Inflammation

VLA, November 6, 2018

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

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.

Types of inflammation

- Acute
- Chronic

- Local
- Systemic

Acute inflammation

- can be caused by microbial agents such as
- infectious inflammatory stimuli (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 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.

Macroscopic appearance of acute inflammation

- The cardinal signs of acute local 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**.

Systemic manifestation of inflammation

→ 1. Increase of body temperature (fever)

→ 2. Acute phase reaction

Systemic effects of acute/chronic 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 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

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.

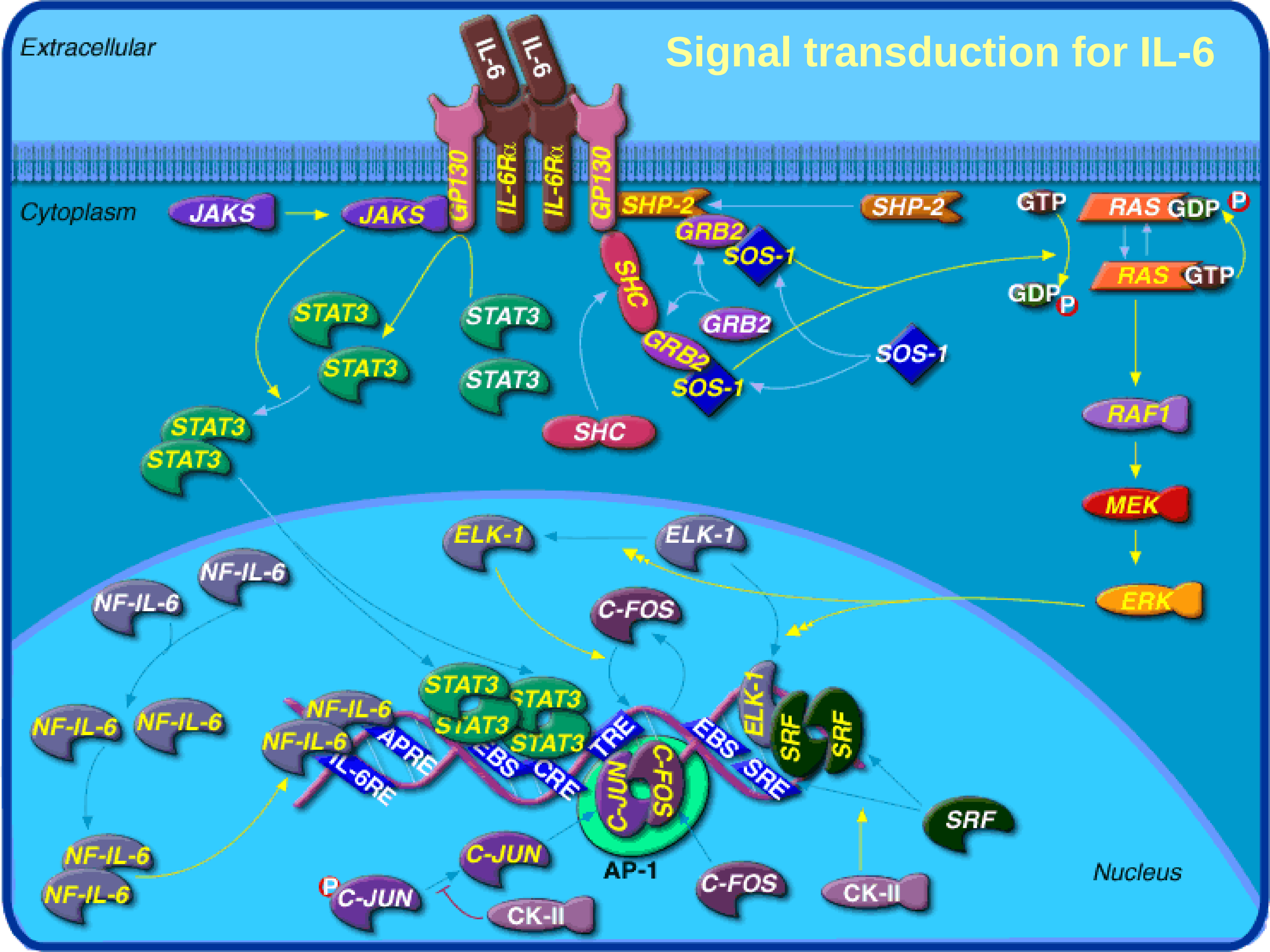
General and local clinical symptoms of the acute phase reaction

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.

Signal transduction for IL-6



The acute phase proteins

- Induction of the acute phase reaction means changes in the synthesis of many proteins in the liver 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.

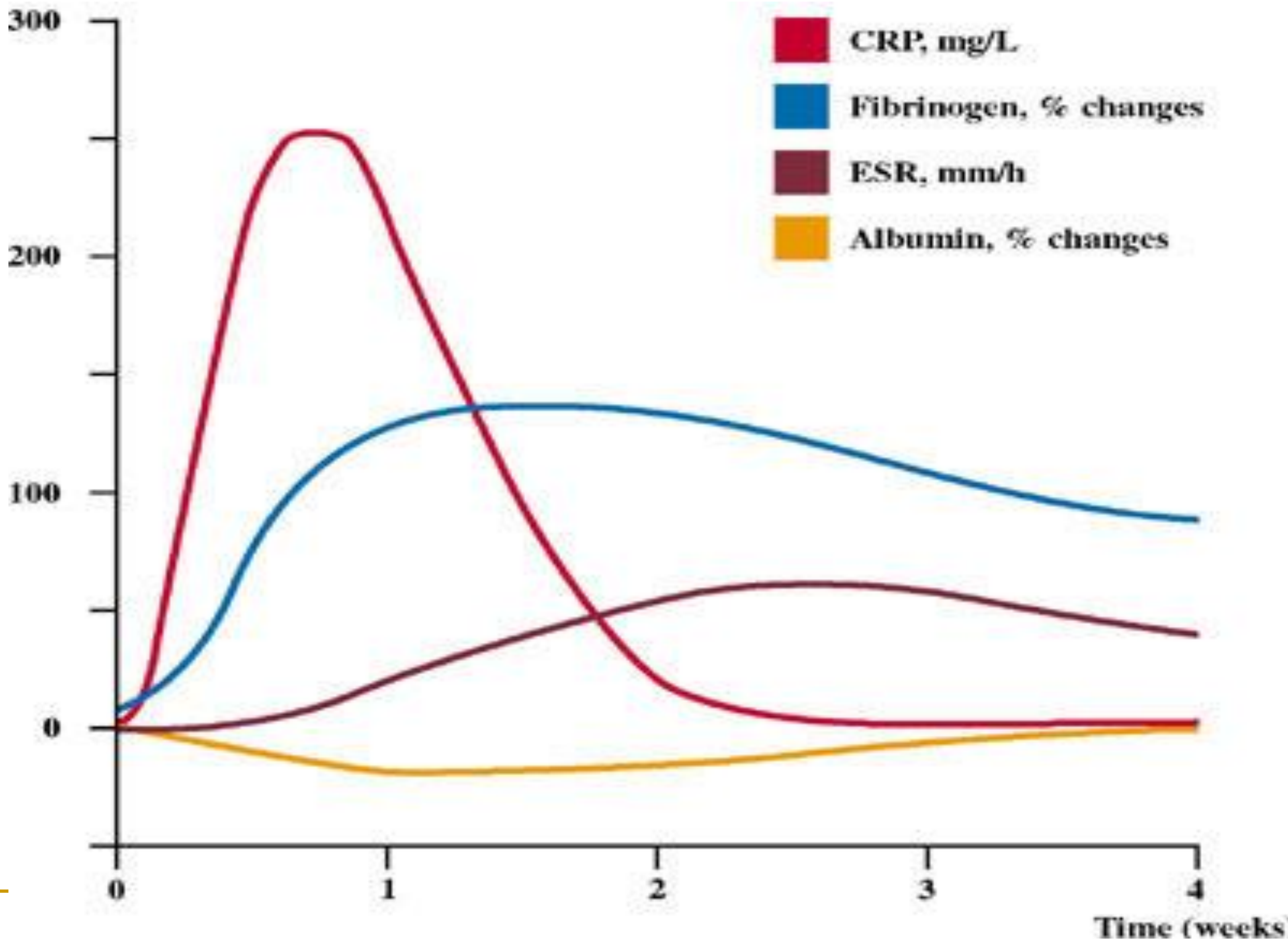
The protein synthesis may be upregulated even if plasma levels are normal, due to increased consumption of acute phase proteins.

