Inflammation

VLA, October 17, 2017

Inflammation

- Inflammation is the response of living tissue to damage. The acute inflammatory response has 3 main functions.
- The affected area is occupied by a transient material called the acute inflammatory exudate. The exudate carries proteins, fluid and cells from local blood vessels into the damaged area to mediate local defences.
- If an infective causative agent (e.g. bacteria) is present in the damaged area, it can be destroyed and eliminated by components of the exudate.
- The damaged tissue can be broken down and partialy liquefied, and the debris removed from the site of damage.

Etiology

- The cause of acute inflammation may be due to physical damage, chemical substances, micro-organisms or other agents.
- The inflammatory response consists of changes in blood flow, increased permeability of blood vessels and escape of cells from the blood into the tissues. The changes are essentially the same whatever the cause and wherever the site.
- Acute inflammation is short-lasting, lasting only a few days.

Inflammation

- In all these situations, the inflammatory stimulus will be met by a series of changes in the human body; it will induce production of certain cytokines and hormones which in turn will regulate haematopoiesis, protein synthesis and metabolism.
- Most inflammatory stimuli are controlled by a normal immune system. The human immune system is divided into two parts which constantly and closely collaborate - *the innate and the adaptive immune system.*

Inflammation

- ***The innate system*** reacts promptly without specificity and memory. *Phagocytic cells* are important contributors in innate reactivity together with *enzymes*, *complement activation and acute phase proteins*.
- When phagocytic cells are activated, the synthesis of different *cytokines* is triggered. These cytokines are not only important in regulation of the innate reaction, but also for induction of the adaptive immune system. There, specificity and memory are the two main characteristics.

Inflammation

- In order to induce a strong ***adaptive immune response***, some *lymphocytes* must have been educated to recognise the specific antigen on the antigen-presenting cell (APC) in context of self *major histocompatibility molecules*. The initial recognition will mediate a *cellular immune reaction, production of antigen-specific antibodies or a combination of both*. Some of the cells which have been educated to recognise a specific antigen will survive for a long time with the memory of the specific antigen intact, rendering the host "immune" to the antigen.

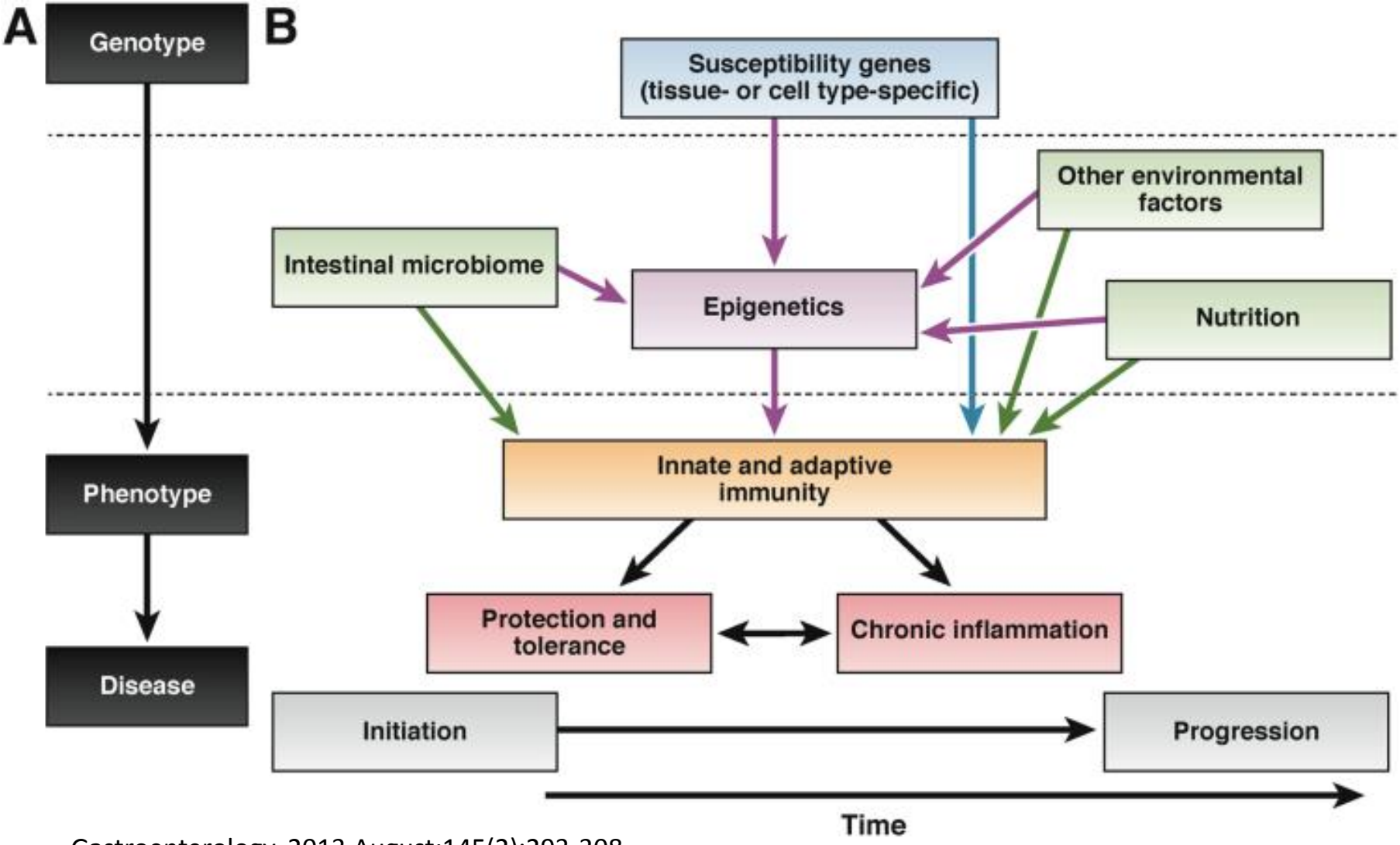
Differences between innate (non-specific) and specific (adaptive) immunologic reaction of organism

- **Non-specific Immunity**
- Response is **antigen-independent**
- There is **immediate** maximal response
- **Not antigen-specific**
- Exposure results in **no immunologic memory**

- **Specific Immunity**
- Response is **antigen-dependent**
- There is a **lag time** between exposure and maximal response
- **Antigen-specific**
- Exposure results in **immunologic memory**

Changes compared with normal state	Increase	Decrease
Cellular	phagocytotic cells (in circulation and at the site of inflammation)	erythrocytes
Metabolic	acute phase proteins serum Cu protein catabolism gluconeogenesis	serum Fe serum Zn albumin synthesis transthyretin transferrin
Endocrinological	glucagon insulin ACTH GH T4 cortisol aldosterone vasopressin	T3 TSH

