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

| C1 | C4 | C2 |

MBLectin Pathway
- MBLectin binding to pathogen surfaces

| MASP | C4 | C2 |

Alternative Pathway
- Activating surfaces

| C3b | Factor B | Factor D |

C3 convertase

| C3a | Anaphylatoxin |
| C3b | Opsonization, Solubilization, Immunoregulation |

C5 convertase

| C5a | Anaphylatoxin |
| C5b |

Terminal Pathway
- C5b, C6, C7, C8, C9

| 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

Flasminogen → Flasmin

Complement system

C3 → C3a

Fibrinolytic system

Fibrin → Fibrinogen

Clotting cascade

Prothrombin → Thrombin

Fibrinopeptides

Fibrin-split products
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
<table>
<thead>
<tr>
<th>Name</th>
<th>Produced by</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradykinin</td>
<td><em>Kinin system</em></td>
<td>induce vasodilation, increase vascular permeability, smooth muscle contraction, induce pain.</td>
</tr>
<tr>
<td>C3</td>
<td><em>Complement system</em></td>
<td>Cleaves to produce C3a, C3b. C3a stimulates histamine release by mast cells: vasodilation. C3b bind to bacterial cell: opsonin</td>
</tr>
<tr>
<td>C5a</td>
<td><em>Complement system</em></td>
<td>Stimulates histamine release by mast cells: vasodilation. chemoattractant to direct chemotaxis</td>
</tr>
<tr>
<td>Factor XII (Hageman Factor)</td>
<td><em>Liver</em></td>
<td>circulates inactively activated by collagen, platelets, or exposed basement membranes activate three plasma systems: the kinin system, fibrinolysis system, and coagulation system.</td>
</tr>
<tr>
<td>Membrane attack complex</td>
<td><em>Complement system</em></td>
<td>C5b, C6, C7, C8, and multiple units of C9 forms the membrane attack complex, insert into bacterial cell walls and causes cell lysis, death.</td>
</tr>
<tr>
<td>Plasmin</td>
<td><em>Fibrinolysis system</em></td>
<td>break down fibrin clots, Cleave C3,</td>
</tr>
<tr>
<td>Thrombin</td>
<td><em>Coagulation system</em></td>
<td>Cleaves fibrinogen bind to cells via protease activated receptors (PAR) to trigger production of chemokines and nitric oxide.</td>
</tr>
</tbody>
</table>
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 recruitment & activation
  C5a
  LTB4
  Chemokines
  IL-1, TNF
  Bacterial products
- Pain
  Prostaglandin
  Bradykinin
- Tissue damage
  Lysosomal enz
  Oxygen metabolites
  NO
The diagram illustrates the complement system, specifically the classical and alternative pathways. The classical pathway starts with C1 activation, which leads to the formation of C4b2b3b C3 convertase. This pathway involves mannose binding lectin, which triggers the alternative pathway.

In the alternative pathway, C3bBb3b C3 convertase is formed, leading to the production of C3bBb3b C5 convertase and ultimately the C5-9 MAC (membrane attack complex).
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 C4, D4, E4
PAF (AGEPC)
oxxygen free radicals

Chemotaxis
C5a
Leukotriene B4
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