From Rubor and Calor to today: An Update on Inflammation

Susan J. Leclaire, Ph.D, CLS(NCA)
Chancellor Professor Emerita
Department of Medical Laboratory Science
University of Massachusetts
Dartmouth, Massachusetts
Inflammation

First Century C.E.
Greeks first described inflammation
Rubor – Calor – Dolor – Tumor
redness  heat  pain  swelling

Second Century
Romans – not to be outdone added
Loss of function
Inflammation

Normal    Necessary   Non-specific
mechanism of response

Primarily a localized process
but can become systemic

Combination of cells and mediators
Causes

◆ anything and everything that will alter the homeostasis of an area
Inflammation at the visible level

- Acute nerve reflex response
- starts within seconds
- causes immediate vasoconstriction
- helps to limit damage
- divides into afferent (dilation) and efferent (constriction)
Inflammation at the visible level

Acute vascular response

- starts within seconds and last for up to 20 minutes
- vasodilation = more blood to the area
  REDNESS
Inflammation at the visible level

Vascular flare

- scratch the skin ~ blanches
- FLARE
  - Enlarged arterioles ~ redness
Inflammation at the visible level

Acute Nerve Reflex Response

- Increased vessel permeability

- WHEAL
  localized swelling due to plasma leakage

- SWELLING
Inflammation at the visible level

**Acute Cellular Response**
- hours to day
- Leukocytes: granulocytes and monocytes
- Platelets and/or fibrin formation
- swelling
Inflammation at the visible level

Combination of increased intravascular blood cell and extravascular fluid accumulation

pressure causes heat
Inflammation at the visible level

Combination of red cell increase, swelling, pressure increase, and damaged tissue

pain
Inflammation at the cellular level

Granulocytes

Diapedesis/chemotaxis
Inflammation at the Cellular level

Glycoproteins
mannose, galactose, fucose and maybe glucose
Bind to neuraminimic aid (sialic acid)residues
Made in the liver
Induced by Interleukin -1
Inflammation at the Cellular level

**L-Selectins and Adhesion molecules**

- Tether granulocytes to site
- Regulates T lymph activity
  1. Low expression - recognition
  2. High expression - increased transcription and surface protein communication
  3. Return to low - memory acquisition
Inflammation at the Cellular level

GlyCan-1
Glycosylation-dependent cell adhesion molecule-1

Found in lymph node endothelial cells

Binds to L-Selectins to stimulate T lymphs
Inflammation at the Cellular level

**E-Selectins**

Bind to neutrophils, monocytes, eosinophils, memory-effector T-like lymphocytes, and natural killer cells

Includes Lewis A and Lewis X
Inflammation at the cellular level

P-Selectins

Found on activated endothelial cells

Bind to neutrophils, monocytes, eosinophils

Stimulated by IL-4 and IL-13
Inflammation at the Cellular level

**CD34**

Cell surface glycoprotein

Enhances individual cell migration and cell-to-cell adhesion
Inflammation at the Cellular level

Various cell adhesion compounds cause granulocytes to engage in tight adhesion to blood vessel endothelial wall.
Inflammation at the Cellular level

Various cell adhesion compounds cause granulocytes to engage in tight adhesion to blood vessel endothelial wall.
Inflammation at the Cellular level

Diapedesis/chemotaxis

Chemoattractants – too many to list
Inflammation at the Cellular level

Diapedesis/chemotaxis

ICAM-1

cell surface glycoprotein
expressed on endothelial cells

binds to granulocytes, Fibrinogen and Factor X
Inflammation at the Cellular level

Diapedesis/chemotaxis

PECAM-1

platelets, monocytes, neutrophils,

makes up a large portion of endothelial intercellular junctions

leukocyte transmigration, angiogenesis, and integrin activation
Inflammation at the Cellular level
Inflammation at both visible and cellular level

Granulocytes accumulation

Dead and dying cells (pus) attract monocytes
Inflammation at the invisible level

First phase – inflammation

- PMN activation
  - Neutrophil recruitment
  - IL-6 receptor shedding
  - Local acute inflammatory response
  - Environmental
  - Chemoattractants recruit neutrophils

Second phase – prolonged inflammation

- Mononuclear shift
  - IL-6
  - sIL-6R complex
  - Monocyte recruitment
  - MCP-1

