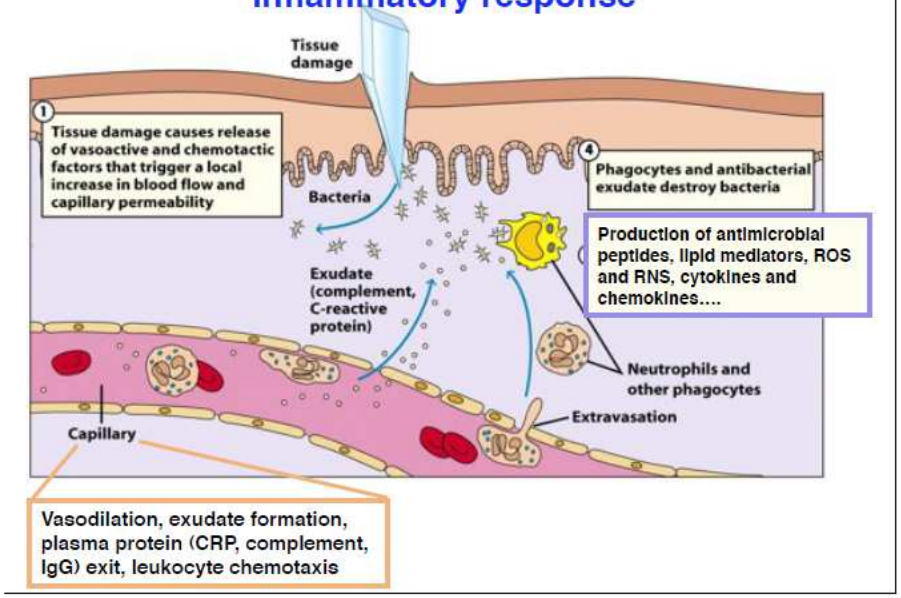
I - Classification of Inflammation

II - mechanisms of resolution

1

Pathogens (or tissue damage) trigger the acute inflammatory response



2

Classifying Inflammatory Reactions

- by duration:
  - acute: days;
  - subacute: weeks;
  - chronic: months-years
- by type of exudate and consequence on tissues

3

Types of acute inflammation:

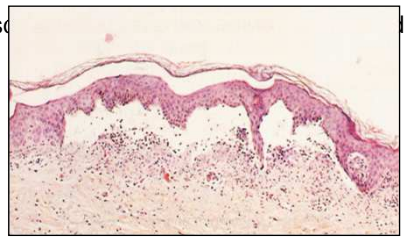
- Serous inflammation
- Fibrinous inflammation
- Purulent inflammation
- Hemorrhagic inflammation
- Gangrenous inflammation

Catharral inflammation

4

Serous Inflammatory Exudate

- Commonly is a clear exudate, serum-like, containing mainly water and salts with small amount of proteins (about 2%) and insufficient fibrinogen conversion to fibrin.
- Very limited number of leukocytes present (few neutrophils)
- Collects in pleural, peritoneal, and pericardial cavities (effusion) or in injured joint spaces, or spreads throughout subcutaneous tissue or along fascial planes.
- Caused by some infecive agents, physical and chemical damage..
- e.g. burned skin, viral blisters, pleuritis, pericarditis,etc.
- eabs

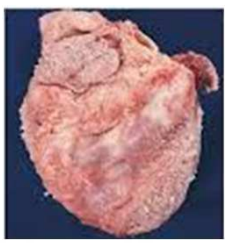


5

Fibrinous Inflammation

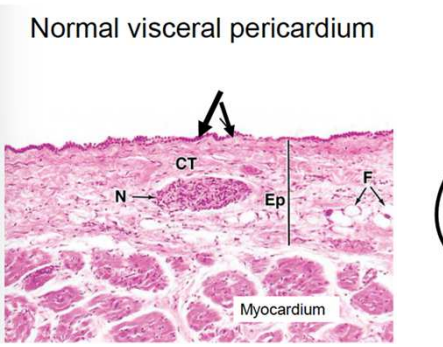
- Greater vascular permeability: exudate with high concentration of plasma protein fraction and substantial amounts of fibrin deposition (eosinophilic threads in a mesh or an amorphous clump)
- It may be present in acute but also in chronic inflammations
- characteristically occurs in an inflammation in serosal lined cavities where the mesothelial cells become covered by fibrin polymerization with a dull surface
  - on the surface of an organ it appears rough, "bread and butter"
- e.g. certain virulent bacterial infections, fibrinous pericarditis (shown here)

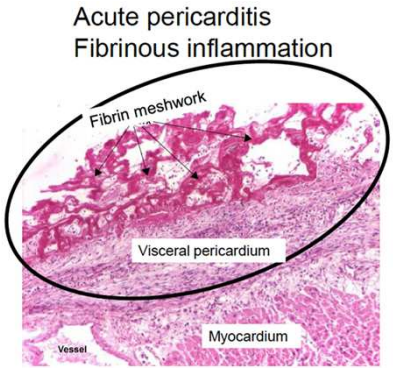
Normal heart



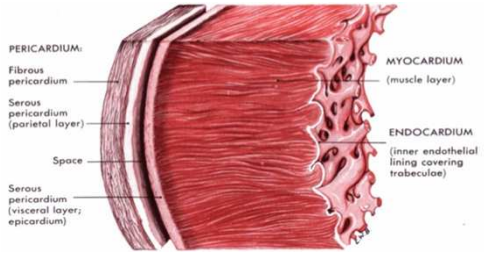
Fibrinous inflammation
Acute Pericarditis

6





Ep=epicardium (visceral pericardium)
CT= connective tissue



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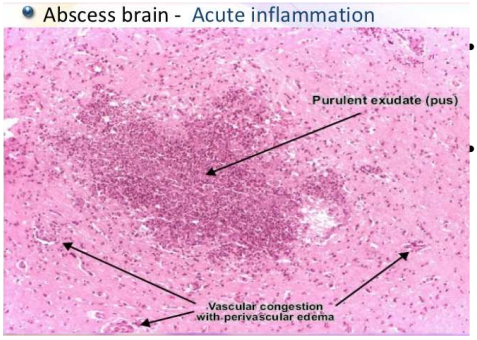
Purulent Inflammation



- Purulent (cell rich), suppurative (large amounts of pus is evident)
- Pus: exhudate – protein rich fluid, typical of infection, formed by microorganisms plus significant local liquifactive necrosis of tissue and neutrophils
- e.g., acute appendicitis or a boil
- typically induced by "pyogenic“ (producing pus) bacteria e.g. *Staphylococcus aureus*

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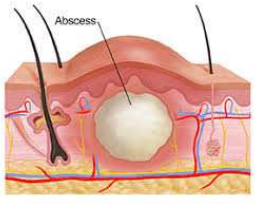
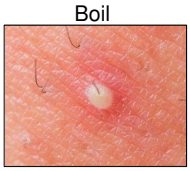
Focal purulent inflammatory reactions contained in a confined space or tissue:

- "**abscess**" accumulation of pus in a tissue/organ
  - A liquefactive **necrotic** center of dead parenchymal **tissue** and dead/dying **neutrophils**, surrounded by **fibrin** and live neutrophils, with an outer area of vascular growth, new collagen fibers, and parenchymal and fibroblastic proliferation. May become walled off by connective tissue.
  - **"Empyema"** if accumulation in a preformed space
  - Often caused by pyogenic bacteria
- **furuncle (boil**) is a single or multiple abscess under the skin; may remain in this state for long periods, but heal faster if drained.





