Plasma derived mediators

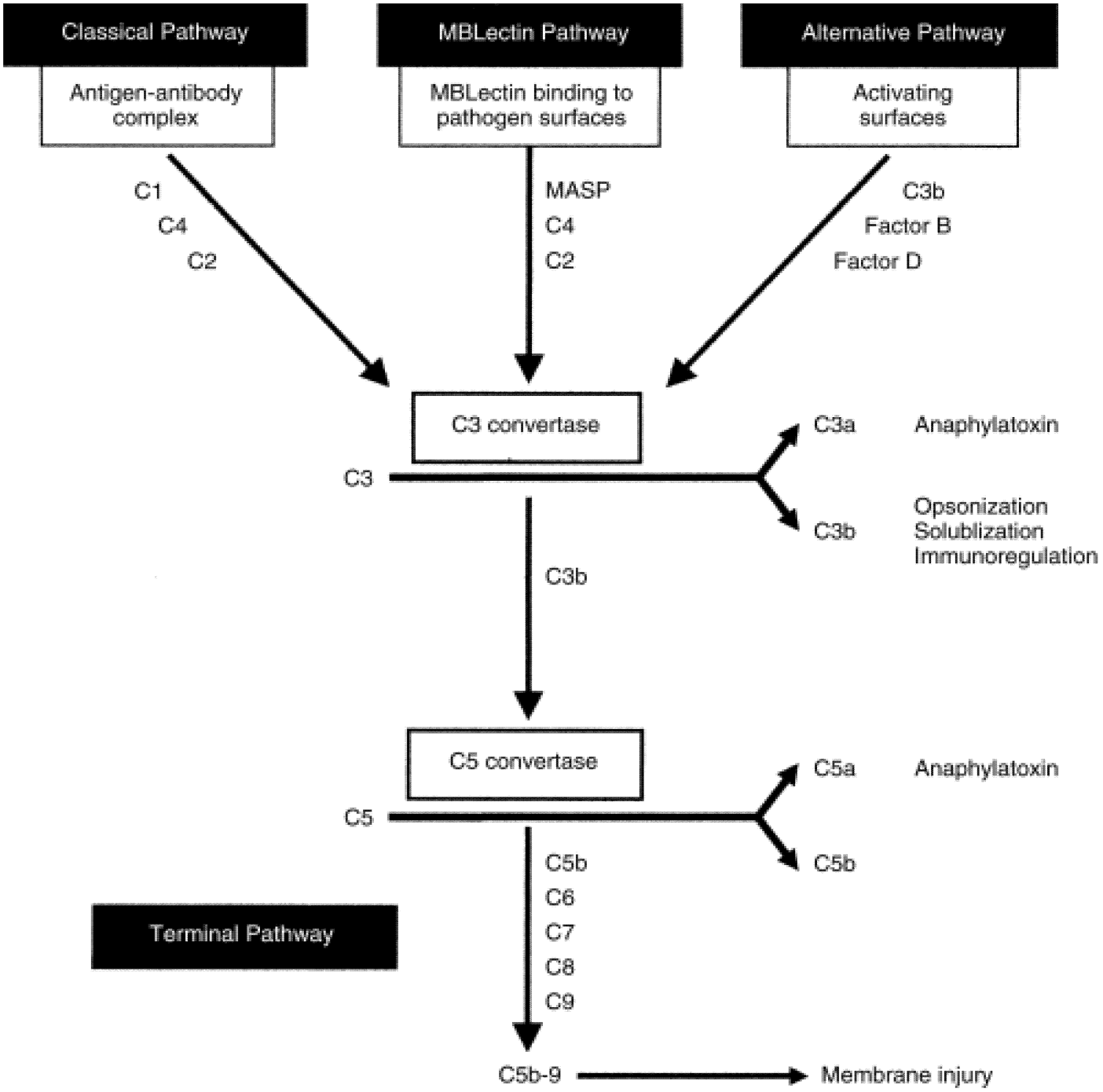
- Complement system
- Kinin system
- Clotting system
- Fibrinolytic system

Plasma cascade systems

- Complement system, when activated, results in the increased removal of pathogens via opsonisation and phagocytosis.
- Kinin system generates proteins capable of sustaining vasodilation and other physical inflammatory effects.
- Coagulation system or *clotting cascade* which forms a protective protein mesh over sites of injury.
- Fibrinolytic system, which acts in opposition to the *coagulation system*, to counterbalance clotting and generate several other inflammatory mediators.

