INFLAMMATIONS II

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MEDIATORS OF INFLAMMATION

- ***Definition:***
- *The mediators of inflammation are substances that initiate and regulate inflammatory reactions.*

Principal Mediators of Inflammation

Table 3.5 Principal Mediators of Inflammation

Mediator	Source	Action
Histamine	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability, endothelial activation
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain, fever
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis, leukocyte adhesion, and activation
Cytokines (TNF, IL-1, IL-6)	Macrophages, endothelial cells, mast cells	Local: endothelial activation (expression of adhesion molecules). Systemic: fever, metabolic abnormalities, hypotension (shock)
Chemokines	Leukocytes, activated macrophages	Chemotaxis, leukocyte activation
Platelet-activating factor	Leukocytes, mast cells	Vasodilation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst
Complement	Plasma (produced in liver)	Leukocyte chemotaxis and activation, direct target killing (membrane attack complex), vasodilation (mast cell stimulation)
Kinins	Plasma (produced in liver)	Increased vascular permeability, smooth muscle contraction, vasodilation, pain

- ***The most important mediators of acute inflammation are:***

1. *Vasoactive amines,*
2. *Lipid products (Arachidonic acid derivatives; prostaglandins and leukotrienes),*
3. *Cytokines (including chemokines), and*
4. *Products of complement activation.*

- ***Mediators may be either:***

1. Produced locally by cells at the site of inflammation, or
2. Derived from circulating inactive precursors that are activated at the site of inflammation.

- ***Cell-derived mediators are:***

1. Rapidly released from intracellular granules (e.g., amines) or
2. Synthesized *de novo* (e.g., prostaglandins, leukotrienes, cytokines) in response to a stimulus.

- ***The major cell types that produce mediators of acute inflammation are:***

1. tissue macrophages,
2. dendritic cells, and
3. mast cells

- Platelets, neutrophils, endothelial cells, and most epithelia also can be induced to elaborate some of the mediators.
- *Cell-derived mediators are important for reactions against offending agents in tissues.*

- ***Plasma-derived mediators*** (e.g., complement proteins) are present in the circulation as inactive precursors
- They must be activated, by a series of proteolytic cleavages, to acquire their biologic properties.
- They are produced mainly in the liver.
- *They are effective against circulating microbes.*
- They also can be recruited into tissues.

- *Active mediators are produced only in response to various molecules that stimulate inflammation, including:*
  1. Microbial products and
  2. Substances released from necrotic cells.
- The usual requirement for microbes or dead tissues as an initiating stimulus ensures that *inflammation is normally triggered only when and where it is needed.*
- Most of the mediators are short-lived.
- *They quickly decay, or are inactivated by enzymes, or they are otherwise scavenged or inhibited.*

- *There is a system of checks and balances that regulates mediator actions (built-in control mechanisms).*
- One mediator can stimulate the release of other mediators.
- Products of complement activation stimulate the release of *histamine*.
- The cytokine *TNF* acts on endothelial cells to stimulate the production of another cytokine, *IL-1*, and many *chemokines*.

- ***The secondary mediators may have:***
  1. The same actions as the initial mediators or
  2. Different and even opposing activities

- ***This provides mechanisms for either:***
  1. *amplifying or,*
  2. *counteracting the initial action of a mediator*

Chemical Mediators of Inflammation

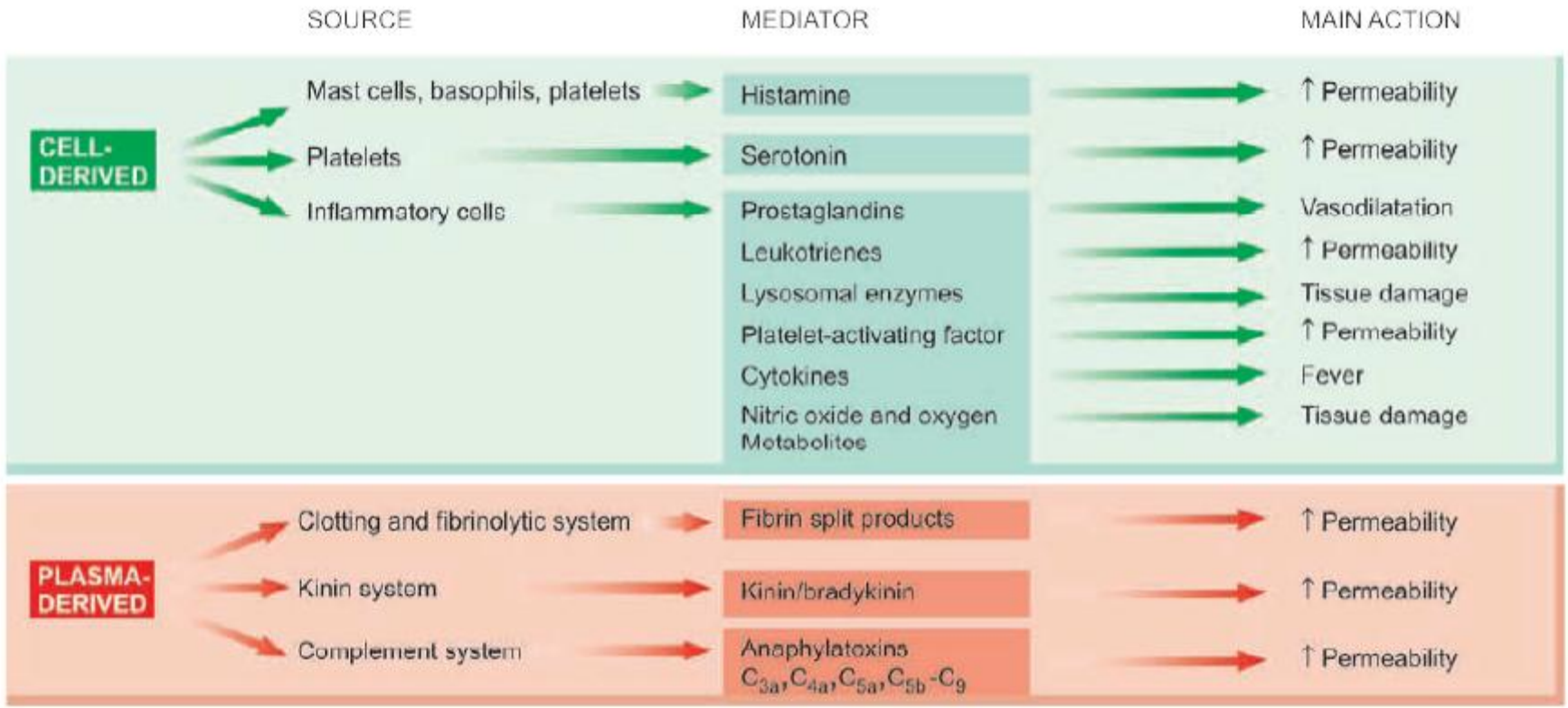

Figure 6.7 Chemical mediators of inflammation.

Chemical Mediators of Acute Inflammation

TABLE 6.2: Chemical Mediators of Acute Inflammation.