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Acute Inflammatory Exudate

- Accumulation of fluid and WBCs at injury site
- Three major anatomic patterns:
  - Serous inflammation
    - Seen in mild, short-term inflammation
    - Watery fluid with decreased protein
    - No/few inflammatory cells
  - Fibrinous inflammation
    - Seen in more severe injuries
    - Thicker, with coagulation factors (fibrin)
    - Neutrophils
  - Suppurative (purulent, pyogenic) inflammation
    - Seen with severe injuries
    - Associated with liquefactive necrosis; pus (dead cells/debris)
    - Frequently associated with bacterial infection

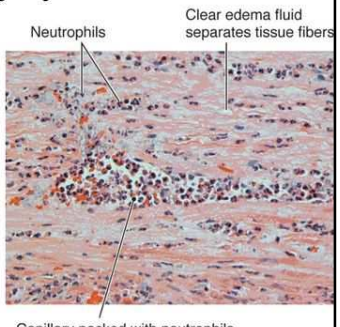

Figure from: McConnell, *The Nature of Disease*, 2nd ed., Wolters Kluwer, 2014

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Morphological types of exudative inflammation

(according to character of exudates and prevailing location):

- **Serous, when the fluid exudate resembles serum or is watery.**
- **Fibrinous, when the fibrin content of the fluid exudates. It can be croupous and diphtheritic.**
- **Purulent or suppurative exudate is formation of pus in infection with pyogenic bacteria.**
- **Hemorrhagic, when there is vascular damage.**
- **Catarrhal, when the surface of epithelium in case of inflammation produces increased amount of mucus.**
- **Mixed**

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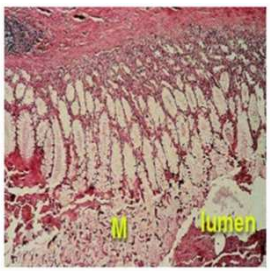
Catarrhal Inflammation

- When mucus hypersecretion accompanies acute inflammation of a mucous membrane, the appearance is described as catarrhal.
- This type of inflammation is usually seen in the acute stage of inflammation in organs that have abundant goblet (mucus producing) cells, such as the respiratory tract and the colon.
- Some allergic reactions and infections of mucosa produce marked mucus production
  - E.g., runny/snotty nose with viral infections

Colon section with excess secretion of Mucus into the colonic lumen



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Hemorrhagic Inflammation

- Hemorrhagic inflammation

  - indicates severe vascular injury. As a result blood predominates in the exudate.

  – a fibrinous reaction with damage to small blood vessels allowing rbc to escape into the extravascular space.
    - E.g., typhus, anthrax, viral influenzal pneumonia

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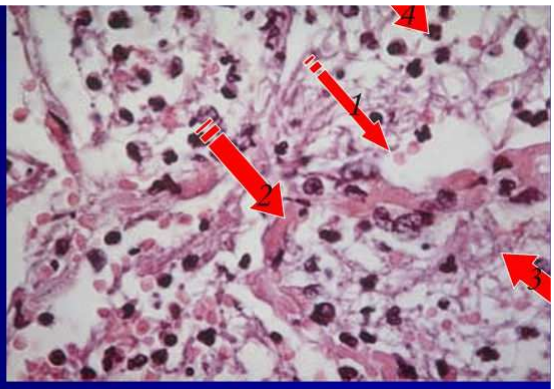
Hemorrhagic Inflammation

the inflammatory exudate consists of

1. Erythrocytes leaked out the permeable
2. and congested capillaries,
3. thin strands of fibrin derived from fibrinogen
4. leukocytes



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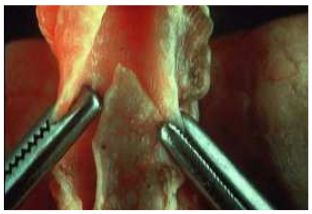
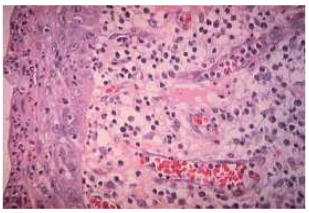
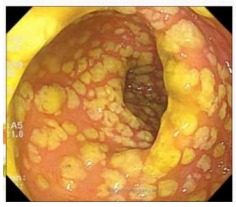
(Pseudo)membranous reactions





- toxins stimulate a necrotic inflammation of mucous membranes
- inflammatory exudate forms an adherent , gray, pseudomembrane on the mucosal surface containing cells, necrotic debris, organisms, fibrin.
- E.g., *Corynebacterium diphtheriae*
- (oropharynx shown above),
- *Clostridium difficile*, *S. typhi.*



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Necrotizing Inflammation

- The products of inflammation (i.e. proteolytic enzymes) and vascular occlusion by thrombosis may result in widespread necrosis of the affected organ.
- The term necrotizing can be used to describe this kind of inflammation.
- As with other types of inflammation, necrotizing can occur in conjunction with an influx of neutrophils (necropurulent) or hemorrhage (necrohemorrhagic).
- The combination of necrosis and bacterial putrefaction is called **gangrene**.

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Gangrene

- It may be caused either **ischemic** or **inflammatory**
- Coagulative Necrosis due to ischaemia
  - gangrene of the bowel,
  - gangrene of limb
- **Gangrenous or necrotising inflammation:** primarily inflammation provoked by virulent bacteria resulting in massive tissue necrosis.
  - Gangrenous appendicitis,
  - Gangrenous stomatitis (noma, cancrum oris)

18

Resolution of inflammation

Complete resolution:

1. Clearance of injurious stimuli
2. Clearance of mediators and acute inflammatory cells
3. Replacement of injured cells
4. Restoration of normal functions

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Mediators of resolution

In recent years, specific pro-resolving mediators were discovered, which activate resolution pathways:

- specialized lipid mediators (lipoxins, resolvins, protectins and maresins)
- proteins (annexin A1, galectins) and peptides
- gaseous mediators (including hydrogen sulphide)
- a purine (adenosine)
- neuromodulator release under the control of the vagus nerve.