Role of epigenetics in pathogenesis of diseases

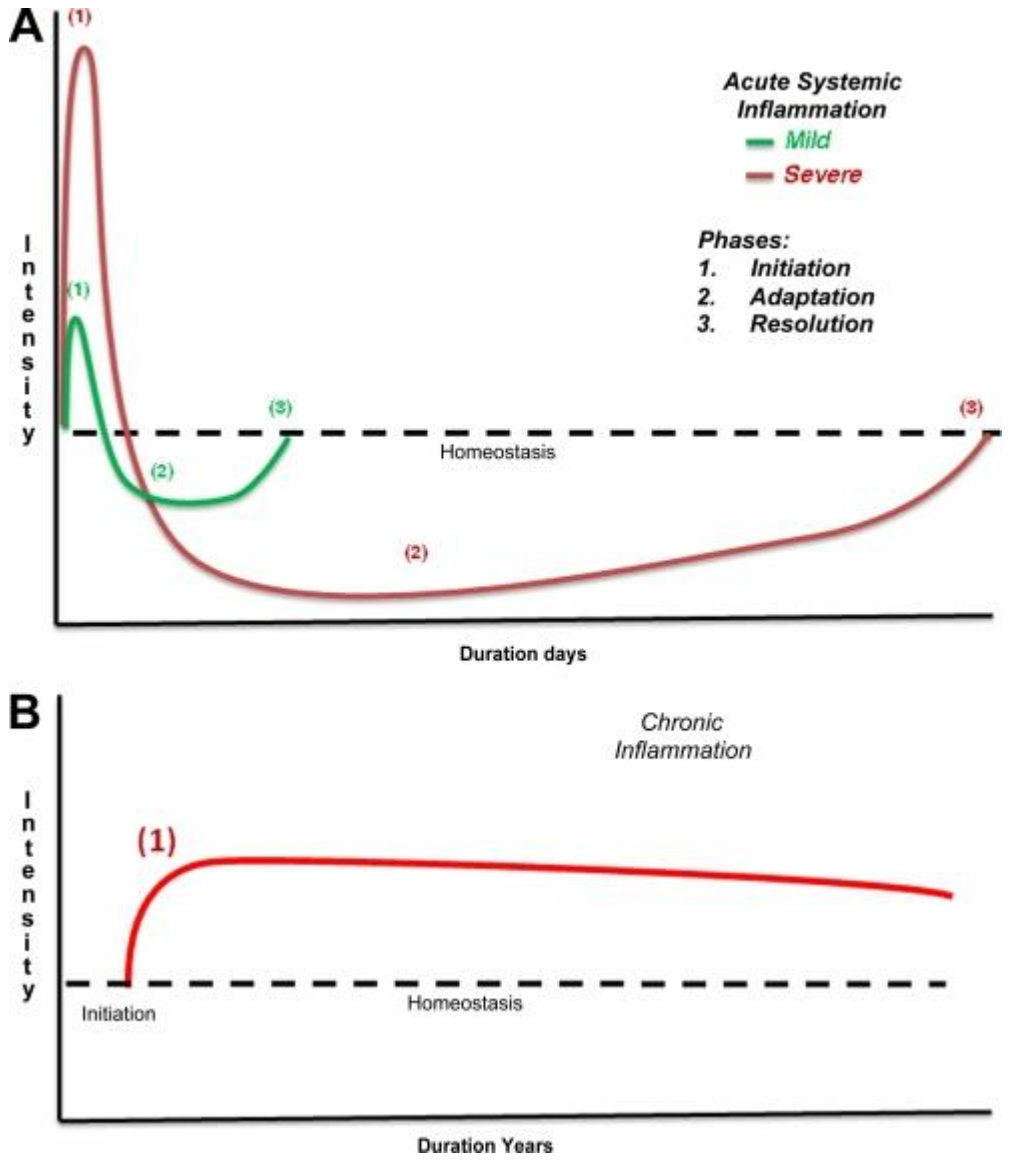


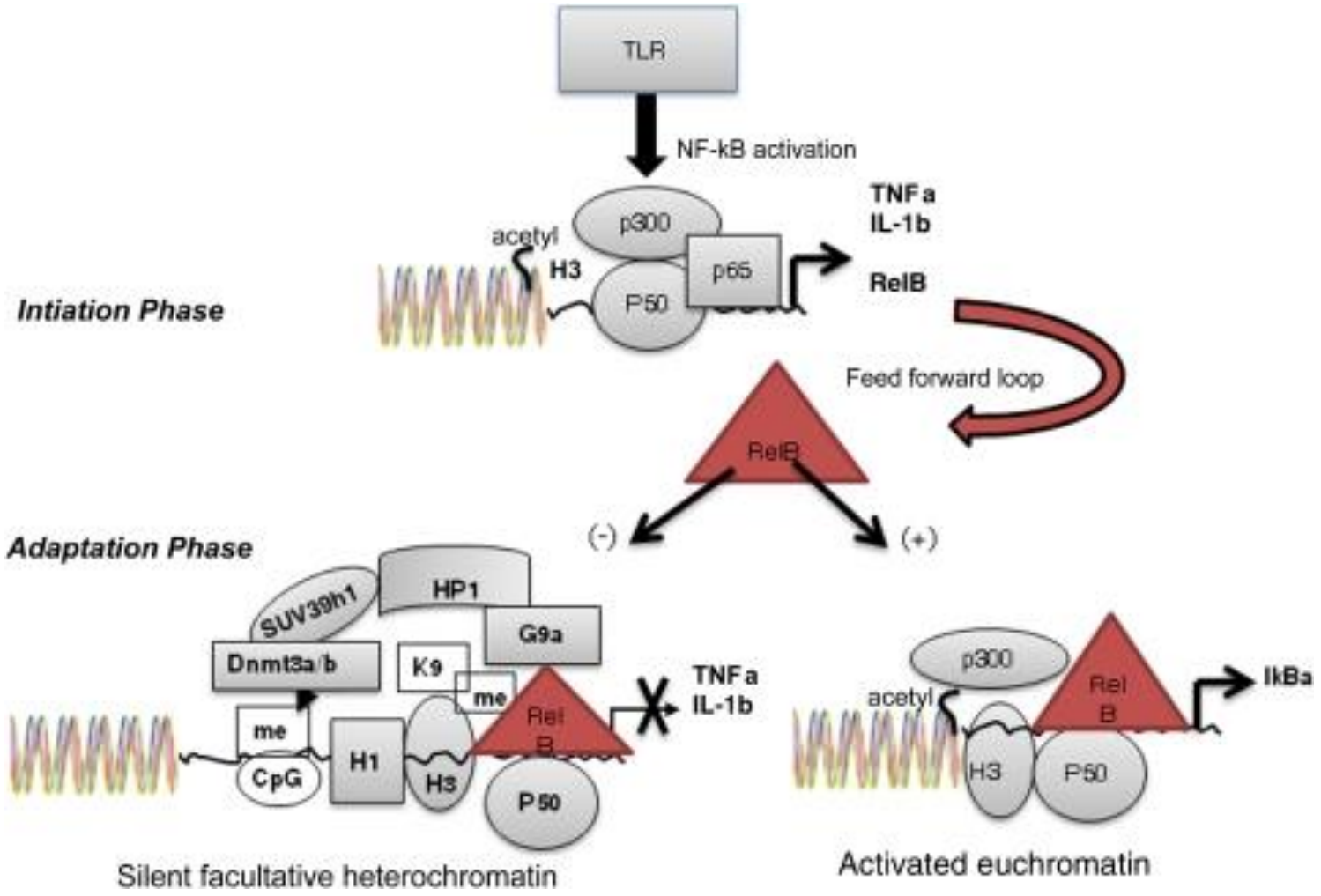
Gastroenterology. 2013 August;145(2):293-308.

TABLE III. Examples of environmental exposure on clinical phenotype mediated through epigenetic modifications: current examples

Effector	Epigenetic regulation	Clinical phenotype	Genes (cell type)	References
Allergens (OVA)	Histone deacetylation	AA, COPD	*LAT* ($CD4^+$)	48
	Histone acetylation	AA	*PDE4E* ($CD4^+$)	
			ACLS3 ($CD4^+$)	
Microbes/farm environment	DNA methylation	AA	*RAD50* (PBMC)	50,51
			IL13 (PBMC)	
			IL4 (PBMC)	
			IFNG ($CD4^+$)	
Tobacco smoke	DNA methylation	COPD	*GSTM1/GSTP* (macrophages)	61-63
	Histone acetylation	COPD	*TNF* (macrophages)	
	Histone deacetylation	COPD		
Diesel exhaust/polycyclic aromatic hydrocarbons	Histone deacetylation	COPD, AA	*FOXP3* ($CD4^+$)	4,60,73,75
	DNA methylation	A	*IFNG* ($CD4^+$)	
			FOXP3 ($CD4^+$)	
			ACSL3 ($CD4^+$)	
Folic acid	DNA methylation	AA	*ZFP57* ($CD4^+$)	83,84
	Histone Acetylation	AA		
Fish oil	Histone deacetylation	Cell-culture analysis	*IL6* (macrophages)	91,92
			TNF (macrophages)	
Lifestyle (obesity)	DNA methylation	AA	*CCL5*, *IL2RA*, and *TBX21* (PBMC)	100
Stress	DNA methylation	AA	*ADCYAP1R1* (PBMC)	102

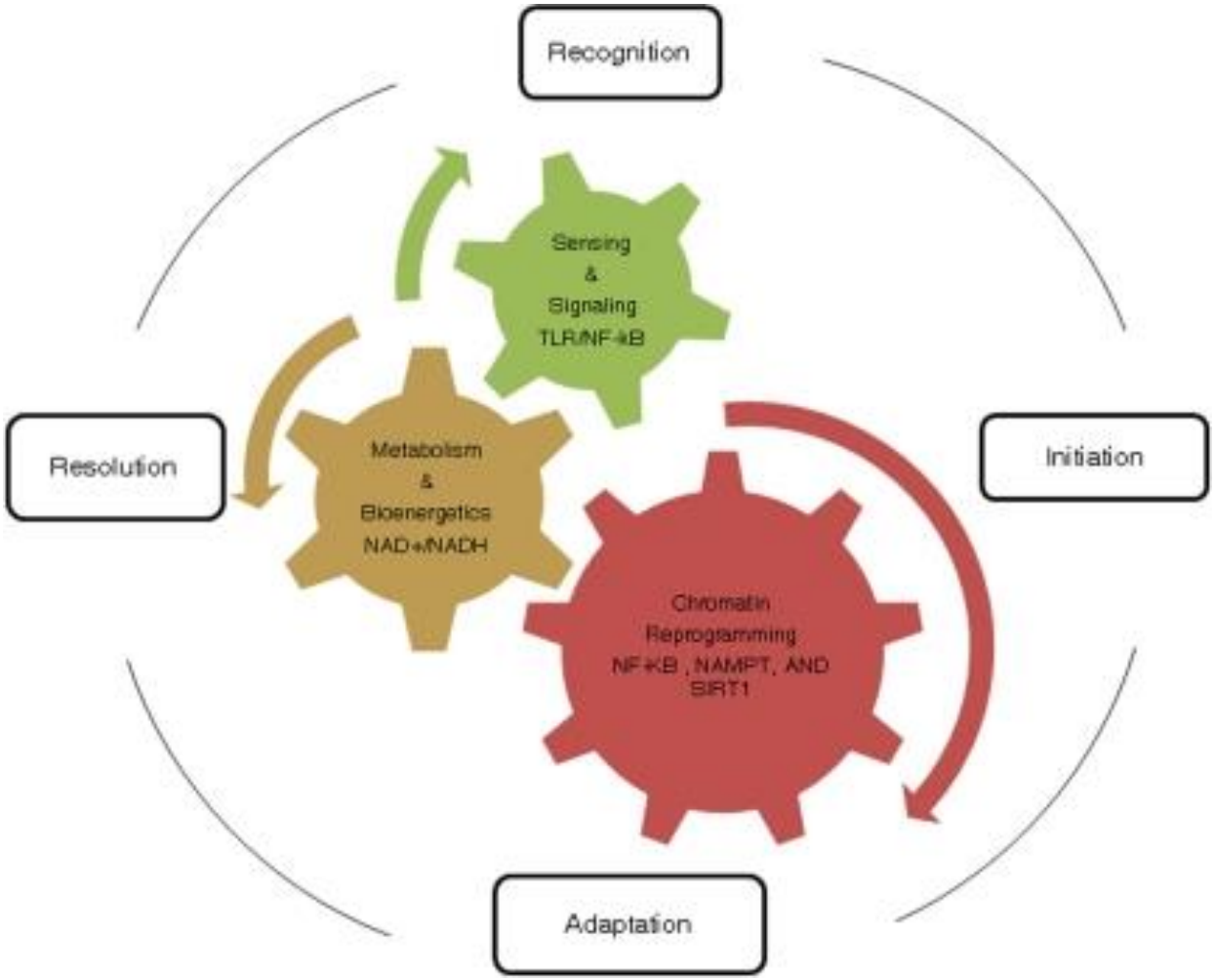
A, Nonallergic asthma; *AA*, allergic asthma; *COPD*, chronic obstructive pulmonary disease; *LAT*, linker for activation of T cells; *TBX21*, T-box transcription factor.


A
(1)
Acute Systemic Inflammation
Mild
Severe
Phases:
1. Initiation
2. Adaptation
3. Resolution
Intensity
(1)
(3)
(3)
(2)
Homeostasis
(2)
Duration days
B
Chronic Inflammation
Intensity
(1)
Initiation
Homeostasis
Duration Years