I. CELL-DERIVED MEDIATORS
1. Vasoactive amines (Histamine, 5-hydroxytryptamine, neuropeptides)
2. Arachidonic acid metabolites (Eicosanoids)
   i. Metabolites via cyclo-oxygenase pathway (prostaglandins, thromboxane A_2, prostacyclin, resolvins)
   ii. Metabolites via lipo-oxygenase pathway (5-HETE, leukotrienes, lipoxins)
3. Lysosomal components (from PMNs, macrophages)
4. Platelet activating factor
5. Cytokines (IL-1, TNF-α, TNF-β, IFN-γ, chemokines)
6. Free radicals (Oxygen metabolites, nitric oxide)

II. PLASMA-DERIVED MEDIATORS (PLASMA PROTEASES)
Products of:
1. The kinin system
2. The clotting system
3. The fibrinolytic system
4. The complement system

Summary of the general properties of the mediators of inflammation and some of the more important molecules

A. Vasoactive Amines: Histamine and Serotonin

- ***The two major vasoactive amines, so named because they have important actions on the blood vessels, are histamine and serotonin.***
- They are stored as preformed molecules in cells.
- They are among the first mediators to be released during inflammation.

1. ***Histamine:***

- The richest sources of ***histamine*** are the ***mast cells***, which are normally present in the connective tissue adjacent to blood vessels.
- Histamine also is found in blood ***basophils*** and ***platelets***.
- It is stored in mast cell granules and is released by degranulation in response to a variety of stimuli, including:

1. Physical injury, such as trauma, cold, or heat, by unknown mechanisms;
2. Binding of antibodies to mast cells, which underlies immediate hypersensitivity (allergic) reactions ; and
3. Products of complement called *anaphylatoxins* (C3a and C5a).

- *Antibodies and complement products bind to specific receptors on mast cells and trigger signaling pathways that induce rapid degranulation.*

- Neuropeptides (e.g., substance P) and cytokines (IL-1, IL-8) also may trigger release of histamine.
- ***Histamine causes dilation of arterioles and increases the permeability of venules.***
- Histamine is the principal mediator of the immediate transient phase of increased vascular permeability, producing inter-endothelial gaps in postcapillary venules.
- Its vasoactive effects are mediated mainly via binding to receptors, called ***H1 receptors,*** on microvascular endothelial cells.

- The *antihistamine drugs* that are commonly used to treat some inflammatory reactions, such as allergies, are *H1 receptor antagonists* that bind to and block the receptor.
- ***Histamine also causes contraction of some smooth muscles***.
- ***Leukotrienes,*** are much more potent than histamine and relevant for causing spasms of bronchial muscles, as in asthma.

2. ***Serotonin (5-hydroxytryptamine):***

- It is a preformed vasoactive mediator present in ***platelets*** and certain ***neuroendocrine cells***, such as in the GIT.
- It is not found in mast cells in humans.

1. Its primary function is a neurotransmitter in the GIT.
2. *It is a vasoconstrictor.*

- *The importance of this action in inflammation is unclear.*

B. Arachidonic Acid Metabolites

- ***Arachidonic acid*** is a 20-carbon polyunsaturated fatty acid that is derived from dietary sources or by conversion from the essential fatty acid linoleic acid.
- The lipid mediators ***prostaglandins*** and ***leukotrienes*** are produced from arachidonic acid present in ***membrane phospholipids.***
- They stimulate vascular and cellular reactions in acute inflammation.

- Most cellular arachidonic acid is esterified and incorporated into ***membrane phospholipids***.
- Mechanical, chemical, and physical stimuli or other mediators (e.g., C5a) trigger the release of arachidonic acid from membranes by activating ***cellular phospholipases***, mainly *phospholipase A2.*
- Once freed from the membrane, arachidonic acid is rapidly converted to ***bioactive mediators.***

- These mediators, also called ***eicosanoids*** (because they are derived from 20-carbon fatty acids; Greek *eicosa* = 20).
- *They are synthesized by two major classes of enzymes:*
  1. Cyclooxygenases which generate prostaglandins, and
  2. Lipoxygenases which produce leukotrienes and lipoxins.
- Eicosanoids bind to G protein-coupled receptors on many cell types and can mediate every step of inflammation.

1. Prostaglandins

- ***Prostaglandins (PGs)*** ***are produced by mast cells, macrophages, endothelial cells, and many other cell types.***
- ***They are involved in the vascular and systemic reactions of inflammation.***
- They are generated by the actions of ***two cyclooxygenases*** called ***COX-1*** and ***COX-2.***

A. ***COX-1*** is produced in response to inflammatory stimuli
- It is constitutively expressed in *most tissues.*
- It may serve a homeostatic function e.g.,
  1. Fluid and electrolyte balance in the kidneys, and
  2. Cytoprotection in the GIT.

B. In contrast, ***COX-2*** is induced by inflammatory stimuli
- It generates the PGs that are involved in inflammatory reactions,.
- It is *low or absent* in *most normal tissues.*

- *Prostaglandins are named based on structural features coded by a letter (e.g., PGD, PGE, PGF, PGG, and PGH) and a subscript numeral (e.g., 1, 2), which indicates the number of double bonds in the compound.*
- The most important ***PGs*** in inflammation are PGE2, PGD2, PGF2a, PGI2 *(prostacyclin), and TXA2 (thromboxane A2).*
- Each of which is derived by the action of a specific enzyme on *an intermediate* in the pathway.

- ***PGD2*** is the major prostaglandin made by mast cells; along with PGE2 (which is more widely distributed)
- *It causes:*
  1. *Vasodilation and*
  2. *Increases the permeability of postcapillary venules*
- This potentiates exudation and results in edema.
- ***PGD2*** also is:
  3. *A chemoattractant for neutrophils*

- ***Platelets*** contain the enzyme *thromboxane synthase,* which is responsible for synthesizing ***TXA2,*** the major platelet eicosanoid.
- ***TXA2*** is a potent platelet-aggregating agent and vasoconstrictor, and thus promotes thrombosis.
- In contrast, ***vascular endothelium*** contains *prostacyclin synthase*, which is responsible for the formation of ***prostacyclin (PGI2)*** and its stable end product ***PGF1a***.
- ***Prostacyclin*** is a vasodilator.
- Thus it serves to prevent thrombus formation on normal endothelial cells.

- *A thromboxane-prostacyclin imbalance* has been implicated in *coronary and cerebral artery thrombosis.*
- In addition to their ***local effects, PGs*** are involved in the pathogenesis of *pain* and *fever*, two common ***systemic manifestations*** of inflammation.
- ***PGE2:***
  1. Makes the *skin hypersensitive to painful stimuli*, and
  2. *Causes fever during infections.*

Arachidonic acid metabolites via cyclooxygenase pathway

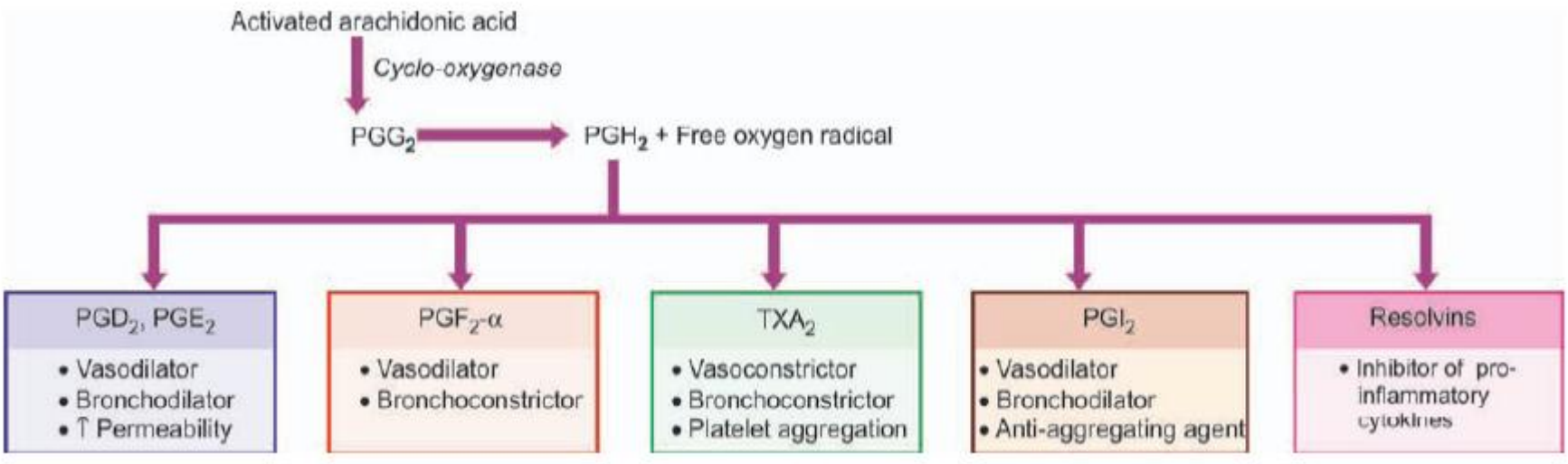

Figure 6.8 Arachidonic acid metabolites via cyclooxygenase pathway.