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Mediators of resolution

Mediators may act:

- to limit further leukocyte recruitment
- induce neutrophil apoptosis
- enhance efferocytosis by macrophages.
- switch macrophages from classical to alternatively activated cells
- promote the return of non-apoptotic cells to the lymphatics
- help initiate tissue repair mechanisms and healing

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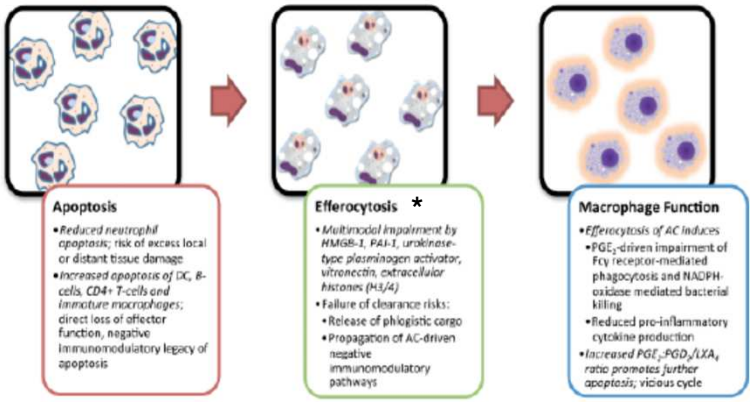
Elimination of the infiltrate



*removal by phagocytic cells

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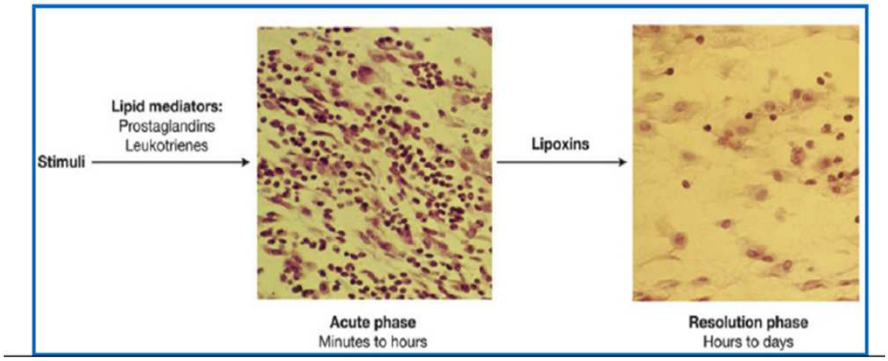
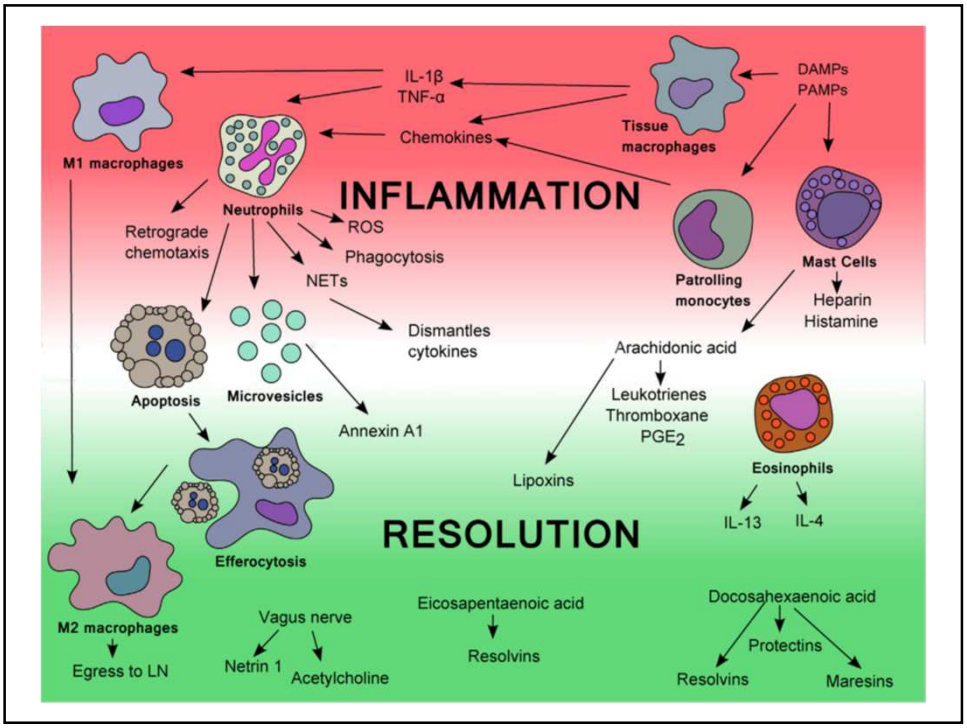
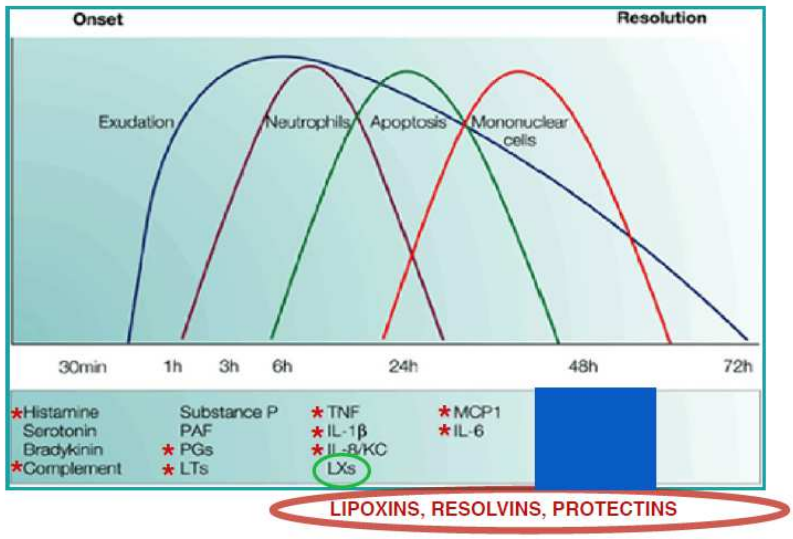

Lipid mediators:
Prostaglandins
Leukotrienes
Stimuli
Lipoxins
Acute phase
Minutes to hours
Resolution phase
Hours to days

23


IL-1β
TNF-α
Chemokines
DAMPs
PAMPs
Tissue macrophages
M1 macrophages
Neutrophils
INFLAMMATION
Retrograde chemotaxis
ROS
Phagocytosis
NETs
Patrolling monocytes
Mast Cells
Heparin
Histamine
Dismantles cytokines
Arachidonic acid
Apoptosis
Microvesicles
Annexin A1
Leukotrienes
Thromboxane
PGE2
Eosinophils
Lipoxins
IL-13
IL-4
RESOLUTION
Efferocytosis
M2 macrophages
Egress to LN
Vagus nerve
Netrin 1
Acetylcholine
Eicosapentaenoic acid
Resolvins
Docosahexaenoic acid
Protectins
Resolvins
Maresins

24

Acute inflammation activation and resolution and associated LIPID mediators!



