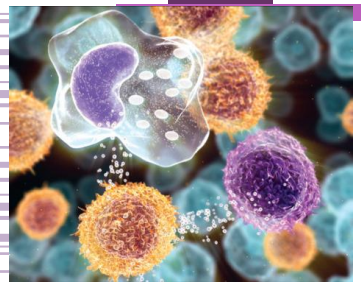

From Rubor and Calor to today:

An Update on Inflammation

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Department of Medical Laboratory Science
University of Massachusetts
Dartmouth, Massachusetts

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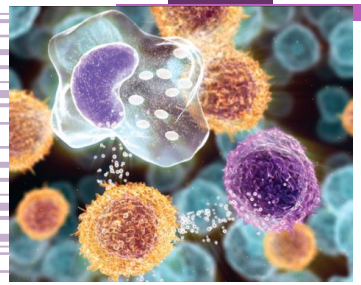

Inflammation

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

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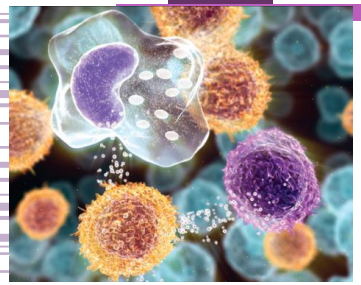
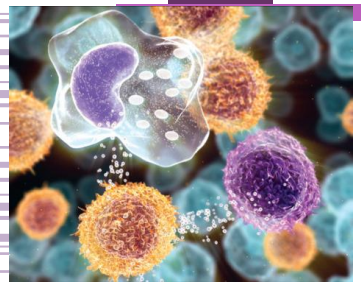


Inflammation

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

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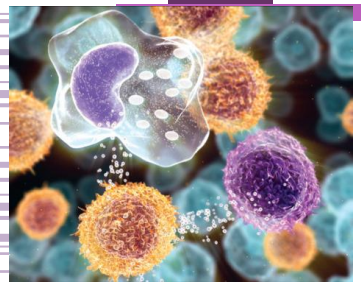

Inflammation at the visible level

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

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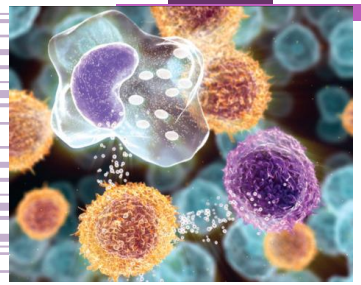
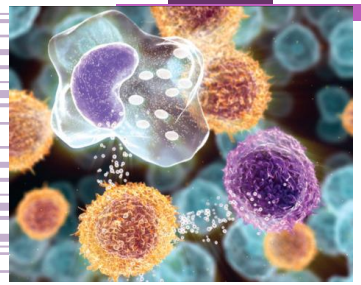


Inflammation at the visible level

Acute vascular response

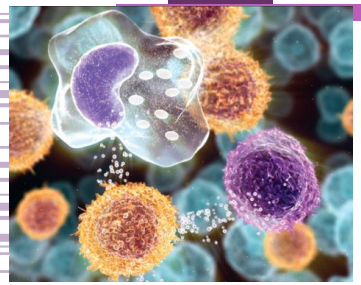
- starts within seconds and last for up to 20 minutes
- vasodilation = more blood to the area

REDNESS



Inflammation at the visible level

- Vascular flare
  - scratch the skin – blanches
  - FLARE
    - Enlarged arterioles – redness



Inflammation at the visible level

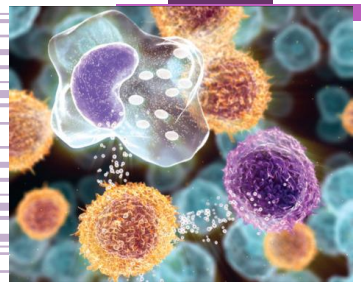
Acute Nerve Reflex Response

- 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

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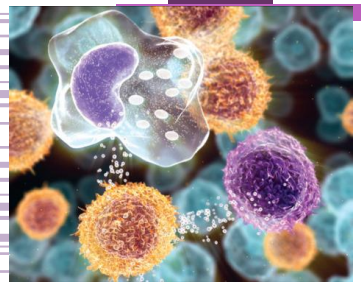

Inflammation at the visible level

Combination of increased intravascular blood cell and extravascular fluid accumulation

pressure causes heat

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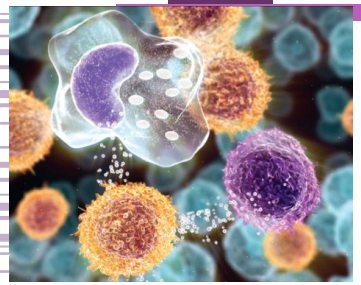
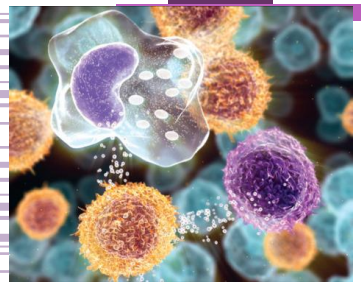