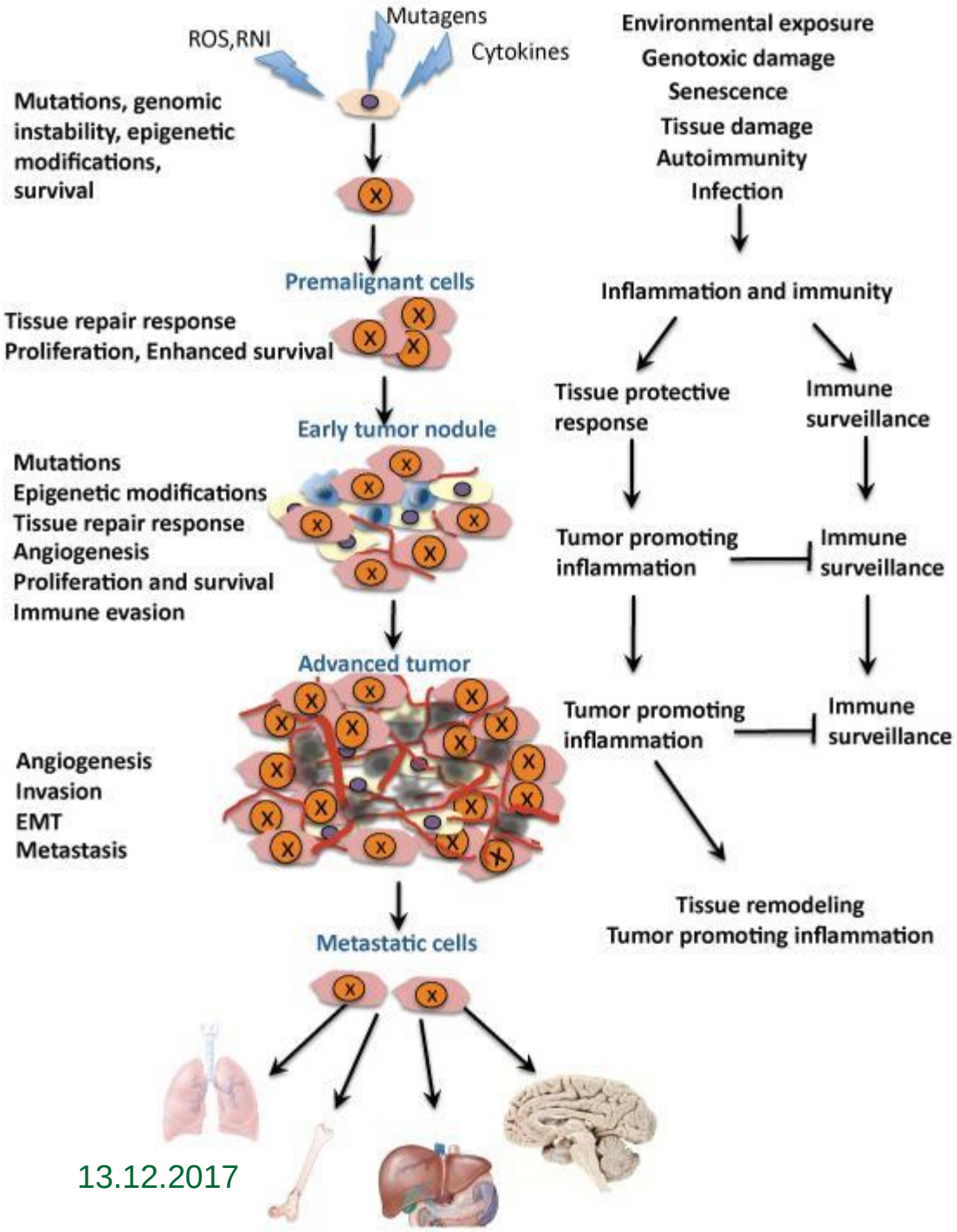
Epigenetic remodelling of chromatin and reprogramming od genes during acute systemic inflammation.

Leukoc Biol. Sep 2011; 90(3): 439–446.



Integration between bioenergetics and epigenetics during acute systemic inflammation

Leukoc Biol. Sep 2011; 90(3): 439–446.



Chronic inflammation potentionally takes part in all phases of tumorigenesis

Systemic manifestation of inflammation

→ 1. Increase of body temperature (fever)

→ 2. Acute phase reaction

Systemic effects of acute inflammation

- **Pyrexia**

  Polymorphs and macrophages produce compounds known as *endogenous pyrogens* which act on the hypothalamus to set the thermoregulatory mechanisms at a higher temperature. Release of endogenous pyrogen is stimulated by phagocytosis, endotoxins and immune complexes.
- **Constitutional symptoms**

  Constitutional symptoms include *malaise, anorexia and nausea*. *Weight loss* is common when there is extensive chronic inflammation.
- Local or systemic lymph node enlargement commonly accompanies inflammation, while splenomegaly is found in certain specific infections (e.g. malaria, infectious mononucleosis).

Systemic effects of acute inflammation

- **Haematological changes**
- *Increased erythrocyte sedimentation rate*. An increased erythrocyte sedimentation rate is a non-specific finding in many types of inflammation.
- *Leukocytosis*. Neutrophilia occurs in pyogenic infections and tissue destruction; eosinophilia in allergic disorders and parasitic infection; lymphocytosis in chronic infection (e .g. tuberculosis), many viral infections and in whooping cough; and monocytosis occurs in infectious mononucleosis and certain bacterial infections (e.g. tuberculosis, typhoid). *Anaemia*. This may result from blood-loss in the inflammatory exudate (e.g. in ulcerative colitis), haemolysis (due to bacterial toxins), and 'the anaemia of chronic disorders' due to toxic depression of the bone marrow.
- **Amyloidosis**
- Longstanding chronic inflammation (for example, in rheumatoid arthritis, tuberculosis and bronchiectasis), by elevating serum amyloid A protein (SAA), may cause amyloid to be deposited in various tissues resulting in secondary (reactive) amyloidosis

Macroscopic appearance of acute inflammation

- The cardinal signs of acute inflammation are modified according to the tissue involved and the type of agent provoking the inflammation. Several descriptive terms are used for the appearances.
- **Serous inflammation**.
- **Catarrhal inflammation**
- **Fibrinous inflammation**
- **Haemorrhagic inflammation**
- **Suppurative (purulent) inflammation**
- **Membranous inflammation**
- **Pseudomembranous inflammation**
- **Necrotising (gangrenous) inflammation**.

Acute inflammation

- can be caused by microbial agents such as
- viruses, bacteria, fungi and parasites
- by non-infectious inflammatory stimuli, as in rheumatoid arthritis and graft-versus-host disease
- by tissue necrosis as in cancer
- by burns and toxic influences caused by drugs or radiation

Early Stages of Acute Inflammation

The acute inflammatory response involves three processes:

- changes in vessel calibre (=vasodilation) and, consequently, slower blood flow
- increased vascular permeability and formation of the fluid exudate
- formation of the cellular exudate by emigration of the neutrophil polymorphs into the extravascular space.

Early Stages of Acute Inflammation

The steps involved in the acute inflammatory response are:

- Small blood vessels adjacent to the area of tissue damage initially become *dilated* with increased blood flow, then flow along them slows down.
- Endothelial cells *swell* and partially *retract* so that they no longer form a completely intact internal lining.
- The vessels become *leaky,* permitting the passage of water, salts, and some small proteins from the plasma into the damaged area ***(exudation).*** One of the main proteins to leak out is the small soluble molecule, fibrinogen.
- Circulating neutrophil polymorphs initially adhere to the swollen endothelial cells (*margination*), then actively migrate through the vessel basement membrane (*emigration*), passing into the area of tissue damage.
- Later, small numbers of blood monocytes (macrophages) migrate in a similar way, as do lymphocytes.

The acute phase reaction

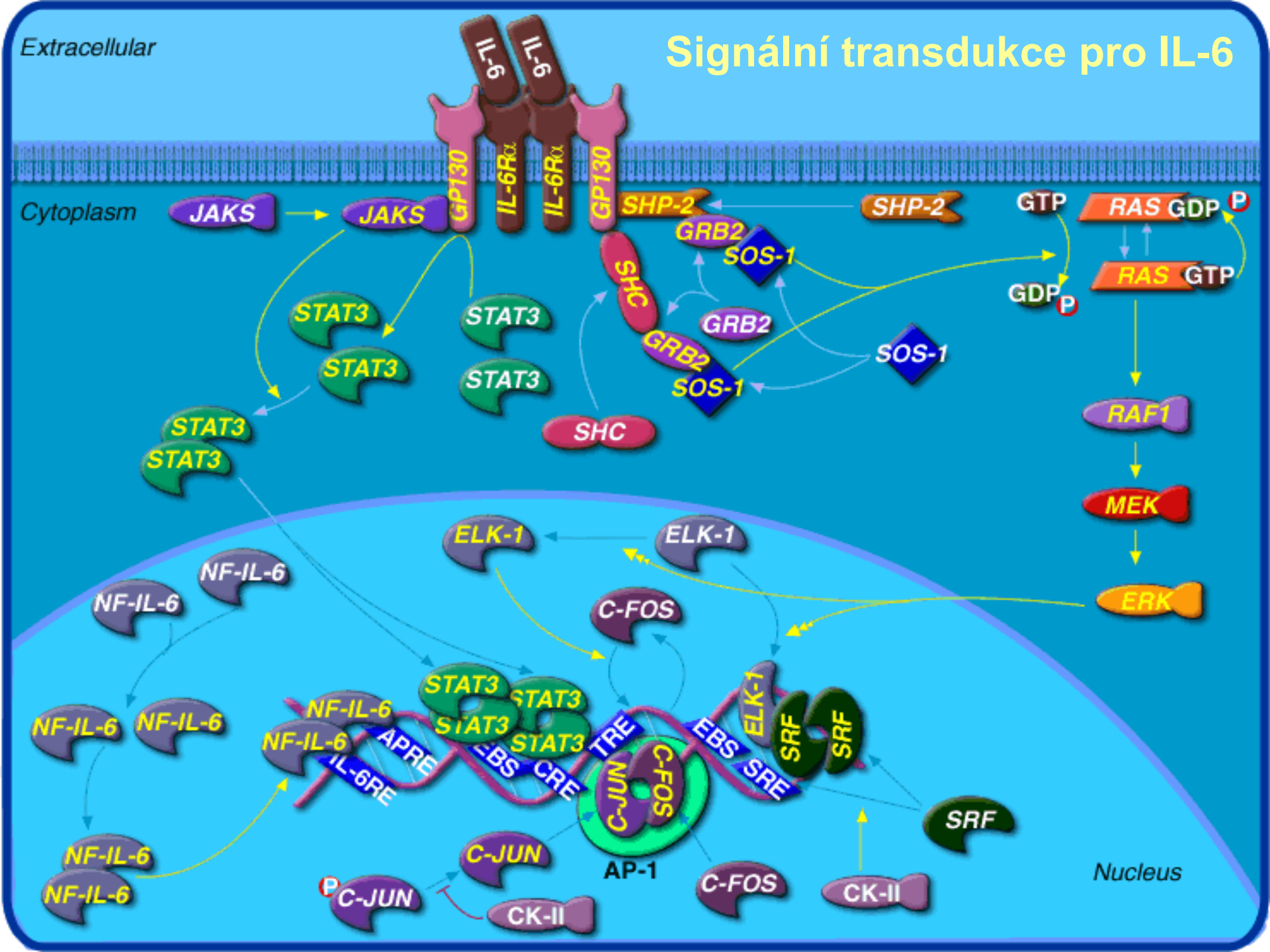
- In the acute phase reaction, several biochemical, *metabolic, hormonal and cellular changes* take place in order to fight the stimulus and re-establish a normal functional state in the body.
- An ***increase in the number of granulocytes*** will *increase the phagocytotic capacity*, *an increase in scavengers* will potentiate the capability to neutralise free oxygen radicals, and *an increase in metabolic rate* will increase the energy available for cellular activities, despite a reduced food intake.
- Some of these changes can explain the symptoms of an acute phase reaction, which are typically fever, tiredness, loss of appetite and general sickness, in addition to local symptoms from the inducer of the acute phase.

General and local clinical symptoms of the acute phase reaction

General symptoms	Local symptoms
fever	calor
increased heart rate	rubor
hyperventilation	dolor
tiredness	tumor
loss of appetite	functio laesa

Biochemistry and physiology of the acute phase reaction

- The acute phase reaction is the body's first-line inflammatory defence system, functioning without specificity and memory, and in front of, and in parallel with, the adaptive immune system.
- *CRP* is a major acute phase protein acting mainly through Ca2+-dependent binding to, and clearance of, different target molecules in microbes, cell debris and cell nuclear material.
- In an acute phase reaction there may be a more than 1000-fold increase in the serum concentration of CRP. CRP is regarded as an important member of the family of acute phase proteins, having evolved almost unchanged from primitive to advanced species.