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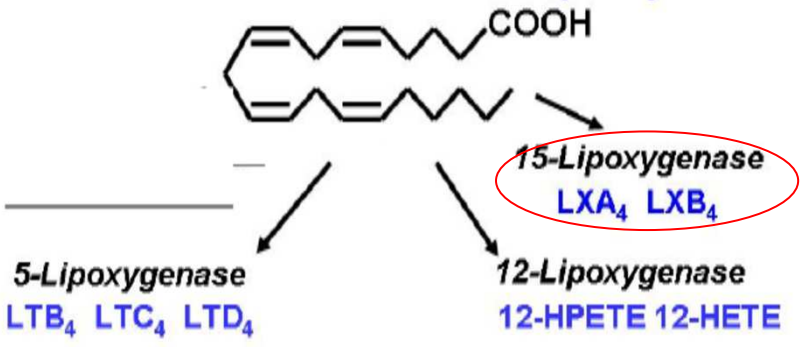
Lipoxins

Arachidonic acid (AA)



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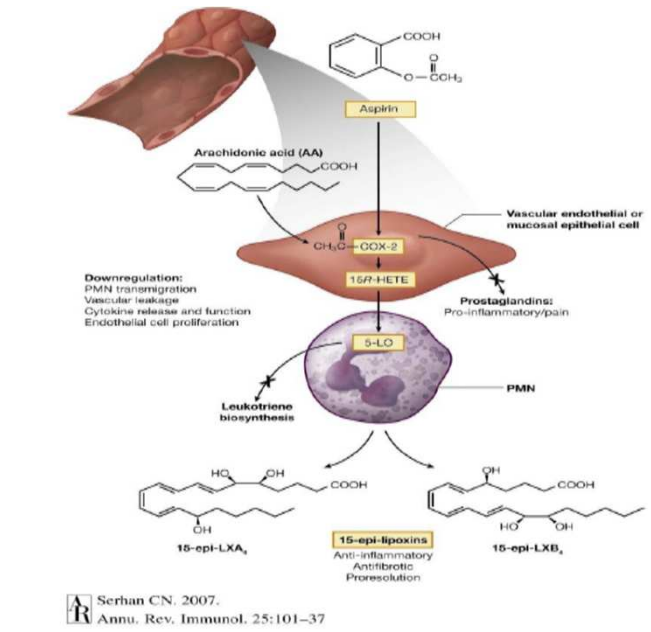
Aspirin-triggered 15-epi-lipoxins (ATL)



Serhan CN. 2007.
Annu. Rev. Immunol. 25:101–37

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Biological (proresolving) properties of lipoxins and aspirin-triggered 15-epi-lipoxins

LXs and ATL were shown to exert their anti-inflammatory and pro-resolution effects by:

(i) stopping infiltration and activation of PMNs (Levy et al., 2001; Perretti et al., 2002)
(ii) stimulating macrophage phagocytosis of apoptotic PMNs (Godson et al., 2000)
(iii) reducing the synthesis of the pro-inflammatory cytokines (TNFα: Hachicha et al., 1999; IL-8: Gronert et al., 1998)
(iv) upregulating the synthesis of anti-inflammatory cytokines TGFβ (Mitchell et al., 2002)

LXs and ATL were shown to exert their anti-inflammatory and pro-resolution effects in various experimental models of inflammations, as well as in human diseases, including:

- **glomerulonephritis (O'Meara & Brady, 1997)**
- **colitis (Gewirtz et al., 2002)**
- **ischemia/reperfusion injury (Leonard et al., 2002)**
- **cutaneous inflammation models (Schottelius et al., 2002)**
- **periodontitis (Pouliot et al., 2000)**
- **acute pleuritis (Paul-Clark et al., 2004)**
- **peritonitis (Bannenberg et al., 2004)**
- **cystic fibrosis (Karp et al., 2005)**
- **asthma (Levy, 2005)**
- **wound healing processes in the eye (Gronert, 2005)**
- **skin edema formation in mice (Guilford & Parkinson, 2005)**
- **inflammation-induced hyperalgesia in rats (Svensson et al., 2007)**

Huwiler A, Pfeilschifter J.
Lipids as targets for novel anti-inflammatory therapies.
Pharmacol Ther 124:96-112, 2009.

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Table 1 Cardinal signs of inflammation: roles of eicosanoids

Signs	"Go" Signals	"Stop" Signals
Chemotaxis, leukocyte	LTB_4, HETEs	LXA_4, LXB_4
Vascular permeability	LTC_4, LTD_4	LXA_4
Pain and hyperalgesia	PGE_2, PGI_2, LTB_4	LXA_4
Local heat and systemic fever	PGE_2, PGI_2	LXA_4
Vasodilation (erythema)	PGI_2, PGE_1, PGE_2, PGD_2	LXA_4, LXB_4, LTB_4
Edema (swelling)	PGE_2, LTB_4	

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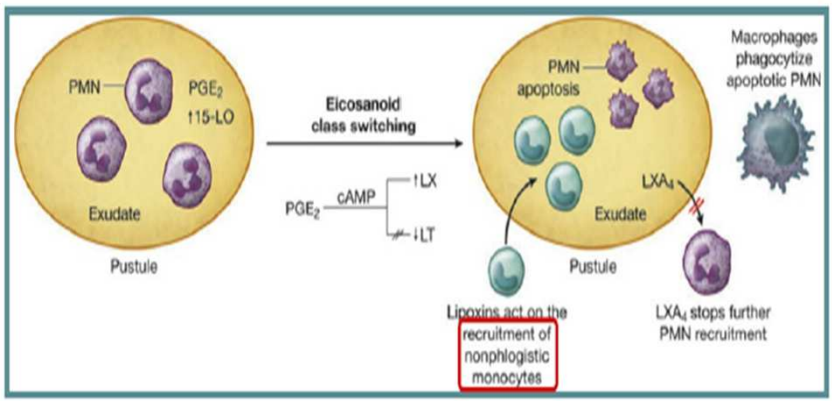

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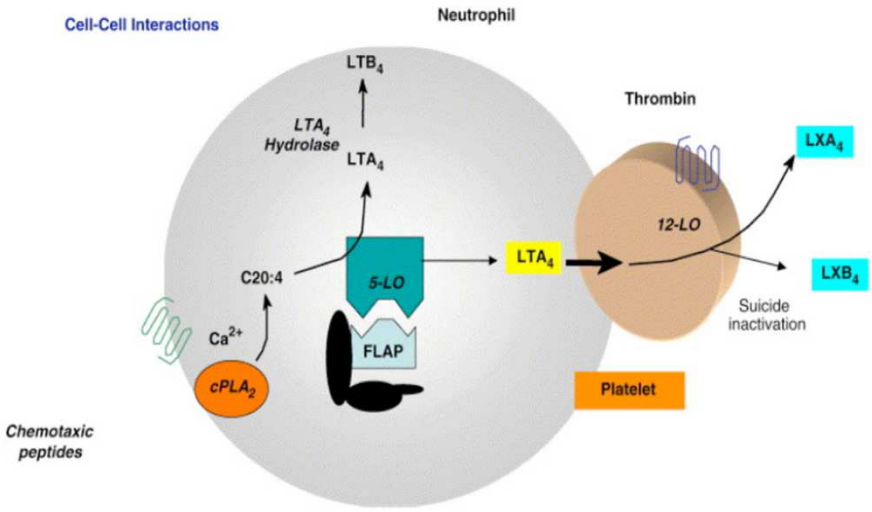
Combinatorial activity of 5-Lipooxygenase and 12- LO, cooperation of neutrophils and platelets