Inflammation at the visible level

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

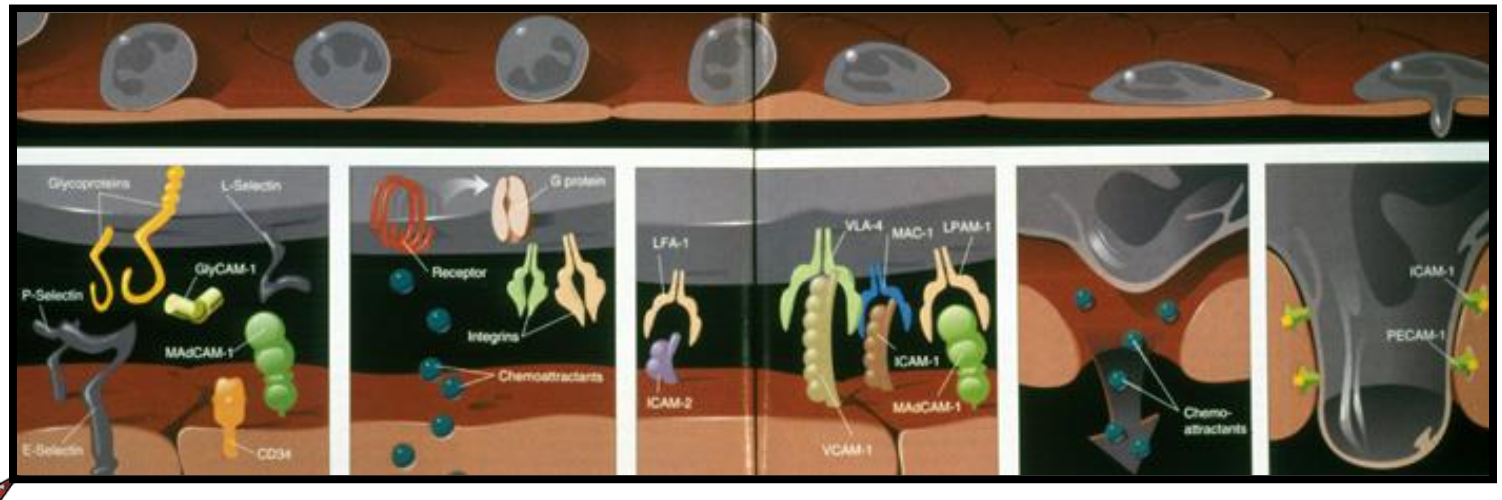
pain



Inflammation at the cellular level

Granulocytes

Diapedesis/chemotaxis



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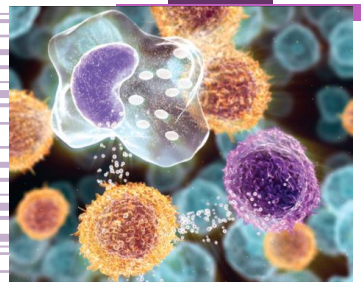
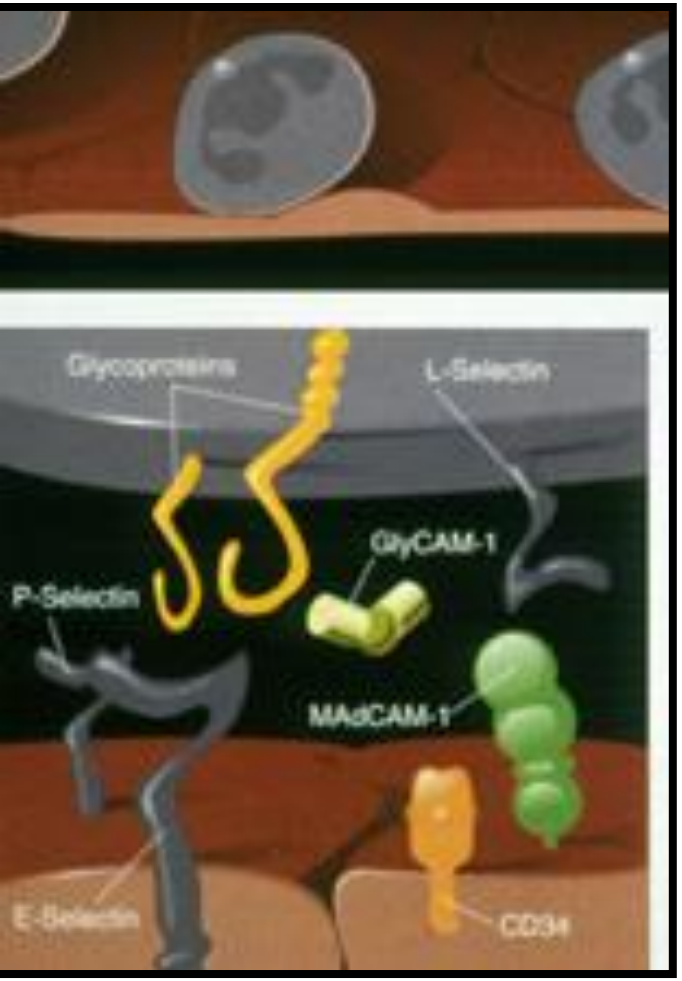


Inflammation at the Cellular level



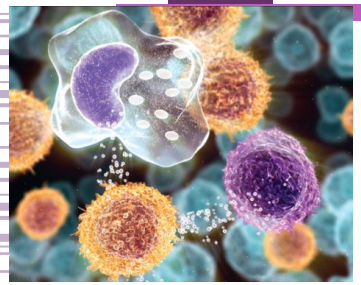
Glycoproteins

mannose, galactose, focuse
and maybe glucose

Bind to neuraminimic aid
(sialic acid)residues

Made in the liver

Induced by Interleukin -1



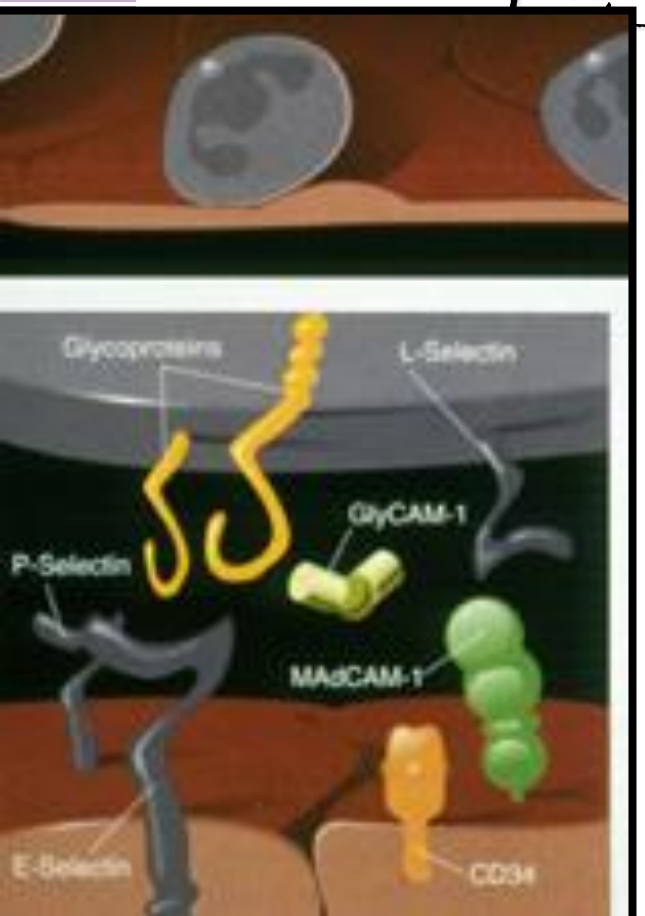
Inflammation at the Cellular level

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



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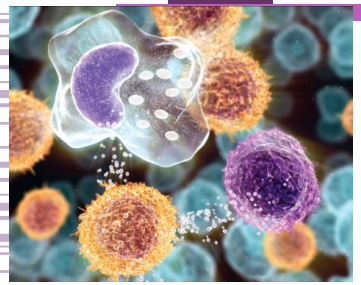
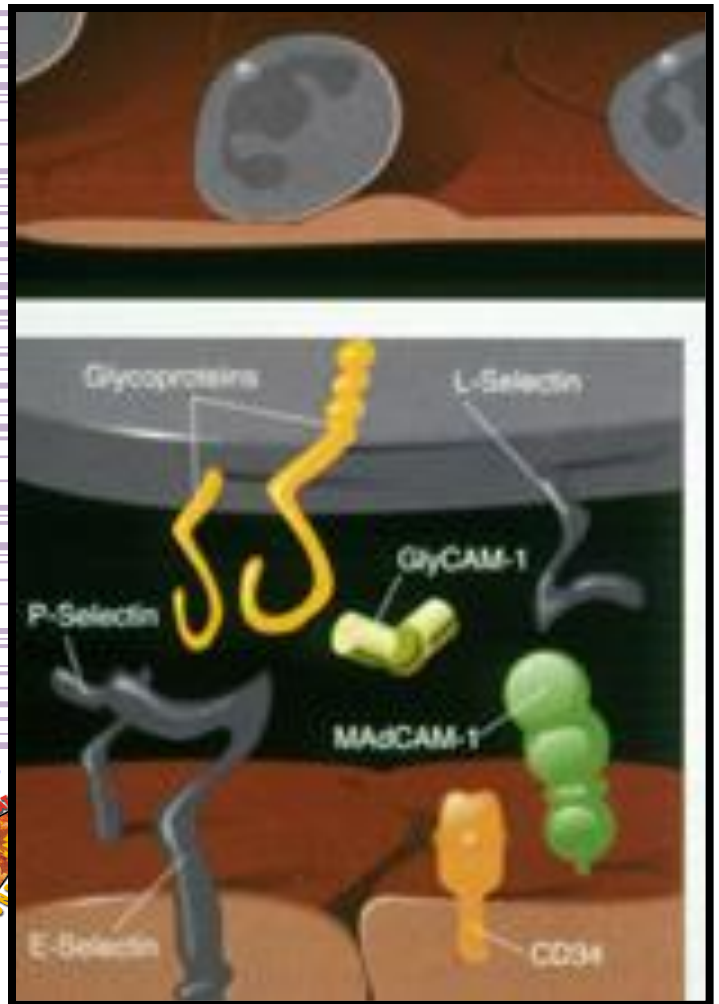


Inflammation at the Cellular level

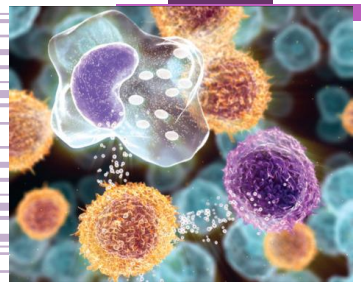


GycCam-1

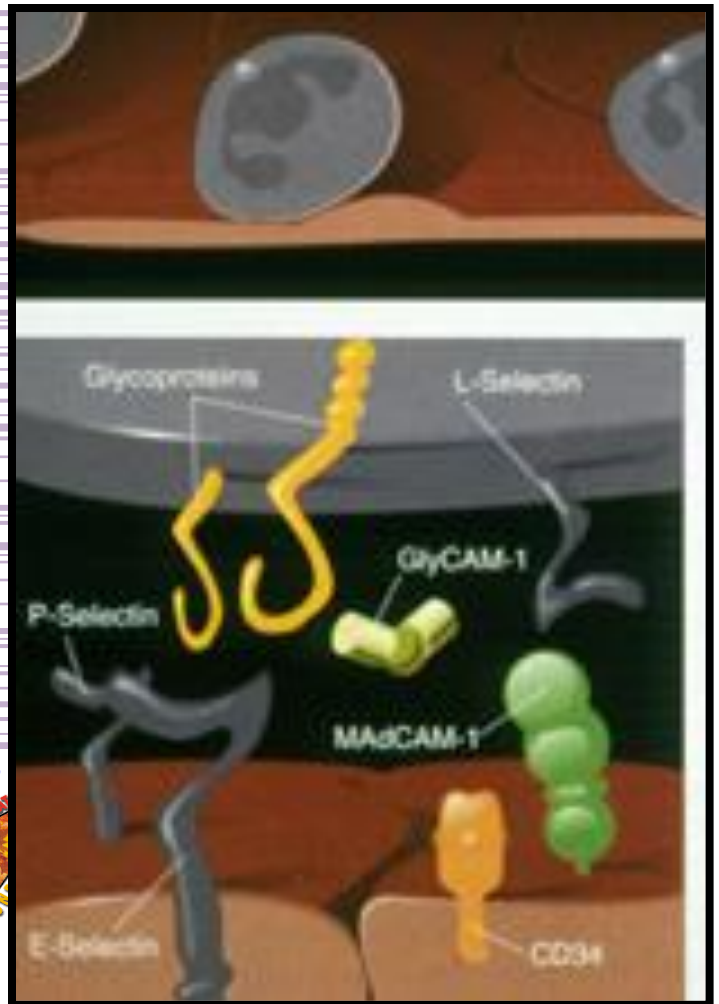
Glycosylation-dependent cell adhesion molecule-1