Signální transdukce pro IL-6
Extracellular
Cytoplasm
Nucleus
IL-6
IL-6
IL-6Rα
IL-6Rα
GP130
GP130
JAKS
JAKS
SHP-2
SHP-2
GRB2
SOS-1
SHC
GRB2
SOS-1
GRB2
SOS-1
SHC
GTP
RAS GDP
P
RAS GTP
GDP
P
RAF1
MEK
ERK
STAT3
STAT3
STAT3
STAT3
STAT3
STAT3
ELK-1
ELK-1
NF-IL-6
NF-IL-6
NF-IL-6
NF-IL-6
NF-IL-6
NF-IL-6
NF-IL-6
NF-IL-6
C-FOS
APRE
IL-6RE
EBS
CRE
TRE
C-JUN
C-FOS
EBS
SRE
ELK-1
SRF
SRF
SRF
AP-1
C-JUN
P
C-JUN
CK-II
CK-II
C-FOS

The acute phase proteins

- Induction of the acute phase reaction means changes in the synthesis of many proteins which can be measured in plasma.
- Regulation of protein synthesis takes place at the level of both transcription (DNA, RNA) and translation to protein.
- The cells have intricate systems for up- and down-regulation of protein synthesis, initiated by a complex system of signals induced in the acute phase reaction.

The acute phase proteins

Most of the proteins with increased serum concentrations have functions which are easily related

- to limiting the negative effects of the acute phase stimulus or
- to the repair of inflammatory induced damage.

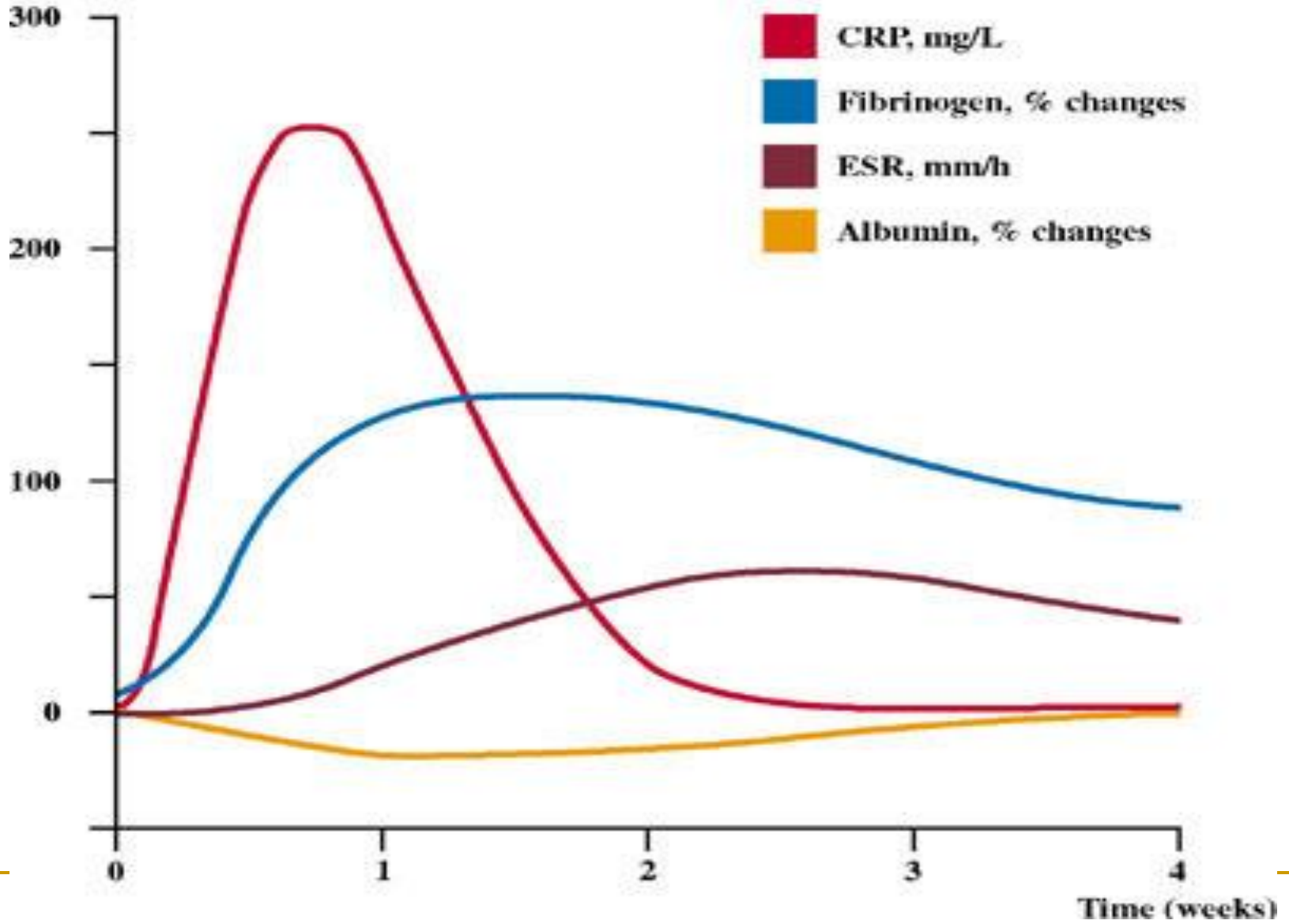
Examples are enzyme inhibitors limiting the negative effect of enzymes released from neutrophils, scavengers of free oxygen radicals, increase in some transport proteins and increased synthesis and activity of the cascade proteins such as coagulation and complement factors. The synthesis may be upregulated even if plasma levels are normal, due to increased consumption of acute phase proteins.

Function	Acute phase protein	Increase up to
Protease inhibitors	"α_1-antitrypsin α"$_1$-antichymotrypsin	4 fold 6 fold
Coagulation proteins	fibrinogen prothrombin factor VIII plasminogen	8 fold
Complement factors	C1s C2b C3, C4, C5 C9 C5b	2 fold
Transport proteins	haptoglobin haemopexin ferritin	8 fold 2 fold 4 fold
Scavenger proteins	ceruloplasmin	4 fold
Miscellaneous	α_1-acid glycoprotein (orosomucoid) serum amyloid A protein C-reactive protein	4 fold 1000 fold 1000 fold