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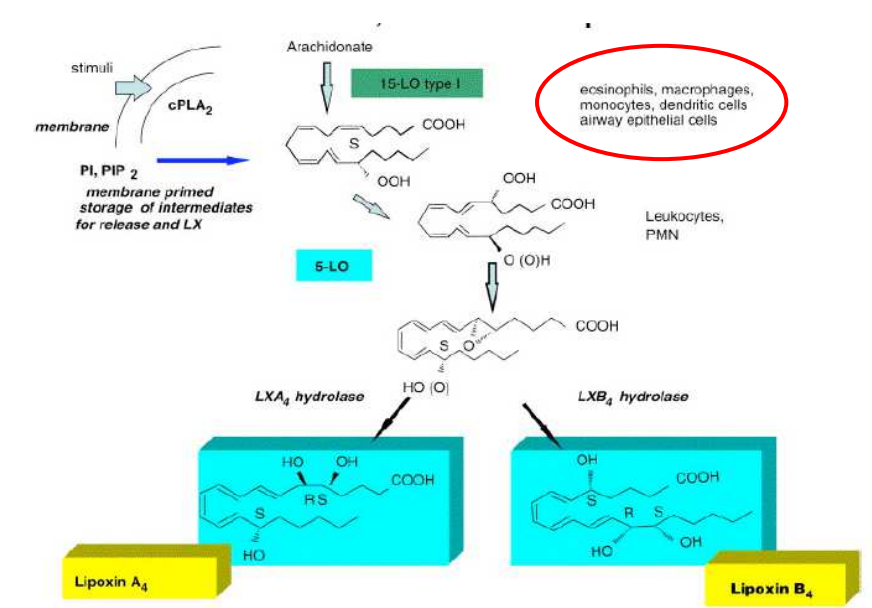

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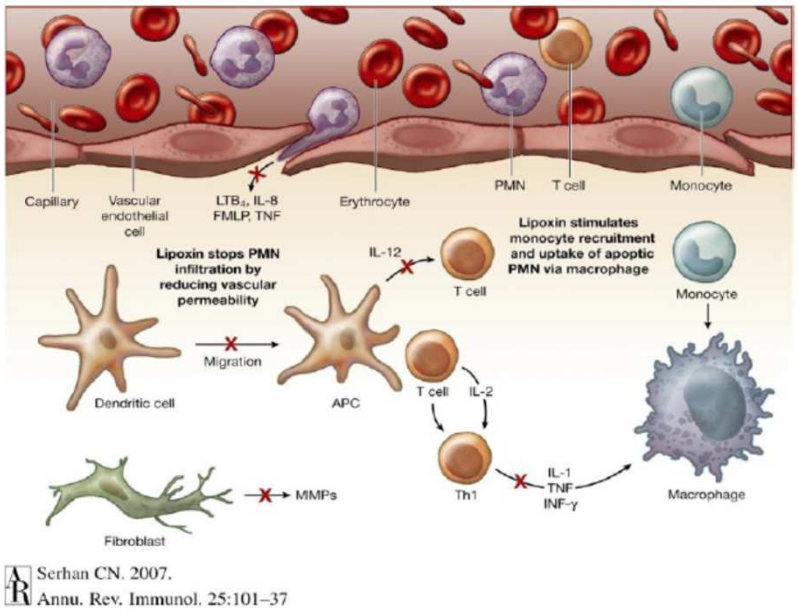

Serhan CN. 2007.
Annu. Rev. Immunol. 25:101–37

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Resolvins

-are metabolic byproducts of omega-3 fatty acids:
primarily eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

They act through G protein-coupled receptors (GPRs), although the mechanism is not yet clarified.

resolvins, together with protectins and maresins are separate classes of specialized pro-resolving lipid mediators with distinct functions, ranging from:

- limiting infection,
- altering neutrophil lifespan
- modulation of the adaptive immune system
- analgesic actions

e.g.: - RvE1, 18(S)-RvE1, and RvE2 inhibit the Leukotriene B4 receptor 1 which is the receptor for inflammation-promoting PUFA metabolites such as LTB4 and the R stereoisomer of 12-HETE

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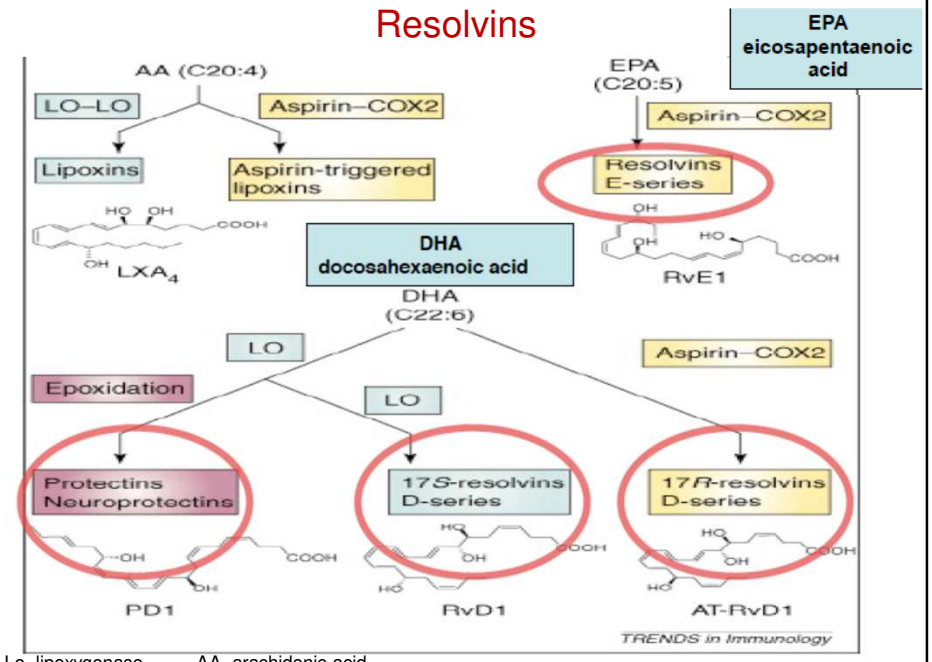

Lo=lipoxygenase AA=arachidonic acid

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Table 1
Summary of the major pro-resolving mediators and their roles as effectors of resolution.

Pro-resolving mediator	Type	Receptor	Broad functions
Annexin A1 and N-terminal peptides	Protein/peptide	FPR2/ALX [28,29].	Halt leukocyte migration [165], Promote bacterial clearance & efferocytosis [166–168]
Resolvins	SPM	7 Transmembrane GPCRs including FPR2/ALX [151], GPR32, BLT1, ChemR23 [28,30,33]	Limit neutrophil recruitment [169]. Prevent tissue and bone loss in models of periodontitis [152,170]. Promote bacterial clearance and efferocytosis. RvE1 regulates neutrophil apoptosis and enhances leukocyte drainage to lymphatics
Protectins	SPM	Not currently known [171,172], likely to be Gαi-coupled GPCR [173].	Inhibits neutrophil recruitment and regulates cytokine and chemokine production [118,174]. Enhances neuroprotection.
Lipoxins	SPM	FPR2/ALX [175], AhR, GPR32.	Halt leukocyte migration [165] and promote bacterial clearance, IL-10 production and efferocytosis [166–168]. Promote monocyte migration. Enhance leukocyte drainage to lymphatics
Maresins	SPM	Unknown, but unlikely to be PPARγ, cannabinoid receptor type I, FPR2/ALX or glucocorticoid receptor [176]	Potently blocks neutrophil recruitment [177], reduces ROS production in neutrophils [176]. Enhances wound healing and tissue regeneration. Switches macrophages from M1 to M2 phenotype.
Chemerin-derived peptides	Peptide	ChemR23 [178]	Limits neutrophil recruitment.
Extracellular Adenosine	Amino acid	A1 adenosine receptor, A2A adenosine receptor, A2B adenosine receptor, A3 adenosine receptor	Alternative macrophage activation [104]
Netrin-1	Secreted neuronal-guidance protein	A2B adenosine receptor	Suppresses hypoxia-elicited inflammation. Attenuates neutrophil transmigration [59,60].
Acetylcholine	Neurotransmitter	α7 nicotinic acetylcholine receptor (AChR)	Down-regulates cytokine synthesis via suppression of nuclear translocation of NFκB [52]