Function	Positive 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



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

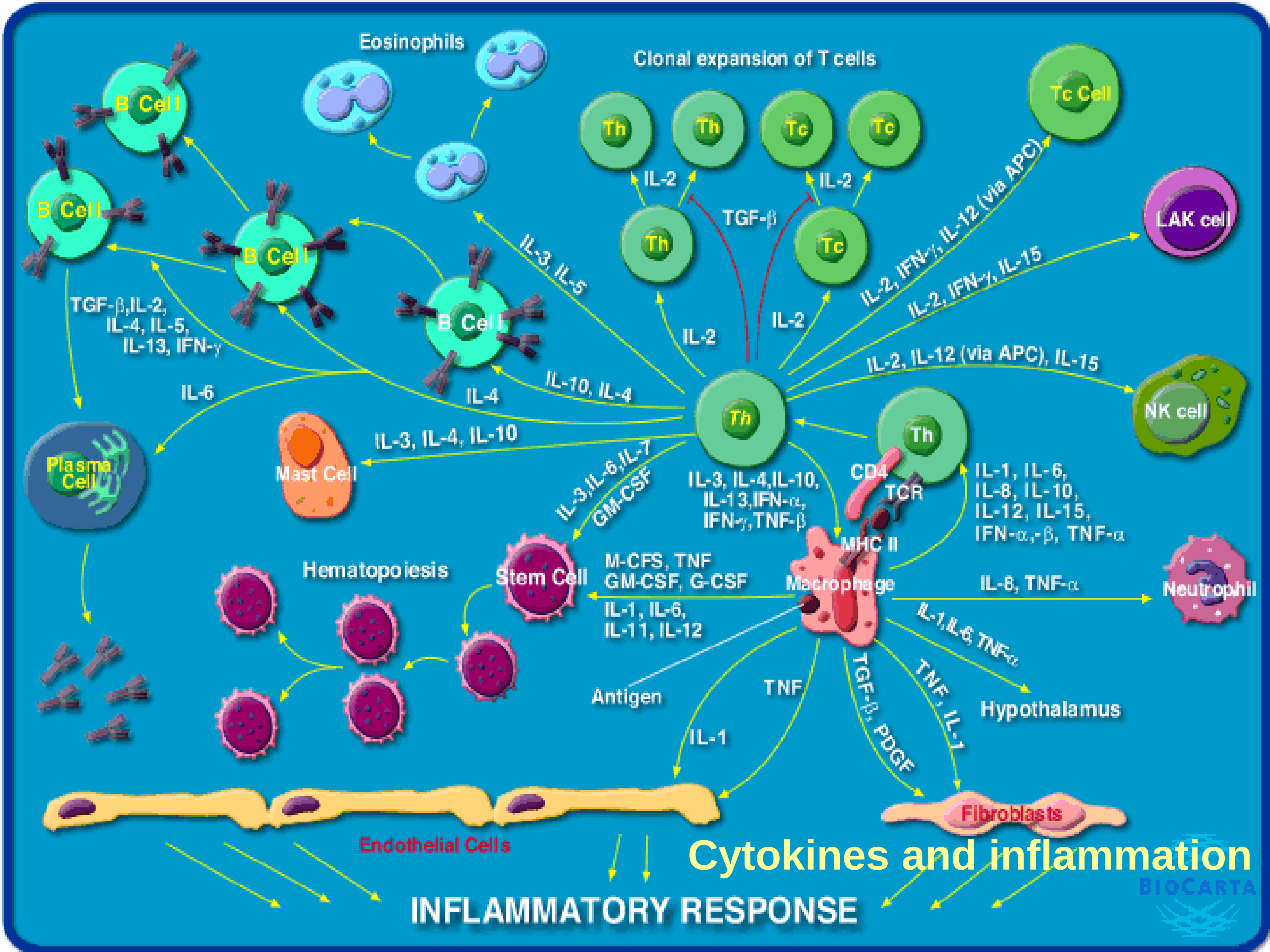
- is directed movement of cells in concentration gradient of soluble extracellular components.
- Chemotaxis factors, **chemotaxins or chemoattractants**
- **Positive chemotaxis** = cells move do the places with higher concentrations of chemotactic factors.
- **Negative chemotaxis** = cells move from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



Cytokines and inflammation

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.

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

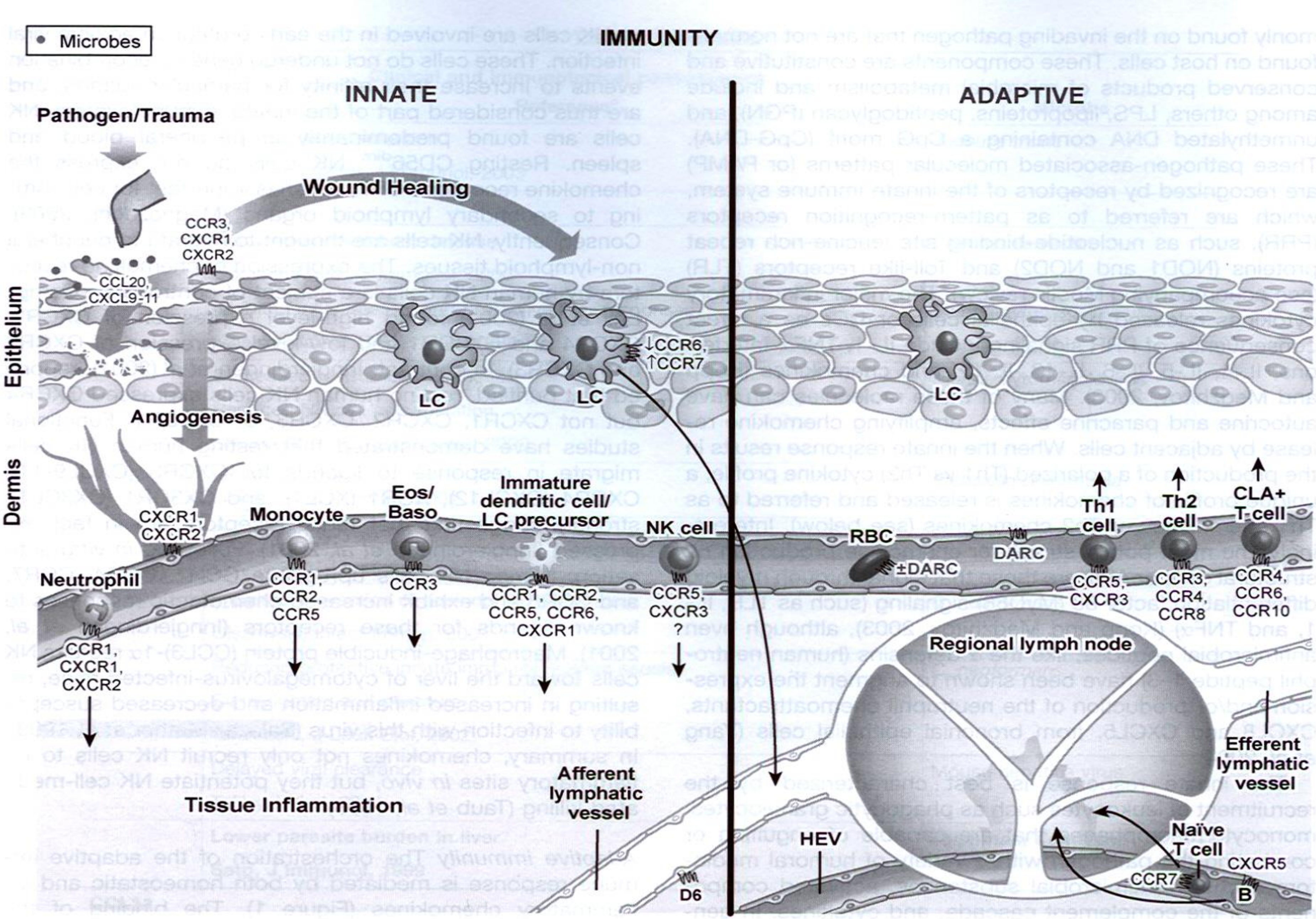
- The biological activities of chemokines are mediated by specific receptors and also by receptors with overlapping ligand specificities that bind several of these proteins, which always belong either to the CC-Chemokines or the group of CXC-Chemokines. Lymphocytes require stimulation to become responsive 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