2. Leukotrienes

- ***Leukotrienes*** **are produced in leukocytes and mast cells by the action of lipoxygenase**
- They are involved in vascular and smooth muscle reactions and leukocyte recruitment.
- ***The synthesis of leukotrienes involves multiple steps:***
- The first of which generates leukotriene A4 (LTA4), which in turn gives rise to LTB4 or LTC4.

- ***LTB4*** is produced by neutrophils and some macrophages, which:
  1. Is a potent chemotactic agent and activator of neutrophils,
  2. Causes aggregation and adhesion of the cells to venular endothelium,
  3. Generation of ROS, and
  4. Release of lysosomal enzymes.
- The cysteinyl-containing leukotriene LTC4 and its metabolites,LTD4 and LTE4, are *produced mainly in mast cells* and *cause*
  1. Intense vasoconstriction,
  2. Bronchospasm (important in asthma), and
  3. Increased permeability of venules.

3. Lipoxins

- ***Lipoxins*** *are generated from arachidonic acid by the lipoxygenase pathway.*
- Unlike prostaglandins and leukotrienes, the lipoxins suppress inflammation by inhibiting the recruitment of leukocytes.
- They inhibit neutrophil chemotaxis and adhesion to endothelium.

- *Two cell populations are required for the transcellular biosynthesis of these mediators.*
- Leukocytes, particularly *neutrophils,* produce intermediates in lipoxin synthesis.
- These are converted to lipoxins by *platelets* interacting with the leukocytes.

Arachidonic acid metabolites via lipooxygenase pathway

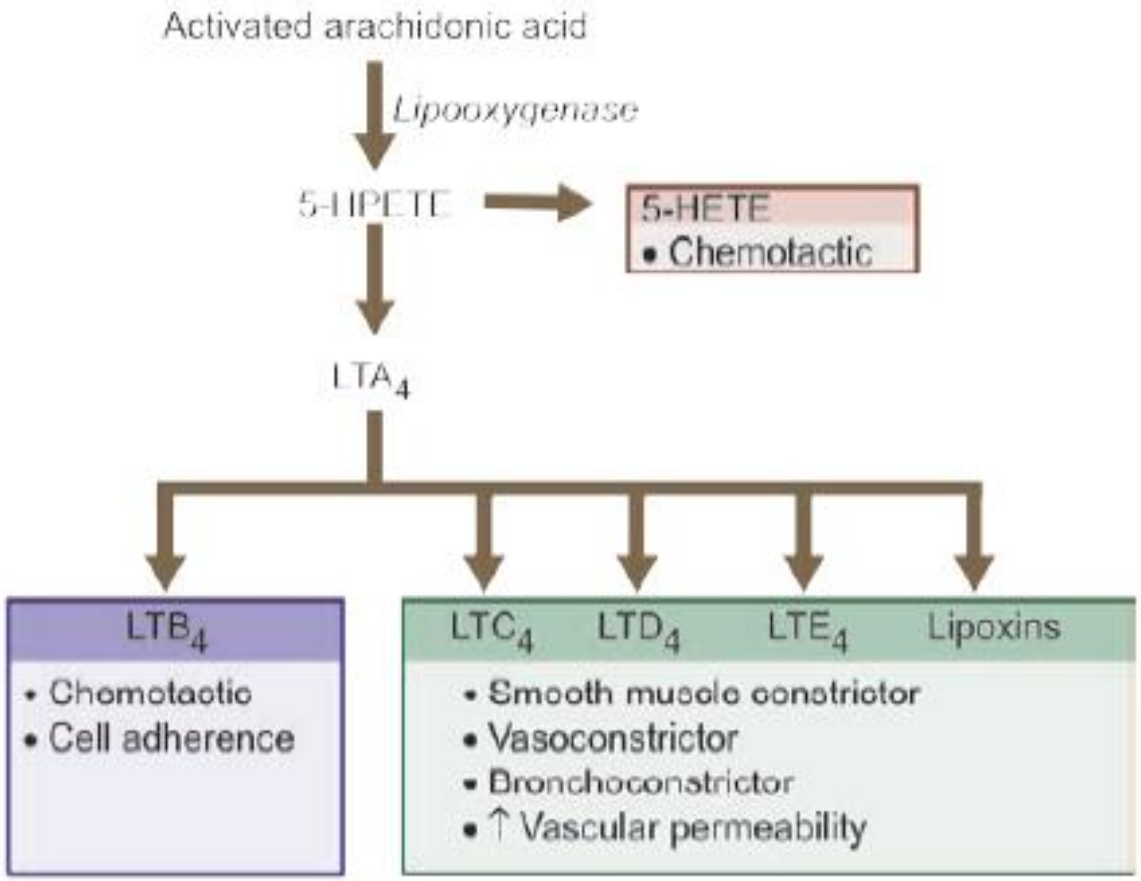

Figure 6.9 Arachidonic acid metabolites via lipooxygenase pathway.

Production of AA metabolites and their roles in inflammation.

