General Pathology

Basic Principles of Cellular and Organ Pathology

Inflammation - I

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Inflammation I - table of contents

- Definition
- Classifications (sense, time view...)
- Causes
- Macroscopy features
- Phases of inflammatory response
- Pathogenesis of inflammation
  - hyperemia
  - inflammatory mediators
  - immune response
- Cells in inflammation
- Systemic inflammatory response
- Inflammation development
Inflammation

Definition:
complex reaction of organism to damage

(aim: homeostasis maintenance)
Inflammation

Sense

defensive  — agent elimination

reparative  — damage reparation
Inflammation - Classification:

**Time view**

- **acute** (days)
- **subacute** (weeks)
- **chronic** (months-years)
Inflammation - Classification:

Causes:

- nonliving
  - physical
  - chemical

- living
  - viral
  - bacterial
  - mycotic
  - parasitic

AUTOIMMUNE
Inflammation

Celsius´ features:

- rubor
- tumor
- calor
- dolor
- functio laesa

Aulus Cornelius Celsus
25 BC – 50 AD;

De Medicina

Galenos, Sydenham, Virchow?
Erysipelas
Laryngitis haemorrhagica et pseudomembranosa
Phases of Inflammatory Response

- alteration
- exsudation
- proliferation
Meningitis purulenta
Colitis pseudomembranosa
Cholelithiasis. Empyema vesicae felleae chronicum.
Phases of Inflammatory Response

- Alteration
- Exsudation
- Proliferation
Phases of Inflammatory Response

- Alteration
- Exsudation
- Proliferation
Vascular Changes in Inflammation

- Flux hyperemia - axonal reflex
- Peristatic hyperemia
- Stasis
- Increased permeability - exsudation
- Inflammatory edema
The reflex arc of **axon reflex** has neither an integration center nor any synapse

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Active Hyperemia

- vasodilatation
- slowing of the circulation
- increased microvasculature permeability – leakage

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- leucocyte emigration
Mast Cell ruling the process

- **Degranulation** (immediate response)
  - histamine-vasodilation-permeability-exsudation
  - neutrophil chemotactic factor (micro)fagocytosis
  - eosinophil chemotactic factor - modulation of the vascular effect

- **Synthesis** (long-term response)
  - leukotriens (SRS-A) - vasodilation-permeability-exsudation
  - prostaglandins - vasodilation-permeability-exsudation - PAIN
Active Hyperemia

- vasodilatation

leakage

Chemical mediators:

**Cells:** histamine, serotonin, catecholamines, lysosomal enzymes

**Plasma:** complement, kinin system, coagulation/fibrinolysis system
Active Hyperemia

- vasodilatation
  - slowing of the circulation
  - increased microvasculature permeability - leakage

- leucocyte emigration

chemotaxis:
  - soluble bact. products
  - complement components esp. C5a
  - products of lipoxygenase pathway of arachidonic acid (esp. leukotriene B4)
axial flow
quiet capillary
vasoconstriction
vasodilation
flux hyperemia
peristatic hyperemia
increased permeability
endothelium swelling
increased permeability
erthro- & leucocytodiape desis
Main Inflammatory Mediators

Vasodilation: prostaglandins, NO
Permeability: vasoactive amines, C3, C5, bradykinin
Chemotaxis: C5a, bacterial products, leucotriens, cytokins
Fever: interleukin 1, 6, TNF, prostaglandins
Pain: prostaglandins, bradykinin
Tissue damage: lysosomal enzymes...
Acne conglobata

Alteration
Exsudation
Proliferation

Acne conglobata
Mechanisms and Morphological Features of Immune Reaction
Mechanisms of Immune Response

- nonspecific
- antigen specific
  - humoral
  - cellular
Barriers
Mechanisms of Immune Response

- nonspecific
  - PHAGOCYTOSIS
  - bactericidal substances (*lysozyme*)
  - complement
  - interferon
  - proteins distinguishing general microbial structures
Complement proteins C2-C9

Chemotactic fragments C3a, C5a

Antibody

Lytic pore C5-C9

Bacterium
Superficial phagocyte membrane

Phagocytosis & Opsonisation

Superficial lectins

Fc receptors of antibodies

1. Particle
2. Particle
3. Particle
4. Particle
“Natural” antibodies starting the immune response
Cytokines

*Def.*:

polypeptides and proteins - regulatory molecules participating by autocrine, paracrine & endocrine function in homeostasis maintenance
Cytokines

Source:
- macrophages
- APC
- T-lympho

Types:
- growth fcs.
- colony stim. fcs.
- chemokins (interleukins)
- TNFα, TNF β – LT
- interferons
Zhang X, Mosser DM.

Macrophage activation by endogenous danger signals.

Most microbes have Pathogen Associated Molecular Patterns (PAMPS) that are recognized by macrophages and trigger this activation response.

Interleukin 4

- Th$_2$ stimulation – antibody mediated immune response
- Th$_1$ + interferon γ suppression
- Inhibition of the T-lymphocytes proliferation
- Inhibition of TNF α + IL6 secretion
Mechanisms of Immune Response

- antigen specific
  - humoral B– lymphocytes
  - cellular T– lymphocytes

INTERACTION

B-lympho–\(T_h\) – affinity maturation – plasmocyte
NK-cell, macrophage, neutrophil, heparinocyte

antibodies

FC receptors
virus
Il-2 receptor
mature T\textsubscript{c} clone creation
cytotoxic vesicules
infected cell
cytotoxic vesicules injection
APC
MHC II
ICAM-1
CD8
CD28
IL-2 receptor
LFA-1
IL-1
MHC I
B7
T\textsubscript{H}

TCR
LFA-1
CD8
CD28
IL-1 receptor
intercellular adhesion molecule-1
interleukin-1
interleukin-2
major histocompatibility complex
intercellular adhesion molecule-1
lymphocyte function-associated antigen-1
CD4
Granzyme B

Apoptosis
Macrophage activation

IFN-γ is secreted by T lymphocytes and NK cells.