Complement system

- 20 component proteins
- Present in inactive form in plasma
- Activation of C3- generation of C3b by cleavage of C3 is the critical step
- *Classic Pathway* - initiated by IgM or IgG immune complexes; (IgM immune complexes are more effective)
- *Alternate Pathway* – triggered by microbial surface molecules, cobra venom, complex polysaccharides
- *Lectin pathway*- plasma mannose –binding lectin binds on microbes & activates C1


Classical Pathway
Antigen-antibody complex
MBLectin Pathway
MBLectin binding to pathogen surfaces
Alternative Pathway
Activating surfaces
C1
C4
C2
MASP
C4
C2
C3b
Factor B
Factor D
C3 convertase
C3
C3a
Anaphylatoxin
C3b
Opsonization
Solublization
Immunoregulation
C3b
C5 convertase
C5
C5a
Anaphylatoxin
C5b
C5b
C6
C7
C8
C9
Terminal Pathway
C5b-9
Membrane injury

Functions of complement system

- **Inflammation**:
  - Vascular phenomenon
  - C3a,C5a (anaphylatoxins) stimulate histamine release →↑ vascular permeability, vasodil
  - C5a activates lipooxygenase pathway
  - Leukocyte adhesion, chemotaxis, activation by C5a
- **Phagocytosis** - C3b acts as opsonin & favor phagocytosis by neutro, macro
- **Cell lysis-** by MAC

- Activation of complement controlled by protein inhibitors-
  - regulation of C3, C5 convertases
  - binding of active complement components by proteins

