflammation are mediated by chemical factors (derived from blood plasma or some cells) & triggered by inflammatory stimulus.

- Tissue injury or death ---> Release mediators
Etiologies

- Microbial infections: bacterial, viral, fungal, etc.
- Physical agents: burns, trauma—like cuts, radiation
- Chemicals: drugs, toxins, or caustic substances like battery acid.
- Immunologic reactions: rheumatoid arthritis.
Cardinal Signs of Inflammation

- Redness: Hyperaemia.
- Warm: Hyperaemia.
- Pain: Nerve, Chemical mediators.
- Swelling: Exudation
- Loss of Function: Pain
• Time course
  – Acute inflammation: Less than 48 hours
  – Chronic inflammation: Greater than 48 hours (weeks, months, years)

• Cell type
  – Acute inflammation: Neutrophils
  – Chronic inflammation: Mononuclear cells (Macrophages, Lymphocytes, Plasma cells).
Pathogenesis: Three main processes occur at the site of inflammation, due to the release of chemical mediators:

- Increased blood flow (redness and warmth).
- Increased vascular permeability (swelling, pain & loss of function).
- Leukocytic Infiltration.
Changes in vascular flow (hemodynamic changes)

- **Slowing of the circulation**
  - outpouring of albumin rich fluid into the extravascular tissues results in the concentration of RBCs in small vessels and increased viscosity of blood.

- **Leukocyte margination**
  - Neutrophils become oriented at the periphery of vessels and start to stick.
Time scale

- Variable
  - minor damage---- 15-30 minutes
  - severe damage---- a few minutes
Lymphatics in inflammation:

- Lymphatics are responsible for draining edema.

**Edema**: An excess of fluid in the interstitial tissue or serous cavities; either a *transudate* or an *exudate*.
Transudate:

• An ultrafiltrate of blood plasma
  – permeability of endothelium is usually normal.
  – low protein content (mostly albumin)
Exudate:

- A filtrate of blood plasma mixed with inflammatory cells and cellular debris.
  - permeability of endothelium is usually altered
  - high protein content.
Pus:

- A purulent exudate: an inflammatory exudate rich in leukocytes (mostly neutrophils) and parenchymal cell debris.
Leukocyte exudation

- Divided into 4 steps
  - Margination, rolling, and adhesion to endothelium
  - Diapedesis (trans-migration across the endothelium)
  - Migration toward a chemotactic stimuli from the source of tissue injury.
  - Phagocytosis
MARGINATION
Phagocytosis

- 3 distinct steps
  - Recognition and attachment
  - Engulfment
  - Killing or degradation
Defects in leukocyte function:

- Margination and adhesion
  - steroids, leukocyte adhesion deficiency
- Emigration toward a chemotactic stimulus
  - drugs
  - chemotaxis inhibitors
- Phagocytosis
  - Chronic granulomatous disease (CGD)
Inflammation Outcome

Injury

Acute Inflammation

Abscess

Ulcer

Fistula

Sinus

Resolutio

Fibrosis/Scar

Chronic Inflammation

Fungus

Virus

Cancers

T.B. etc.
Chemical Mediators:

Chemical substances synthesised or released and mediate the changes in inflammation.

- **Histamine** by mast cells - vasodilatation.

- **Prostaglandins** – Cause pain & fever.

- **Bradykinin** - Causes pain.
Morphologic types of acute inflammation

- **Exudative** or catarrhal Inflammation: excess fluid.
  
  TB lung.

- **Fibrinous** – pneumonia – fibrin

- **Membranous** (fibrino-necrotic) inflammation

- **Suppuration/Purulent** – Bacterial - neutrophils
- Serous – excess clear fluid – Heart, lung
- Allergic inflammation
- Haemorrhagic – b.v. damage - anthrax.
- Necrotising inflammation.
Acute inflammation has one of four outcomes:

- Abscess formation
- Progression to chronic inflammation
- Resolution—tissue goes back to normal
- Repair—healing by scarring or fibrosis
Abscess formation:

• "A localized collection of pus (suppurative inflammation) appearing in an acute or chronic infection, and associated with tissue destruction, and swelling."
- **Site:** skin, subcutaneous tissue, internal organs like brain, lung, liver, kidney, ......

- **Pathogenesis:** the necrotic tissue is surrounded by pyogenic membrane, which is formed by fibrin and help in localize the infection.
Carbuncle

- It is an extensive form of abscess in which pus is present in multiple loci open at the surface by sinuses.

- Occur in the back of the neck and the scalp.
Furuncle or boil

- It is a small abscess related to hair follicles or sebaceous glands, could be multiple furunclosis.
Cellulitis

- It is an acute diffuse suppurative inflammation caused by streptococci, which secrete hyaluronidase & streptokinase enzymes that dissolve the ground substances and facilitate the spread of infection.

- Sites:
  - Areolar tissue; orbit, pelvis, …
  - Lax subcutaneous tissue