

Cell Death

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Cell death- more historical aspects

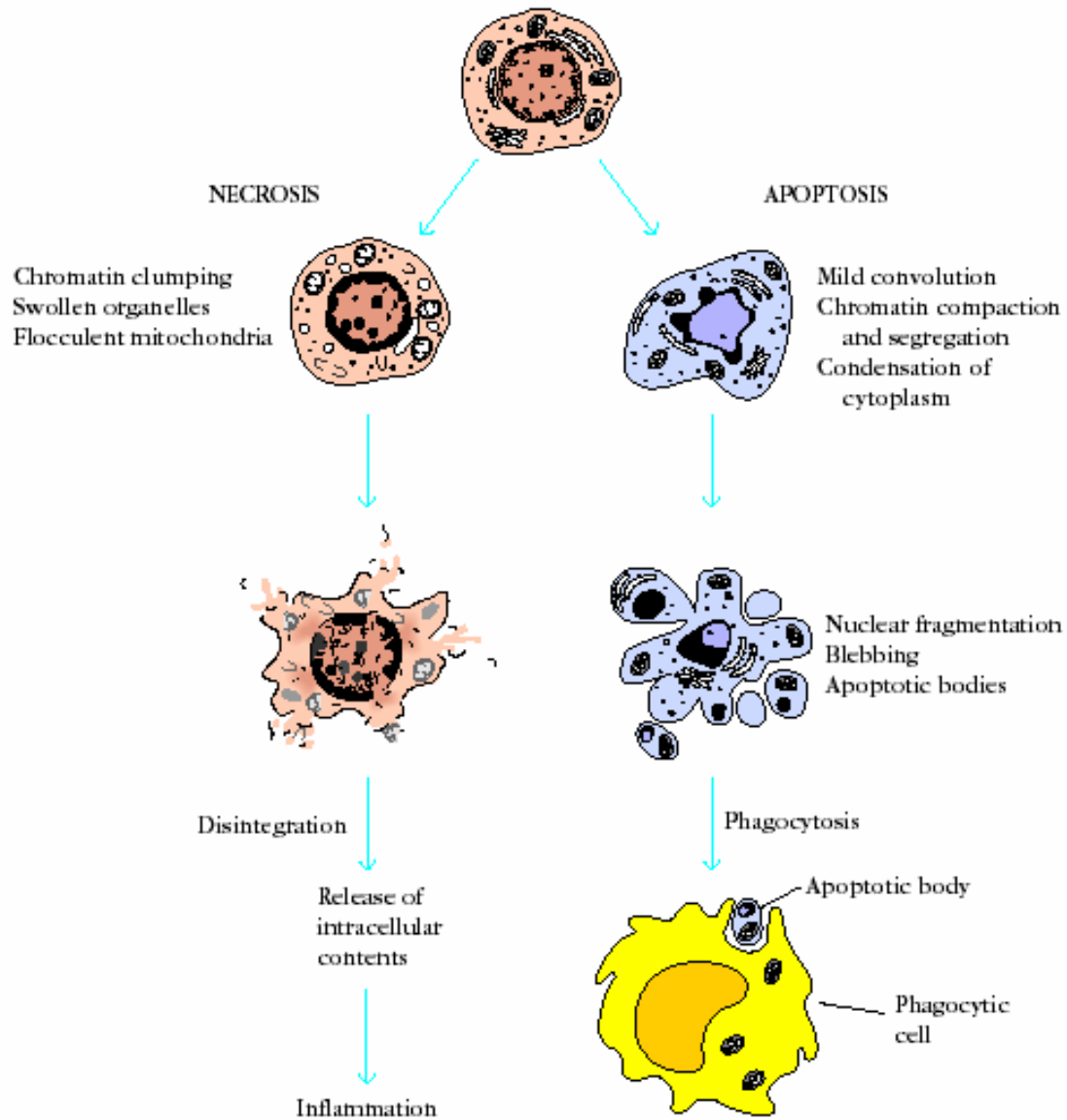
- 1950s - discovery of lysosomes, concept of cell suicide
- 1964 (Lockshin and Williams) – “programmed cell death”
- 1971 (Kerr and Wyllie) - apoptosis: **apo = away from,**
ptosis = falling

Major types of cell death

Apoptosis – (appropriate, programmed) is an active and physiologic mechanism of programming cell death.

Necrosis – (inappropriate, accidental) is an accidental death due to stress:hypothermic shock, changes in pH...