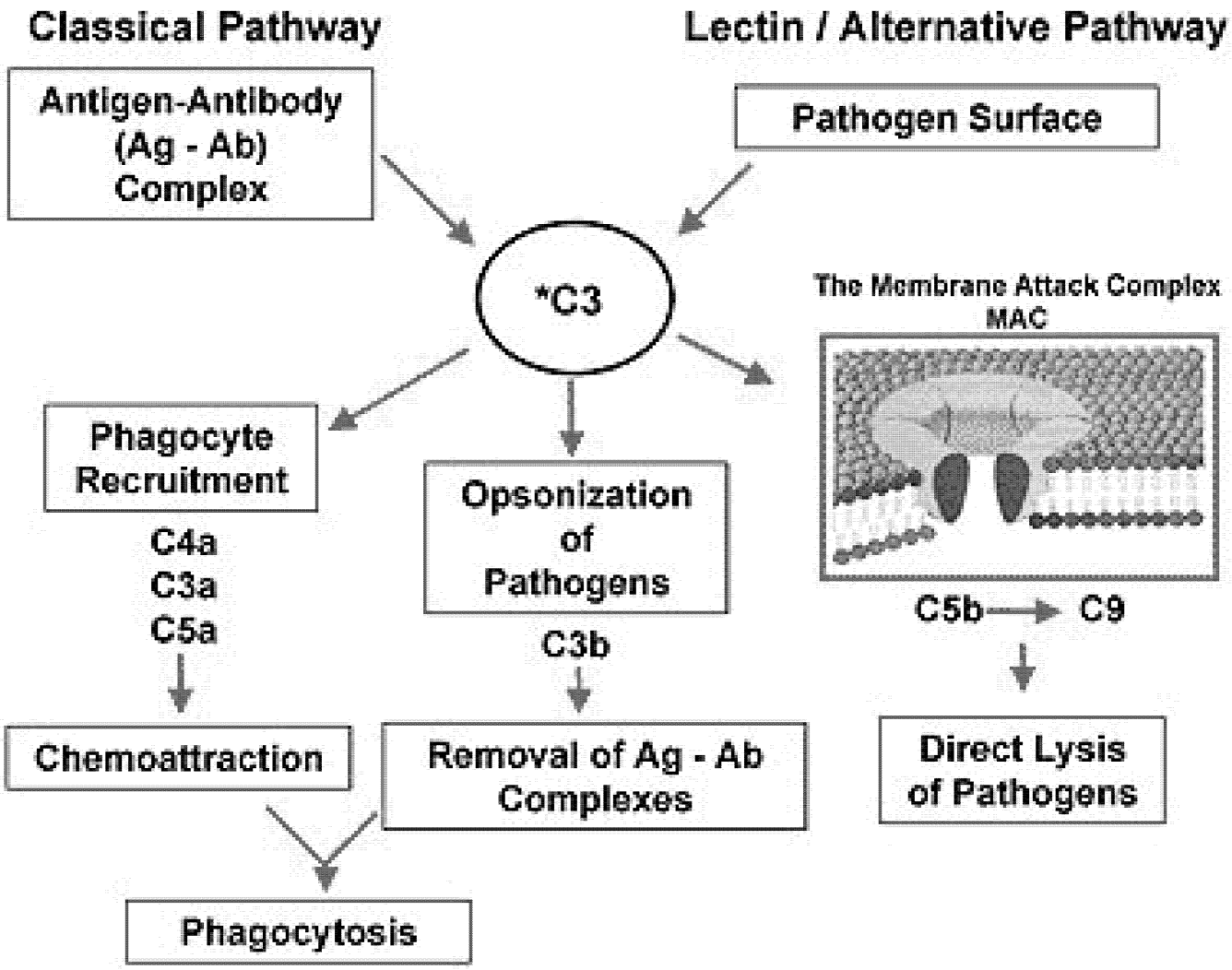