Found in lymph node endothelial cells

Binds to L-Selectins to stimulate T lymphs



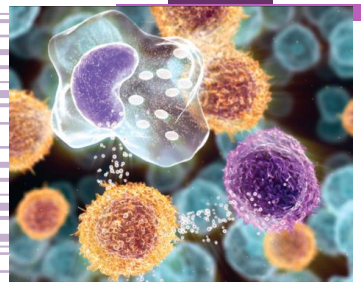
Inflammation at the Cellular level



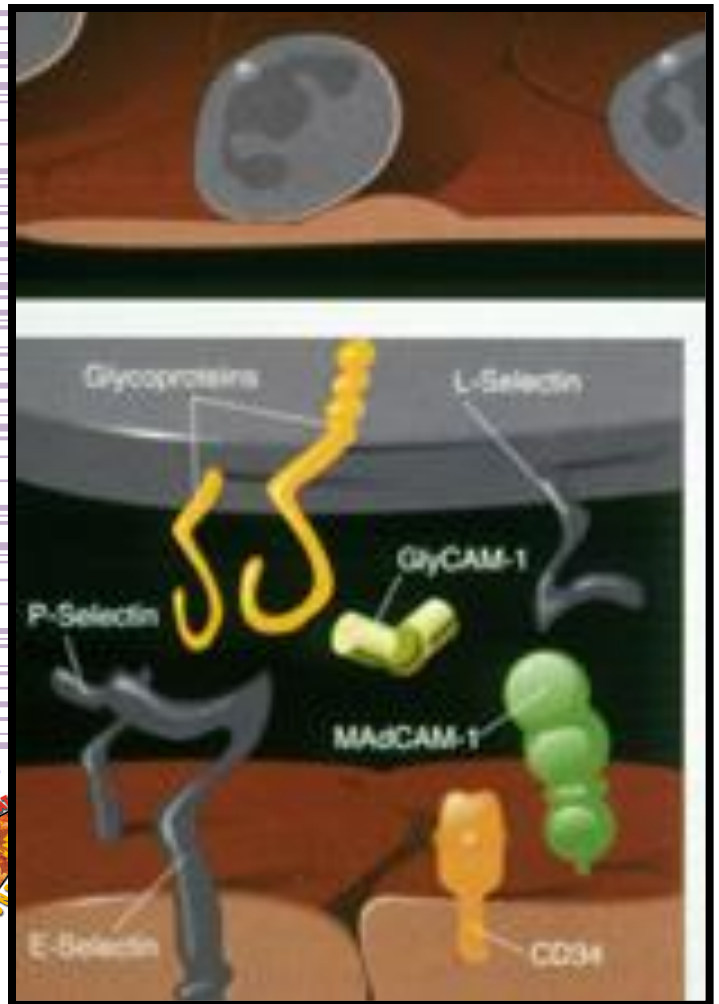
E-Selectins

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

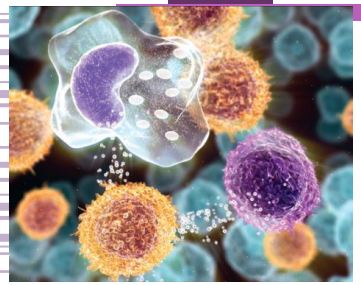


P-Selectins

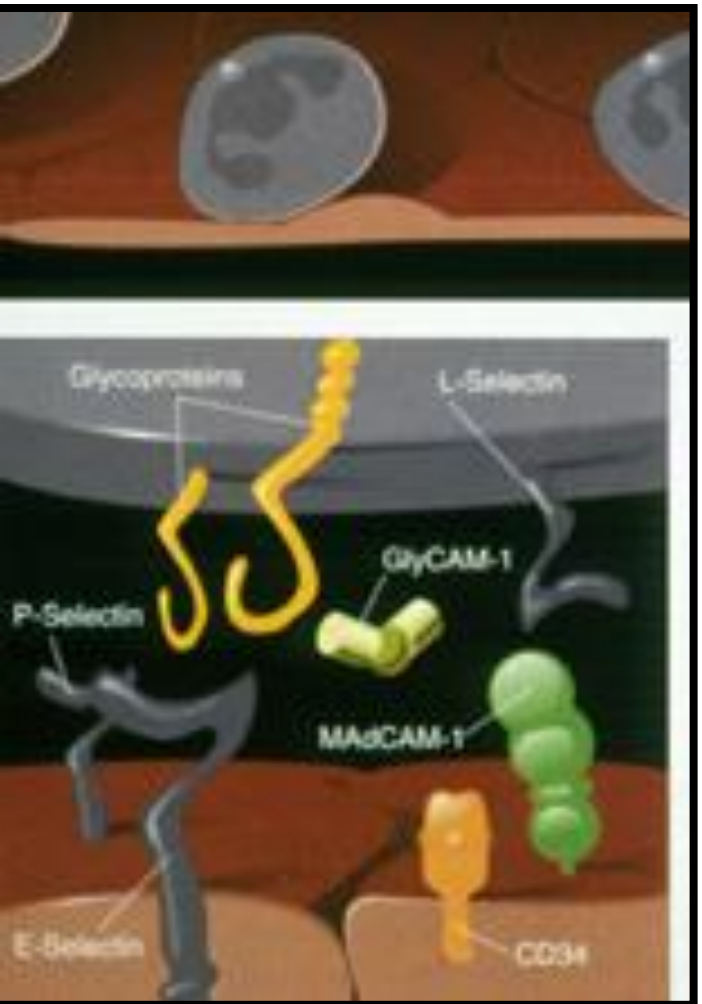
Found on activated endothelial cells

Bind to neutrophils, monocytes, eosinophils

Stimulated by IL-4 and IL-13



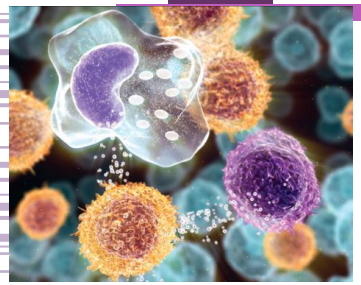
Inflammation at the Cellular level



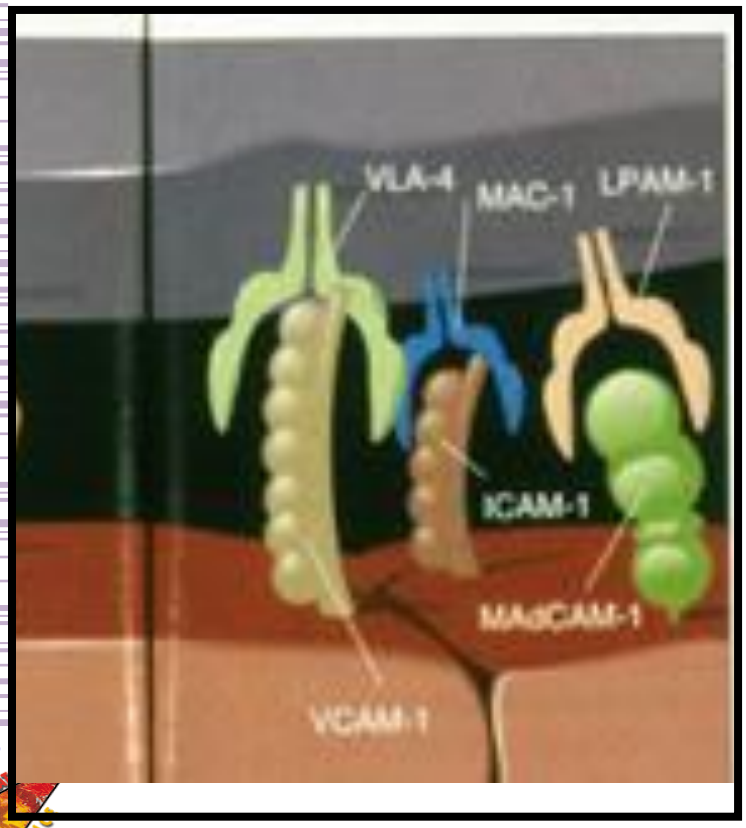
CD34

Cell surface glycoprotein

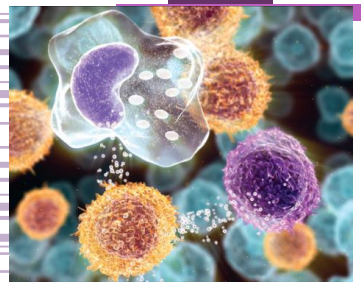
Enhances individual cell migration and cell-to-cell adhesion