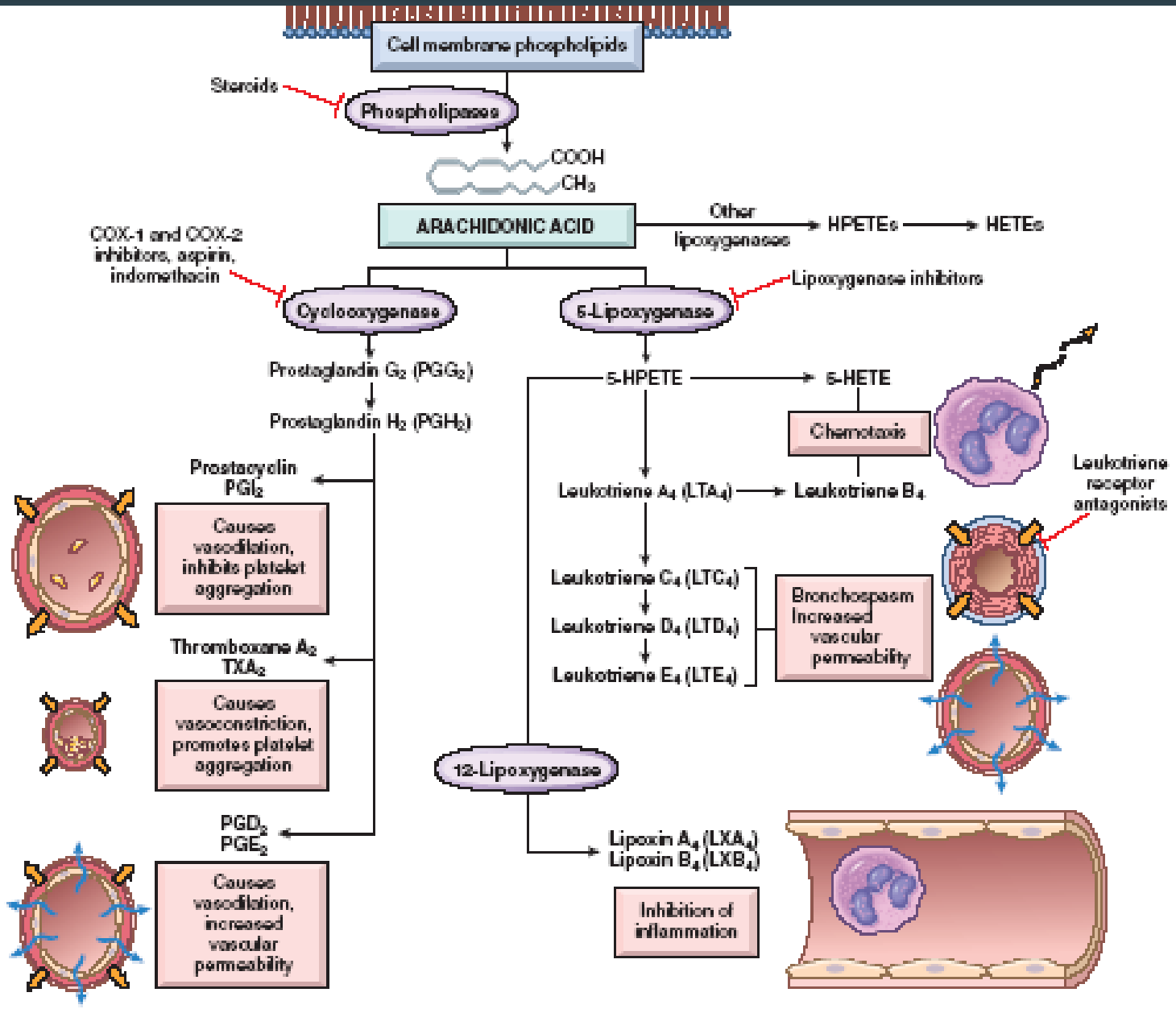

Fig. 3.9 Production of AA metabolites and their roles in inflammation. Clinically useful antagonists of different enzymes and receptors are indicated in red. While leukotriene receptor antagonists inhibit all actions of leukotrienes, they are used in the clinic to treat asthma, as shown. *COX-1, COX-2*, Cyclooxygenase 1 and 2; *HETE*, hydroxyeicosatetraenoic acid; *HPETE*, hydroperoxyeicosatetraenoic acid.

Principal Actions of Arachidonic Acid Metabolites in Inflammation

Table 3.6 Principal Actions of Arachidonic Acid Metabolites in Inflammation

Action	Eicosanoid
Vasodilation	Prostaglandins PGI_2 (prostacyclin), PGE_1, PGE_2, PGD_2
Vasoconstriction	Thromboxane A_2, leukotrienes C_4, D_4, E_4
Increased vascular permeability	Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte adhesion	Leukotriene B_4
Smooth muscle contraction	Prostaglandins PGC4, PGD4, PGE4

C. Cytokines and Chemokines

1. ***Cytokines:***

- They are proteins secreted by many cell types (*principally activated lymphocytes, macrophages, and dendritic cells*).
- Endothelial, epithelial, and connective tissue cells that mediate and regulate immune and inflammatory reactions also secrete cytokines.
- ***Growth factors*** that act on epithelial and mesenchymal cells are not grouped under cytokines.

- ***Cytokines involved in acute inflammation are: Tumor Necrosis Factor (TNF) and Interleukin-1 (IL-1).***
- *TNF and IL-1 serve critical roles in* leukocyte recruitment *by promoting adhesion of leukocytes to endothelium and their migration through vessels.*
- *Activated macrophages and dendritic cells* mainly produce these cytokines.
- ***TNF*** is also produced by *T lymphocytes* and *mast cells.*
- *Some epithelial cells produce IL-1* as well.
- *Microbial products, foreign bodies, necrotic cells,* and a variety of other inflammatory stimuli can *stimulate the secretion of TNF and IL-1.*

- The production of ***TNF*** is induced by signals through ***TLRs*** and other microbial sensors.
- The synthesis of ***IL-1*** is stimulated by the same signals, but the generation of the biologically active form of this cytokine is dependent on the ***inflammasome.***
- ***TNF and IL-1*** contribute to the local and systemic reactions of inflammation.
- *The most important roles of these cytokines in inflammation are the following:*

A. ***Endothelial activation:***

- Both ***TNF and IL-1*** act on endothelium to induce a spectrum of changes referred to as *endothelial activation*.
- ***These changes include increased:***

1. Expression of endothelial adhesion molecules, mostly ***E- and P-selectins*** and ligands for leukocyte ***integrins***;
2. Production of other cytokines, chemokines, and eicosanoids; and
3. Procoagulant activity of the endothelium.

B. ***Activation of leukocytes and other cells:***

1. TNF augments responses of neutrophils to bacterial endotoxin and stimulates the microbicidal activity of macrophages.
2. IL-1 activates fibroblasts to synthesize collagen and stimulates proliferation of synovial cells and other mesenchymal cells.
3. ***IL-1 and IL-6*** stimulate the generation of a subset of ***CD4+ helper T cells*** called ***TH17 cells.***

C. ***Systemic acute-phase response:***

1. ***IL-1 and TNF as well as IL-6*** induce the systemic acute-phase responses associated with infection or injury, including ***fever.***
2. ***IL-1 and TNF*** are implicated in the pathogenesis of the systemic inflammatory response syndrome (SIRS), resulting from disseminated bacterial infection ***(sepsis).***

3. ***TNF*** regulates energy balance by:
   A. *Promoting lipid and protein catabolism and*
   B. *Suppressing appetite.*

- Therefore, sustained production of TNF contributes to ***cachexia.***
- ***Cachexia*** *is a pathologic state characterized by:*
  A. *Weight loss,*
  B. *Muscle atrophy, and*
  C. *Anorexia*
- It accompanies some chronic infections and cancers.

2. *Chemokines*

- Chemokines are a family of small (8-10 kD) proteins that act primarily as chemo-attractants for specific types of leukocytes.
- About 40 different chemokines and 20 different receptors for chemokines are identified.
- *They are classified into four major groups, according to the arrangement of cysteine (C) residues in the proteins:*

1) ***C-X-C chemokines:***

- *They* have one amino acid residue separating the first two of the four conserved cysteines.
- *These chemokines act primarily on neutrophils.*
- ***IL-8;*** now called ***CXCL8*** is typical of this group.
- It is secreted by activated macrophages, endothelial cells, and other cell types.
- *It causes activation and chemotaxis of neutrophils.*
- *It has limited activity on monocytes and eosinophils.*
- *Its most important inducers are microbial products and cytokines, mainly IL-1 and TNF.*

2) C-C chemokines:

- They have the first two conserved cysteine residues adjacent.
- The C-C chemokines, include:
  A. *Monocyte chemo-attractant protein (MCP-1, CCL2),*
  B. *Eotaxin (CCL11), and*
  C. *Macrophage inflammatory protein-1α (MIP-1α, CCL3).*
- They mainly serve as chemoattractants for monocytes, eosinophils, basophils, and lymphocytes.
- Although most of the chemokines in this class have overlapping actions, eotaxin selectively recruits eosinophils.