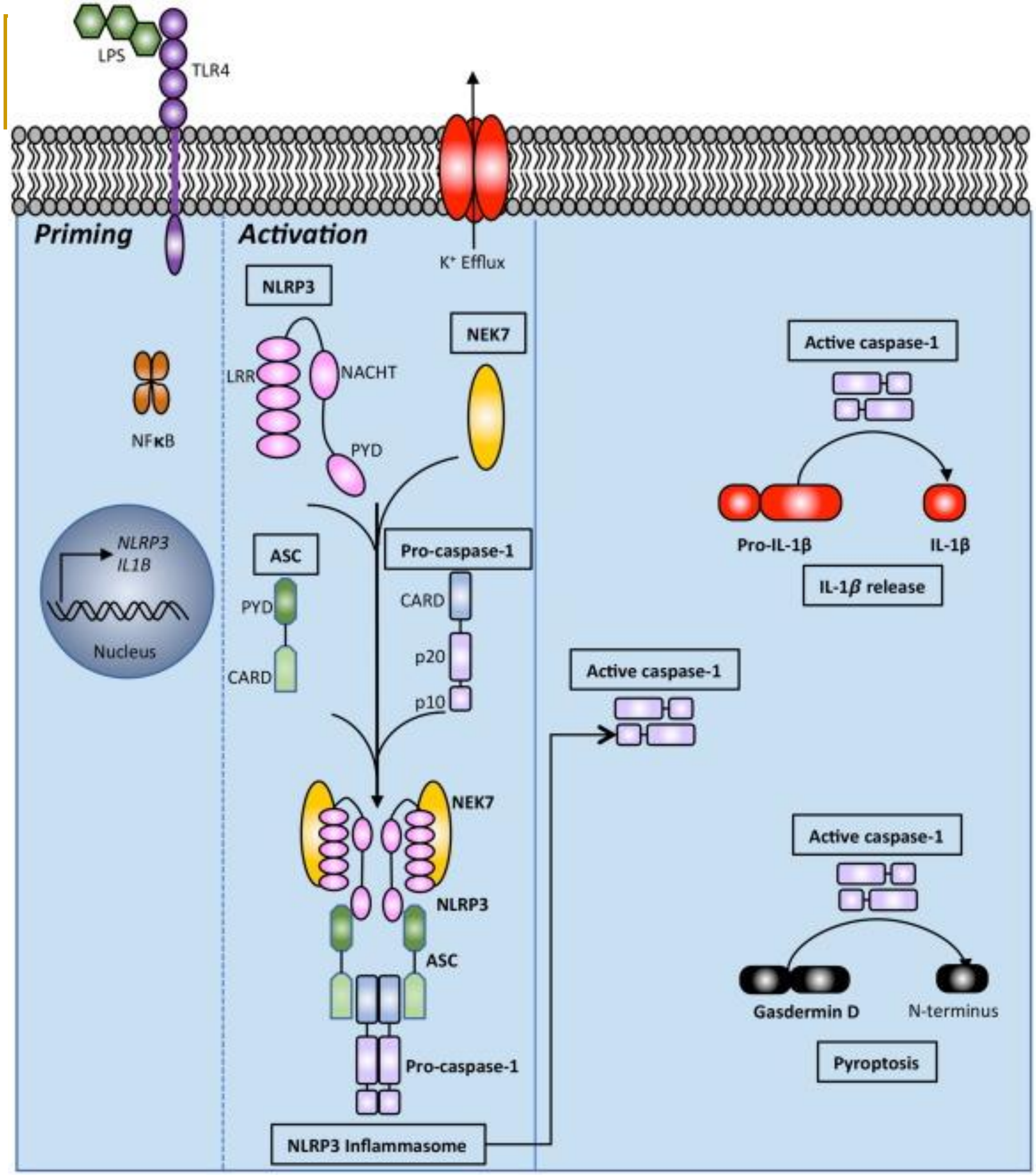
- Erythrocytes through their promiscuous chemokine receptor play an important role in regulating the chemokine network. Chemokines bound to the receptor on erythrocytes are known to be inaccessible to their normal target cells. This appears to provide a sink for superfluous chemokines and may serve to 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
↓CCR6,
↑CCR7
LC
LC
LC
Angiogenesis
Dermis
CXCR1,
CXCR2
Monocyte
Eos/
Baso
Immature
dendritic cell/
LC precursor
NK cell
RBC
DARC
±DARC
Th1
cell
Th2
cell
CLA+
T-cell
Neutrophil
CCR1,
CCR2,
CCR5
CCR3
CCR1, CCR2,
CCR5, CCR6,
CXCR1
CCR5,
CXCR3
?
CCR5,
CXCR3
CCR3,
CCR4,
CCR8
CCR4,
CCR6,
CCR10
CCR1,
CXCR1,
CXCR2
Regional lymph node
Efferent
lymphatic
vessel
Afferent
lymphatic
vessel
Tissue Inflammation
HEV
D6
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 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.

J Mol Biol. 2017 Oct 12. pii: S0022-2836(17)30471-0. doi: 10.1016/j.jmb.2017.10.001

THE SYSTEMIC inflammatory response syndrome (SIRS)

- a clinical expression of nonspecific inflammation, is a major cause of morbidity and mortality and is a leading cause of death in intensive care units.
- SIRS can be initiated by a variety of causes, including infection, and may vary in severity from mild to life threatening.

Severe injury or infection

- Severe injury or infection begins with the recognition of alarmins, primarily consisting of microbial products and damaged tissue.
- The innate immune system relies on germ line-encoded pattern-recognition receptors (PRRs) to sense components of foreign pathogens and damaged cells to mount host-protective responses.

Front Immunol. 2018; 9: 595.

Severe injury or infection

- These PRRs are expressed on a variety of host cells, including cells of myeloid, endothelial, and epithelial lineages. These PRRs detect conserved microbial components called pathogen-associated molecular patterns (PAMPs) as well as host molecules derived from damaged cells, known as damage-associated molecular patterns (DAMPs).

Front Immunol. 2018; 9: 595.

PRRs

- Major classes of PRRs include Toll-like receptors (TLRs), C-type lectin receptors (CLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), retinoic-acid-inducible gene-I (RIG-I)-like receptors (RLRs), and receptor for advanced glycation end products (RAGE).
- The sheer number, diversity, and redundancy of these pathogen-recognition receptors emphasize their essential role in host-protective immunity.

Front Immunol. 2018; 9: 595.

PRRs

- Upon host recognition of PAMPs or DAMPs, PRRs initiate a complex set of downstream signaling events that induce a host-protective response.
- This includes recruitment and phosphorylation of intracellular intermediates leading in part to the activation of immediate response genes.

Front Immunol. 2018; 9: 595.

PRRs

- Pattern-recognition receptors activation and downstream signaling result in both nonspecific and pathogen-specific host cellular responses to prevent or eliminate host stressors, such as microbial infection or tissue damage .
- The suppression of microbial replication, tissue invasion, and dissemination from the site of infection involves multiple innate immune cells: neutrophils (PMNs), monocytes/macrophages (Mφ), dendritic cells (DCs), natural killer (NK) cells, and innate lymphoid cells (ILCs) .