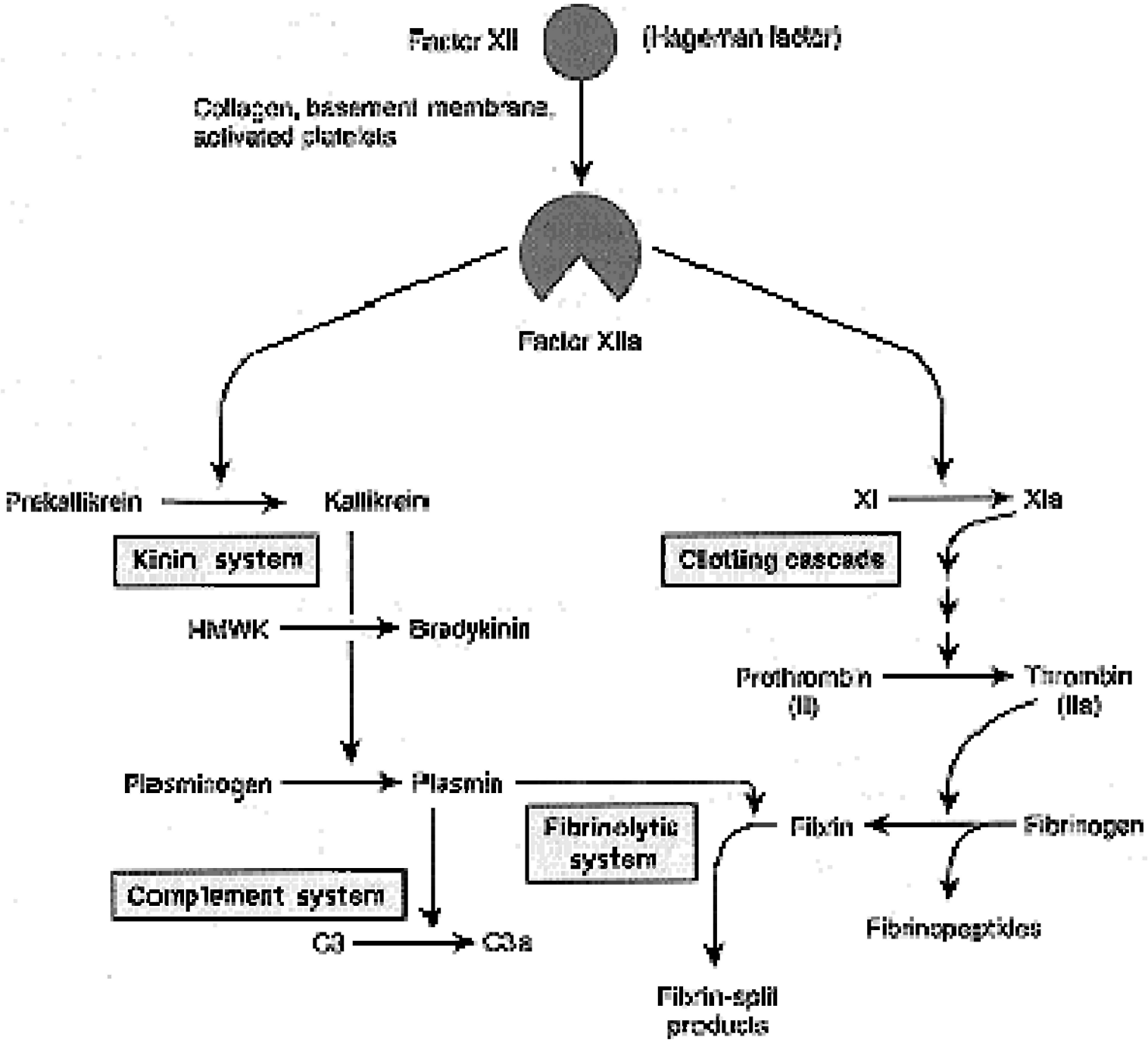