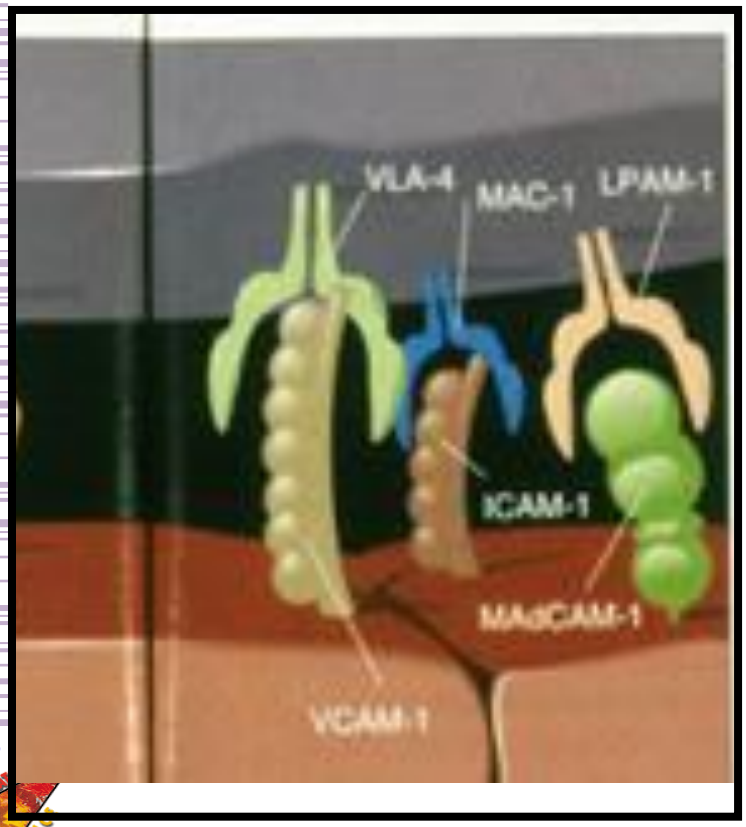
Inflammation at the Cellular level



Various cell adhesion compounds cause granulocytes to engage in tight adhesion to blood vessel endothelial wall



Inflammation at the Cellular level



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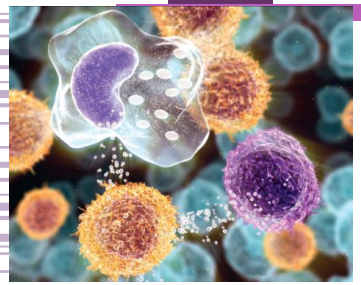
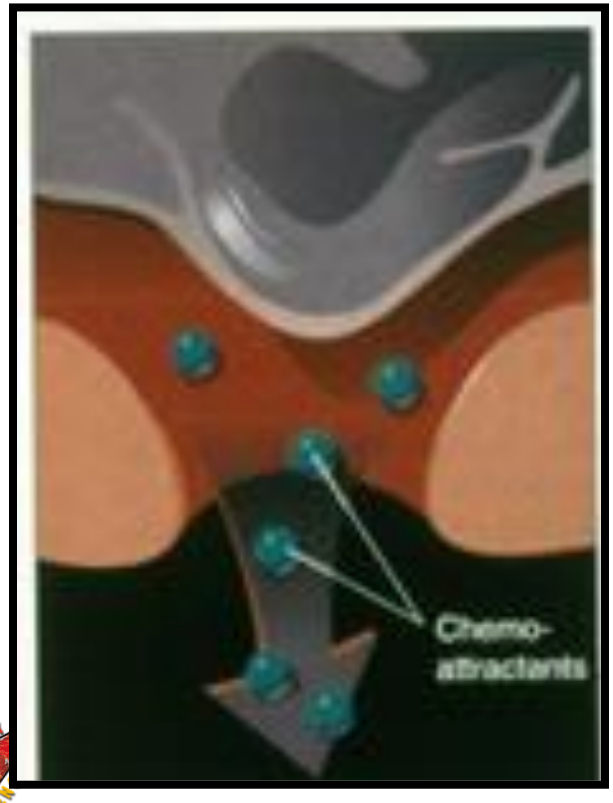
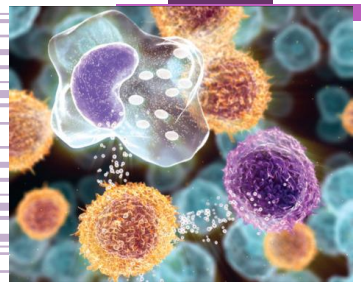