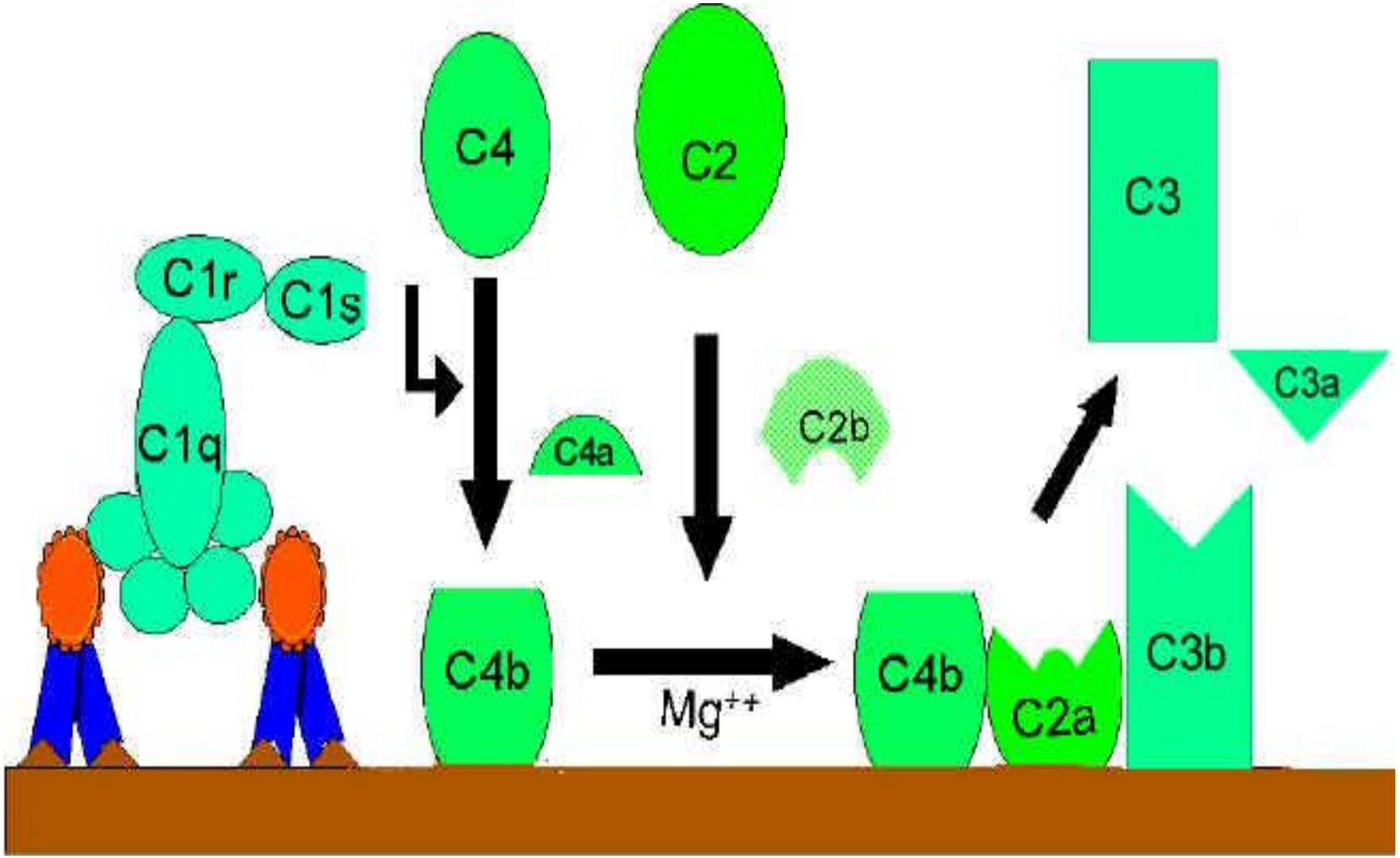
CRP functions

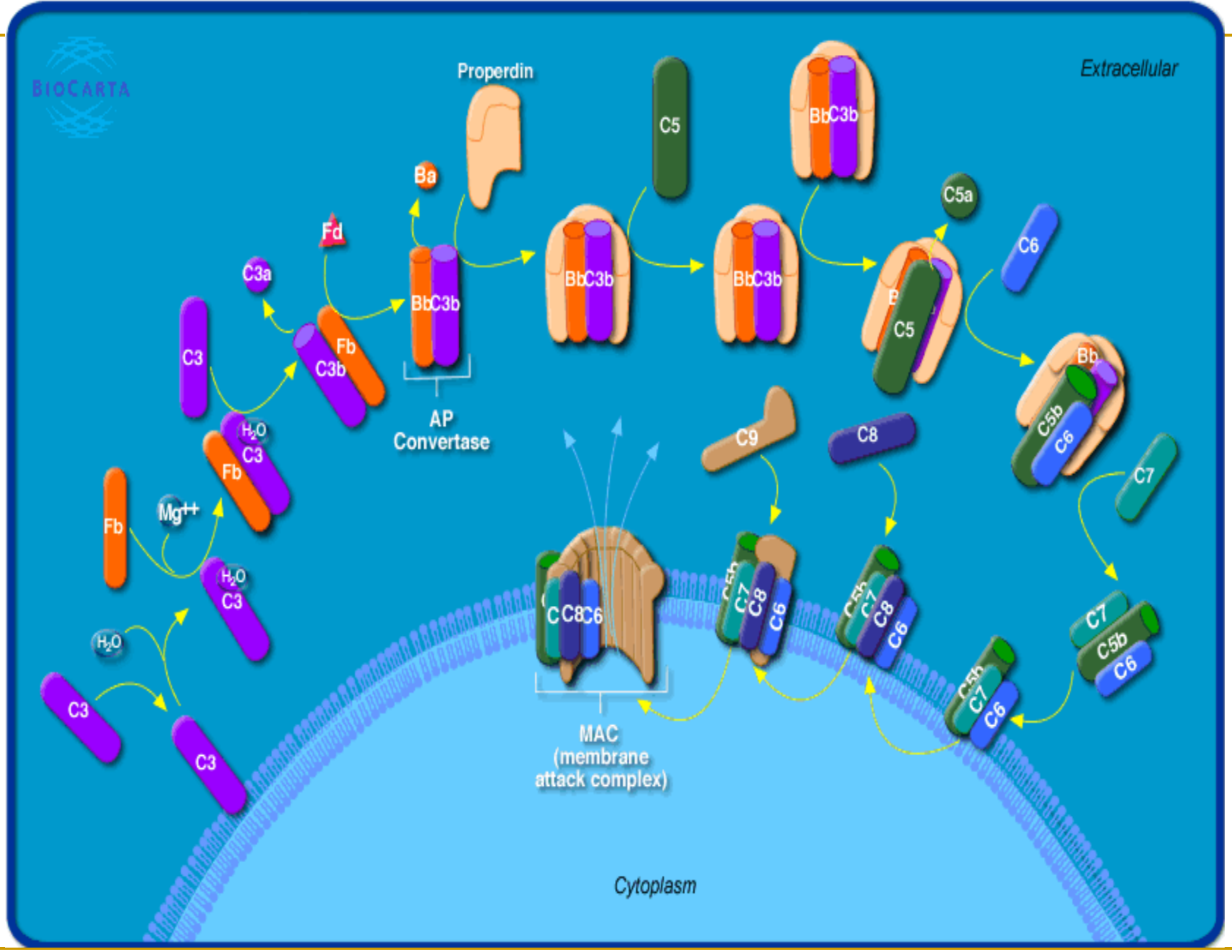
- Most functions of CRP are easily understood in the context of the body's defences against infective agents.
- The bacteria are ***opsonised*** by CRP and ***increased phagocytosis*** is induced.
- CRP ***activates complement*** with the split product being ***chemotactic***, increasing the number of phagocytes at the site of infection. Enzyme inhibitors protect surrounding tissue from the damage of enzymes released from the phagocytes.
- CRP ***binds to chromatin from dead cells and to cell debris*** which are cleared from the circulation by phagocytosis, either directly or by binding to Fc-, C3b- or CRP-specific receptors. ***Platelet aggregation is inhibited***, decreasing the possibility of thrombosis.
- CRP ***binds to low density lipoprotein (LDL)*** and may clear LDL from the site of atherosclerotic plaques by binding to cell surface receptors on phagocytic cells.

Typical changes of CRP, fibrinogen, ESR (erythrocyte sedimentation rate) and albumin during an acute phase reaction



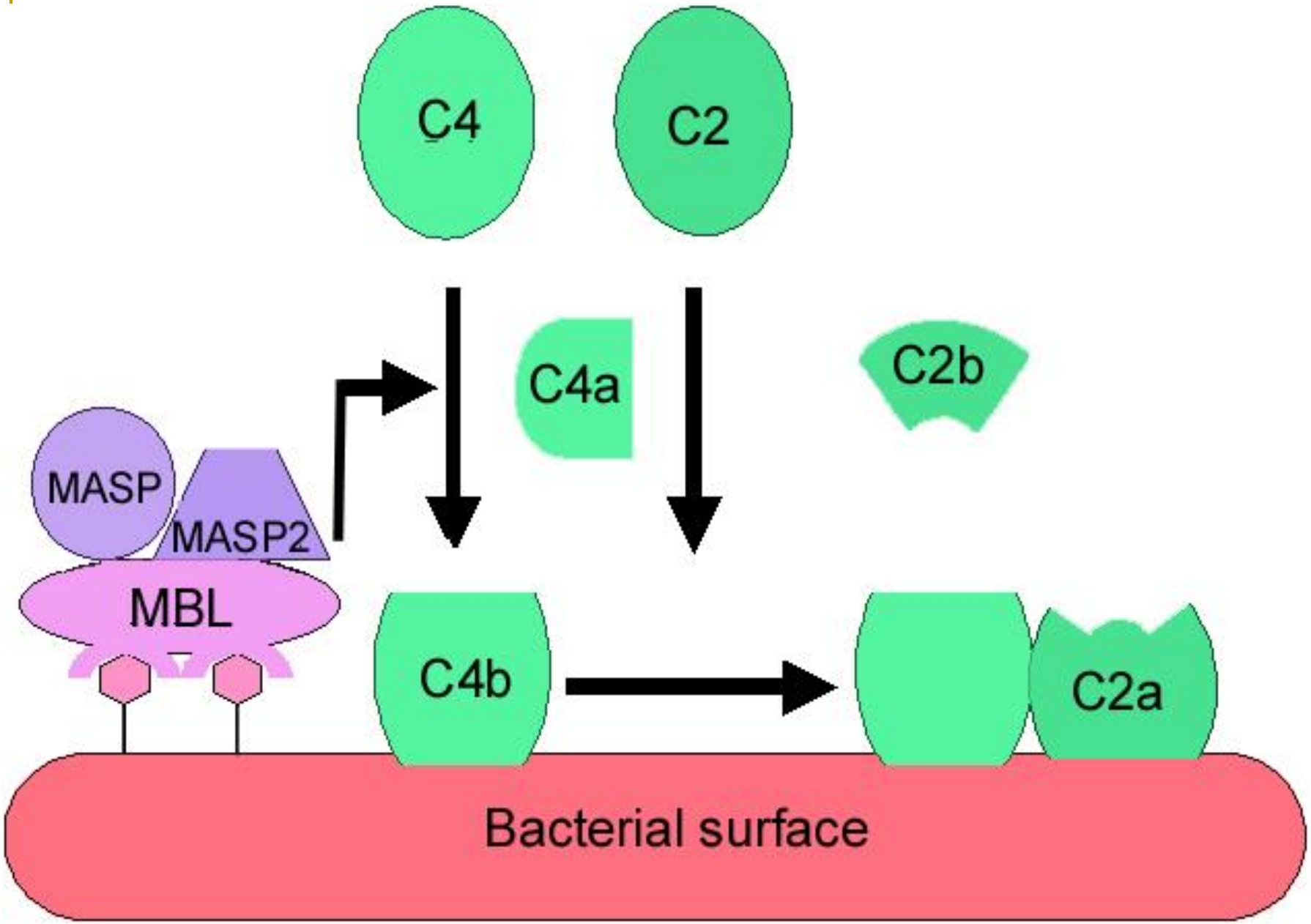
Classical pathway activation





Alternative pathway of complement activation

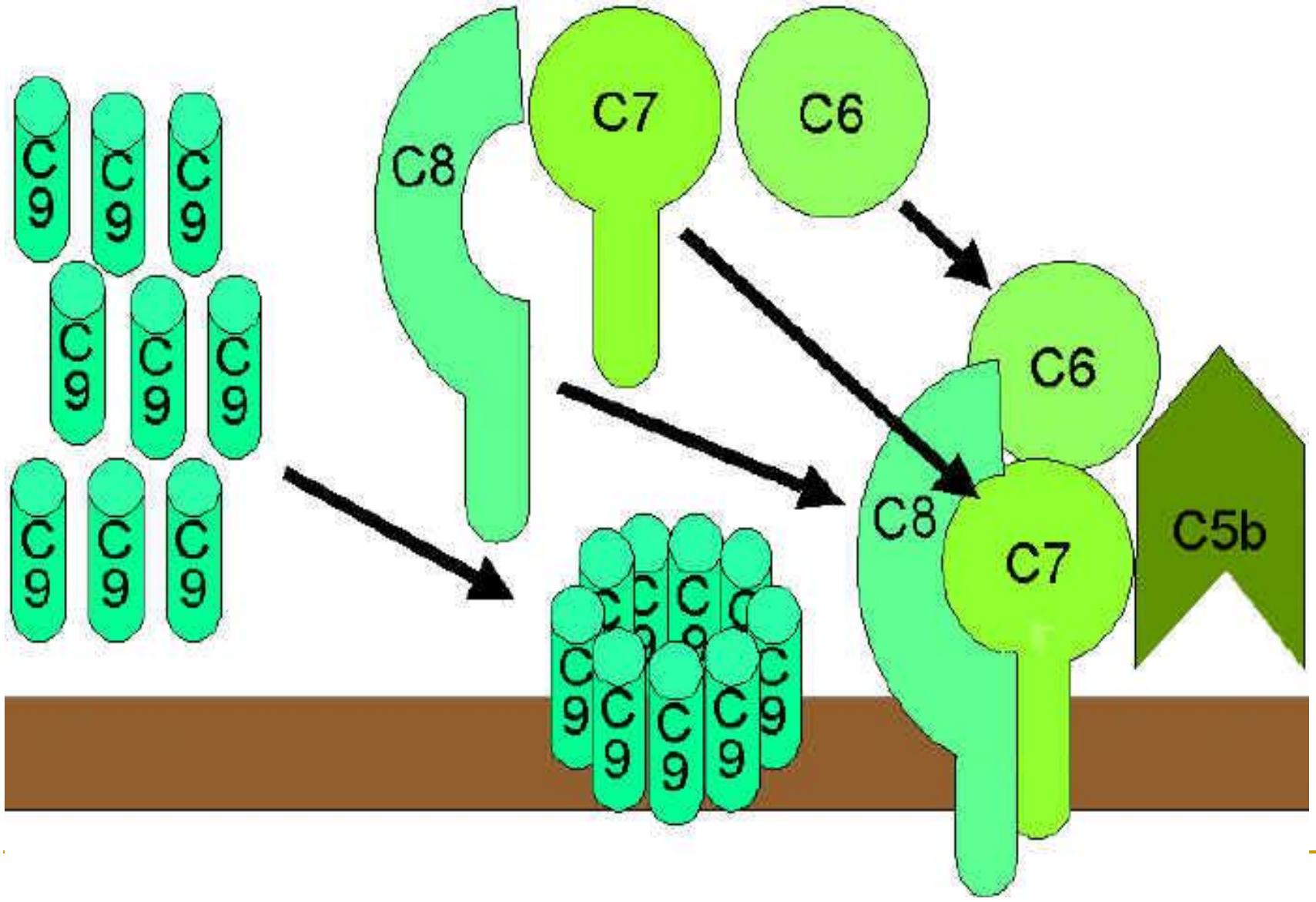
Lectin pathway activation



Lytic pathway

- The lytic (membrane attack) pathway involves the C5-9 components. C5 convertase generated by the classical or alternative pathway cleaves C5 into C5a and C5b. C5b binds C6 and subsequently C7 to yield a hydrophobic C5b67 complex which attaches quickly to the plasma membrane. Subsequently, C8 binds to this complex and causes the insertion of several C9 molecules. bind to this complex and lead to formation of a hole in the membrane resulting in cell lysis.
- The lysis of target cell by C5b6789 complex is nonenzymatic and is believed to be due to a physical change in the plasma membrane. C5b67 can bind indiscriminately to any cell membrane leading to cell lysis. Such an indiscriminate damage to by-standing cells is prevented by protein S (vitronectin) which binds to C5b67 complex and blocks its indiscriminate binding to cells other than the primary target