INF-γ is secreted by T lymphocytes and NK cells

cytokins & bactericid subst. secretion

activated macrophage
Inflammatory cells

- neutrophile granulocytes
- eosinophil granulocytes
- basophil granulocytes & heparinocytes
- lymphocytes & plasmocytes
- monocytes – macrophages
- erythrocytes
- platelets
Heparinocytes

- IgE receptors
- Mediators production (heparin, histamin, serototnin, catecholamins…)
- Cytokinin production IL4, TNF α
- Chemotactic factors for neutrophils & eosinophils
Heparinocytus
Heparinocyte Degranulation

IgE receptors

antigen
Heparinocytes
Heparinocyte degranulation

- **physical**
  - heat, mech., UV light, x-rays
- **chemical**
  - venoms, enzymes
- **immune**
  - IgE binding, complement
Neutrophilic granulocytes

- **pavementing** *(selectins, integrins)*
- **emigration** *(chemotactic factors from bacteria, complement 3a, 5a, kinins, histamin*.....)
- **fagocytosis** *(both non specific without opsonisation and specific IgG + compl.*)
Neutrophilic granulocytes

- ingestion & digestion of bacteria
- H$_2$O$_2$ & myeloperoxidase
- lysozyme - mucopeptide digestion

DEATH in a few hours

- elastase, colagenase
- plasminogen activator
- complement activation

- neutrophil extracellular traps - NETs
Neutrophil (polymorphonuclear) granulocyte
Neutrophil (polymorphonuclear) granulocyte
NG disorders

- migration & chemotaxis
  - lazy leucocytes syndrome
  - diabetes (locomotion)
  - Chédiak - Higashi syndrome (bacteria killing, lack of elastase, locomotion)
  - β2-integrin defect (adhaesion)

- locomotion
  - serum changes
  - corticoids
  - phenylbutazone
NG disorders

- **phagocytosis**
  - opsonins & IgG in sickle cell anaemia
  - morphin abusers
  - lysosom fusion (corticoids, antimalaric drugs, CH-H sy...)

- **bactericid effect**
  - chronic granulomatosis in children
    - cytochrom oxidase & $H_2O_2$ defects
    - recurences of staphylococcus and aspergillus infection
Eosinophilic Granulocytes

- allergic response
- IgA receptors
- anti parasites defence
- peroxidase, histamininase, acid phophatase, cytokins
Mechanisms of Immune Response

- antigen specific
  - cellular  T- lymphocytes

APC – CD8+ precursors – $T_h, T_c$
Programmed Cell Death in the Normal Thymus

Immature T-Lymphocyte (recognizes self)

CD3

"self-antigen"

dendritic antigen-presenting cell at cortico-medullary junction

T-cell death by apoptosis
Inflammatory cells

- neutrophile granulocytes
- eosinophil granulocytes
- basophil granulocytes & heparinocytes
- lymphocytes & plasmocytes
- monocytes – macrophages
- erythrocytes
- platelets
Macrophage
Macrophages - Function

- phagocytosis
- bacteria killing
- mediators production
- antigen processing & presentation
- modulation of fibroblast proliferation – IL-1
- modulation of endothelia proliferation – TNFα
Macrophages - secretion

- acid & neutral proteases
- cytokins IL-1, TNF
- $O_2$, NO
- complement components
Granuloma lipophagicum
Sinus pilonides
Giant cells - I

- Foreign body giant cell
- Langhans giant cell
- Touton giant cell
- Capillary
- Epulis giant cell
- Aschoff giant cell
- Megakaryocyte
Giant cells - II

Hodgkin-cell

Reed-Sternberg giant cell

Osteoclasts

Placental giant cell

Tumor giant cells
Megakaryocytes & Platelets
Thrombocytes

- mediators production
  - vasoactive substances, thrombosis, mesenchymal cell proliferation
  - granules: serotonin, ADP, acid phosphatase, thromboxan, Ca cationic protein...
Collagen fibres creation

1. Amino acids including glycine, proline & lysine
2. Assembly and hydroxylation of polypeptide (procollagen) chain with terminal segments
3. Association of procollagen chains through terminal segments
4. Assembly of three procollagen chains into one procollagen molecule with helical conformation
5. Passage of procollagen molecules to extracellular space, & subsequent removal of terminal segments to leave tropocollagen
6. Aggregation of tropocollagen to form collagen fibrils
7. Aggregation of collagen fibrils to form collagen fibres & fasciculi of fibres
Collagen fibres
Systemic Inflammatory Response

- lymphatic tissue activation
- fever – IL 1, prostaglandins
- leucocytosis
- lymphocytosis in viral infections
- eosinophilia in parasitic diseases
Inflammation Development

No – death

Complete resolution - ad integrum
  vessel permeability normalized
  migration stopped
  necrosis resorption
  tissue regeneration

Healing with a defect - per defectum
  regeneration impossible – extensive necrosis
  granulation tissue – scar

Progression towards a chronic inflammation
Thank You