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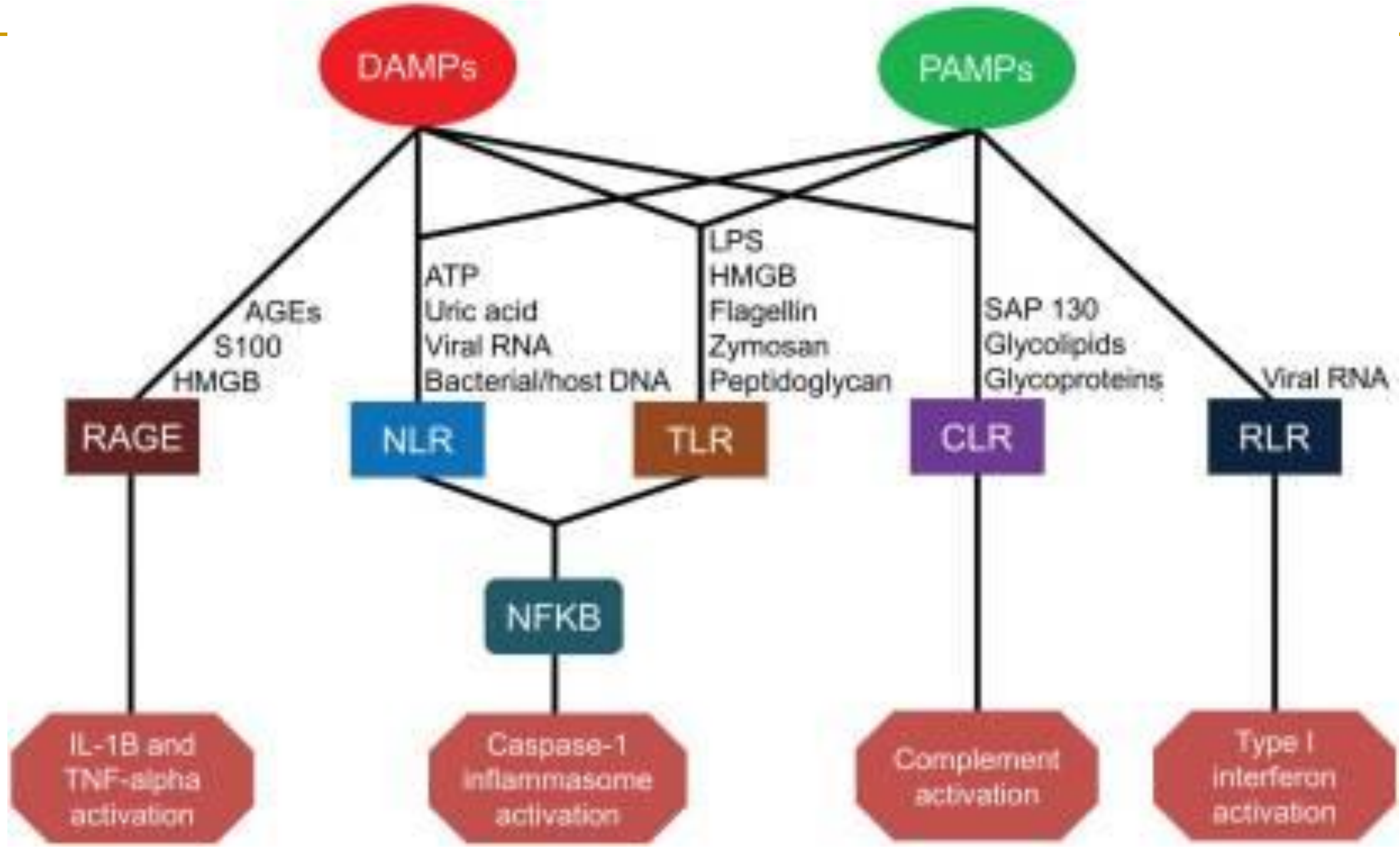

Pattern-recognition receptor pathways for damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). AGEs, advanced glycosylation end products; HMGB, high-mobility group box; ATP, adenosine triphosphate; RNA, ribonucleic acid; DNA, deoxyribonucleic acid; LPS, lipopolysaccharide; RAGE, receptor for advanced glycation end products; NLR, nucleotide-binding oligomerization domain-like receptors; TLR, toll-like receptors; CLR, C-type lectin receptors; RLR, retinoic-acid-inducible gene-I-like receptors; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; IL, interleukin; TNF, tumor necrosis factor.

Toll-like receptors

- To date, 13 different TLRs have been identified in humans, with slight differences in receptor type and function between species.
- While some TLRs are expressed on the plasma membrane (TLRs 1, 2, 4, 5, and 6) to constantly sample the local environment,
- others are located within endosomal compartments (TLRs 3, 7, 8, 9, 11, 12, and 13) to sense host danger signals or microbial proteins and nucleic acids .

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TLRs

- TLRs located on the plasma membrane detect external microbial components and circulating damage signals such as lipopolysaccharide (LPS), phospholipids, zymosan, flagellin, peptidoglycan, S100A8/9, and endogenous high-mobility group box (HMGB) nuclear proteins from distressed cells.
- TLRs located in cytoplasm, however, detect viral or microbial nucleic acids as well as the mitochondrial nucleic acids associated with cell injury .
- TLRs play a central role in initiating the innate immune response in cooperation with other PRRs through diverse and overlapping signaling pathways.

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Innate immunity cells

- All these cells can play a crucial role in the early inflammatory response . PMNs primed by cytokines such as TNF-a eliminate invading pathogens through phagocytosis, the production of reactive oxygen species (ROS), and the release of neutrophil extracellular traps (NETs) in a process known as NETosis.
- Mφ also contribute significantly to the host defense against infection. M1 Mφ, or classically activated Mφ, are activated by microbial stimuli alone or in combination with other endogenous or exogenous inflammatory signals, such as IFN-γ and LPS, respectively, to produce high levels of pro-interleukines (e.g., IL-6, IL-12, and TNF-a), ROS, and reactive nitrogen species.

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Cell type	Mφ		PMN	DCs	ILCs			
	M1	M2			Group 1		Group 2	Group 3
					NK cells	ILC 1	ILC 2	ILC 3
Products	IL-1β IL-6 IL-12 IL-23 TNFα iNOS	IL-1 IL-4 IL-13 IL-10 TGFβ Arg 1	IL-6 TNFα IFNγ RNS ROS	IL-1β IL-6 IL-12 IL-23 IFNα/β	TNFα IFNγ Perforin Granzyme	TNFα IFNγ	IL-4 IL-5 IL-13 AREG	IL-17A/IL-17F
Main Immunological function	Phagocytosis Bactericidal activity Type 1 inflammation	Efferocytosis Killing parasites Type 2 inflammation	Phagocytosis Respiratory burst NET formation	Phagocytosis Antigen presentation	Direct Cytolysis	Weak cytotoxity Mainly in mucosal barrier surface (e.g. intestine, airway)	Th2, Th17	Th2, Th17

Efferocytosis is a process by which macrophages and other phagocytes recognize, bind to, and engulf dying cells

Arginase (Arg) catalyzes the hydrolysis of arginine to ornithine and urea. At least two isoforms of mammalian arginase exist (types I and II) which differ in their tissue distribution, subcellular localization, immunologic crossreactivity and physiologic function. The type I isoform encoded by this gene, is a cytosolic enzyme and expressed predominantly in the liver as a component of the urea cycle.