The lytic pathway



Biologically active products of complement activation

- *Chemotactic factors*
  C5a and MAC (membrane attack complex C5b67) are both chemotactic. C5a is also a potent activator of neutrophils, basophils and macrophages and causes induction of adhesion molecules on vascular endothelial cells.
- *Opsonins*
  C3b and C4b in the surface of microorganisms attach to C-receptor (CR1) on phagocytic cells and promote phagocytosis.
- *Other biologically active products of C activation*
  Degradation products of C3 (iC3b, C3d and C3e) also bind to different cells by distinct receptors and modulate their function.

Biologically active products of complement activation

- Activation of complement results in the production of several biologically active molecules which contribute to resistance, anaphylaxis and inflammation.
- *Kinin production*
  C2b generated during the classical pathway of C activation is a prokinin which becomes biologically active following enzymatic alteration by plasmin.
- *Anaphylotoxins*
  C4a, C3a and C5a (in increasing order of activity) are all anaphylotoxins which cause basophil/mast cell degranulation and smooth muscle contraction.

Chemotaxis

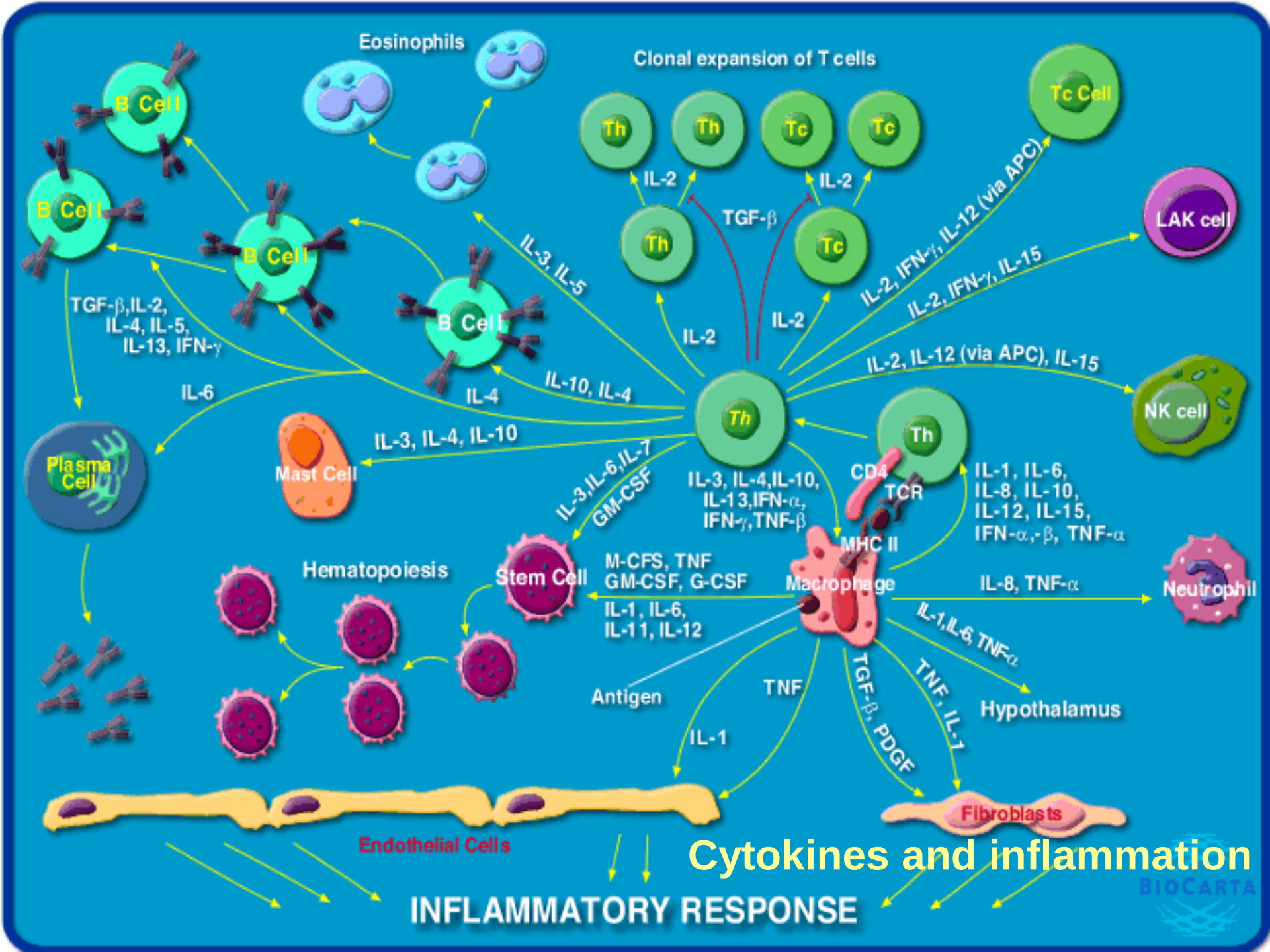
- is directed movement of cells in concentration gradient of soluble extracellular components.
- Chemotaxis factors, **chemotaxins or chemoattractants**
- **Positive chemotaxis** = cells move do the places with higher concentrations of chemotactic factors.
- **Negative chemotaxis** = cells move from the places with higher conentrations of chemotactioc factors
- **Chemoinvasion** = cells move through basal membrane

Cytokines

- The term ***cytokine*** is used as a generic name for a diverse group of soluble proteins and peptides which act as humoral regulators at nano- to picomolar concentrations and which, either under normal or pathological conditions, modulate the functional activities of individual cells and tissues. These proteins also mediate interactions between cells directly and regulate processes taking place in the extracellular environment.

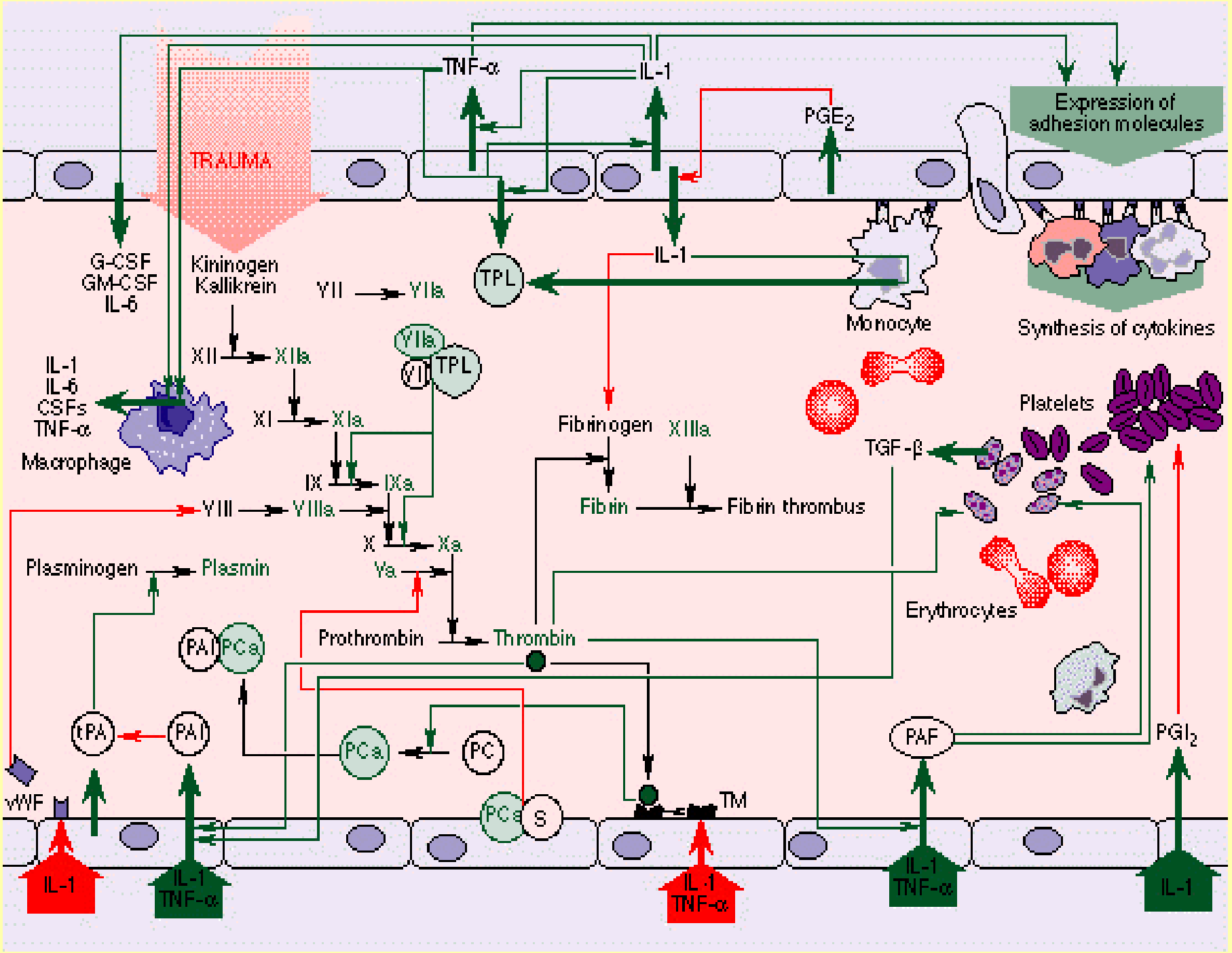
Cytokine network

- This term essentially refers to the extremely complex interactions of cytokines by which they induce or suppress their own synthesis or that of other cytokines or their receptors, and antagonize or synergise with each other in many different and often redundant ways.
- These interactions often resemble Cytokine cascades with one cytokine initially triggering the expression of one or more other cytokines that, in turn, trigger the expression of further factors and create complicated feedback regulatory circuits.
- Mutually interdependent pleiotropic cytokines usually interact with a variety of cells, tissues and organs and produce various regulatory effects, both local and systemic.