From: Seminars in Immunology 27 (2015) 149–160

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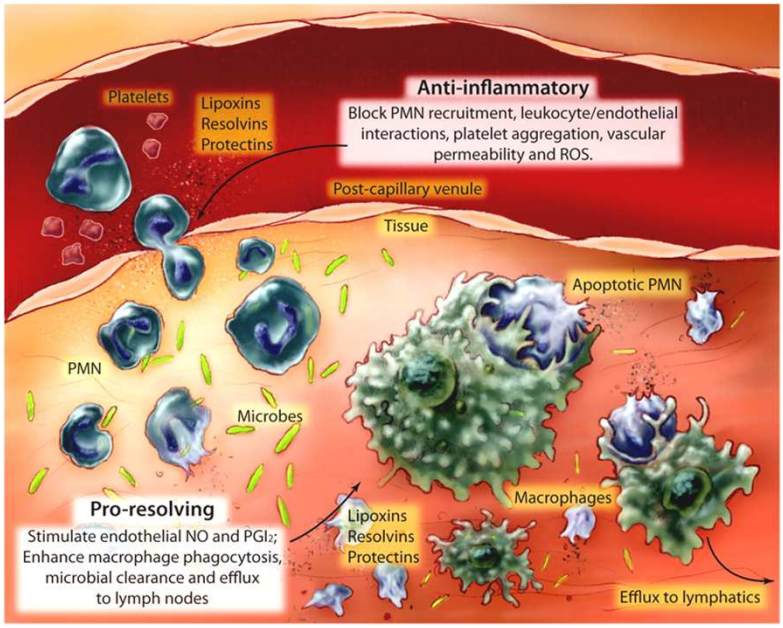
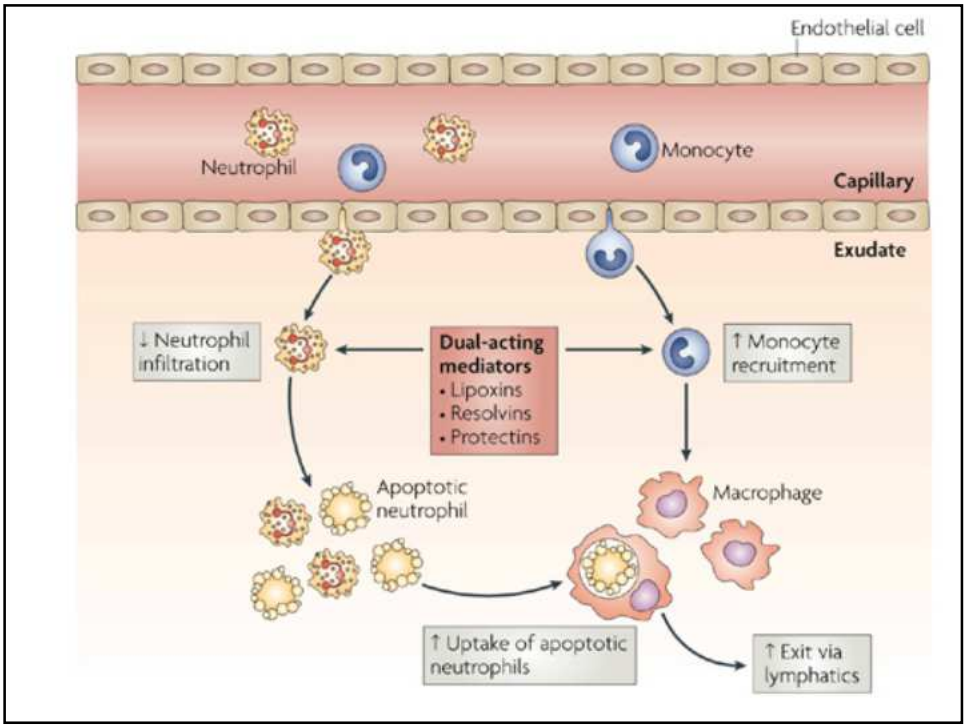

Platelets
Lipoxins
Resolvins
Protectins
Anti-inflammatory
Block PMN recruitment, leukocyte/endothelial interactions, platelet aggregation, vascular permeability and ROS.
Post-capillary venule
Tissue
Apoptotic PMN
PMN
Microbes
Macrophages
Pro-resolving
Stimulate endothelial NO and PGI2; Enhance macrophage phagocytosis, microbial clearance and efflux to lymph nodes
Lipoxins
Resolvins
Protectins
Efflux to lymphatics

37


Endothelial cell
Neutrophil
Monocyte
Capillary
Exudate
↓ Neutrophil infiltration
Dual-acting mediators
• Lipoxins
• Resolvins
• Protectins
↑ Monocyte recruitment
Apoptotic neutrophil
Macrophage
↑ Uptake of apoptotic neutrophils
↑ Exit via lymphatics