APOPTOSIS Vs NECROSIS



Apoptosis

Necrosis

Patterns of death

Single cells

Groups of neighboring cells

Cell size

Shrinkage
Fragmentation

Swelling

Plasma membrane

Preserved continuity
Blebbled
Phosphatidylserine on surface

Smoothing
Early lysis

Mitochondria

Increased membrane permeability
Contents released into cytoplasm
Cytochrome c; Apaf1
Structure relatively preserved

Swelling
Disordered structure

Organelle shape

Contracted
"Apoptotic bodies"

Swelling
Disruption

Nuclei

Chromatin:
Clumps & Fragmented

Membrane disruption

DNA degradation

Fragmented
Internucleosomal cleavage
Free 3' ends
Laddering on electrophoresis
DNA appears in cytoplasm

Diffuse & Random

Cell degradation

Phagocytosis
No inflammation

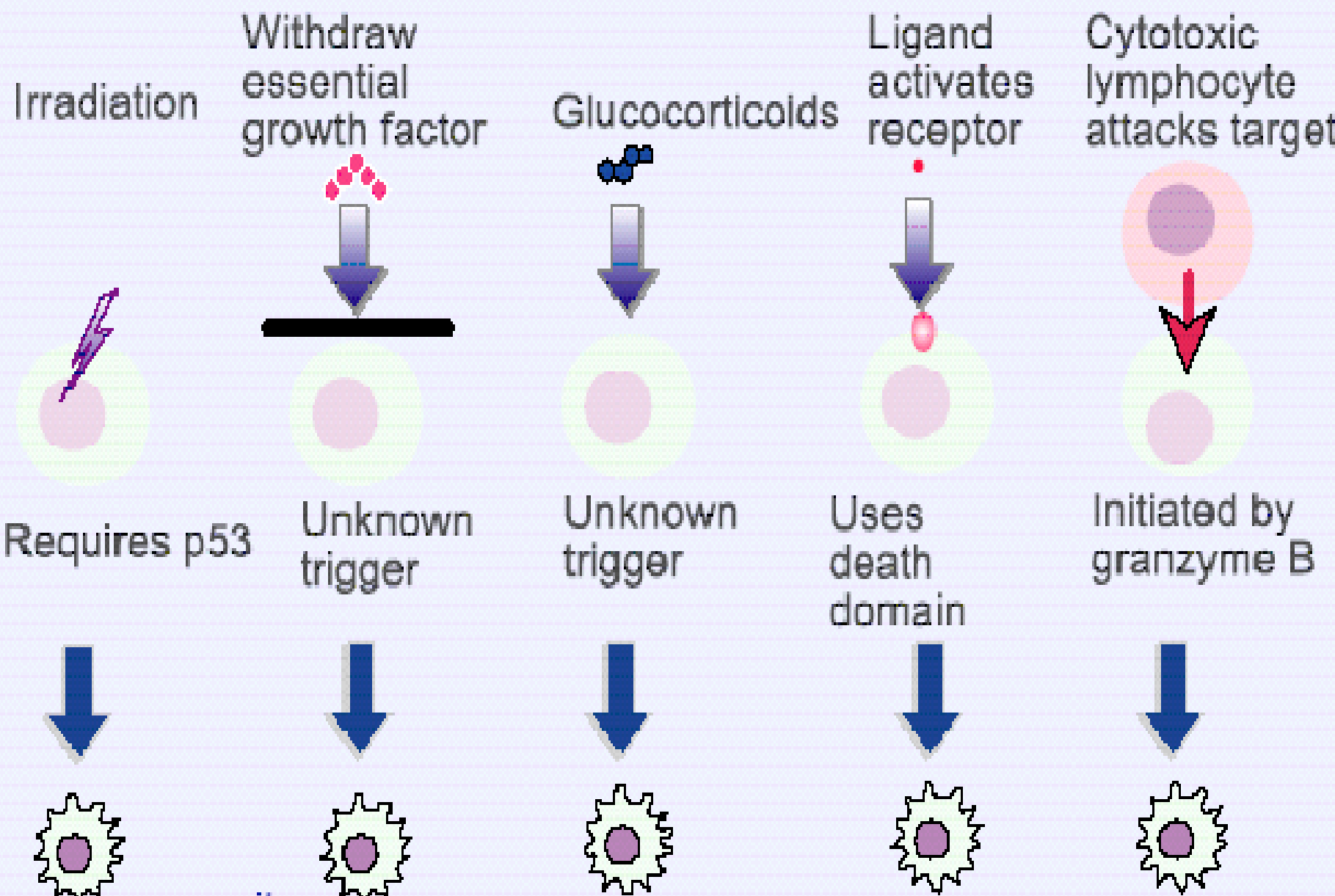
Inflammation
Macrophage invasion

PATHOLOGICAL FEATURES

MECHANISMS

<p>General stimuli</p>	<p>Developmental programs Endogenous signals Intercellular signals Disease processes</p>	<p>Disease processes</p>
<p>Specific stimuli</p>	<p>Toxic: Hormones; Radiation; Mild ischemia Oxidants in cell: Increased DNA damage</p>	<p>Toxic Severe ischemia Radiation</p>
<p>Cellular processes</p>	<p>Programmed cascade of reactions Caspase activation Internucleosomal endonucleases Transglutaminase activation Requires New RNA transcription Protein synthesis <u>ATP</u></p>	<p>No protein synthesis No RNA transcription Energy independent ATP depletion</p>
<p>Apoptosis Inhibitors</p>	<p>Protease inhibitors NAIP ₁; crmA; p35 Human IAP-1 ₁, IAP-2 ₁ & IAP3 Bcl-2 family (Some) Bcl-2 ₁; Mcl-1 ₁; Bcl-w ₁; Bcl-xL</p>	
<p>Apoptosis Promoters</p>	<p>Bcl-2 family (Some) Bax ₁; Bcl-xS; Hrk ₁; Bak ₁; Bid ₁; Bik ₁; Bad</p>	