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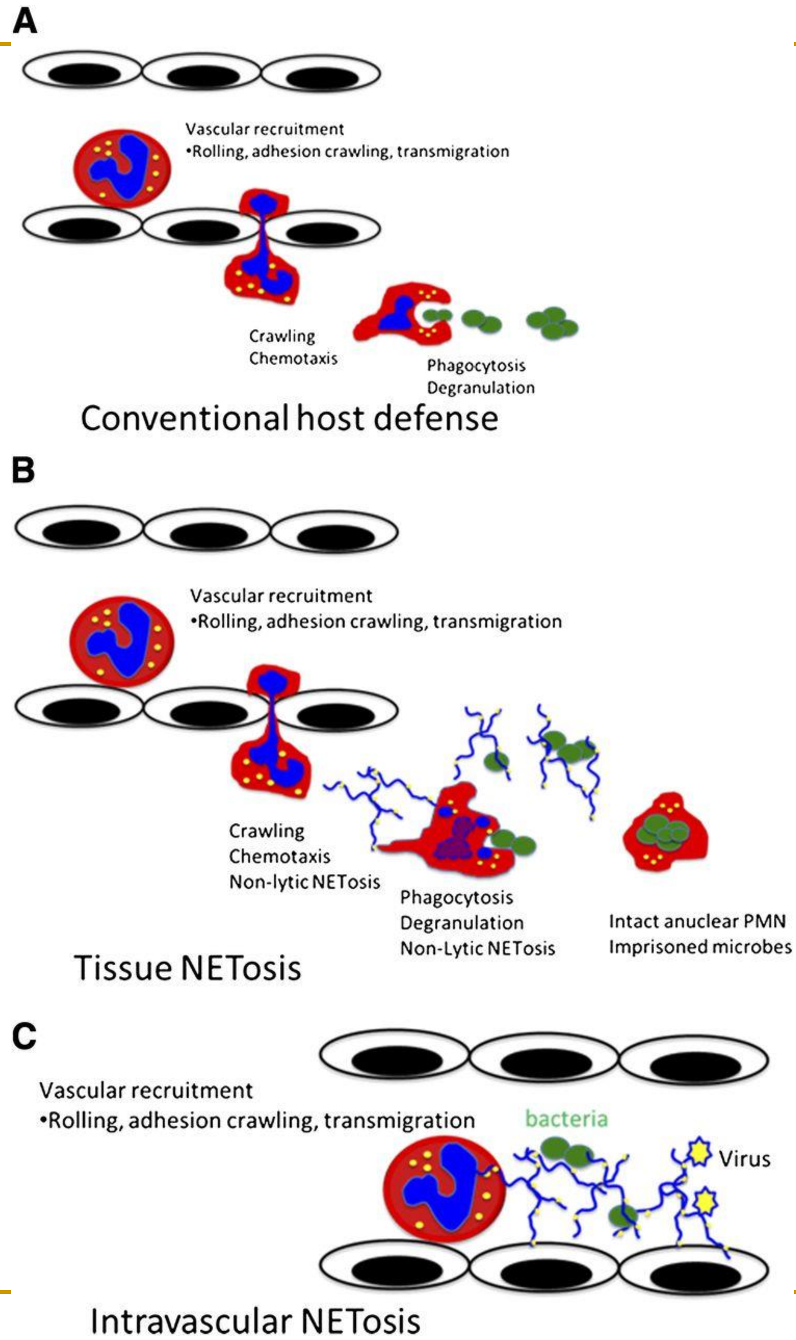
NETosis

- Stimulated PMNs could release extracellular nucleic acids decorated with histones and granular proteins capable of entrapping exogenous bacteria.
- Suicidal vs. vital NETosis



Vital NETosis allows PMNs to maintain conventional host defensive functions.

(A) Conventional neutrophil host response incudes the recruitment cascade, emigration, chemotaxis, phagocytosis, and microbial killing.

(B) Vital NETosis aids in containing local infections, such as gram-positive cellulitis, by allowing PMNs to rapidly release NETs and continue to chemotax and phagocytose live bacteria. Additionally, the live NET-releasing PMNs are able to maintain their membrane integrity, thereby imprisoning the captured bacteria.

(C) Intravascular NET release optimizes the capture of both bacteria and viruses within the blood stream. Intravascular NETosis may also contribute to immunothrombosis.

Blood. 2013 Oct 17;122(16):2784-94

Early cytokine response

- These early cytokine responses serve two primary purposes:
- (1) to signal the host regarding the type and magnitude of the infection and
- (2) to delay microbial expansion and colonization until T- and B-lymphocytes are able to initiate an adaptive immune response, which ultimately contributes to pathogen elimination. DCs are known as professional APCs.
- DCs present pathogen-derived antigenic peptides to $CD4^+$ T cells in lymph nodes, leading to the activation and differentiation of antigen-reactive T-effector cells. The NK cell is also an effector cell of innate immunity, producing cytokines such as IFN-γ during the early phase of inflammation. In addition, these cells have a direct cytotoxic activity *via* the induction of apoptosis from the release of perforin, granzymes, TNF-a, Fas ligand (FasL), and TNF-related apoptosis-inducing ligand (TRAIL).

Front Immunol. 2018; 9: 595.

Early cytokine response

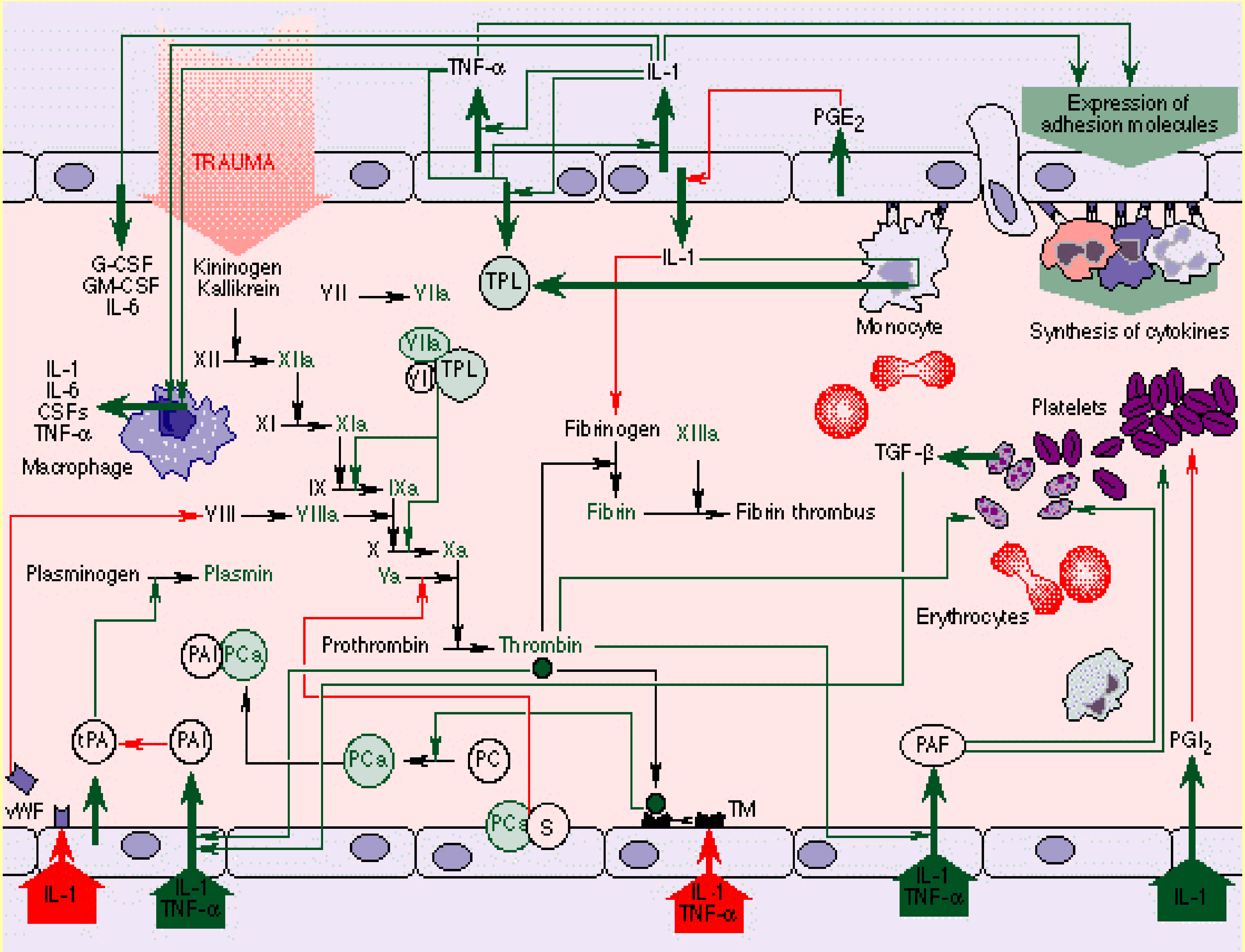
- Finally, ILCs are another newly described population of innate immune cells.
- ILC1 cells are weakly cytotoxic but can express several interleukines.
- ILC2 and ILC3 cells are thought to promote T_H2 and T_H17 responses, respectively, and are critical for the crosstalk between innate and adaptive immunity.

Front Immunol. 2018; 9: 595.