Eosinophils
Clonal expansion of T cells
B Cell
B Cell
B Cell
B Cell
Th
Th
Tc
Tc
Tc Cell
IL-2
IL-2
TGF-β
Th
Tc
IL-2, IFN-γ, IL-12 (via APC)
LAK cell
IL-2, IFN-γ, IL-15
IL-3, IL-5
TGF-β,IL-2,
IL-4, IL-5,
IL-13, IFN-γ
IL-2
IL-2
IL-2, IL-12 (via APC), IL-15
IL-6
IL-4
IL-10, IL-4
Th
NK cell
Plasma Cell
Mast Cell
IL-3, IL-4, IL-10
IL-3,IL-6,IL-7
GM-CSF
IL-3, IL-4,IL-10,
IL-13,IFN-α,
IFN-γ,TNF-β
Th
CD4
TCR
IL-1, IL-6,
IL-8, IL-10,
IL-12, IL-15,
IFN-α,-β, TNF-α
MHC II
Hematopoiesis
Stem Cell
M-CFS, TNF
GM-CSF, G-CSF
IL-1, IL-6,
IL-11, IL-12
Macrophage
IL-8, TNF-α
Neutrophil
IL-1,IL-6,TNF-α
Antigen
TNF
TGF-β, PDGF
TNF, IL-1
Hypothalamus
IL-1
Fibroblasts
Endothelial Cells
INFLAMMATORY RESPONSE
Cytokines and inflammation
BIOCARTA

Cytokines

- In many respects the biological activities of cytokines resemble those of classical hormones produced in specialized glandular tissues. Some cytokines also behave like classical hormones in that they act at a systemic level, affecting, for example, biological phenomena such as inflammation , systemic inflammatory response syndrome , and acute phase reaction , wound healing , and the neuroimmune network .
- In general, cytokines act on a wider spectrum of target cells than hormones. Perhaps the major feature distinguishing cytokines from mediators regarded generally as hormones is the fact that, unlike hormones, cytokines are not produced by specialized cells which are organized in specialized glands, i. e. there is not a single organ source for these mediators.
- The fact that cytokines are secreted proteins also means that the sites of their expression does not necessarily predict the sites at which they exert their biological function.


TNF-α
IL-1
PGE2
Expression of adhesion molecules
TRAUMA
G-CSF
GM-CSF
IL-6
Kininogen
Kallikrein
VII → VIIa
TPL
IL-1
Monocyte
Synthesis of cytokines
XII → XIIa
XI → XIa
IX → IXa
VIII → VIIIa
X → Xa
Va
IL-1
IL-6
CSFs
TNF-α
Macrophage
Fibrinogen
XIIIa
Fibrin
Fibrin thrombus
Platelets
TGF-β
Erythrocytes
Plasminogen
Plasmin
Prothrombin
Thrombin
PA
PCa
tPA
PAI
PC
PCa
S
TM
vWF
PAF
PGI2
IL-1
IL-1
TNF-α
IL-1
TNF-α
IL-1

Chemokines

- New generic name given to a family of pro-inflammatory activation-inducible cytokines. These proteins are mainly chemotactic for different cell types.
- All chemokines possess a number of conserved cysteine residues involved in intramolecular disulfide bond formation, which allows chemokines to be grouped into families according to the presence or absence of one or more conserved cysteine residues.

Chemokines

- According to the chromosomal locations of individual genes two different subfamilies of chemokines are distinguished.
- Members of the **Alpha-Chemokines** are referred to also as the **4q chemokine family** because the genes encoding members of this family map to human chromosome 4q12-21. The first two cysteine residues of members of this family are separated by a single amino acids and these proteins, therefore, are called also **CXC-Chemokines**. Some members of the subgroup of the human CXC-Chemokines are defined by the conserved **ELR sequence motif** (glutamic acid-leucine-arginine) immediately preceding the first cysteine residue near the amino-terminal end. Chemokines with an ELR sequence motif have been found to chemoattract and activate primarily neutrophils. Chemokines without the ELR sequence motif appear to chemoattract and activate monocytes, dendritic cells, T-cells, NK-cells, B-lymphocytes, basophils, and eosinophils.
- Members of the **Beta-Chemokines** or **17q chemokine family** map to human chromosome 17q11-32. The first two cysteine residues are adjacent and, therefore, these proteins are called also **CC-Chemokines.**

Chemokines

- Members of the small group of chemokines with a **CXXXC cysteine signature motif** are referred to as **Delta-Chemokines** or **CX3C-Chemokines** or **CXXXC-Chemokines**).

Chemokines

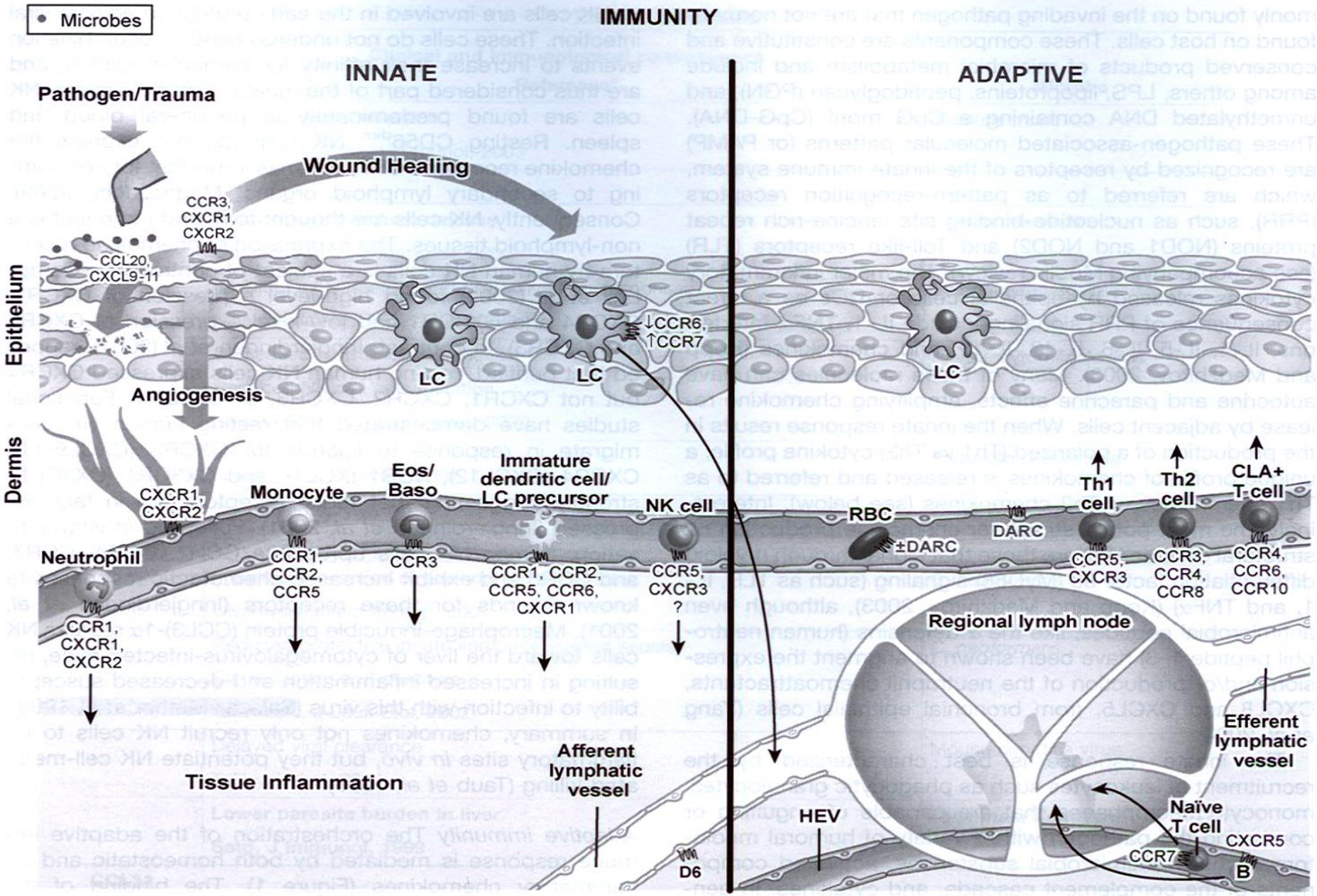
- The biological activities of chemokines are mediated by specific receptors and also by receptors with overlapping ligand specificities that bind several of these proteins, which always belong either to the CC-Chemokines or the group of CXC-Chemokines. Lymphocytes require stimulation to become responsive to most known chemokines, and this process is linked closely to chemokine receptor expression. Chemokine receptors belong to the large group of G-protein-coupled seven transmembrane domain receptors that contain seven hydrophobic alpha-helical segments that transverse the membrane.
- The receptors that bind CXC-Chemokines are designated **CXCR** followed by a number (**CXCR1**, **CXCR2**, **CXCR3**, **CXCR4**, **CXCR5**, **CXCR6**) while those binding CC-Chemokines are designated **CCR** followed by a number (**CCR1**, **CCR2**, **CCR3**, **CCR4**, **CCR5**, **CCR6**, **CCR7**, **CCR8**, **CCR9**, **CCR10**, **CCR10A**, **CCR10B**, **CCR11**). The "R" nomenclature is used for receptors that bind chemokines and elicit intracellular signaling in response to binding of a ligand.

Chemokines

- According to their mode of expression and function, chemokines have been categorized as inflammatory chemokines and homeostatic chemokines.
- Inflammatory chemokines are expressed usually by leukocytes or related cells only upon cell activation. These factors mediate emigration of leukocytes.
- Homeostatic chemokines are expressed constitutively and are involved usually in relocation of lymphocytes or other cell types.
- Dual-function chemokines can act as inflammatory cytokines or homeostatic cytokines.