3) *C chemokines:*

- They lack the first and third of the four conserved cysteines.
- The C chemokines e.g., ***lymphotactin, XCL1*** are relatively specific for lymphocytes.

4) ***CX3C chemokines:***

- They contain three amino acids between the first two cysteines.
- The only known member of this class is called ***fractalkine (CX3CL1).***
- ***This chemokine exists in two forms:***

A. ***A cell surface-bound protein*** induced on endothelial cells by inflammatory cytokines that promote strong adhesion of monocytes and T cells, and

B. ***A soluble form,*** derived by proteolysis of the membrane-bound protein, that has potent chemoattractant activity for the same cells.

- *Chemokines mediate their activities by binding to seven-transmembrane G protein–coupled receptors.*
- These receptors usually exhibit overlapping ligand specificities, and leukocytes generally express multiple receptors.
- Certain chemokine receptors (CXCR4, CCR5) act as *co-receptors for a viral envelope glycoprotein of HIV virus of AIDS, and are thus involved in binding and entry of the virus into cells.*

- Chemokines bind to proteoglycans and are displayed at high concentrations on the surface of endothelial cells and in the extracellular matrix.
- ***They have two main functions:***

I. **Acute inflammation:**

- Most chemokines stimulate leukocyte attachment to endothelium by:

A. Acting on leukocytes to increase the affinity of integrins, and

B. Serving as chemoattractants, thereby guiding leukocytes to sites of infection or tissue damage.

- Because they mediate aspects of the inflammatory reaction, they are called ***inflammatory chemokines.***
- Their production is induced by microbes and other stimuli.

II. Maintenance of tissue architecture:

- Some chemokines are produced by stromal cells in tissues and are sometimes called ***homeostatic chemokines.***
- *These organize various cell types in different anatomic regions of the tissues, such as T and B lymphocytes in discrete areas of the spleen and lymph nodes.*

- ***Other Cytokines in Acute Inflammation***
- The list of cytokines implicated in inflammation is huge and constantly growing.
- Two that have received considerable interest are:
- ***IL-6,*** made by macrophages and other cells.
- It is involved in local and systemic reactions.
- IL-6 receptor antagonists are used in the treatment of rheumatoid arthritis.
- ***IL-17,*** produced mainly by T lymphocytes.
- It promotes neutrophil recruitment.
- IL-17 antagonists are very effective in psoriasis.
- ***Type I interferons,*** whose normal function is to inhibit viral replication. It contribute to some of the systemic manifestations of inflammation.

Cytokines in Inflammation

Table 3.7 Cytokines in Inflammation

Cytokine	Principal Sources	Principal Actions in Inflammation
In Acute Inflammation		
TNF	Macrophages, mast cells, T lymphocytes	Stimulates expression of endothelial adhesion molecules and secretion of other cytokines; systemic effects
IL-1	Macrophages, endothelial cells, some epithelial cells	Similar to TNF; greater role in fever
IL-6	Macrophages, other cells	Systemic effects (acute phase response)
Chemokines	Macrophages, endothelial cells, T lymphocytes, mast cells, other cell types	Recruitment of leukocytes to sites of inflammation; migration of cells in normal tissues
IL-17	T lymphocytes	Recruitment of neutrophils and monocytes
In Chronic Inflammation		
IL-12	Dendritic cells, macrophages	Increased production of IFN-γ
IFN-γ	T lymphocytes, NK cells	Activation of macrophages (increased ability to kill microbes and tumor cells)
IL-17	T lymphocytes	Recruitment of neutrophils and monocytes

The most important cytokines involved in inflammatory reactions are listed. Many other cytokines may play lesser roles in inflammation. There is also considerable overlap between the cytokines involved in acute and chronic inflammation. Specifically, all the cytokines listed under acute inflammation may also contribute to chronic inflammatory reactions.

IFN-γ, Interferon-γ; *IL-1*, interleukin-1; *NK*, natural killer; *TNF*, tumor necrosis factor.

Major Roles of Cytokines

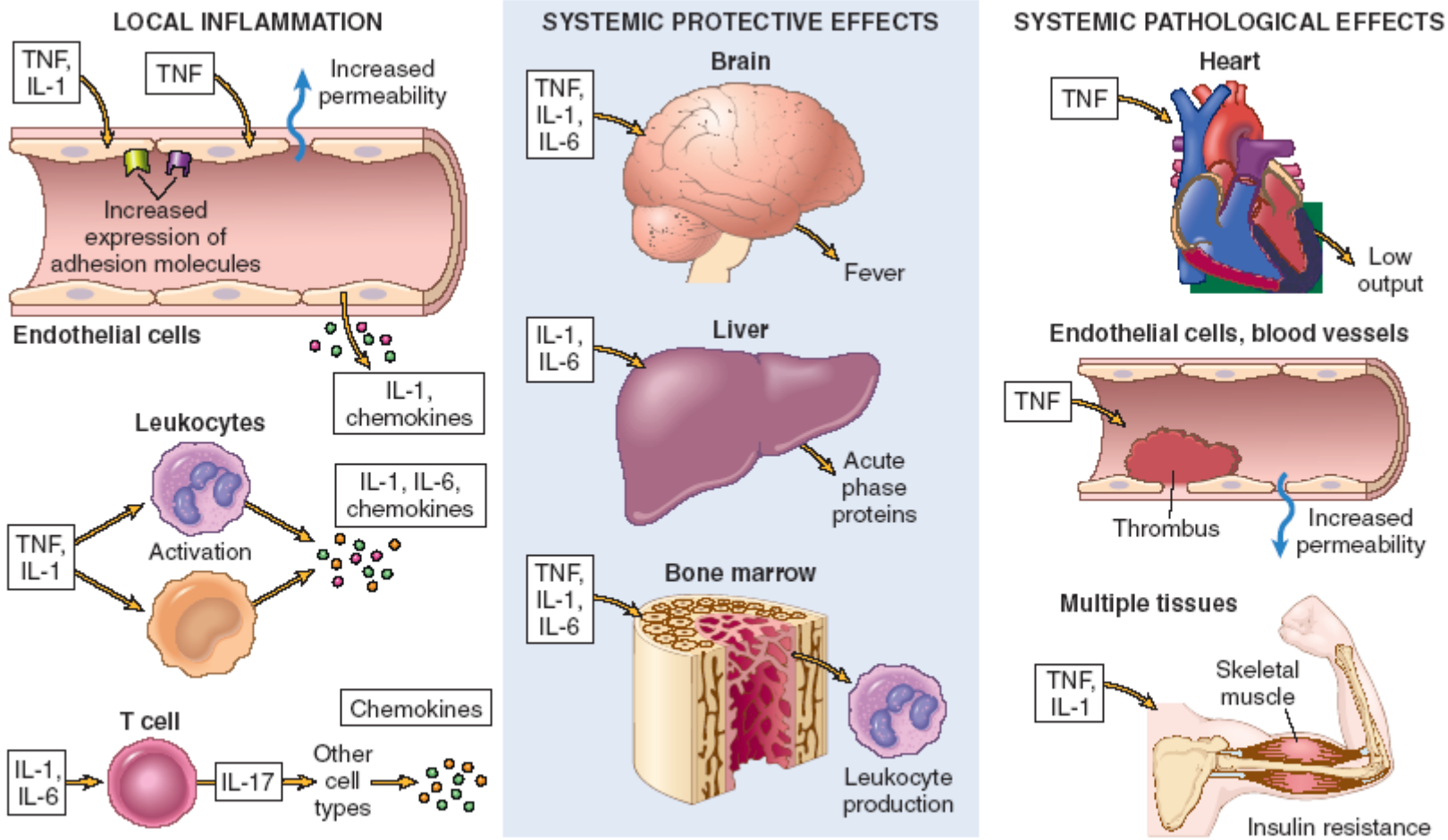

Fig. 3.10 Major roles of cytokines in acute inflammation. *PDGF*, Platelet-derived growth factor; *PGE*, prostaglandin E; *PGI*, prostaglandin I.