Hypercoagulable state

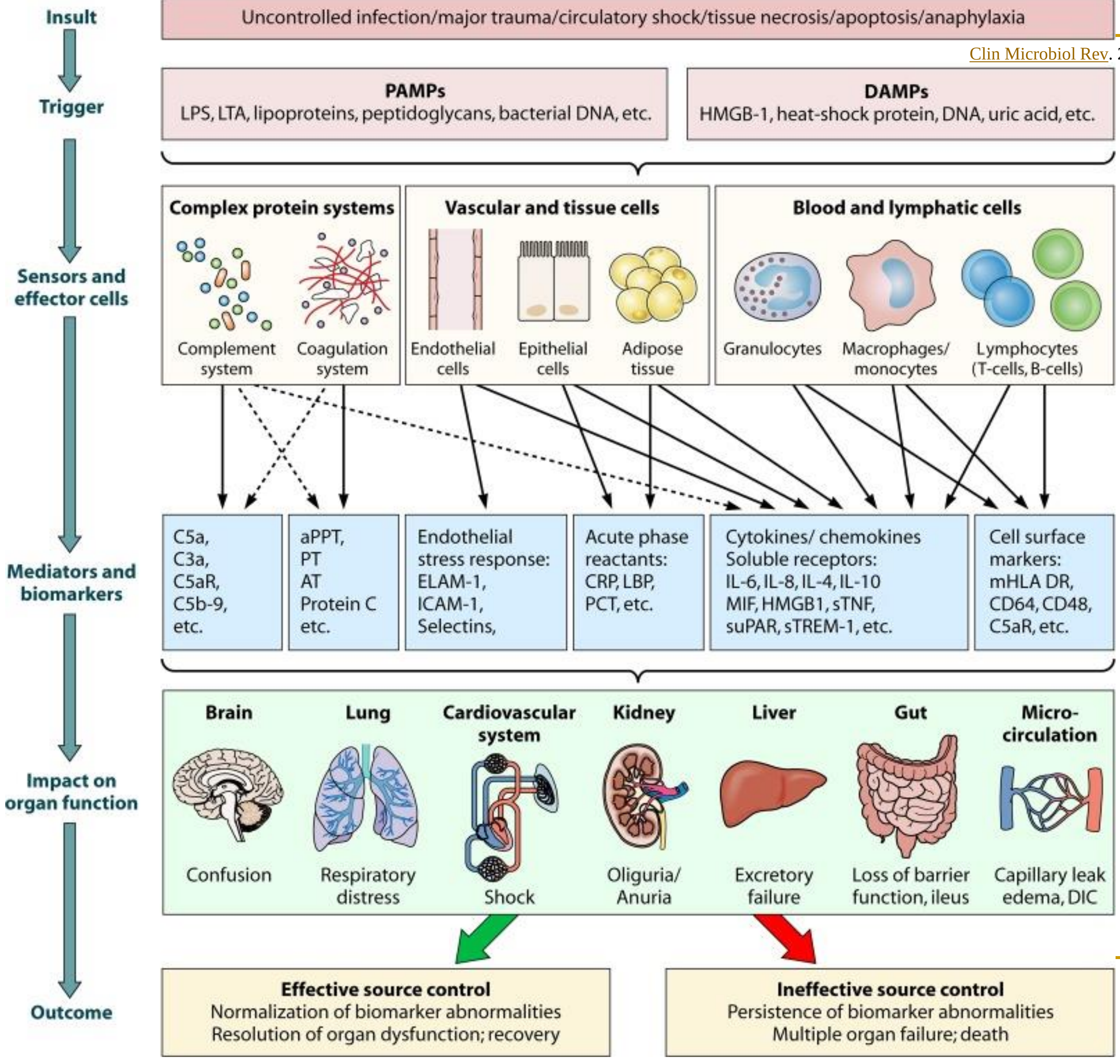
- In a further attempt to control local infections or tissue damage, an endothelial cell-target hypercoagulable state occurs with the presumed intent of reducing blood loss and trapping microbial pathogens.
- Tissue factor (TF), an important trigger of coagulation, is upregulated and decrypted in response to chemical or physical damage, cytokines (such as TNF-a and IL-1β), and infectious agents.
- TF upregulation leads to the activation of platelets and induction of protease-activated receptor-mediated signaling, resulting in the production of additional cytokines and the expression of cell adhesion molecules. These responses result in the formation of NETs within the vasculature, which bind platelets and promote thrombosis.

Front Immunol. 2018; 9: 595.

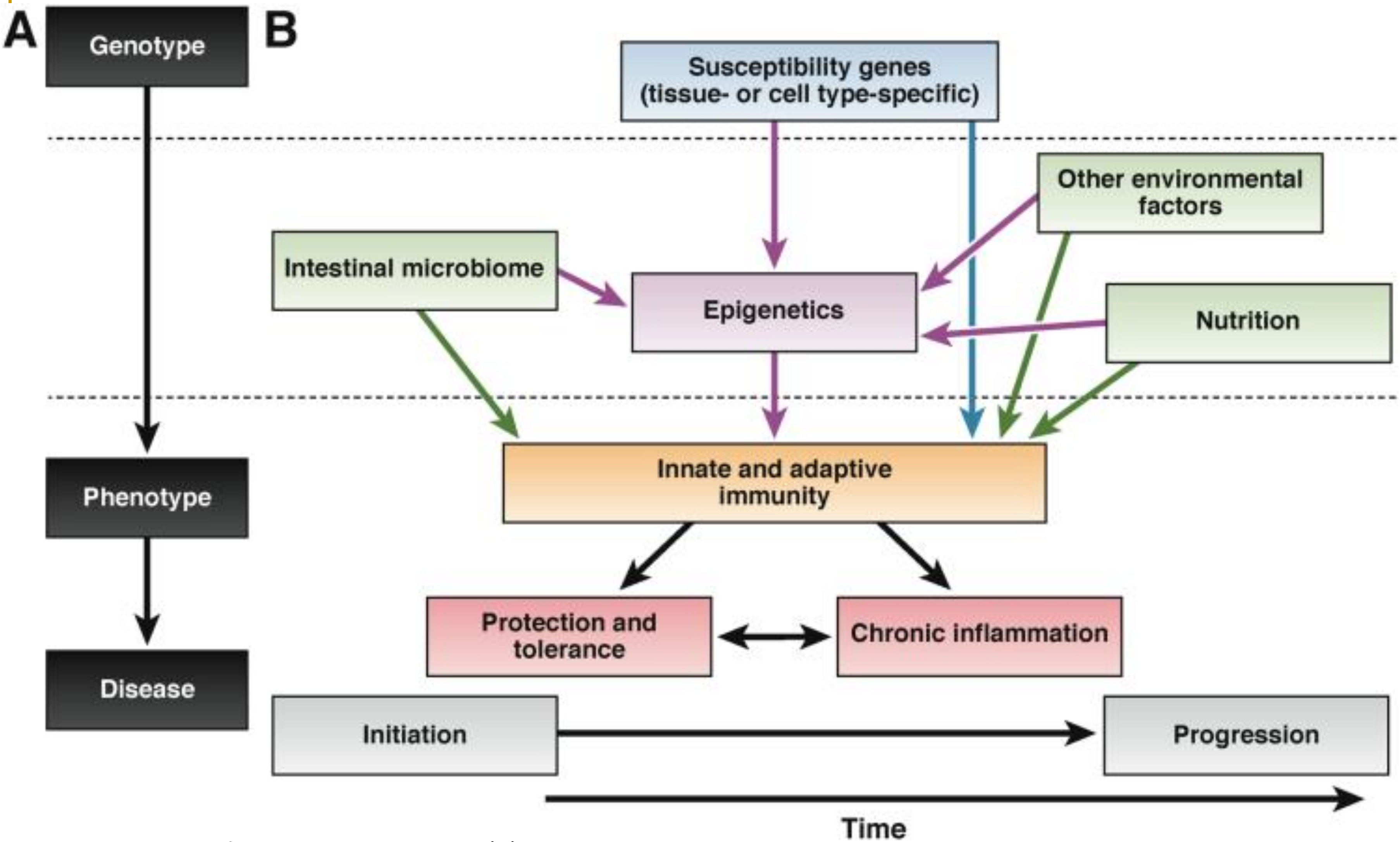


TNF-α
IL-1
Expression of adhesion molecules
PGE$_2$
TRAUMA
G-CSF
GM-CSF
IL-6
Kininogen
Kallikrein
VII
VIIa
TPL
IL-1
Monocyte
Synthesis of cytokines
XII
XIIa
VIIa
VII
TPL
IL-1
IL-6
CSFs
TNF-α
Macrophage
XI
XIa
Fibrinogen
XIIIa
Platelets
TGF-β
IX
IXa
VIII
VIIIa
Fibrin
Fibrin thrombus
X
Xa
Plasminogen
Plasmin
Va
Erythrocytes
PAI
PCa
Prothrombin
Thrombin
tPA
PAI
PCa
PC
PAF
PGI$_2$
vWF
PCa
S
TM
IL-1
IL-1
TNF-α
IL-1
TNF-α
IL-1
TNF-α
IL-1

