Inflammation
and
Introduction to Wound Healing

Approved

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Objectives

- Understand basic concepts of acute, chronic, and granulomatous inflammation
- Recognize key leukocytes participating in inflammatory responses
- Distinguish acute, chronic, and granulomatous inflammation
What is Inflammation?

- Response to injury (including infection)
- Reaction of blood vessels leads to:
  - Accumulation of fluid and leukocytes in extravascular tissues
- Destroys, dilutes, or walls off the injurious agent
- Initiates the repair process
What is Inflammation?

- Fundamentally a protective response
- May be potentially harmful
  - Hypersensitivity reactions to insect bites, drugs, contrast media in radiology
  - Chronic diseases: arthritis, atherosclerosis
  - Disfiguring scars, visceral adhesions

He told a story of a woman in her 40s given penicillin by a nurse even though her penicillin allergy was written in her chart. Med errors can be fatal, people! Maybe electronic records can help fix this...
What is Inflammation?

- Components of inflammatory response
  - Vascular reaction
  - Cellular reaction
- How: Chemical mediators
  - Derived from plasma proteins
  - Derived from cells inside and outside of blood vessels
Historical Highlights

- Celsus, a first century A.D. Roman, listed four cardinal signs of acute inflammation:
  - **Rubor** (erythema [redness]): vasodilatation, increased blood flow
  - **Tumor** (swelling): extravascular accumulation of fluid
  - **Calor** (heat): vasodilatation, increased blood flow
  - **Dolor** (pain)
Types of Inflammation

- **Acute inflammation**
  - Short duration
  - Edema
  - Mainly neutrophils

- **Chronic inflammation**
  - Longer duration
  - Lymphocytes & macrophages predominate
  - Fibrosis
  - New blood vessels (angiogenesis)
Types of Inflammation

- Granulomatous inflammation
  - Distinctive pattern of chronic inflammation
  - Activated macrophages (epithelioid cells) predominate
  - +/- Multinucleated giant cells
Acute Inflammation

• Three major components:
  » Increase in blood flow (redness & warmth)
  » Edema results from increased hydrostatic pressure (vasodilation) and lowered intravascular osmotic pressure (protein leakage)
  » Leukocytes emigrate from microcirculation and accumulate in the focus of injury

• Stimuli: infections, trauma, physical or chemical agents, foreign bodies, immune reactions
Neutrophil Morphology

- Hallmark: multilobulated nuclei with light pink cytoplasm
- Bright pink granular cytoplasm
Mechanisms of Increased Vascular Permeability - 1

Gaps due to endothelial contraction

- Venules
- Vasoactive mediators (histamine, leukotrienes, etc.)
- Most common
- Fast and short-lived (minutes)

think allergic rxn

Figure 2-4 Robbins and Cotran Pathologic Basis of Disease, 7th Ed.
Mechanisms of Increased Vascular Permeability - 2

Direct injury

- Arterioles, capillaries, and venules
- Toxins, burns, chemicals
- Fast and may be long-lived (hours to days)

To the vessel wall (i.e. stick a knife into you)

e.g. if a vein is cut (cut a major artery and you bleed out faster, not long-lived)
Mechanisms of Increased Vascular Permeability - 3

Leukocyte-dependent injury

- Mostly venules
- Pulmonary capillaries
- Late response
- Long-lived (hours)
Mechanisms of Increased Vascular Permeability - 4

Increased transcytosis

- Venules
- Vascular endothelium-derived growth factor

Less imp component of increased vascular permeability

pinocytic vesicles form and move across cell and leak fluid
Most tissues and diseases exhibit increased vascular permeability. In the eye, diabetic retinopathy results in angiogenesis and extravasation of blood cells. This mechanism is also important in macular degeneration.
A. NORMAL

- Leukocytes
- Plasma proteins
- Endothelium

B. RETRACTION OF ENDOTHELIAL CELLS

- Occurs mainly in venules
- Induced by histamine, NO, other mediators
- Rapid and short-lived (minutes)

C. ENDOTHELIAL INJURY

- Occurs in arterioles, capillaries, venules
- Caused by burns, some microbial toxins
- Rapid; may be long-lived (hours to days)

D. LEUKOCYTE-MEDIATED VASCULAR INJURY

- Occurs in venules, pulmonary capillaries
- Associated with late stages of inflammation
- Long-lived (hours)

E. INCREASED TRANSCYTOSIS

- Occurs in venules
- Induced by VEGF
Leukocyte Extravasation

• **Extravasation**: delivery of leukocytes from the vessel lumen to the interstitium
  » In the lumen: margination, rolling, and adhesion
  » Migration across the endothelium (**diapedesis**)
  » Migration in the interstitial tissue (**chemotaxis**)