Inflammation at the Cellular level

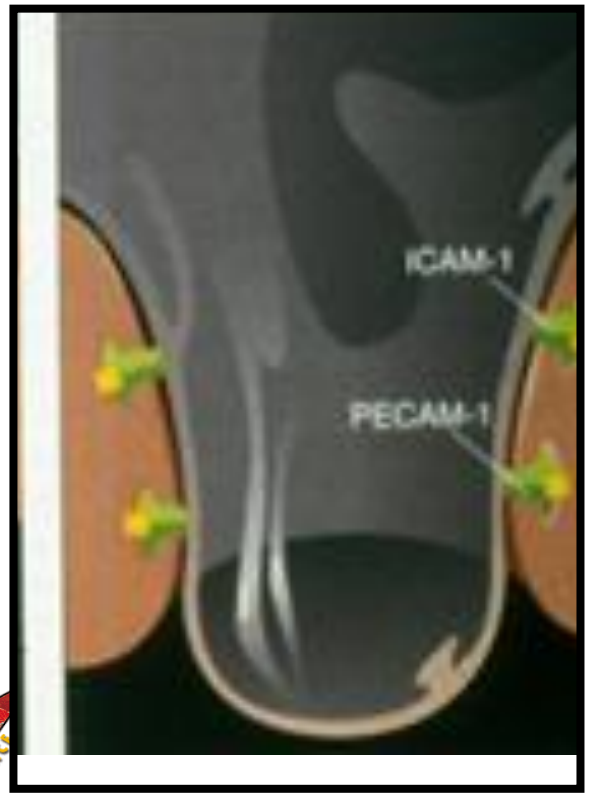
Diapedesis/chemotaxis



Chemoattractants –
too many to list



Inflammation at the Cellular level



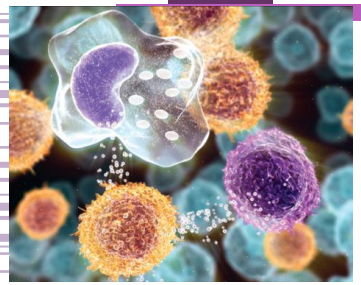
Diapedesis / chemotaxis

ICAM-1

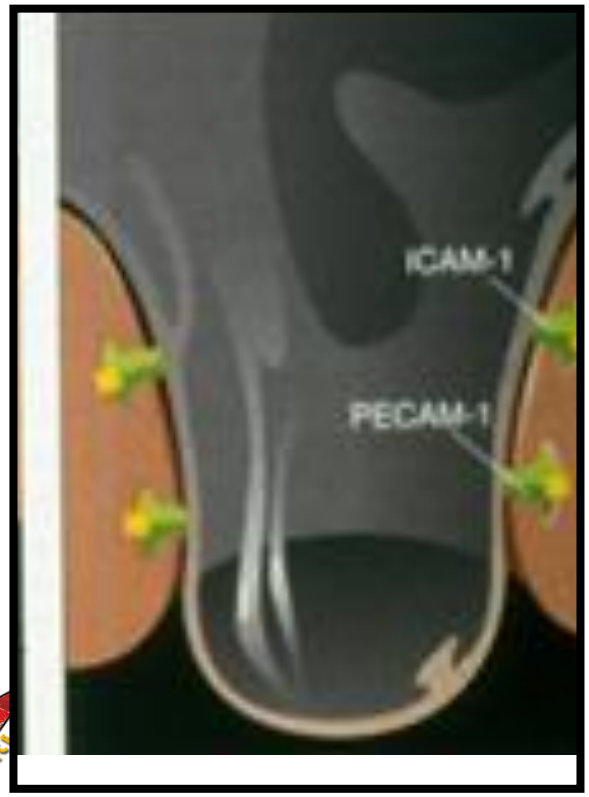
cell surface glycoprotein

expressed on endothelial cells

binds to granulocytes, Fibrinogen and Factor X



Inflammation at the Cellular level



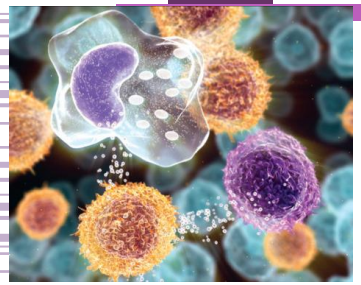
Diapedesis/chemotaxis

PECAM-1

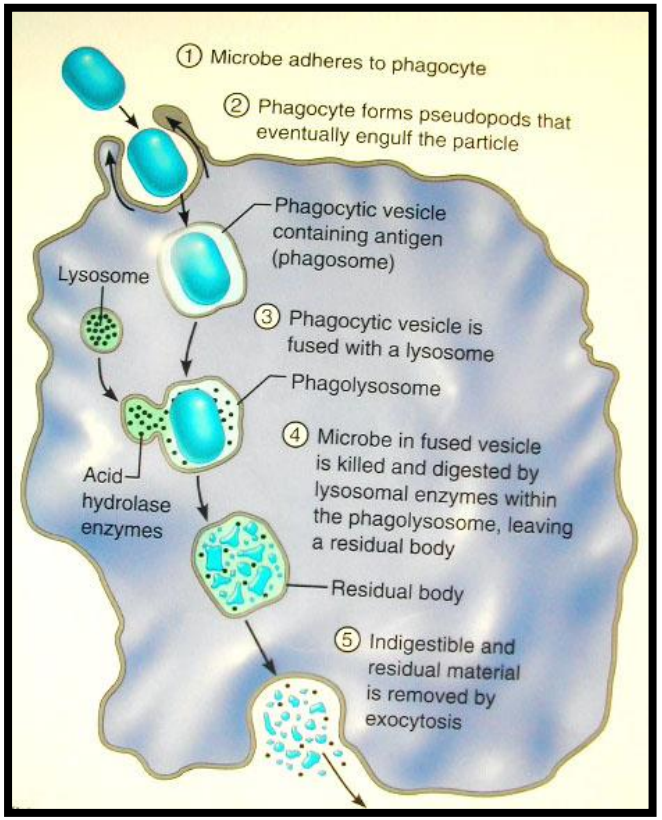
platelets, monocytes, neutrophils,

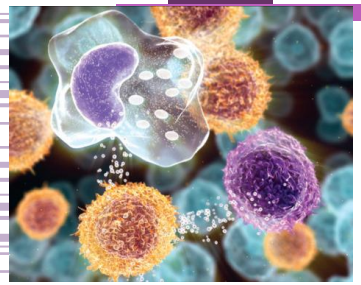
makes up a large portion of endothelial intercellular junctions

leukocyte transmigration, angiogenesis, and integrin activation



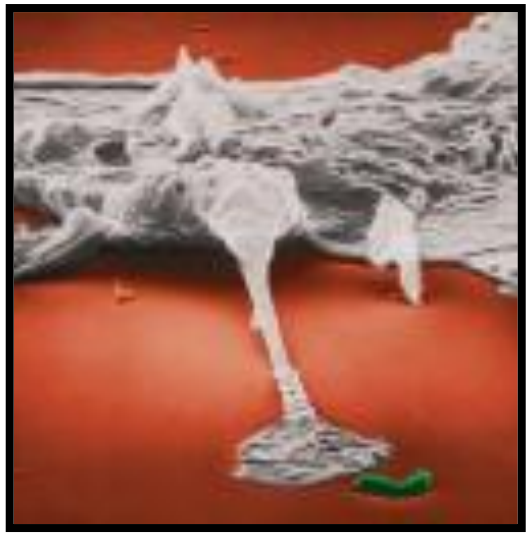
Inflammation at the Cellular level





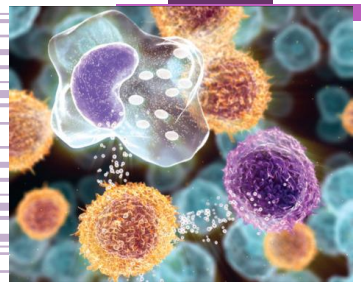
Inflammation at both visible and cellular level