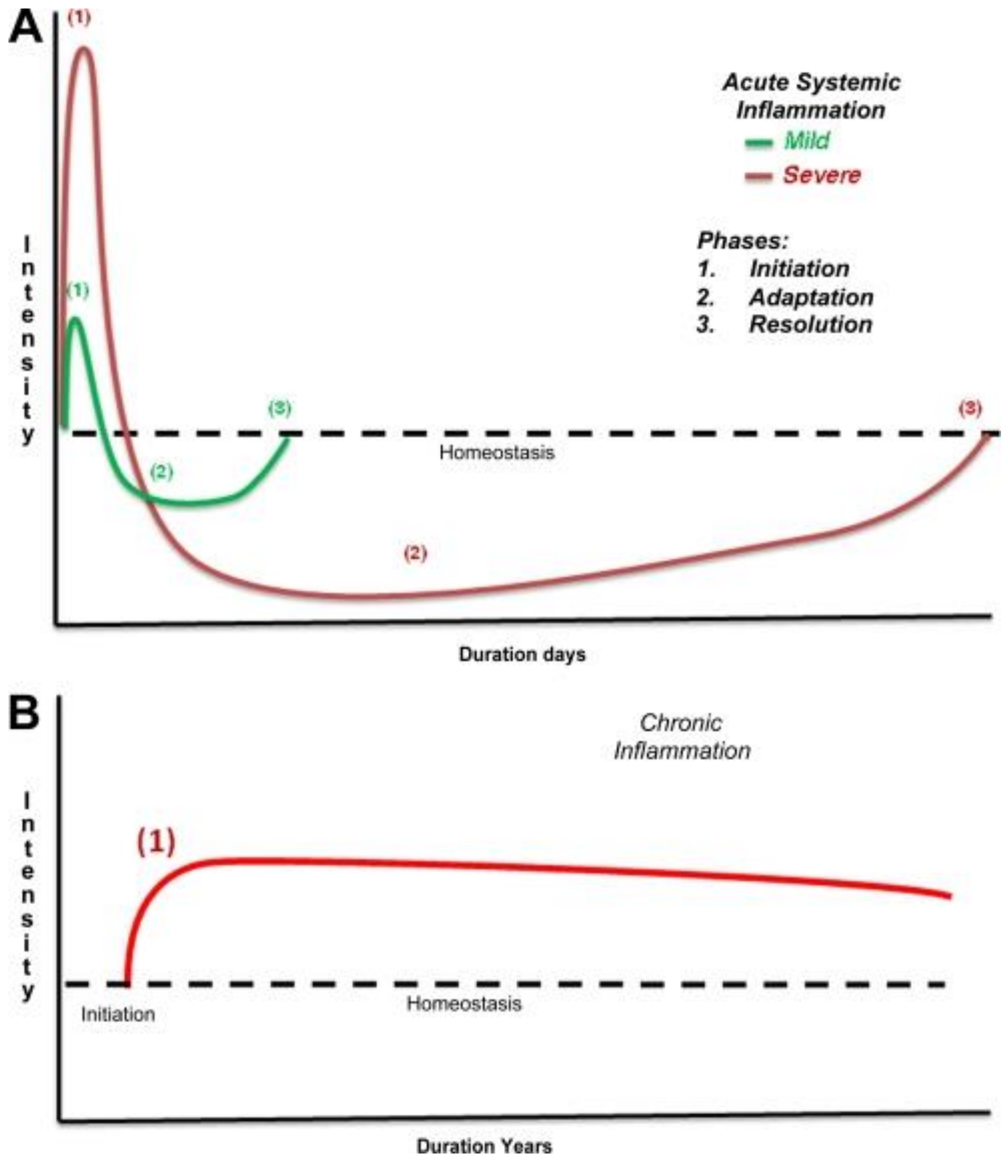
Clin Microbiol Rev. 2012 Oct; 25(4): 609–634.



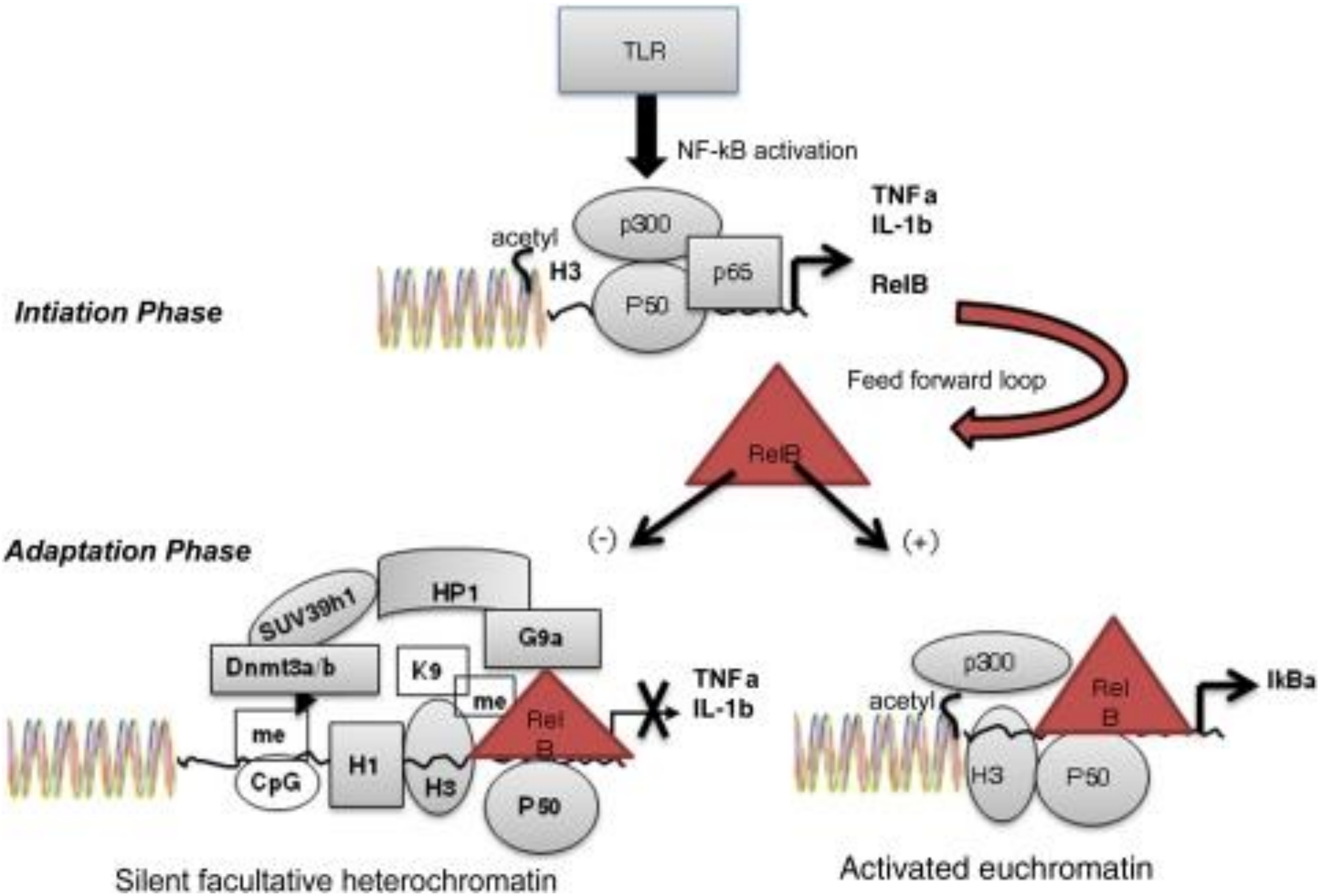
Role of epigenetics in pathogenesis of diseases