Autoantigen

Promotion of neutrophilic apoptosis

Macrophage phagocytosis

gp130 mediated trans-signaling

gp130

JAKs

Umass Dartmouth
Elimination prior to repair

Removal of dead/dying cells occurs prior to replacement with newer cells

Prime time for re-injury

Inappropriate replacement = scarring
Acute vs chronic

Chronic Inflammation

• The result of a balance between continuing tissue damage on the one hand and eradication of the damaging stimulus followed by healing and scar formation on the other
  – If the damaging stimulus eradicated or neutralized then further tissue necrosis does not occur and the repair response progresses to complete scarring
  – If the damaging stimulus cannot be eradicated or neutralized the balance between tissue damage and tissue repair is maintained in a stalemate and thus chronic inflammation will persist, often for years
Continuation of Inflammation

Granulocytes transmit inflammation by releasing ASC specks (Apoptosis-associated Speck protein with a Caspase Recruitment domain)

bacteria-sized clumps of protein key for cytokine maturation
The release of the pro-inflammatory cytokines IL-1β and IL-18 in their mature/active forms is dependent upon the proteolytic cleavage of their precursors pro-IL-1β and pro-IL-18 by active Caspase-1. Caspase-1 itself must be cleaved from its precursor (pro-Caspase-1) by the inflammasome, a multimeric protein complex. This process is dependent upon 2 distinct signals. The first signal is the action of agonists on the TLR receptors, an example of this being LPS, leading to NFκB activation and formation of the IL-1β precursor finally driving the activation of the inflammasome. The second signal is the dependent on the activation of the ATP-dependent P2X7 purinoceptor, a ligand-gated ion channel, leading to K+ efflux driving the activation of the inflammasome.
Continuation of Inflammation

ASC specks accumulate outside the cells at the same time the cells were undergoing pyroptosis, a strategic form of cell death that allows infected cells to kill themselves.
Protein aggregates are components of inflammasomes, which sense pathogens and cell damage and set off innate immune inflammation.
CONtinuation of Inflammation

ASC specks stimulate IL1-β extracellularly. Macrophages ingest the ASC specks from the extracellular space.
CONtinuation of Inflammation

Macrophages can take up released ASC specks, perpetuating the immune response.
ASC specks activate macrophage inflammasomes, restarting the whole process and multiplying inflammation.
Atherosclerosis

Monocytes migrating into the intima

Arterial Lumen

VCAM-1

Intima

Monocyte differentiated to a macrophage

Foam Cell

LDL being taken up by macrophage

Dying macrophage

Apoptotic bodies

Tissue factor

Lipid droplets

M-CSF

ROS

Cytokines

MMPs
Chronic Inflammation Can Lead To...

- Pulmonary diseases
- Diabetes II
- Autoimmune diseases
- Arthritis
- Cancer
- Cardiovascular diseases
- Alzheimer
- Neurological diseases
We have

erythrocyte sedimentation rate

valid only if inflammation is present for more than ~1 week

valid as comparison only – not the specific value but the delta from the last time and the time before
We have Cross-Reactive Protein

reflects acute stages of inflammation
limited associations with physical performance
is associated with mortality risk
We have Interleukin 6

controls the transition from acute to chronic inflammation by changing from polymorphonuclear neutrophils to monocyte/macrophages.

exerts stimulatory effects on T- and B-cells, thus favoring chronic inflammatory responses.
We have

**Serum Amyloid**

is positively associated with chronic inflammation
such as *Chronic Heart Disease*

is lowered with anti-cholesterol medication use
We have

- Individual cytokine release
- Multiplex cytokine profiling
- Superoxide release
- Neutrophil elastase assay
- Cyclic nucleotide accumulation
- Gene expression profiling
- Cytotoxicity assays

BUT expensive and time consuming

ELISAs, Western blots and micro-arrays, real-time PCR, cell cytometry, manual patch clamping and specific activity assays
We will (eventually) have

Soluble adhesion molecules

E-selectin,
P-selectin,
intracellular adhesion molecule-1,
vascular cell adhesion molecule-1

Cytokines

interleukin-1β, -6, -8, and -10
tumor necrosis factor-α