Granulocytes accumulation

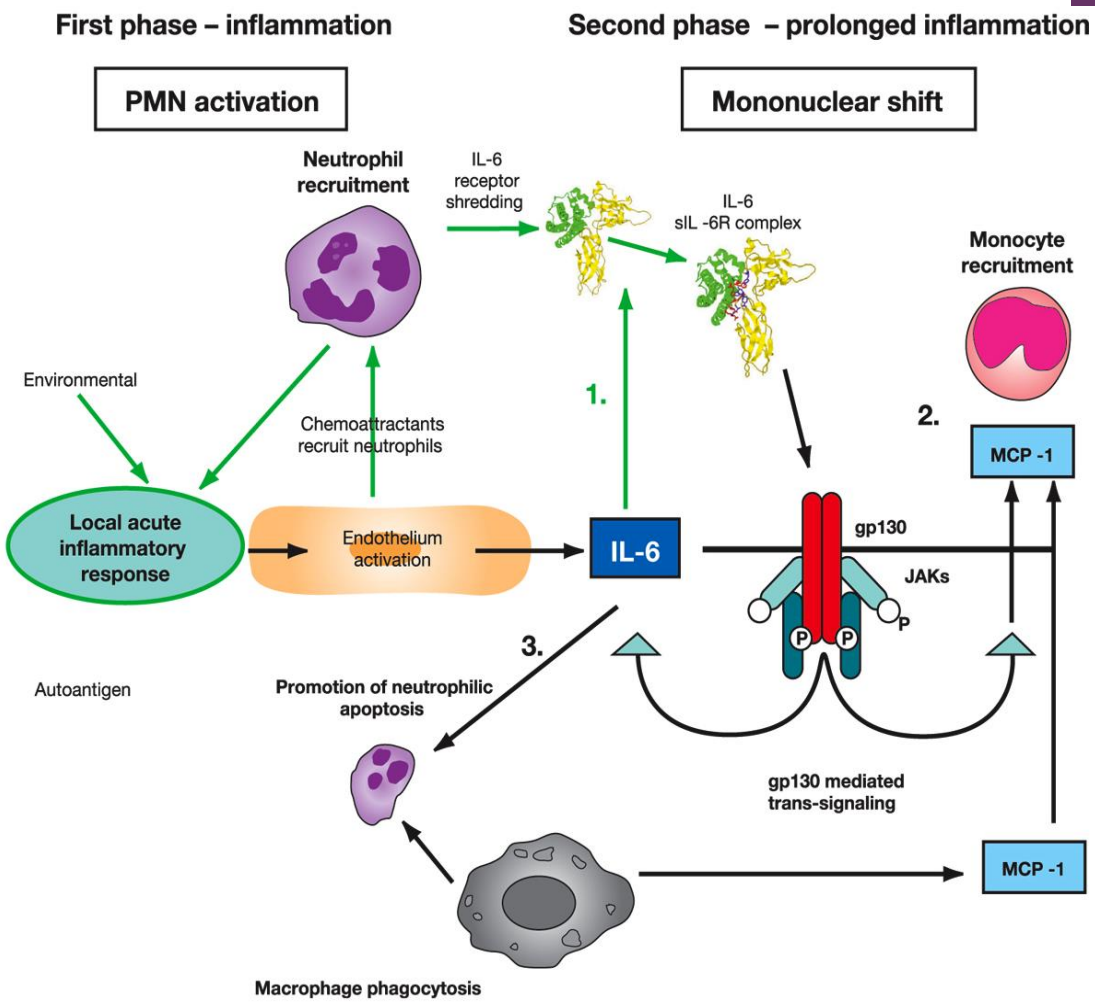


Dead and dying cells

(pus) attract monocytes



Inflammation at the invisible level



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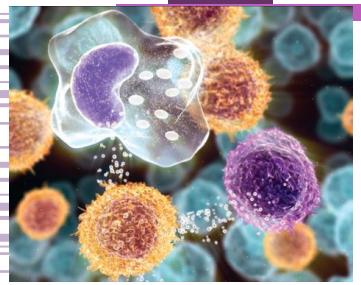
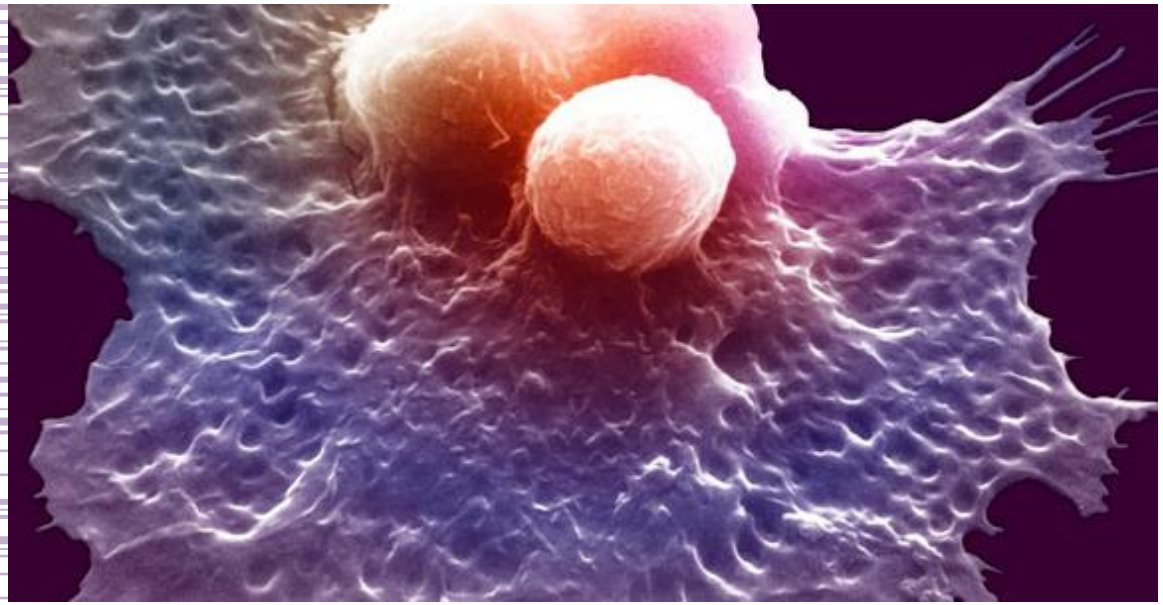


Elimination prior to reapir



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

Prime time for re-injury

inappropriate replacement = scarring

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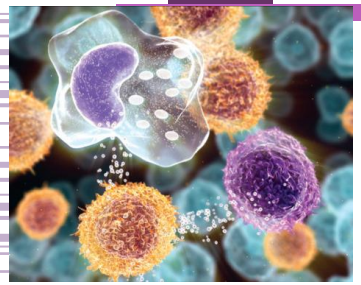
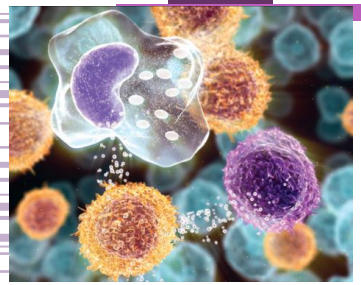


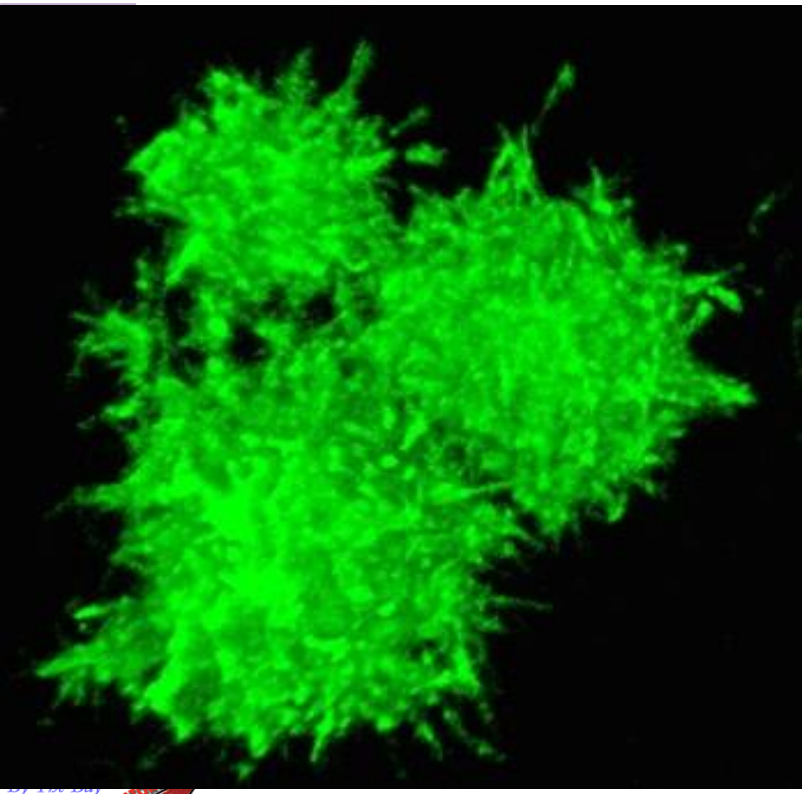
Acute vs chronic

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



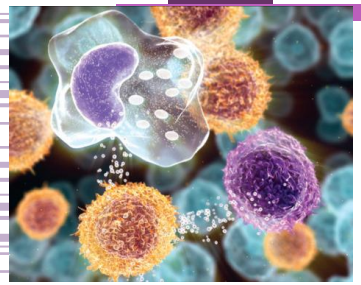
Continuation of Inflammation



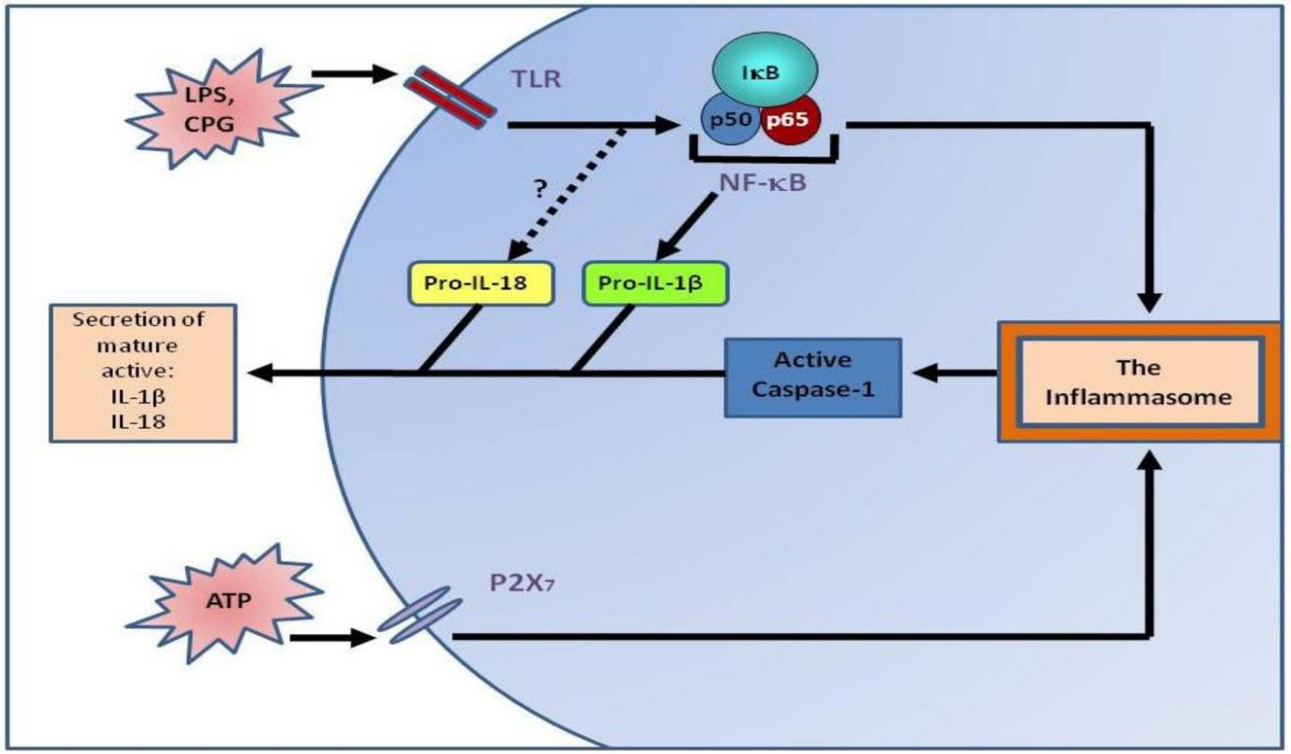
Granulocytes transmit inflammation by releasing ASC specks