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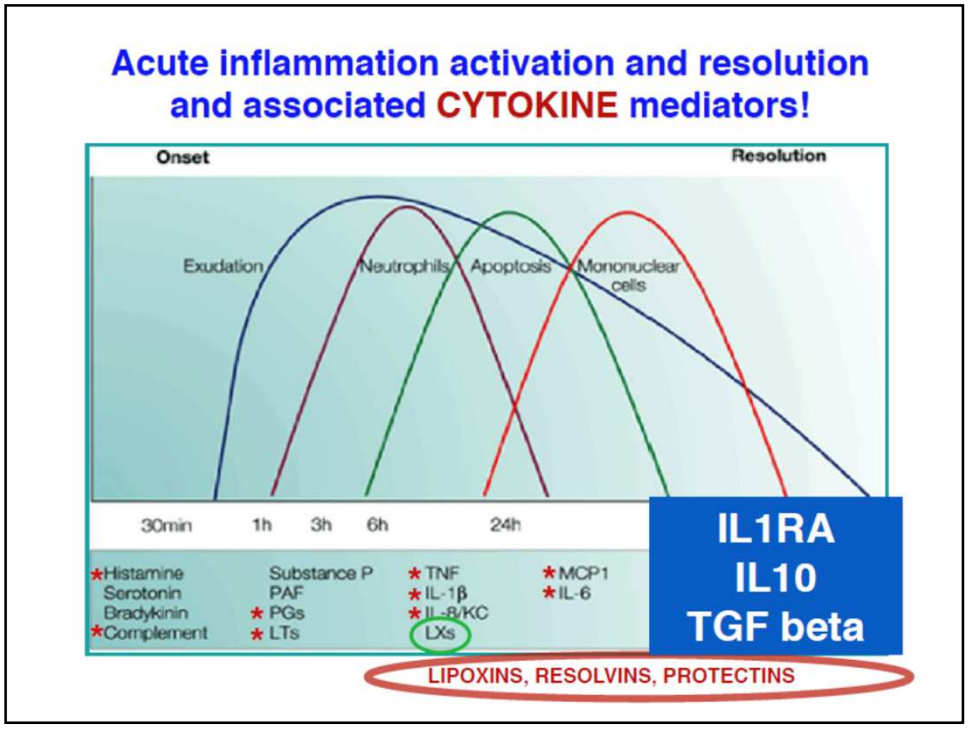
Acute inflammation activation and resolution
and associated CYTOKINE mediators!
Onset
Resolution
Exudation
Neutrophils
Apoptosis
Mononuclear cells
30min
1h
3h
6h
24h
*Histamine
Serotonin
Bradykinin
*Complement
Substance P
PAF
* PGs
* LTs
* TNF
* IL-1β
* IL-8/KC
LXs
* MCP1
* IL-6
IL1RA
IL10
TGF beta
LIPOXINS, RESOLVINS, PROTECTINS

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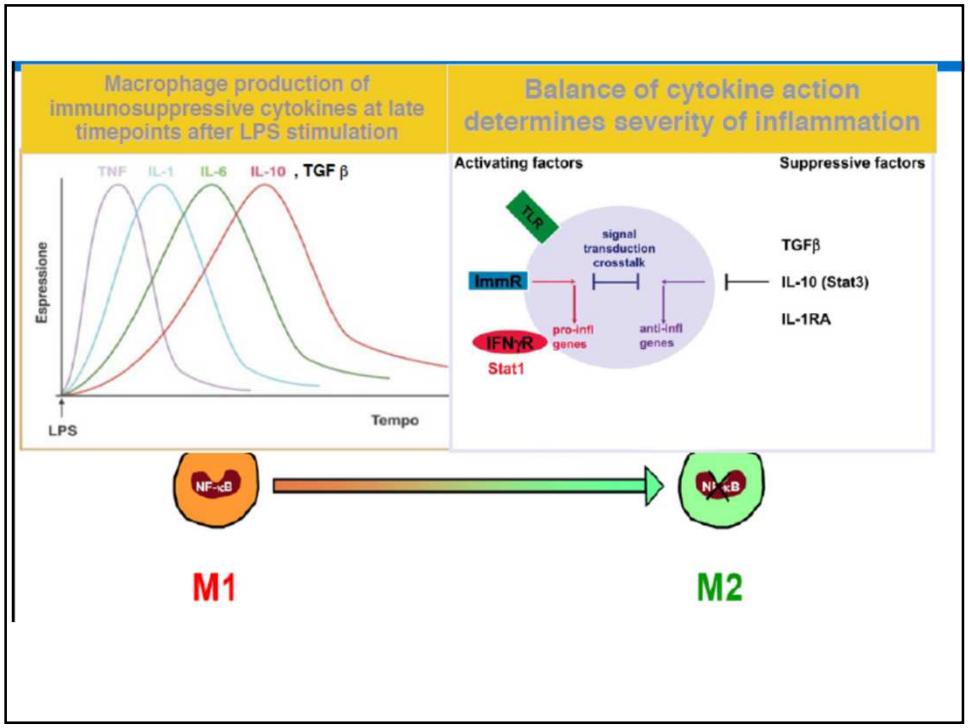
Macrophage production of immunosuppressive cytokines at late timepoints after LPS stimulation
TNF
IL-1
IL-6
IL-10
, TGF β
Espressione
LPS
Tempo
Balance of cytokine action determines severity of inflammation
Activating factors
Suppressive factors
TLR
ImmR
IFNγR
Stat1
signal transduction crosstalk
pro-infl genes
anti-infl genes
TGFβ
IL-10 (Stat3)
IL-1RA
NF-κB
M1
M2

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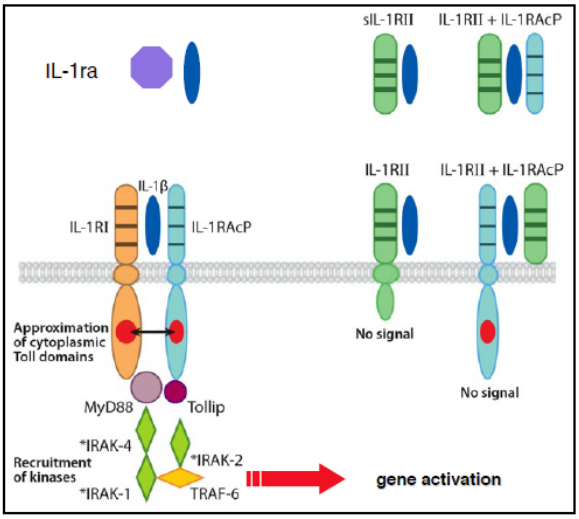
In the inflammation resolution, macrophages M2 produce the soluble IL-1 receptor antagonist (IL-1ra)



The expression of different receptor molecules and of signalling modulators is regulated!

IL-1 RI: functional receptor
IL-1 RII: "decoy" receptor
IL-1ra: soluble receptor antagonist
IL-1RAcP: accessory protein for IL-1 RI and IL-1 RII

Tollip: inhibitor of IL-1R signalling pathway

A family of IL-1 receptors!

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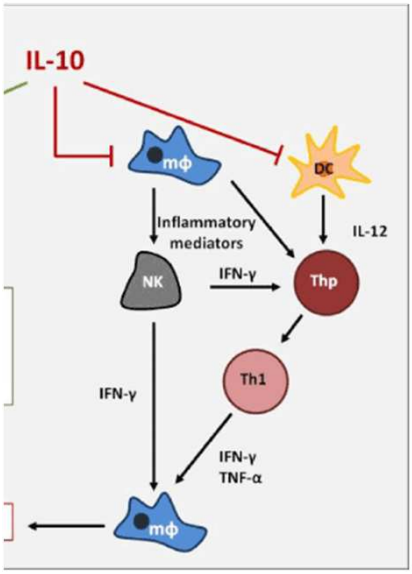

IL-10 not only inhibits the production of pro-inflammatory mediators but also augments the production of anti-inflammatory factors including soluble TNF-α receptors and IL-1RA.

IL-10 down-regulates the expression of MHC class II molecules (both constitutive and IFN-γ-induced), as well as that of co-stimulatory molecule, CD86, and adhesion molecule, CD58.