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

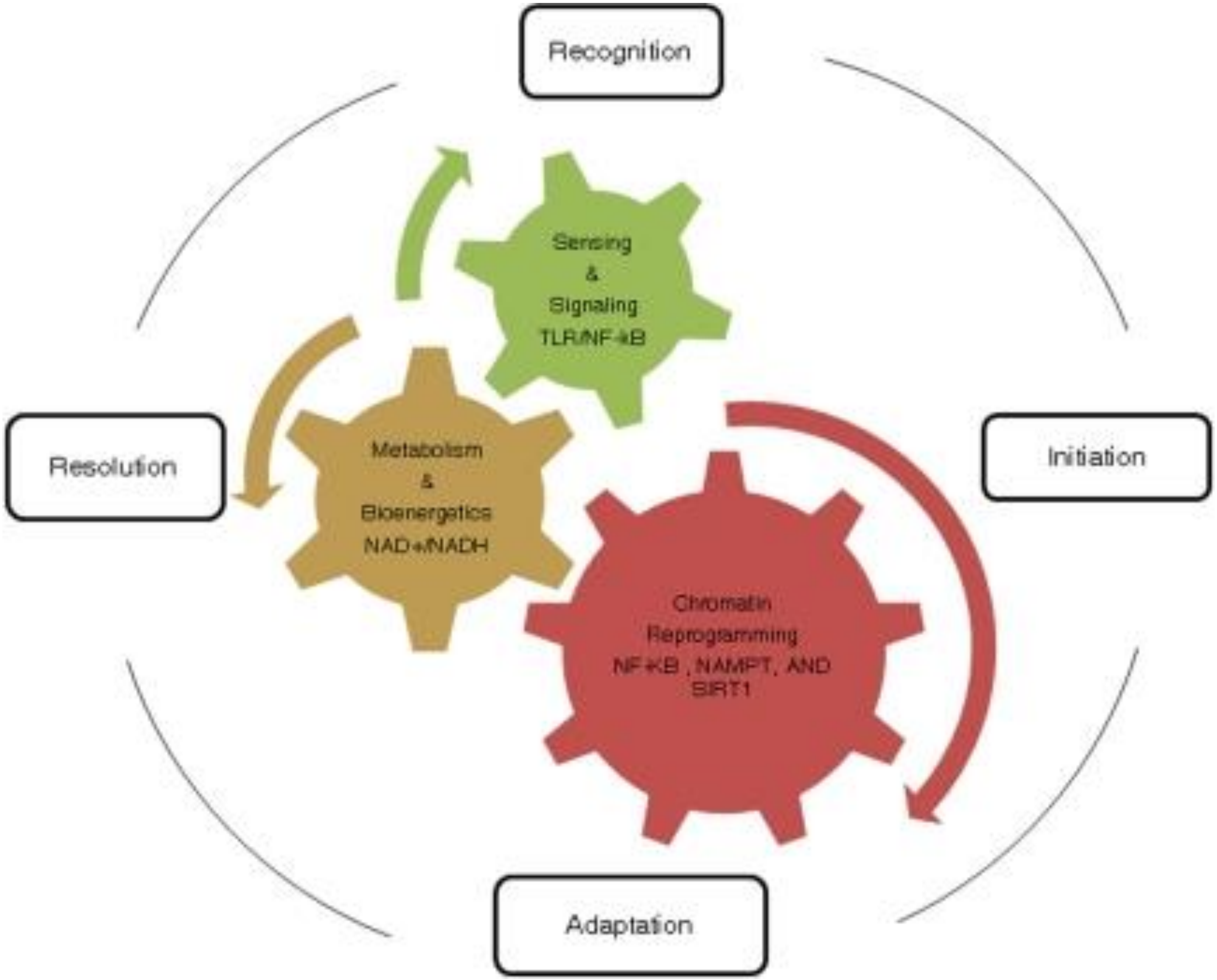


A
(1)
Acute Systemic
Inflammation
Mild
Severe
Phases:
1. Initiation
2. Adaptation
3. Resolution
Intensity
(1)
(3)
(3)
Homeostasis
(2)
(2)
Duration days
B
Chronic
Inflammation
Intensity
(1)
Initiation
Homeostasis
Duration Years



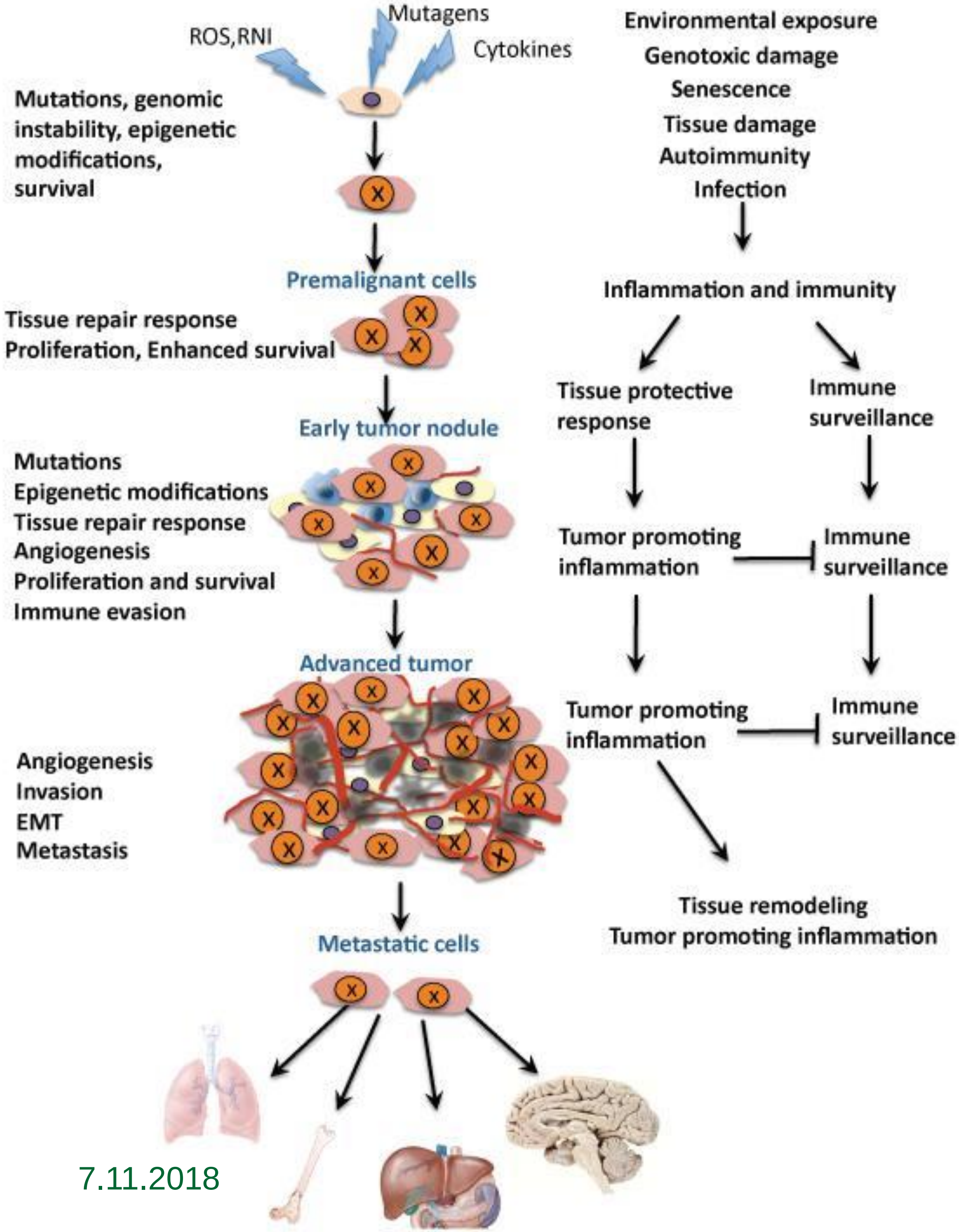
Epigenetic remodelling of chromatin and reprogramming od genes during acute systemic inflammation.

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

Thank you for your attention