- This complex is able to bind caspase-9 (critical initiator caspase of the mitochondrial pathway)

b *Extrinsic (death receptor-initiated) pathway of apoptosis*:

- Initiated by engagement of plasma membrane death receptors, which are present on variety of cells
- Best known death receptors are type 1 TNF receptor (TNFR1) and a related protein called Fas (CD95)
- The ligand for Fas is called Fas ligand (FasL)
- *FasL* is expressed on T-cells that recognize self-antigens
- When FasL binds to Fas, three or more molecules of Fas are brought together, resulting in formation of FADD (Fas-associated death domain)
- FADD that is attached to the death receptors binds with inactive form of caspase-8 (caspase-10 in humans), via a death domain
- Inactive form of caspase-8 and caspase-10 are brought into active form
- Extrinsic pathway can be inhibited by a protein called *FLIP*.

2. *Execution phase*

- Mitochondrial pathway leads to activation of the initiator caspase-9
- Death receptor pathway leads to activation of initiator caspases-8 and -10
- Both pathways lead to activation of executioner caspases, i.e. caspase-3 and -6
- These enzymes cleaves DNA into nucleosome-sized pieces

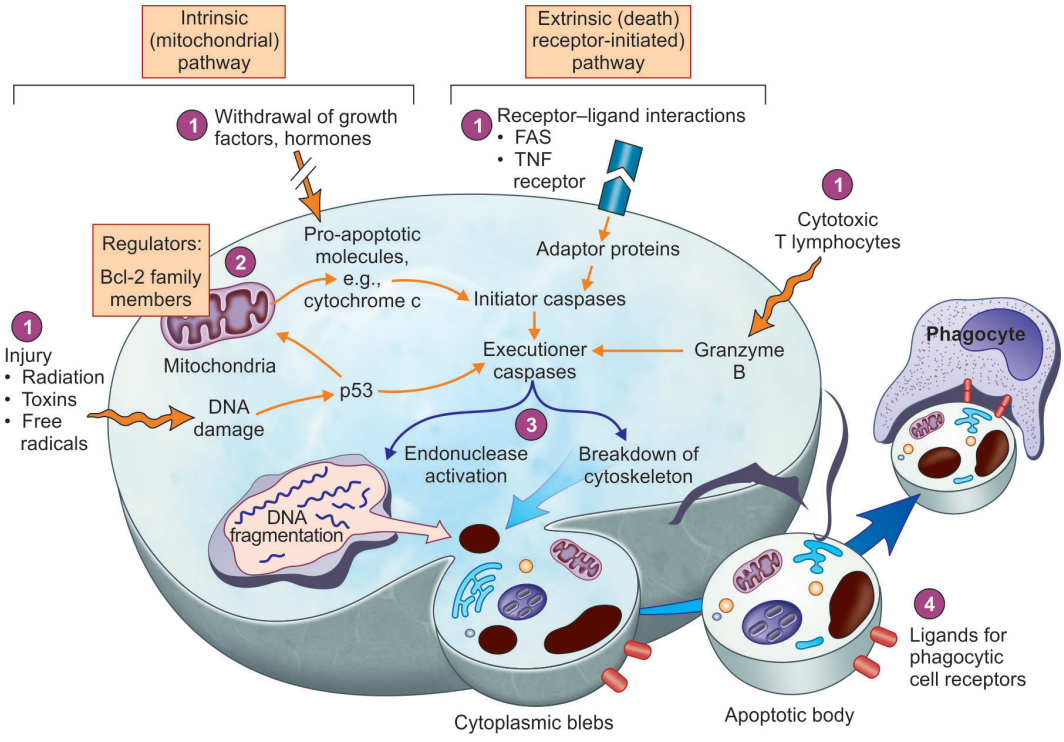

Fig. 2.2: Phases of apoptosis

c. *C chemokines (γ chemokines)*
- Includes lymphotactin which is specific for lymphocytes

d. *CX3C chemokines*
- For example, fractalkine
- Promotes strong adhesion of monocyte and T-cells

Q5. Mention functions of complement pathway system.

Ans.

Functions of complement system

a. Inflammation
- C3a, C5a are called anaphylotoxins, because they stimulate histamine release from mast cells
- C5a-powerful chemotactic agent for neutrophils, monocytes, eosinophils, and basophils

b. Phagocytosis: C3b, acts as opsonins and promotes phagocytosis by neutrophils and macrophages

c. Cell lysis: Deposition of membrane attack complex (MAC) on the cells result in death of the cells

