Inappropriate inflammatory response (with no foreign substances to remove) is the basis of autoimmune inflammation.

Inflammatory process must be tightly regulated by the immune system to avoid excessive tissue damage and spillover to normal tissue.
What is Acute Inflammation?

- The reaction of vascularized tissue to injury
- The culmination of a tightly regulated, complex series of interactions between:
  - Pathogen/Injury
  - Host inflammatory cells
  - Complement and coagulation cascades
  - Chemokines and cytokines
- The end game?
  - Neutralization of the injuring agent and allowing repair (healing)
- A potentially harmful process
  - Components of inflammation that kill microbes may also injure normal tissue in the process

Acute Inflammation

- Immediate tissue reaction characterized by accumulation of:
  - Fluid
  - Plasma proteins
  - Innate immune cells
- The intensity of the response is determined by:
  - The stimulus
  - Duration of the stimulus
  - Genetics of the host local factors
  - Medical interventions

Causes of Inflammation

- Infections (bacterial, viral, fungal, parasitic)
  - Mild to fatal
- Tissue necrosis (ischemia, thermal injury, etc.)
- Foreign bodies (splinters, dirt, sutures)
- Immune reactions (hypersensitivity)
Recognition by the Innate Immune System

- DAMPS/PAMPs activate TLRs and other recognition receptors on monocytes
- This forms the INFLAMMASOME:
  - A multi-protein complex characterized by activation of CASPASE 1
  - Cleavage of IL-1 to an active form sets the inflammatory cytokines in action

A multi-phase cellular inflammatory sequence ensues......
The Critical Components...

- Vascular
  - Regulated by cytokines, chemokines and other inflammatory mediators
  - Logic: expedite innate responses to the offending agent
- Nitric oxide mediated vasodilatation increases flow and increased vascular permeability
- Plasma proteins like complement and antibodies access extracellular space
- Cytokine/chemokine induced endothelial changes allow innate cells access to the inflammatory site

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(1) Vascular dilation and increased blood flow (causing erythema and warmth)
(2) Extravasation of plasma fluid and proteins (edema)
(3) Leukocyte (mainly neutrophil) emigration and accumulation
Gap formation in monolayers of porcine endothelial cells induced by the combination of antibody and complement.
How do PMNs move from a blood vessel to point of injury?

- **Chemotaxis**
- Unidirectional movement along a chemical gradient
  - Bacterial peptides
  - Complement components, esp. C5a
  - The pro-inflammatory cytokine tetrad
- The chemoattractants activate membrane receptors on the innate cells that then activate cytoskeleton (actin is critical) changes that move the cell along the gradient to the site of inflammatory stimulus
Phase 2

NEUTROPHIL DEGRANULATION
PROMOTES MONOCYTE CHEMOTAXIS

Phase 3

APOPTOTIC NEUTROPHILS
INHIBITS
“FIND ME” CYTOKINES, ETC
ATTRACT SCAVENGERS

FACT: Smoking inhibits the neutrophil turn off signal

Modified from original image by JOHN A. ROBINSON

Sequence of Cell Traffic

Ischemic necrosis of myocardium
A. Early (neutrophilic) infiltrates and congested blood vessels.
B. Later (mononuclear) cellular infiltrates.
White cells during acute inflammation

- Rheologic: increased delivery of cells/unit time increases the chance that a leucocyte can respond to a signal
- Cytokine signals from the responding cells at the site induce changes in the endothelium
- This in turn regulates families of receptors that coax innate inflammatory cells across the endothelial lining to undergo:
  - Margination
  - Adhesion
  - Transmigration
- The vast majority of responding cells are neutrophils

Neutrophils, PMNs, “Polys”

- Most numerous leukocyte in circulation
- Signature cell of acute inflammation
- Marrow capable of rapid production and release
- Half life if ~12’ in blood, 1-2” at inflammatory site

Neutrophils are Rapid Responders

- Cytokines and growth factors → the marrow → more cells!
- Marrow responds by pushing mature & slightly immature but functional PMNs out early and in vast amounts
- The clinical correlate of this is elevated leucocyte counts and the presence of young cells that are called “bands”
- Common clinical parlance is “left shift” or bandemia”
Neutrophils at the Site of Injury

- Phagocytosis:
  - Series of complex steps that leads to death/neutralization of the danger signal

- Recognition/attachment:
  - Antibody & C3b coating bind the pathogen to FcR and C3bR

- Engulfment/degranulation:
  - Formation of the phagolysosome

- Killing/degradation:
  - Oxidative burst that generates killing molecules

- NETs (neutrophil extracellular traps):
  - Chromatin spray to the outside of the cell to trap bacteria and fungi

Oxidative Burst and Killing

- Killing/degradation
  - Degranulation
  - Oxidative burst
  - Activation of NADPH generated H2O2
  - Lysosomal enzymes donate MPO
  - MPO + halide = HOCl
Neutrophils Extracellular Traps (NETs)

- PMN sacrifices its nucleus by casting its chromatin laden with killer granules out of the cell as a net to trap bacteria and fungi

Sequence of Cell Traffic

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Monocytes/Macrophages

- Monocytes, largest leukocyte in blood, circulate for ~16 hours
- Can have granules, large golgi and indented nucleus
- Exit into tissue where they become tissue histiocytes
- Some home to specific organs and take up residence as ‘fixed’
Phase IV

Control of Acute Inflammation

- Control is highly dependent on macrophages
- When the inflammatory stimulus is destroyed or neutralized, acute inflammation subsides:
  - No TLR or phagocytic receptor activation leads to:
    - Decreased pro-inflammatory mediator synthesis and release
    - Macrophages sense this as they clean up dying neutrophils
    - Now the predominant cytokines are TGF-β & IL-10
  - The "anti-inflammatory" cytokines establish the correct milieu for appropriate healing and wound repair

Possible Outcomes of Acute Inflammation

- Resolution and repair with restoration of normal tissue architecture
- Transition to chronic inflammation – (next lecture)
Morphology of Acute Inflammation

- Least severe: SEROUS
  - Protein poor transudate from capillary to a space - peritoneal, pericardial or pleural. Known clinically as a transudate

- Intermediate: FIBRINOUS
  - Fluid with larger molecules dominated by fibrinogen which converts to fibrin and potential scarring

- Severe: SUPPURATIVE/ABSCESS
  - Protein rich fluid with inflammatory cells, alive and dead necrotic debris. Known clinically when in a body space as an exudate

- Special category: ULCERATIVE
  - Underlying inflammation cause excavation of a mucosal or skin surface
Serous Inflammation

Low-power view of a cross-section of a skin blister showing the epidermis (E) separated from the dermis (D) by a focal collection of serous effusion (SE).

Fibrinous Inflammation

Fibrinous pericarditis. A, Deposits of fibrin on the pericardium. B, A pink meshwork of fibrin exudate (F) overlies the pericardial surface (P).

Purulent Inflammation

Ulcerative Inflammation

A. Chronic duodenal ulcer

B. Low-power cross-section of a duodenal ulcer crater with an acute inflammatory exudate in the base

Questions?
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