D. Complement System

- ***The complement system is a collection of soluble proteins and their membrane receptors.***
- There are more than 20 complement proteins.
- Some of which are numbered C1 through C9.

1. *They function mainly in host defense against microbes and in pathological inflammatory reactions.*
2. *They function in both innate and adaptive immunity for defense against microbial pathogens.*

- During complement activation, several cleavage products of ***complement proteins*** are elaborated.
- *They cause increased vascular permeability, chemotaxis, and opsonization.*
- Complement proteins are present in inactive forms in the plasma.
- Many of them are activated to become proteolytic enzymes that degrade other complement proteins.
- They form an enzymatic cascade capable of tremendous ***amplification.***
- ***The critical step in complement activation is the proteolysis of the third and most abundant component, C3.***

- **Cleavage of C3 can occur by one of three pathways:**

1. ***The classical pathway,*** which is triggered by fixation of C1 to antibody (IgM or IgG) that has combined with antigen.
2. ***The alternative pathway,*** which can be triggered by microbial surface molecules e.g., endotoxin, or LPS in the absence of antibody
3. ***The lectin pathway,*** in which plasma mannose-binding lectin binds to carbohydrates on microbes and directly activates C1.

- *All three pathways of complement activation lead to the formation of an enzyme called the **C3 convertase,** which splits **C3** into two functionally distinct fragments, **C3a and C3b.***
- C3a is released, and C3b becomes covalently attached to the cell or molecule where the complement is being activated.
- More C3b then binds to the previously generated fragments to form ***C5 convertase***, which cleaves C5 to release ***C5a*** and leave ***C5b*** attached to the cell surface.

- ***C5b*** binds the late components ***(C6–C9),*** culminating in the formation of the membrane attack complex ***(MAC,*** *composed of multiple C9 molecules).*
- The enzymatic activity of complement proteins provides tremendous amplification that *millions of molecules of* ***C3b*** can deposit on the surface of a microbe *within 2 or 3 minutes.*

- ***The complement system has three main functions:***

I. **Inflammation:**

- ***C5a***, and, to a lesser extent, ***C4a*** and ***C3a***, are cleavage products of the corresponding complement components.
- They stimulate histamine release from mast
- This leads to increase vascular permeability and cause vasodilation.
- They are called ***anaphylatoxins*** because they have effects similar to those of mast cell mediators that are involved in ***anaphylaxis.***

- ***C5a*** *also is a* *chemotactic agent* *for neutrophils, monocytes, eosinophils, and basophils.*
- In addition, ***C5a*** activates the *lipoxygenase pathway* of arachidonic acid metabolism in neutrophils and monocytes, causing release of more inflammatory mediators.

II. Opsonization and phagocytosis:

- ***C3b*** and its cleavage product ***iC3b*** *(inactive C3b)*, when fixed to a microbial cell wall, act as opsonins and promote phagocytosis by neutrophils and macrophages, which bear cell surface receptors for these complement fragments.

III. Cell lysis:

- The deposition of the ***MAC*** on cells drills holes in the cell membrane, making them permeable to water and ions and resulting in their osmotic death ***(lysis).***
- This function is important for killing microbes with thin cell walls, such as *Neisseria* bacteria.
- Hence, *deficiency of the terminal components of complement* predisposes to infections by the *Neisseria* species meningococci and gonococci.
- In patients with complement deficiencies, these microbes can cause serious disseminated infections.

- ***The activation of complement is tightly controlled by cell-associated and circulating regulatory proteins.***
- Different ***regulatory proteins*** inhibit the production of active complement fragments or remove fragments that deposit on cells.
- *These regulators are expressed on normal host cells and thus prevent healthy tissues from being injured at sites of complement activation.*
- Regulatory proteins can be overwhelmed when large amounts of complement are deposited on host cells and in tissues, as happens in autoimmune diseases, in which individuals produce ***complement-fixing antibodies*** against their own cell and tissue antigens.

- ***The most important of these regulatory proteins are the following:***

1. ***C1 inhibitor*** blocks the activation of C1, the first protein of the classical complement pathway.
   - Inherited deficiency of this inhibitor is the cause of ***hereditary angioedema***.

2. ***Decay accelerating factor (DAF) and CD59*** are two proteins that are linked to plasma membranes by a glycophosphatidyl (GPI) anchor.
   - ***DAF prevents formation of C3 convertases.***
   - ***CD59 inhibits formation of the MAC.***
   - An acquired deficiency of the enzyme that creates GPI anchors leads to deficiency of these regulators and *excessive complement activation and lysis of red cells*.
   - *This gives rise to a disease called* ***paroxysmal nocturnal hemoglobinuria (PNH)*.**

- Other complement regulatory proteins *proteolytically* cleave active complements.

3. ***Factor H*** is a plasma protein that serves as a cofactor for proteolysis of C3 convertase.

- ***Factor H deficiency*** results in excessive complement activation.
  - ***Mutations in Factor H*** are associated with:
  - ***Hemolytic uremic syndrome,*** and
  - Increased permeability of retinal vessels in ***wet macular degeneration of the eye.***

- ***The complement system contributes to disease in several ways:***

1. Activation of complement by antibodies or
2. Antigen-antibody complexes deposited on host cells and tissues
- These are important mechanisms of cell and tissue injury.
3. Inherited deficiencies of complement proteins cause increased susceptibility to infections, and
1. Deficiencies of regulatory proteins cause a variety of disorders.