Figure 9. The complement cascade.

Kinin system

- Bradykinin formed by cleavage of HMWK
  - ↑ vas permeability
  - smooth ms contraction
  - dil of bld vessels
  - pain
- Action short lived, inactivated by kininase & ACE in lungs


Factor XII
(Hageman factor)
Collagen, basement membrane, activated platelets
Factor XIIa
Prekallikrein
Kallikrein
Kinin system
HMWK
Bradykinin
Plasminogen
Plasmin
Complement system
C3
C3a
Fibrinolytic system
Fibrin-split products
XI
XIa
Clotting cascade
Prothrombin (II)
Thrombin (IIa)
Fibrin
Fibrinogen
Fibrinopeptides

Clotting & fibrinolytic system

- Activation of thrombin & formation of fibrin

  -↑ vas permeability, chemotaxis, anticoagulant

  - chemokines, cytokines

  - induction of CO2, PAF, NO

- Actions of plasmin

- lyses fibrin to form fibrin split products
- activation of factor XII to stimulate kinin system
- splits C3 to form C3 fragments

Plasma derived mediators

** non-exhaustive list*

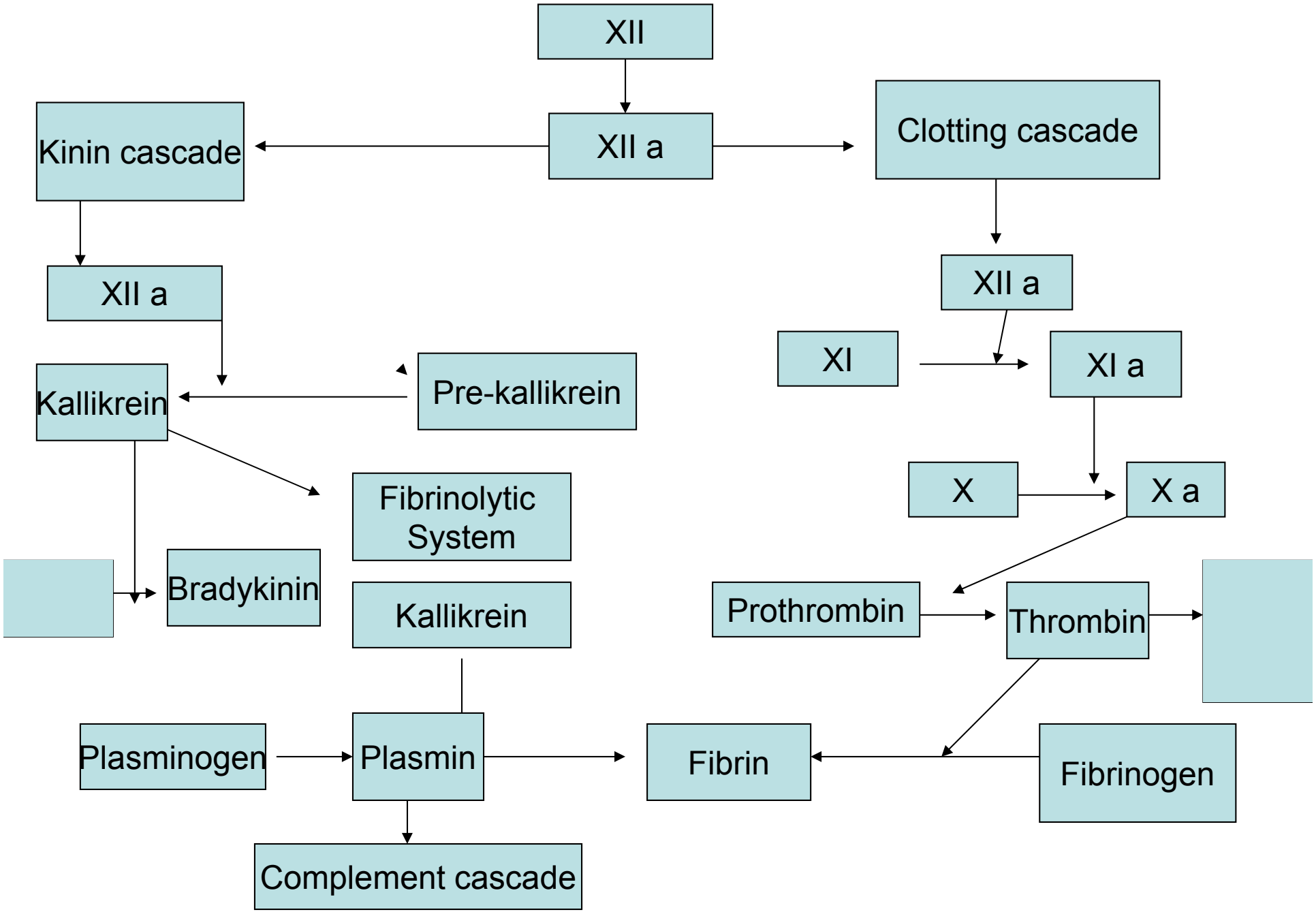
Name	Produced by	Description
Bradykinin	*Kinin system*	induce vasodilation, increase vascular permeability, smooth muscle contraction, induce pain.
C3	*Complement system*	Cleaves to produce *C3a* ,*C3b*. C3a stimulates histamine release by mast cells: vasodilation. C3b bind to bacterial cell : opsonin
C5a	*Complement system*	Stimulates histamine release by mast cells: vasodilation. chemoattractant to direct chemotaxis
Factor XII (*Hageman Factor*)	*Liver*	circulates inactively activated by collagen, platelets, or exposed basement membranes activate three plasma systems : the kinin system, fibrinolysis system, and coagulation system.
Membrane attack complex	*Complement system*	C5b, C6, C7, C8, and multiple units of C9forms the *membrane attack complex*, insert into bacterial cell walls and causes cell lysis, death.
Plasmin	*Fibrinolysis system*	break down fibrin clots, Cleave C3,
Thrombin	*Coagulation system*	Cleaves fibrinogen bind to cells via protease activated receptors (PAR) to trigger production of chemokines and nitric oxide.