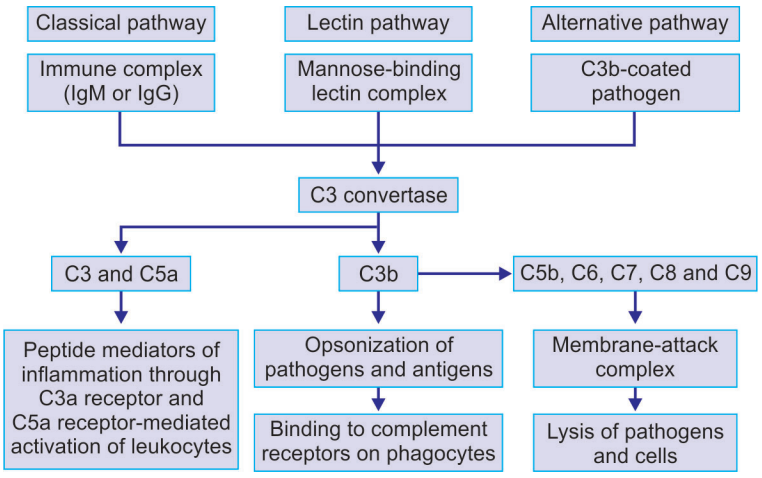

Fig. 3.3: Complement system

Q6. Write a short note on granulomatous inflammation.

Ans.

Granulomatous inflammation
- Chronic inflammation, characterized by collection of activated macrophages, T lymphocytes, and central necrosis
- Epithelioid cells: Activated macrophages with abundant cytoplasm
- Multinucleate giant cells: Fusion of activated macrophages

Fate of Thrombus

a. **Propagation:** Thrombi accumulate additional platelets and fibrin
b. **Embolization:** Thrombi dislodge and travel to other sites in the vasculature
c. **Dissolution:** As a result of fibrinolysis, there can be rapid shrinkage of recent thrombi
d. **Organization and recanalization:** Organized by the in-growth of endothelial cells, smooth muscle cells, and fibroblasts

Q4. Write a short note on heparin-induced thrombocytopenia.

Ans.

Heparin-induced thrombocytopenia (HIT) syndrome

- Occurs following the administration of **unfractionated heparin**
- **Unfractionated heparin** induces the formation of antibodies against complexes of **heparin and platelet factor 4**
- Binding of antibodies to platelets results in their activation, aggregation, and consumption and hence **thrombocytopenia**
- This leads to a **prothrombotic state**, even in face of heparin administration and low platelet counts
- **Low-molecular weight heparin** preparations are at **lower risk** to induce antibody formation

Q5. Write a short note on antiphospholipid antibody syndrome.

Ans.

Antiphospholipid antibody syndrome (lupus anticoagulant syndrome)

- Present with recurrent thrombosis, repeated miscarriages, cardiac valve vegetations and thrombocytopenia
- Fetal loss occurs because of antibody-mediated interference with the growth and differentiation of trophoblasts, leading to a failure of placentation
- Antibodies frequently give a false-positive serologic test for syphilis as the antigen in the standard assay is embedded in cardiolipin

Two types

A. **Primary antiphospholipid syndrome**—presence of a hypercoagulable state without any evidence of other autoimmune disorders
B. **Secondary antiphospholipid syndrome (lupus anticoagulant syndrome)**—individuals have an associated autoimmune disease, such as **SLE**

Q6. Enumerate types of embolism. Write a note on Caisson disease.

Ans.

Types of embolism

a. Pulmonary embolism
b. Systemic thromboembolism
c. Fat and marrow embolism
d. Air embolism
e. Amniotic fluid embolism

b. Ocular changes

- Ectopia lentis: Bilateral subluxation or dislocation (usually **outward and upward**) of the lens

c. Cardiovascular lesions:

- Mitral valve prolapse
- Aortic dissection

Q5. Write a note on familial hypercholesterolemia.

Ans.

Familial hypercholesterolemia

- Occurs due to mutation in the gene encoding LDL receptor, involved in the transport and metabolism of cholesterol
- Elevated plasma cholesterol levels, results in tendinous xanthomas and premature atherosclerosis

LDL metabolism

- Liver secrete very-low density lipoproteins (VLDLs) into the bloodstream
- Lipolysis of VLDL molecule in capillaries occurs by lipoprotein lipase, resulting in formation of intermediate-density lipoprotein (IDL)
- VLDL molecule comprises Apo C, E, B-100, whereas IDL molecule comprises Apo E, B-100
- IDL can be taken up by liver by LDL receptors, resulting in formation of VLDL or is converted to LDL, which is taken up by liver
- IDL is the immediate and major source of plasma LDL
- LDL molecule comprises Apo B-100

LDL receptor pathway and regulation of cholesterol metabolism

- 70% of plasma LDL is cleared by liver
- Binding of LDL to cell surface receptors, present in coated pits
- Receptor-bound LDL are internalized by invagination to form coated vesicles
- These coated vesicles inside the cytoplasm of the cell fuse with the lysosomes
- In the lysosome, LDL molecule is degraded into cholesterol and ApoB-100 is degraded into amino acids
- Free cholesterol exits through the lysosome, with the help of NPC1 and NPC2 proteins
- LDL receptor mutations results in increased LDL levels in blood, resulting in increased deposition of cholesterol in tissues (hypercholesterolemia) and atherosclerosis