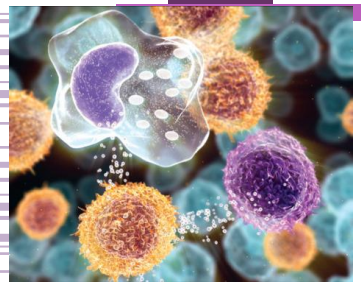
(Apoptosis-associated Speck protein with a Capase Recruitment domain)

bacteria-sized clumps of protein key for cytokine maturation

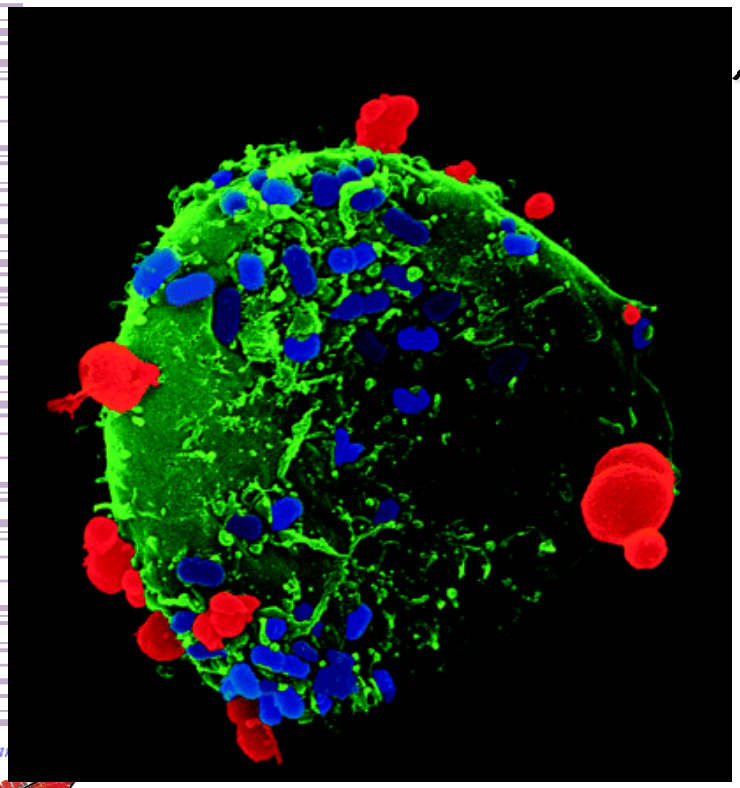


The release of the pro-inflammatory cytokines IL-1b and IL-18 in their mature/active forms is dependent upon the proteolytic cleavage of their precursors pro-IL-1b and pro-IL-18 by active Caspase-1. Caspase-1 itself must be cleaved from its precursor (pro-Caspase-1) by the inflammasome, a multimeric 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 NFkB activation and formation of the IL-1b 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.

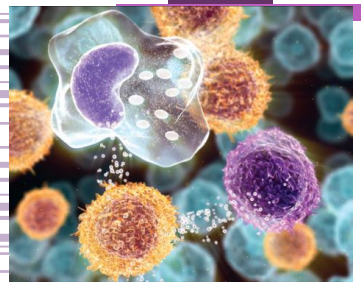




Continuation of Inflammation



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.



CONtinuation of Inflammation

Protein aggregates are components of inflammasomes, which sense pathogens and cell damage and set off innate immune inflammation

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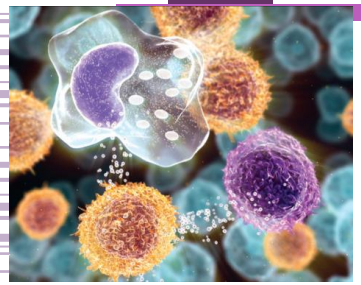
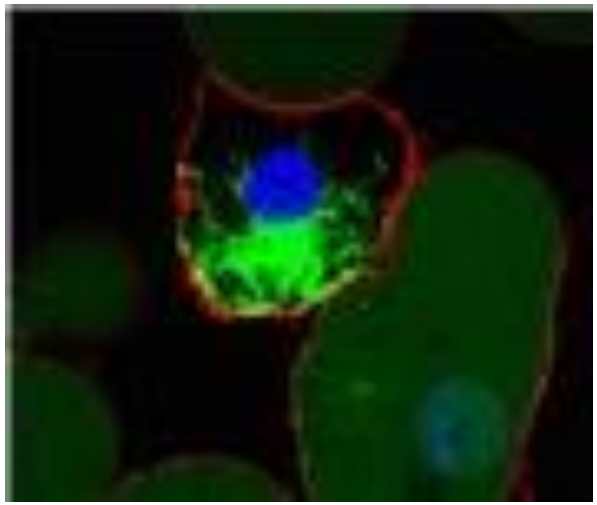


CONtinuation of Inflammation



ASC specks stimulate IL 1-β extracellularly.

Macrophages ingest the ASC specks from the extracellular space

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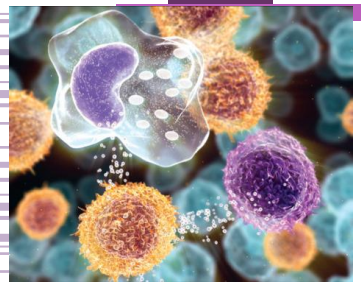
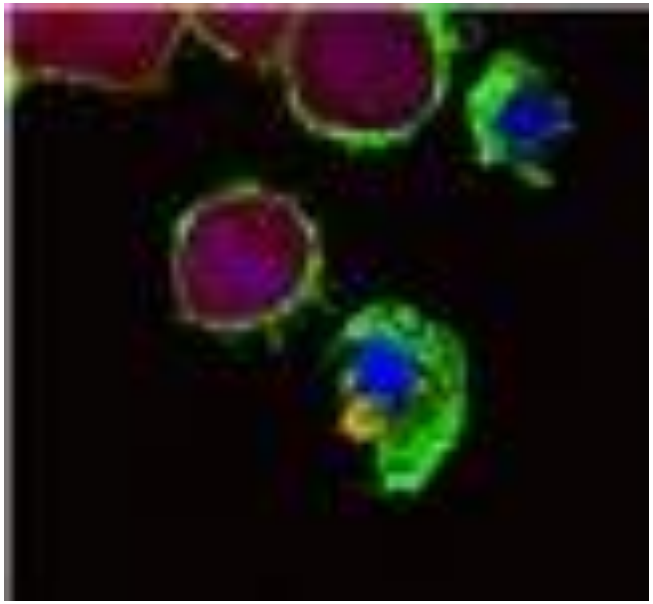


CONtinuation of Inflammation



Macrophages can take up released ASC specks, perpetuating the immune response.

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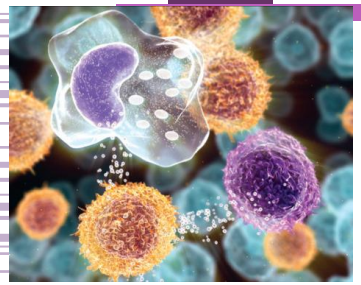
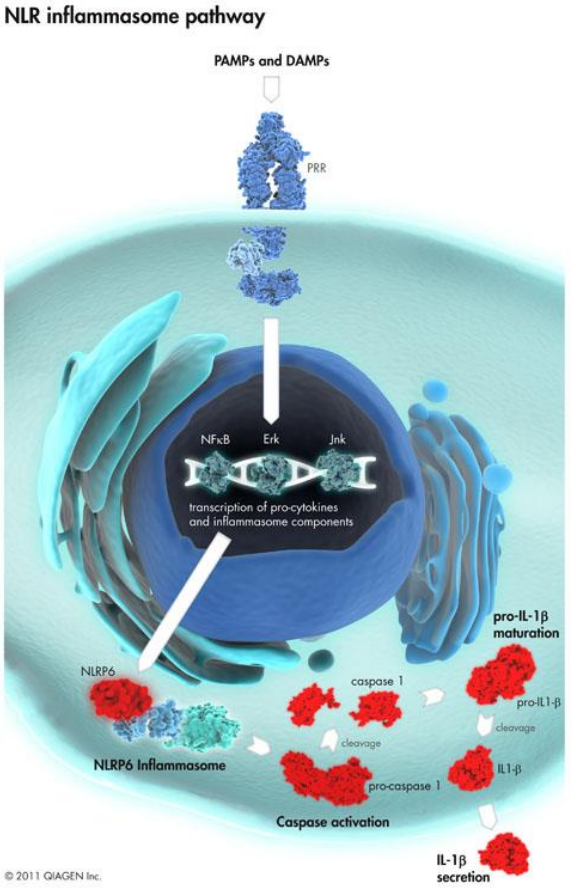
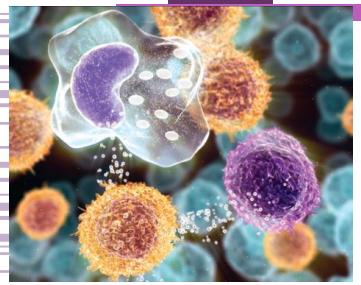