• Leukocytes ingest offending agents (**phagocytosis**), kill microbes, and degrade necrotic tissue and foreign antigens

• There is a balance between the helpful and harmful effects of extravasated leukocytes
Leukocyte Margination

Photomicrograph courtesy of Dr. James G. Lewis

neutrophils with polymorphic nuclei moving to vessel wall

in heart after MI
Leukocyte Diapedesis

Photomicrograph courtesy of Dr. James G. Lewis
Leukocyte Adhesion

- Leukocyte adhesion and migration across vessel wall determined largely by binding of complementary adhesion molecules on the leukocyte and endothelial surfaces.

- Chemical mediators affect these processes by modulating the expression or avidity of the adhesion molecule.

big word for binding properties
Sequence of Leukocyte Emigration

- Neutrophils predominate during the first 6 to 24 hours
- Monocytes in 24 to 48 hours
- Induction/activation of different adhesion molecule pairs and specific chemotactic factors in different phases of inflammation
Sequence of Events - Injury

Shows sequence described in last slide. Neutrophils become apparent at 12 hrs and peak at around day 1. By day 2 we start to get monocyte presence.

Adapted from Robbins and Cotran Pathologic Basis of Disease, 7th Ed.
Sequence of Events

Figure 2-8 Robbins and Cotran Pathologic Basis of Disease, 7th Ed.
Neutrophils go up early, like in injury, but they PERSIST this time b/c they must fight infectious agent.

Sequence of Events - Infection

Edema    Neutrophils    Monocytes / Macrophages

Lymphocytes / Plasma Cells

Amount

Days

1  2  3  4  5  6  7

Proia©/DUMC 24
Outcomes of Acute Inflammation

- Complete resolution
  - with mild injury to cells that have the capacity to enter the cell cycle - e.g. first degree burn

- Abscess formation

- Fibrosis
  - After substantial tissue destruction
  - In tissues that do not regenerate - i.e. the heart
  - After abundant fibrin exudation, especially in serous cavities (pleura, peritoneum)

- Chronic inflammation
Figure 2-21 Robbins and Cotran Pathologic Basis of Disease, 7th Ed.
Morphologic Patterns of Acute Inflammation

- **Serous inflammation**: Outpouring of thin fluid (serous effusion, blisters)
- **Fibrinous inflammation**: Body cavities; leakage of fibrin; may lead to scar tissue (adhesions)
- **Suppurative (purulent) inflammation**: Pus or purulent exudate (neutrophils, debris, edema fluid); abscess: localized collections of pus
- **Ulcers**: Local defect of the surface of an organ or tissue produced by the sloughing (shedding) of inflammatory necrotic tissue
Fibrinous Pericarditis

green due to jaundice
Fibrinous Pericarditis

due to lupus in pt
Fibrinous Pleuritis

pink lamellar architecture on surface -- typical of fibrin on surface of serous cavity
Abscess

so many neutrophils!

dead cells, debris
Gastric Ulcer

lost mucosa. stomach eroded down into submucosa
Gastric Ulcer

this area shown in high-res on next slide
Gastric Ulcer

reactive b/c it's starting to heal
cells proliferating to try to cover the ulcer as appear bluer

normal stomach epithelium
Gastric Ulcer

Typical Appearance. Ulcer that is trying to heal but is not completely successful.

- Neutrophils on surface
- Fiber & necrotic debris at base of ulcer
Systemic Manifestations

- **Endocrine and metabolic**
  - Secretion of acute phase proteins by the liver
  - Increased production of glucocorticoids (stress response)
  - Decreased secretion of vasopressin leads to reduced volume of body fluid to be warmed

- **Fever**
  - Improves efficiency of leukocyte killing
  - Impairs replication of many offending organisms
Systemic Manifestations

● Autonomic
  » Redirection of blood flow from skin to deep vascular beds minimizes heat loss
  » Increased pulse and blood pressure
  » Decreased sweating

● Behavioral
  » Shivering (rigors), chills (search for warmth), anorexia (loss of appetite), somnolence, and malaise
Systemic Manifestations

- **Leukocytosis**: increased leukocyte count in the blood
  - Neutrophilia: bacterial infections
  - Lymphocytosis: infectious mononucleosis, mumps, measles
  - Eosinophilia: Parasites, asthma, hay fever

- **Leukopenia**: reduced leukocyte count
  - Typhoid fever, some viruses, rickettsiae, protozoa
Chronic Inflammation

- Inflammation of prolonged duration (weeks or months)
  - Active inflammation, tissue destruction, and attempts at repair are proceeding simultaneously