The functions of the complement system

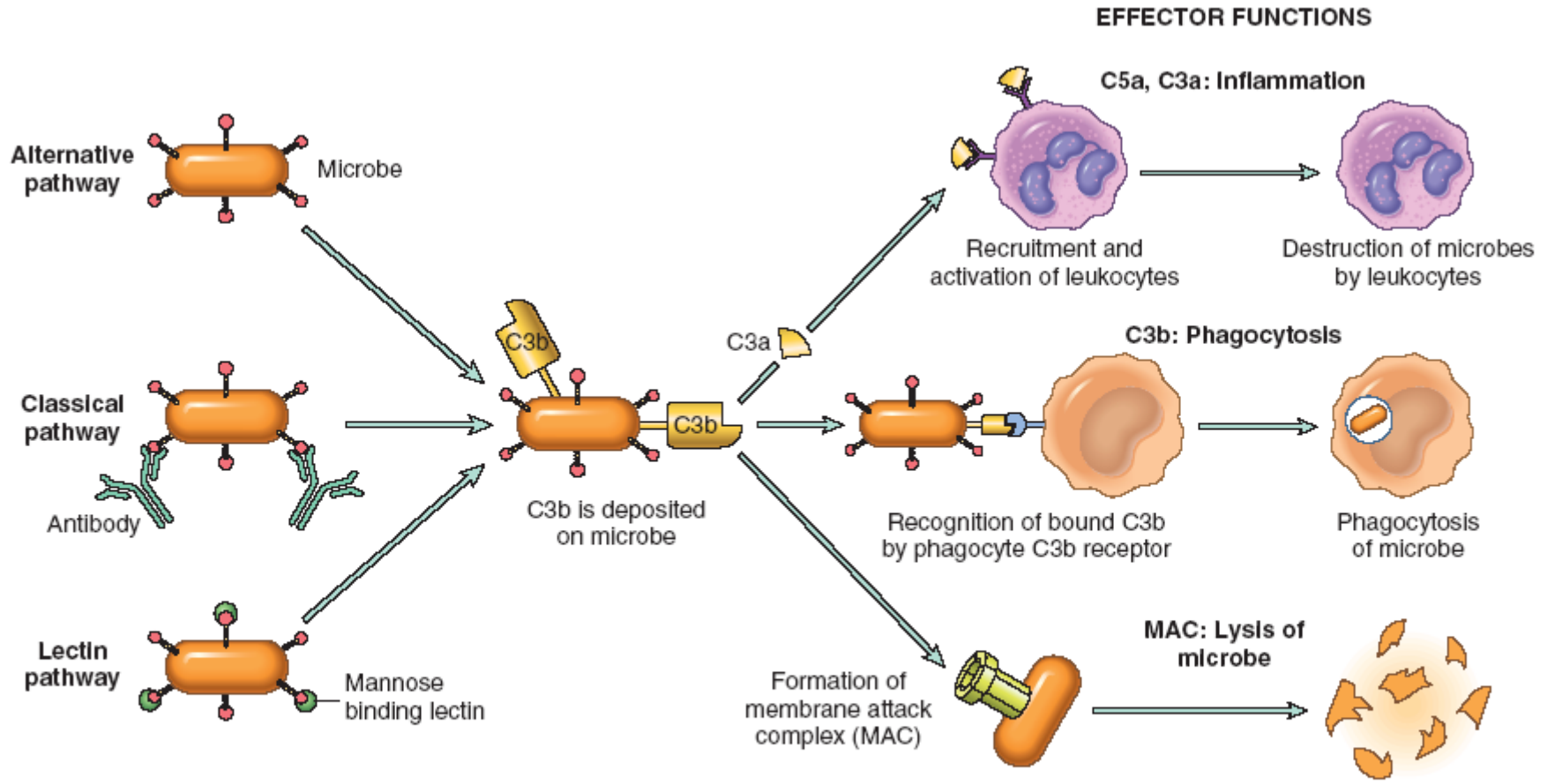

Fig. 3.11 The activation and functions of the complement system. Activation of complement by different pathways leads to cleavage of C3. The functions of the complement system are mediated by breakdown products of C3 and other complement proteins, and by the membrane attack complex (MAC).

Other Mediators of Inflammation
A. Platelet-Activating Factor

- ***Platelet-Activating Factor (PAF)*** is a phospholipid-derived mediator.
- A variety of cell types, can elaborate PAF including platelets themselves, basophils, mast cells, neutrophils, macrophages, and endothelial cells.

- ***Function of PAF:***

1. It causes *platelet aggregation*.
2. It has multiple inflammatory effects.
3. It causes *vasoconstriction and broncho-constriction.*
4. At low concentrations it *induces vasodilation and increased vascular permeability.*

B. Products of Coagulation

- Studies suggested that *inhibiting coagulation reduced the inflammatory reaction to some microbes.*
- This leads to the idea that *coagulation and inflammation are linked processes.*
- This concept was supported by discovery of ***protease-activated receptors (PARs).***
- These receptors are activated by ***thrombin*** *(the protease that cleaves* ***fibrinogen*** *to produce a* ***fibrin*** *clot).*

- PARs are expressed on leukocytes, suggesting a role in inflammation.
- Their clearest role is in platelets.
- *Thrombin activation of PAR is a potent trigger of platelet aggregation during the process of clot formation.*
- It is difficult to dissociate clotting and inflammation, because *all forms of tissue injury that lead to clotting also induce inflammation, and inflammation causes changes in endothelial cells that increase abnormal clotting (thrombosis).*
- Whether the products of coagulation, *per se,* have a significant role in stimulating inflammation is still not established.

C. Kinins

- **Definition:**
- ***Kinins*** are vasoactive peptides derived from plasma proteins, called ***kininogens,*** by the action of specific proteases called ***kallikreins.***
- The enzyme kallikrein cleaves a plasma glycoprotein precursor, high-molecular-weight kininogen, to produce ***bradykinin.***

- ***Bradykinin*** increases vascular permeability and causes contraction of smooth muscle, dilation of blood vessels, and pain when injected into the skin.
- These effects are similar to those of histamine.
- The action of bradykinin is short-lived, because it is quickly inactivated by an enzyme called ***kininase.***
- Bradykinin has been implicated as a mediator in some forms of allergic reaction, such as anaphylaxis.

Inter-relationship among clotting, fibrinolytic, kinin and complement systems

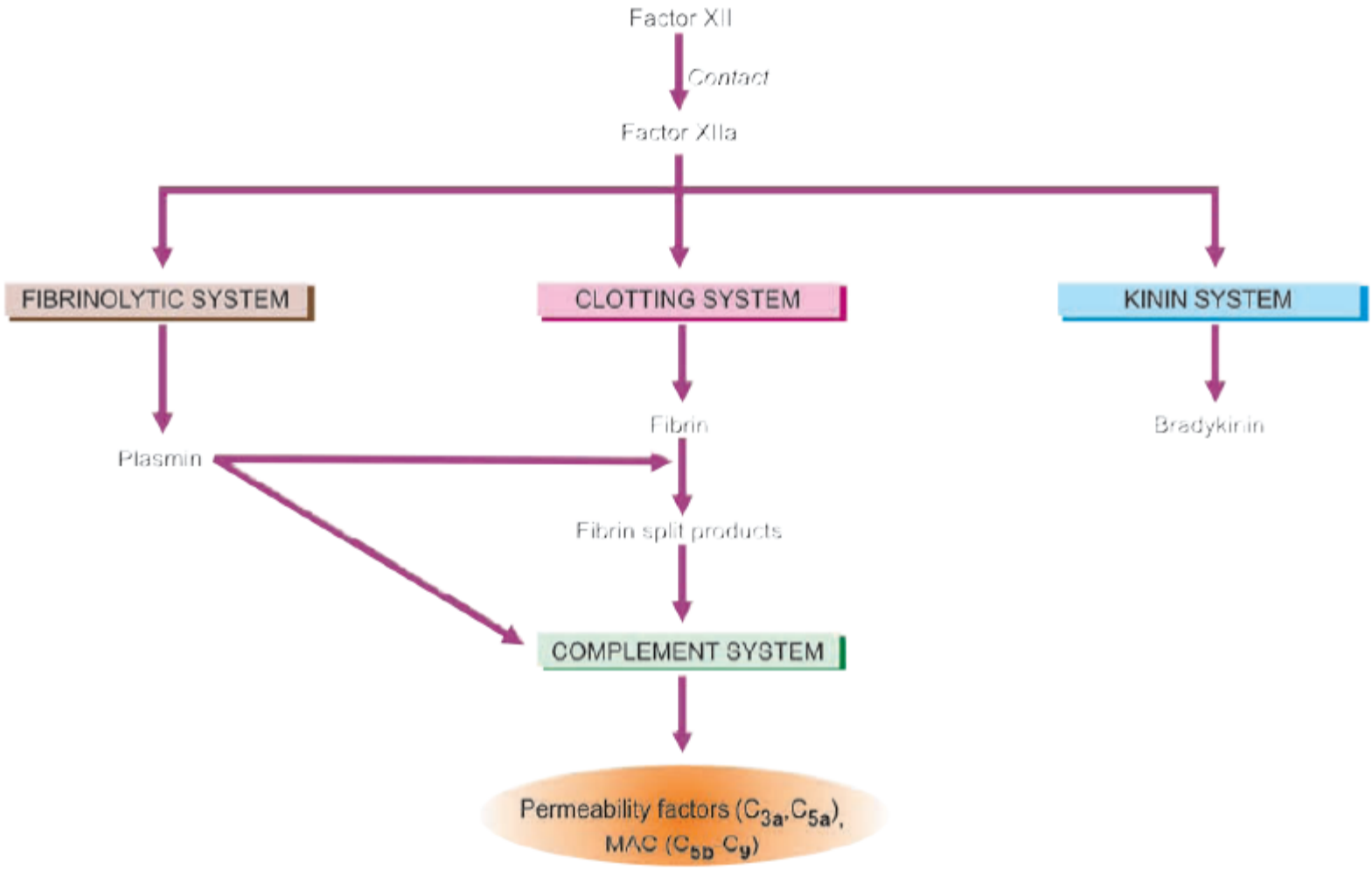

Figure 6.10 Inter-relationship among clotting, fibrinolytic, kinin and complement systems.