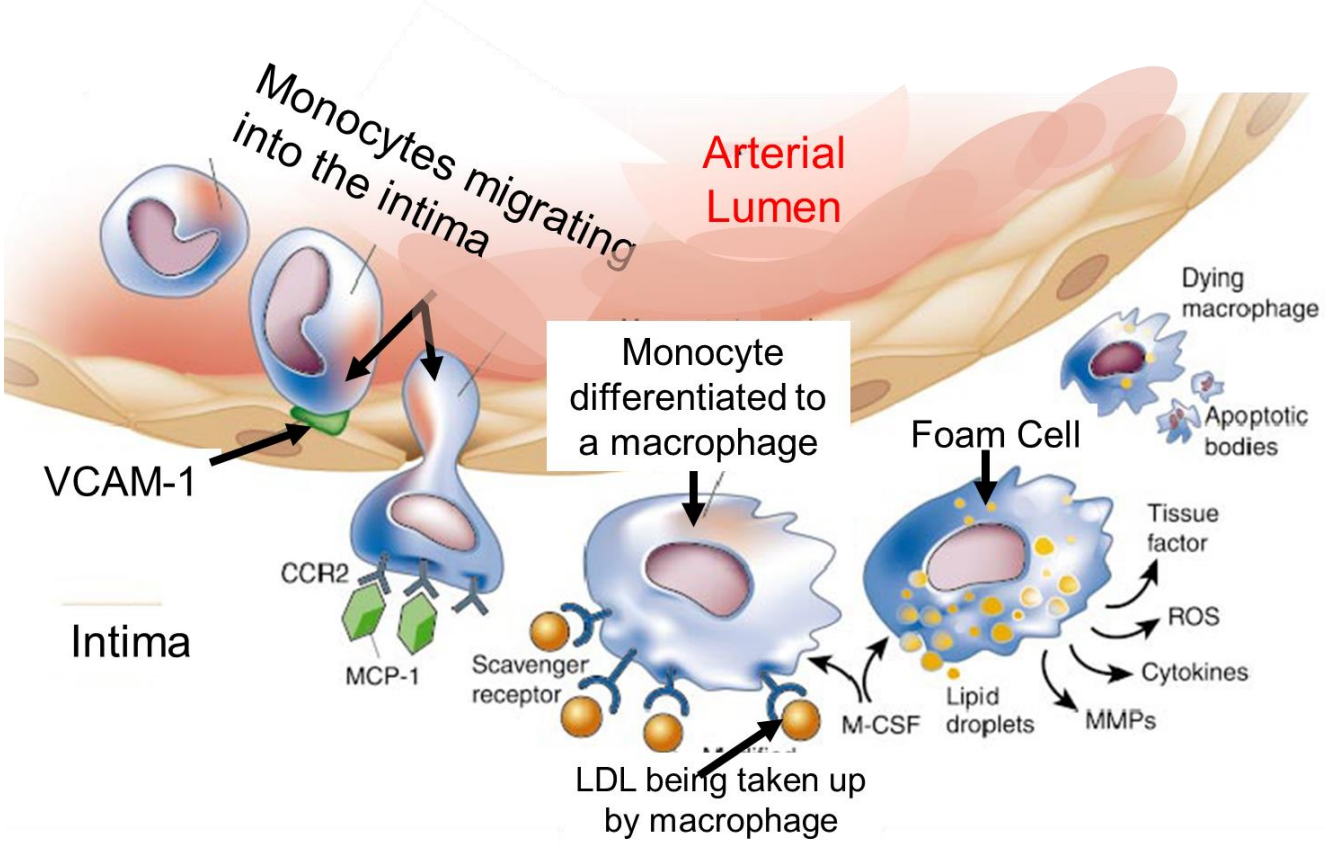
CONtinuation of Inflammation

ASC specks activate macrophage inflammasomes, restarting the whole process and multiplying inflammation.





Atherosclerosis



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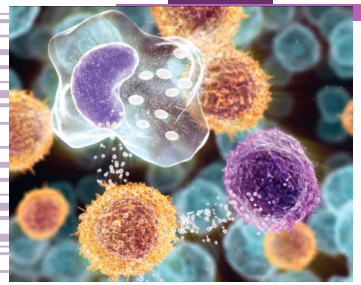
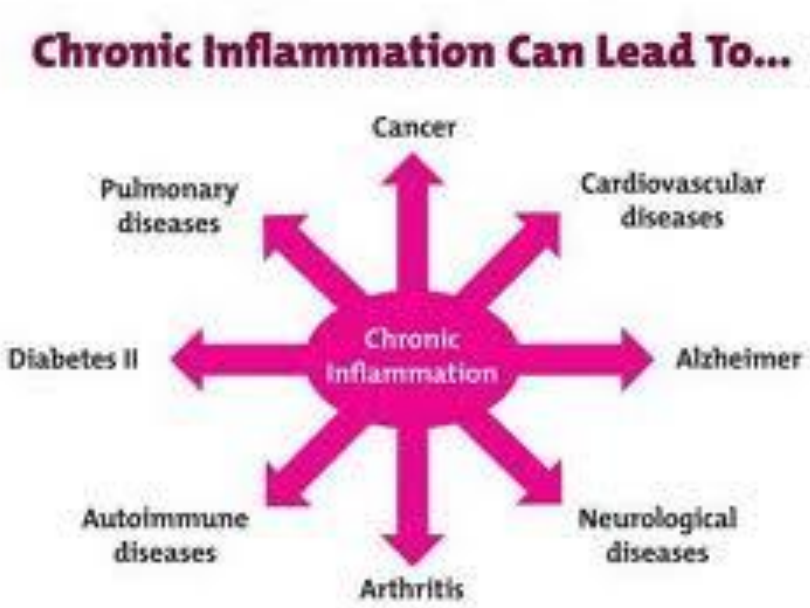
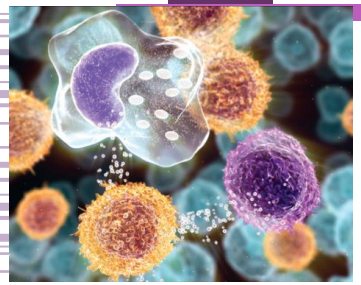



Chronic Inflammation Can Lead To...
Cancer
Pulmonary diseases
Cardiovascular diseases
Diabetes II
Chronic Inflammation
Alzheimer
Autoimmune diseases
Neurological diseases
Arthritis



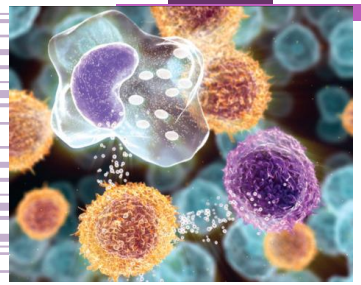
Testing?

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



Testing?

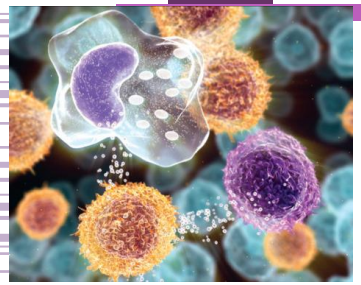
We have

Cross- Reactive Protein

reflects acute stages of inflammation

limited associations with physical performance

is associated with mortality risk



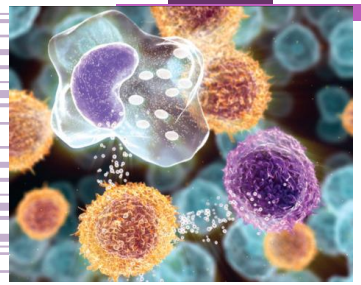
Testing?

We have

Interleukin 6

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

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



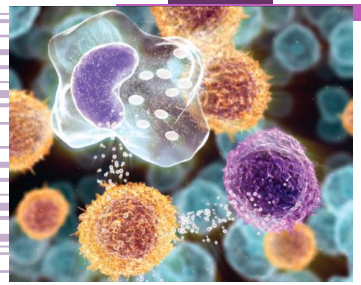
Testing?

We have

Serum Amyloid

is positively associated with chronic inflammation such as Chronic Heart Disease

is lowered with anti-cholesterol medication use



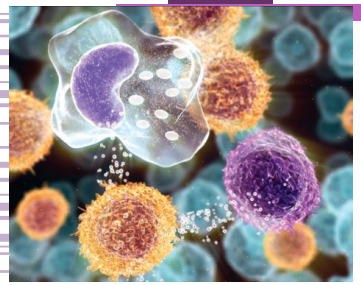
Testing?

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



Testing?

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

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