- May follow acute inflammation or begin insidiously and often asymptotically
  - Persistent infections, exposure to toxic agents such as silica (silicosis), or by autoimmunity

i.e. in arthritis
Chronic Inflammation

- Persistent infections
  - *Treponema pallidum* [syphilis], viruses, fungi, parasites

- Exposure to toxic agents
  - Exogenous: silica (silicosis)
  - Endogenous: toxic plasma lipid components (atherosclerosis)

- Autoimmunity
  - Rheumatoid arthritis, systemic lupus erythematosus
Chronic Inflammation

● Histological features
  » Infiltration with mononuclear cells
     (macrophages, lymphocytes, and plasma cells)
  » Tissue destruction
     (induced by the inflammatory cells)
  » Healing by replacement of damaged tissue by
     connective tissue (fibrosis)
     and new blood vessels (angiogenesis)
Chronic Inflammatory Cells

- **Macrophages**: large, irregular nuclei that stain paler than lymphocyte nuclei.
- **Lymphocytes**: dark nuclei, round.

*Hard to ID. Use process of elim -- it's not a neutrophil or leukocyte, it's an inflammatory response -- think macrophage. Big cells with large, irregular nuclei that stain paler than do lymphocyte nuclei.*
Chronic Inflammation

in orbit

all fibrosis

inflammatory cells
Chronic Inflammation

lymphocyte, no neutrophils

macrophage
Macrophages

- Monocytes begin to emigrate into tissues early in inflammation where they transform into the larger phagocytic cell known as the macrophage.
- Macrophages predominate by 48 hours
  - Recruitment (circulating monocytes); division; immobilization
- Activation results in secretion of biologically active products
Figure 2-28
Robbins and Cotran
Pathologic Basis of Disease, 7th Ed.
Circulating monocyte → Adherent → Emigrating → Tissue macrophage

Immune response: Activated T cell
- Microbes, cytokine (IFN-γ)
  - IL-4, other cytokines
  - Activated macrophages

**INFLAMMATION AND TISSUE INJURY**
- Reactive oxygen and nitrogen species
- Proteases
- Cytokines, including chemokines
- Coagulation factors
- AA metabolites

**REPAIR**
- Growth factors (PDGF, FGF, TGFβ)
- Fibrogenic cytokines
- Angiogenic factors (FGF)
- “Remodelling” collagenesis
Macrophages

brown pigment = melanin that had been released from iris and are being engulfed by macrophages. Clue that the other cells are actually macrophages b/c "macrophages like to eat"

adhering to the back of the cornea here
Other Cells in Chronic Inflammation

- Lymphocytes
  » Produce inflammatory mediators
  » Participate in cell-mediated immune reactions
  » Plasma cells produce antibody
  » Lymphocytes and macrophages interact in a bi-directional fashion
Chronic Inflammatory Cells

- Plasma cells: nucleus pushed to side of cell, pink/blue cytoplasm. This is more typical to see.
- Russell bodies: swollen with pink protein which are antibodies. Unusual to see.
Other Cells in Chronic Inflammation

- **Eosinophils**
  - Immune reactions mediated by IgE (i.e. allergies)
  - Parasitic infections
    - Eosinophil granules contain a protein that is toxic to parasites
- **Mast cells**
  - Release mediators (histamine) and cytokines
Eosinophil Morphology

very bright pink granular cytoplasm. Nucleus can appear to have 1 or 2 lobes
Chronic Cellulitis

Usually eosinophils are seen in chronic inflammation when it happens in the gallbladder, abdomen.
Granulomatous Inflammation

- Distinctive pattern of chronic inflammation
  - Predominant cell type is an activated macrophage with a modified epithelial-like (epithelioid) appearance
  - Giant cells may or may not be present

- **Granuloma:**
  Focal area of granulomatous inflammation

Easiest type to ID
Granulomatous Inflammation

- **Foreign body granulomas:**
  Form when foreign material is too large to be engulfed by a single macrophage

- **Immune granulomas:**
  Insoluble or poorly soluble particles elicit a cell-mediated immune response
Granulomatous Response to Suture

multinucleate giant cell trying to eat suture that is w/in this giant cell
Aspiration Pneumonia

piece of food stuck in giant cell

other giant granuloma cell
Ruptured Dermoid Cyst

Keratin escapes and elicits granulomatous immune response

ex of epithelioid macrophage
Ruptured Dermoid Cyst
Sarcoidosis

granuloma
Sarcoidosis - Lacrimal Gland

granulomas circled
Sarcoidosis - Lacrimal Gland

macrophages fused together to form synctitium. Don't see cell borders here -- This is a typical of granulomatous response