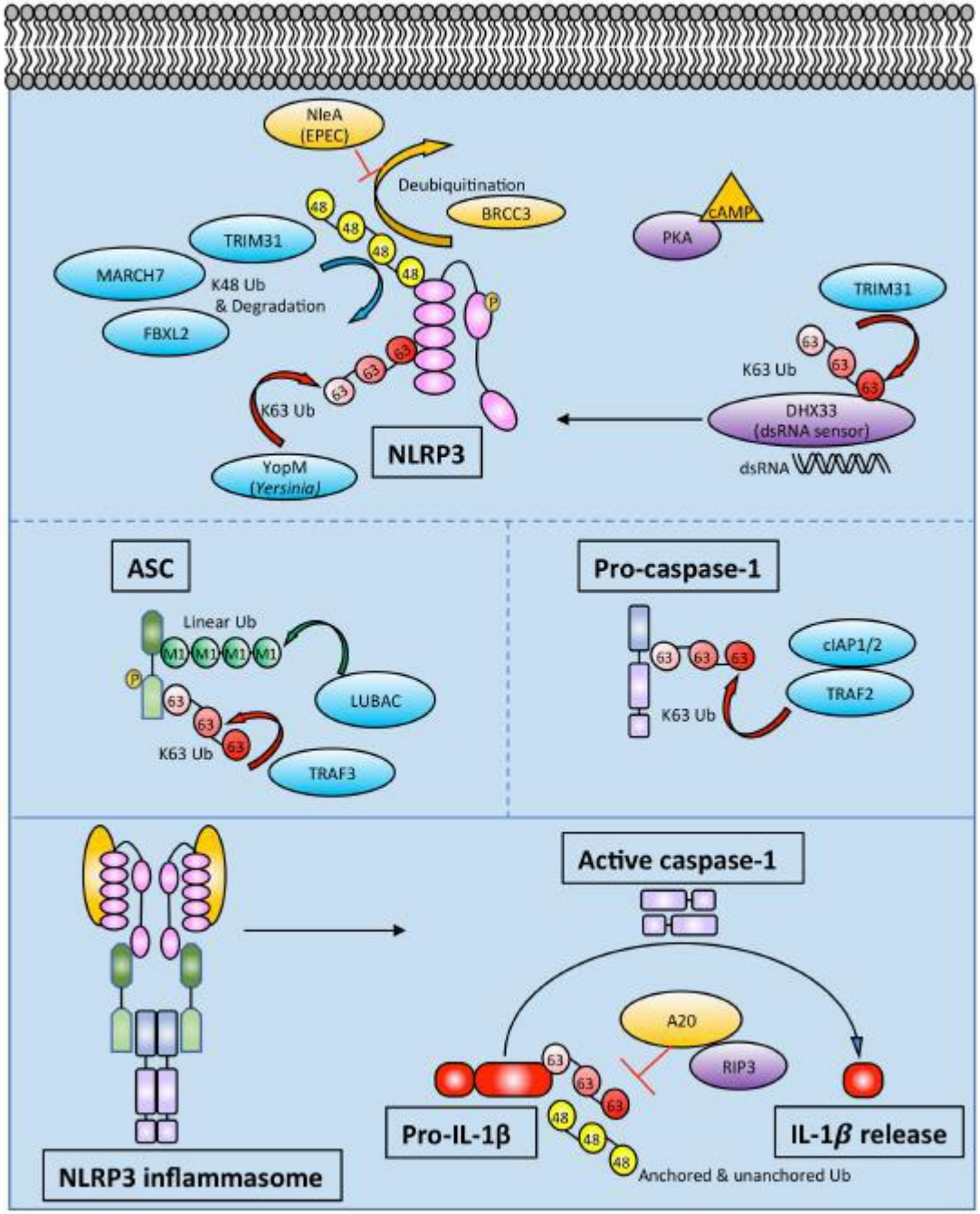
Chemokines

- Erythrocytes through their promiscuous chemokine receptor play an important role in regulating the chemokine network. Chemokines bound to the receptor on erythrocytes are known to be inaccessible to their normal target cells. This appears to provide a sink for superfluous chemokines and may serve to limit the systemic effects of these mediators without disrupting localized processes taking place at the site of inflammation.
- Many genes encoding chemokines are expressed strongly during the course of a number of pathophysiological processes including autoimmune diseases, cancer, atherosclerosis, and chronic inflammatory diseases.


Microbes
IMMUNITY
INNATE
ADAPTIVE
Pathogen/Trauma
Wound Healing
CCR3, CXCR1, CXCR2
CCL20, CXCL9-11
Epithelium
Dermis
↓CCR6, ↑CCR7
LC
LC
LC
Angiogenesis
CXCR1, CXCR2
Neutrophil
CCR1, CXCR1, CXCR2
Monocyte
CCR1, CCR2, CCR5
Eos/ Baso
CCR3
Immature dendritic cell/ LC precursor
CCR1, CCR2, CCR5, CCR6, CXCR1
NK cell
CCR5, CXCR3 ?
RBC
±DARC
DARC
Th1 cell
CCR5, CXCR3
Th2 cell
CCR3, CCR4, CCR8
CLA+ T cell
CCR4, CCR6, CCR10
Tissue Inflammation
Afferent lymphatic vessel
D6
HEV
Regional lymph node
Efferent lymphatic vessel
Naïve T cell
CCR7
CXCR5
B

Inflammasomes

- Inflammasomes are multiprotein complexes.
- An inflammasome mainly consists of cytoplasmic sensor molecule, such as NLRP3, the adaptor (apoptosis associated speck-like protein containing caspase recruitment domain) protein along with effector procaspase-1.
- The inflammasome regulates caspase-1 activation, resulting in secretion of interleukin- 1β and interleukin-18. The inflammasome activation is linked with infection, stress, or other immunological signals involved in inflammation.
- The pathophysiological role of NLRP3 inflammasome in immune regulation, inflammatory receptor-ligand interactions, microbial-associated molecular patterns, danger as well as pathogen associated molecular patterns has been demonstrated in last few years.
- The role of the inflammasome in peripheral and central nervous system involved with cytokine and chemokine inflammatory responses has been demonstrated in preclinical and clinical studies.



Schematic of ubiquitin (Ub)-modifying enzymes and ubiquitination events regulating NLRP3 inflammasome activity.

In addition to upregulating NLRP3 and IL1β mRNA, priming also leads to NLRP3 deubiquitination.
NLRP3 is modified by K48- and K63-linked Ub. Phosphorylation of NLRP3 may be linked to its ubiquitination status.
Prior to NLRP3 inflammasome assembly, ASC gets phosphorylated and linearly ubiquitinated. ASC can also undergo K63-linked ubiquitination by TRAF3.
Pro-caspase-1 undergoes K63-linked polyubiquitination by cIAP1, cIAP2, and TRAF2. After NLRP3 inflammasome assembly, active caspase-1 cleaves pro-IL-1β to IL-1β. Pro-IL-1β undergoes K63-linked polyubiquitination and binds unanchored Ub chains. A20 restricts polyubiquitination of pro-IL-1β in a RIPK3-dependent manner. T he exact character and composition of heterogeneous Ub chains in the inflammasome are not well understood.

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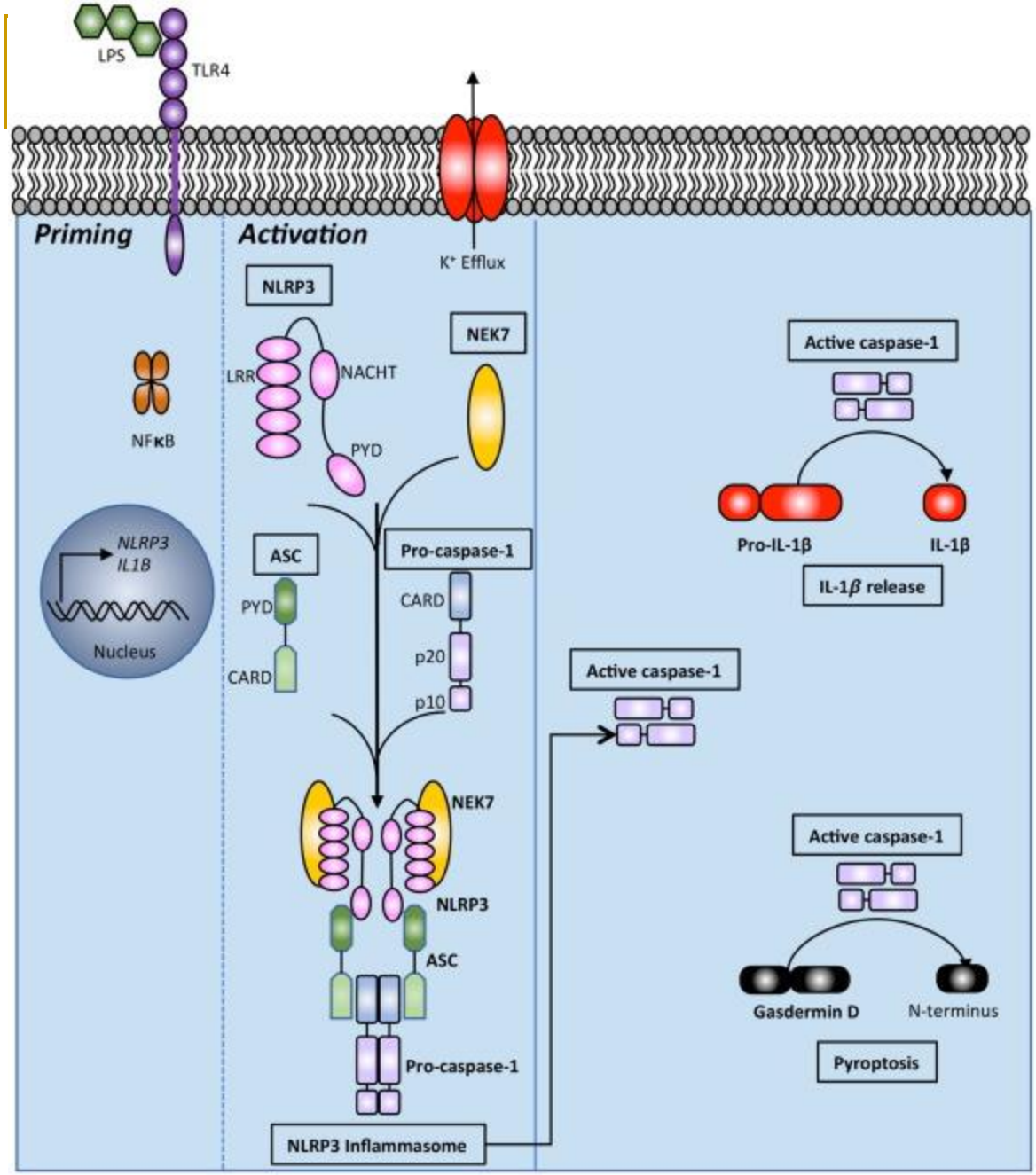

Schematic of NLRP3 inflammasome activation.

LPS signaling through TLR4 or other priming signal activates NFκB and upregulates NLRP3 and IL1β mRNA. A second signal such as potassium efflux then activates the inflammasome. NLRP3, NEK7, ASC, and pro-caspase-1 assemble to form the NLRP3 inflammasome. This leads to autoproteolytic cleavage of pro-caspase-1 yielding active caspase-1. Active caspase-1 cleaves pro-IL-1β to mature IL-1β for release. Cleavage of pro-IL-18 into mature IL-18 is not pictured. Caspase-1 can also cleave gasdermin D, releasing the N-terminal fragment that drives pyroptosis.

PYD, pyrin domain; NACHT, NAIP, CIITA, HET-E, and TP1 domain; LRR, leucine-rich repeat domain; CARD, caspase recruitment domain.

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Thank you for your attention