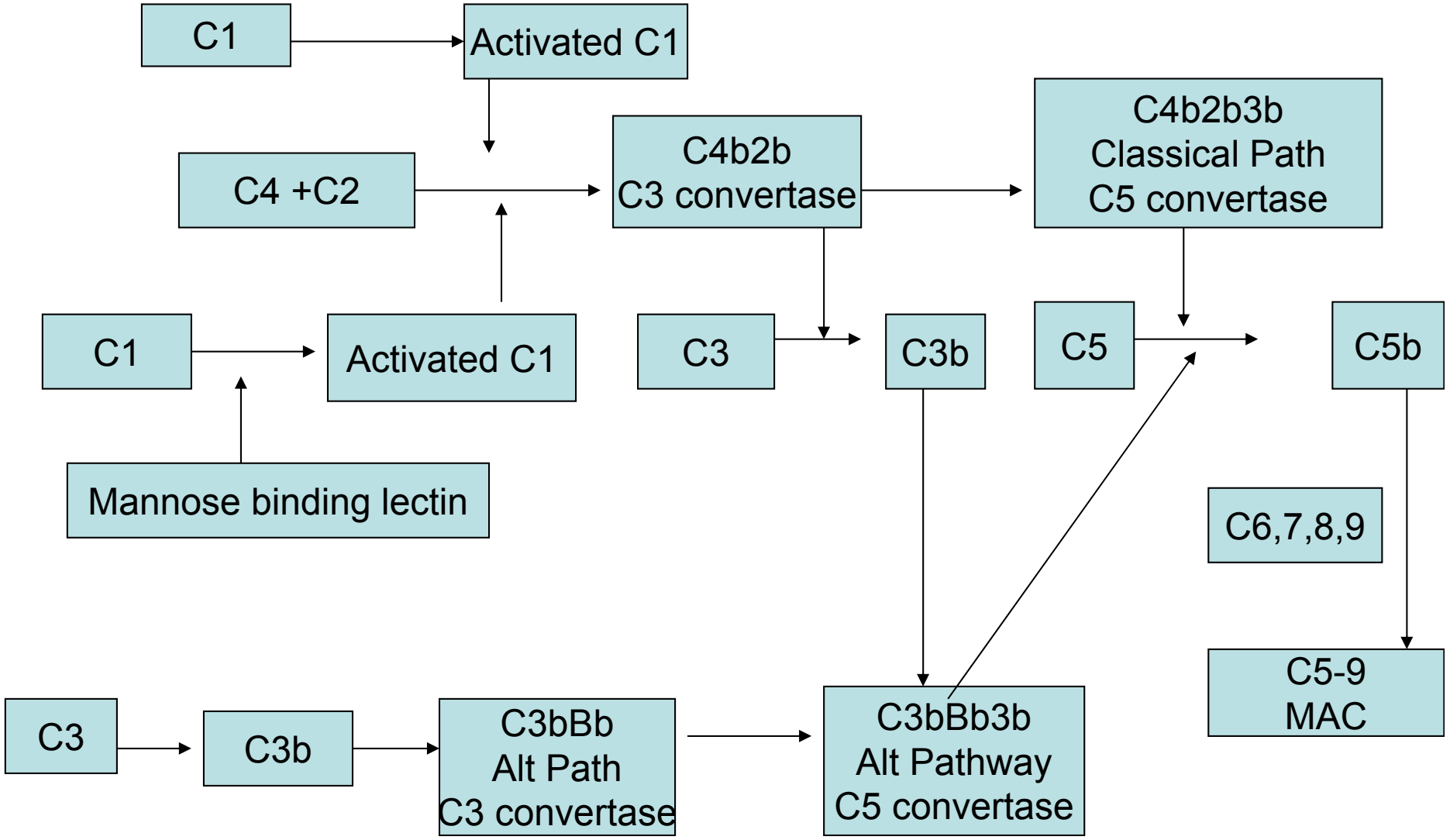
Role of mediators in different reactions of inflammation

- Vasodilation
  - Prostaglandins
  - Nitric oxide
  - Histamine
- Increased vascular permeability
  - C3a & C5a
  - Vasoactive Amines
  - Bradykinin
  - LT C4, D4, E4
  - PAF
- Fever
  - IL-1, TNF
  - Prostaglandins

Role of mediators in different reactions of inflammation

- Chemotaxis, leukocyte recruitement & activation
  - C5a
  - LTB4
  - Chemokines
  - IL-1, TNF
  - Bacterial products
- Pain
  - Prostaglandin
  - Bradykinin
- Tissue damage
  - Lysosomal enz
  - Oxygen metabolites
  - NO


XII
XII a
Kinin cascade
Clotting cascade
XII a
XI
XI a
Kallikrein
Pre-kallikrein
X
X a
Fibrinolytic System
Bradykinin
Kallikrein
Prothrombin
Thrombin
Plasminogen
Plasmin
Fibrin
Fibrinogen
Complement cascade


C1
Activated C1
C4 +C2
C4b2b
C3 convertase
C4b2b3b
Classical Path
C5 convertase
C1
Activated C1
C3
C3b
C5
C5b
Mannose binding lectin
C6,7,8,9
C5-9
MAC
C3
C3b
C3bBb
Alt Path
C3 convertase
C3bBb3b
Alt Pathway
C5 convertase

Vasodilation

Prostaglandins E_2, D_2, $F_{2\alpha}$, I_2

Nitric Oxide

Increased Vascular Permeability

Histamine, Serotonin

Bradykinin

C3a and C5a (through liberating amines)

Leukotrienes C_4,D_4,E_4

PAF (AGEPC)

oxygen free radicals

Chemotaxis

C5a

Leukotriene B_4

IL-8

Bacterial products

Pain

PGE_2

Bradykinin

Fever

IL-1, IL-6, TNF

PGE_2

Tissue Damage

Neutrophil and macrophage lysosomal enzymes

Oxygen derived free radicals

Nitric Oxide