D. Neuropeptides

- Neuropeptides are secreted by sensory nerves and various leukocytes.
- *They play a role in the initiation and regulation of inflammatory responses.*
- These small peptides, including ***substance P*** and ***neurokinin A,*** are produced in the central and peripheral nervous system.

- Nerve fibers containing ***substance P*** are prominent in the lung and GIT.
- ***Substance P*** has many biologic functions, including the transmission of pain signals, regulation of blood pressure, stimulation of hormone secretion by endocrine cells, and in increasing vascular permeability.

Role of Mediators in Different Reactions of Inflammation

Table 3.8 Role of Mediators in Different Reactions of Inflammation

Reaction of Inflammation	Principal Mediators
Vasodilation	Histamine Prostaglandins
Increased vascular permeability	Histamine C3a and C5a (by liberating vasoactive amines from mast cells, other cells) Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte recruitment and activation	TNF, IL-1 Chemokines C3a, C5a Leukotriene B_4
Fever	IL-1, TNF Prostaglandins
Pain	Prostaglandins Bradykinin
Tissue damage	Lysosomal enzymes of leukocytes Reactive oxygen species

Regulation of Inflammation

- The onset of inflammatory responses may have potentially damaging influence on the host tissues as evident in hypersensitivity conditions.
- Such self-damaging effects are kept in check by the host mechanisms in order to resolve inflammation.
- ***These mechanisms are as follows:***

A. Acute phase reactants:

- A variety of acute phase reactant (APR) proteins are released in plasma in response to tissue trauma and infection.
- Their major role is to protect the normal cells from harmful effects of toxic molecules generated in inflammation and to clear away the waste material.

- **APRs include the following:**

i. *Cellular protection factors e.g. α1-antitrypsin, α1- chymotrypsin, α2-antiplasmin, plasminogen activator inhibitor:*

- They protect the tissues from cytotoxic and proteolytic damage.

ii. *Some coagulation proteins* (e.g. fibrinogen, plasminogen, von Willebrand factor; factor VIII):

- They generate factors to replace those consumed in coagulation.

iii. *Transport proteins* (e.g. ceruloplasmin, haptoglobin):

- They carry generated factors.

iv. *Immune agents* (e.g. serum amyloid A and P component, C-reactive protein):

- CRP is an opsonizing agent for phagocytosis and its levels are a useful indictor of inflammation in the body.

v. *Stress proteins* (e.g. heat shock proteins-HSP, ubiquitin):

- They are accompanying molecule who carry the toxic waste within the cell to the lysosomes.

vi. *Antioxidants* (e.g. ceruloplasmin are active in elimination of excess of oxygen free radicals).

- The APR are synthesized mainly in the liver, and to some extent in macrophages.
- APR along with systemic features of *fever* and *leucocytosis* is termed ***'acute phase response'.***
- Deficient synthesis of APR leads to severe form of disease in the form of chronic and repeated inflammatory responses.

B. **Glucosteroids:**

- The endogenous glucocorticoids act as anti-inflammatory agents.
- Their levels are raised in infection and trauma by self-regulating mechanism.

C. **Free cytokine receptors:**

- The presence of freely circulating soluble receptors for cytokines in the serum correlates directly with disease activity.

D. **Anti-inflammatory chemical mediators:**

- PGE2 or prostacyclin have both pro-inflammatory as well as anti-inflammatory actions.

Factors Determining Variation In Inflammatory Response

- Although acute inflammation is typically characterized by vascular and cellular events with emigration of neutrophilic leucocytes, not all examples of acute inflammation show infiltration by neutrophils.
- On the other hand, some chronic inflammatory conditions are characterized by neutrophilic infiltration.
- For example, *typhoid fever* is an example of acute inflammatory process but the cellular response in it is lymphocytic.

1. Factors Involving the Organisms

1. ***Type of injury and infection:***

- For example, skin reacts to herpes simplex infection by formation of vesicle and to streptococcal infection by formation of boil.
- Lung reacts to pneumococci by occurrence of lobar pneumonia while to tubercle bacilli it reacts by granulomatous inflammation.

2. ***Virulence:***

- Many species and strains of organisms may have varying virulence e.g. the three strains of *C. diphtheriae (gravis, intermedius and mitis)* produce the same diphtherial exotoxin but in different amount.

3. ***Dose:***

- The concentration of organism in small doses produces usually local lesions while larger dose results in more severe spreading infections.

4. ***Portal of entry:***

- Some organisms are infective only if administered by particular route e.g. *Vibrio cholerae* is not pathogenic if injected subcutaneously but causes cholera if swallowed.

4. ***Product of organisms:***

- Some organisms produce enzymes that help in spread of infections e.g. hyaluronidase by *Clostridium welchii*, streptokinase by streptococci, staphylokinase and coagulase by staphylococci.

2. Factors Involving the Host

1. ***Systemic diseases:***

- Certain acquired systemic diseases in the host are associated with impaired inflammatory response e.g. diabetes mellitus, chronic renal failure, cirrhosis of the liver, chronic alcoholism, bone marrow suppression from various causes (drugs, radiation, idiopathic).
- These conditions render the host more susceptible to infections.

2. ***Immune status of host:***

- Patients who are immunosuppressed from congenital or acquired immunodeficiency have lowered inflammatory response and spread of infections occurs rapidly e.g. in AIDS, congenital immunodeficiency diseases, protein calorie malnutrition, starvation.

3. ***Congenital neutrophil defects:***

- Congenital defects in neutrophil structure and functions result in reduced inflammatory response.

4. ***Leukopenia:***

- Patients with low WBC count with neutropenia or agranulocytosis develop spreading infection.

5. ***Site or type of tissue involved:***

- For example, the lung has loose texture as compared to bone and, thus, both tissues react differently to acute inflammation.

6. ***Local host factors:***

- For instance, ischemia, presence of foreign bodies and chemicals cause necrosis and are thus cause more harm.

3. Type of Exudation

- *The appearance of escaped plasma determines the morphologic type of inflammation as under:*

1. ***Serous:*** When the fluid exudate resembles serum or is watery e.g. pleural effusion in tuberculosis, blister formation in burns.
2. ***Fibrinous:*** When the fibrin content of the fluid exudate is high e.g. in pneumococcal pneumonia and rheumatic pericarditis.

3. ***Purulent or suppurative exudate:*** It is formation of creamy pus as seen in infection with pyogenic bacteria e.g. abscess, acute appendicitis.
4. ***Hemorrhagic:*** When there is vascular damage e.g. acute hemorrhagic pneumonia in influenza.
5. ***Catarrhal:*** When the surface inflammation of epithelium produces increased secretion of mucous e.g. common cold.


Thank You