It is an inhibitor of IL-12 production from monocytes, which is required for the production of specific cellular defense response

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In the inflammation resolution, macrophages M2 produce TGF-beta

Angiogenic or angiostatic effects
Reduced adhesion molecule expression
Macrophage deactivation
Chemokine and cytokine repression
Myofibroblast differenciation
Fibroblast proliferation
Extracellular matrix protein synthesis

Transforming growth factor-ß (TGF-ß) has been considered an anti-inflammatory cytokine responsible for the bland removal of apoptotic cells. To date both decreased (favoring predominance of inflammation) and increased (favoring resolution of inflammation but potentially pro-fibrotic) responses have been demonstrated

The inflammatory response and cardiac repair after myocardial infarction.
Nah DY, Rhee MY.
Korean Circ J. 2009, 39(10):393-8.

Clearance of apoptotic cells: TGF-ß in the balance between inflammation and fibrosis
Robert M. Clancy and Jill P. Buyon
J Leukoc Biol. 2003 Dec;74(6):959-60.

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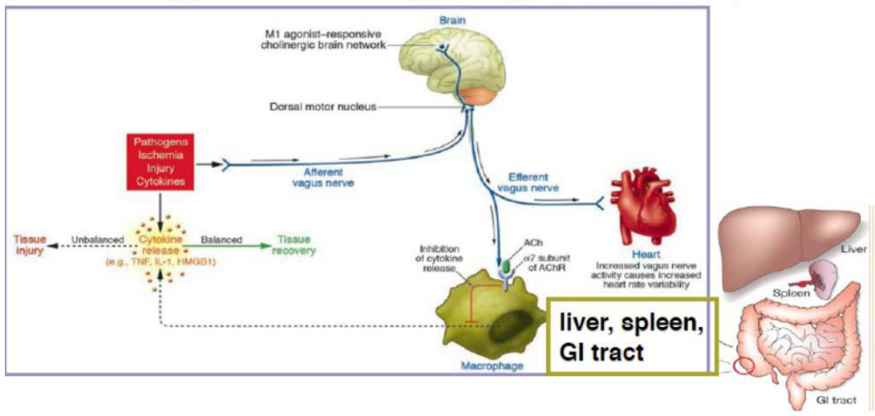
The cholinergic anti-inflammatory pathway: The inflammatory reflex!



Inflammatory products produced in damaged tissues activate afferent signals that are relayed to the nucleus tractus solitarius. Subsequent activation of vagus efferent activity inhibits cytokine synthesis through the activation of a cholinergic anti-inflammatory pathway ('the inflammatory reflex') mediated by signals delivered by the α7 subunit of the AChR on macrophages.

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The crosstalk between immune system and autonomic nervous system regulates inflammation

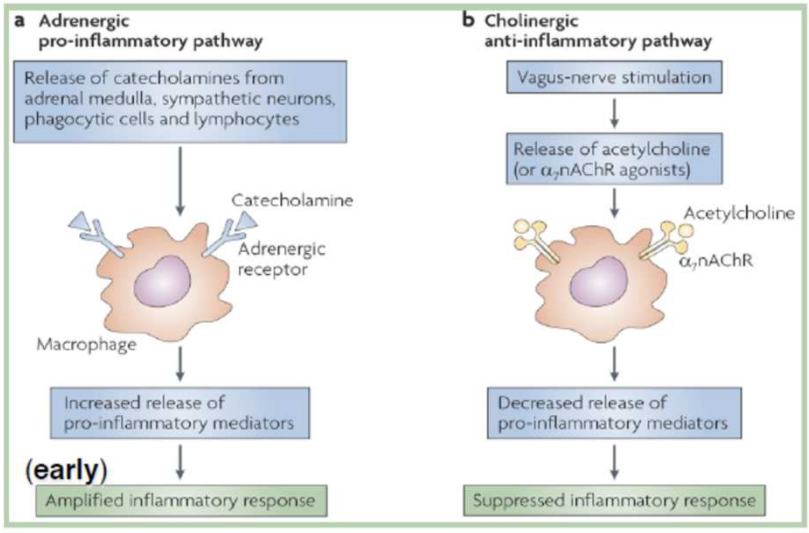

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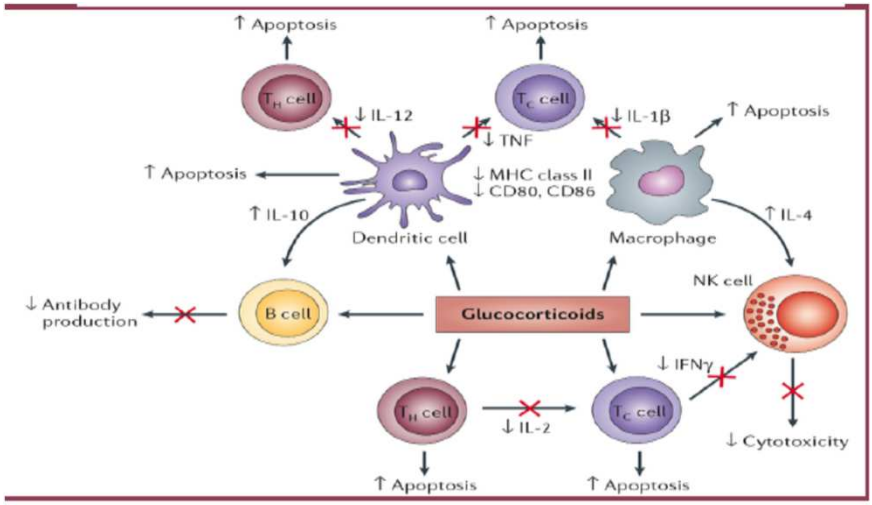
Figure 2 | **Effects of glucocorticoids on immune-cell populations.** Glucocorticoids act on immune cells both directly and indirectly to suppress the induction of pro-inflammatory responses. They inhibit the production of pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and tumour-necrosis factor (TNF), while promoting the production of anti-inflammatory cytokines, such as IL-10, by macrophages and dendritic cells. They also promote apoptosis of macrophages, dendritic cells and T cells, leading to inhibition of immune responses. IFNγ, interferon-γ; NK cell, natural killer cell; T_C, cytotoxic T cell; T_H, T helper cell.



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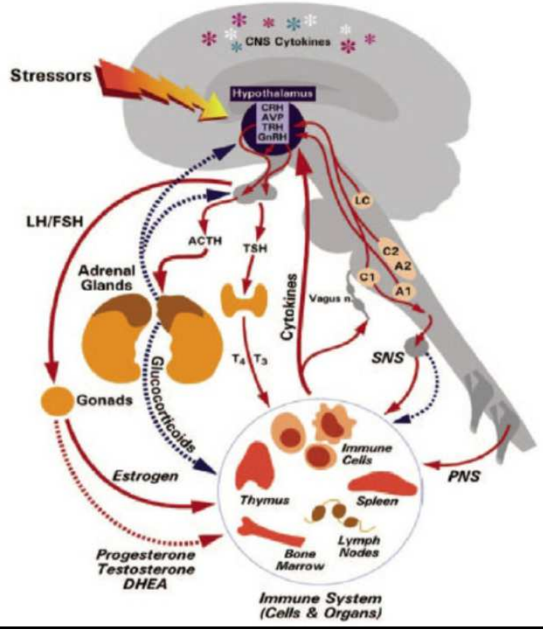
The complexity of the bidirectional communication between the hypothalamic-pituitary axes, the nervous system, and the immune system!!!!!



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