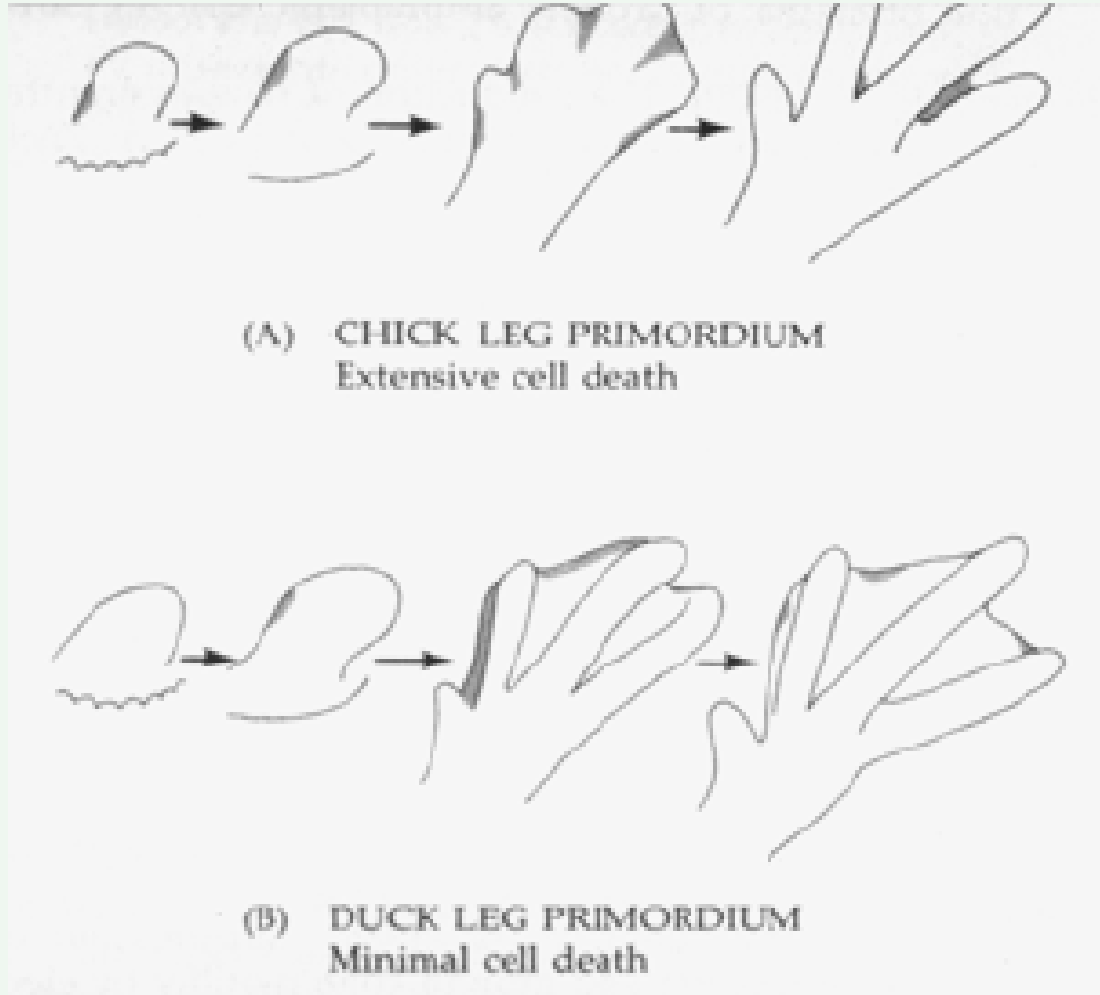
Several pathways trigger apoptosis or kill target cells



Physiological examples of apoptosis

- Embryonic development (deletion of interdigital webs)
- Cell turnover in adult tissues (intestinal crypts)
- T-cell clonal deletion
- Normal involution processes (ovary, breast, endometrium)

Apoptosis during Development



Diseases Associated with Increased Apoptosis

- 1. AIDS**
- 2. Neurodegenerative disorders**
 - Alzheimer's disease**
 - Parkinson's disease**
 - Amyotrophic lateral sclerosis**
 - Retinitis pigmentosa**
 - Cerebellar degeneration**
- 3. Myelodysplastic syndromes**
 - Aplastic anemia**
- 4. Ischemic injury**
 - Myocardial infarction**
 - Stroke**
 - Reperfusion injury**
- 5. Toxin-induced liver disease**
 - Alcohol**

Diseases Associated with the Inhibition of Apoptosis:

1. Cancer

Follicular lymphomas

Carcinomas with p53 mutations

Hormone-dependent tumors

Breast cancer

Prostate cancer

Ovarian cancer

2. Autoimmune disorders

Systemic lupus erythematosus

Immune-mediated glomerulonephritis

3. Viral infections

Herpesviruses

Poxviruses

Adenoviruses

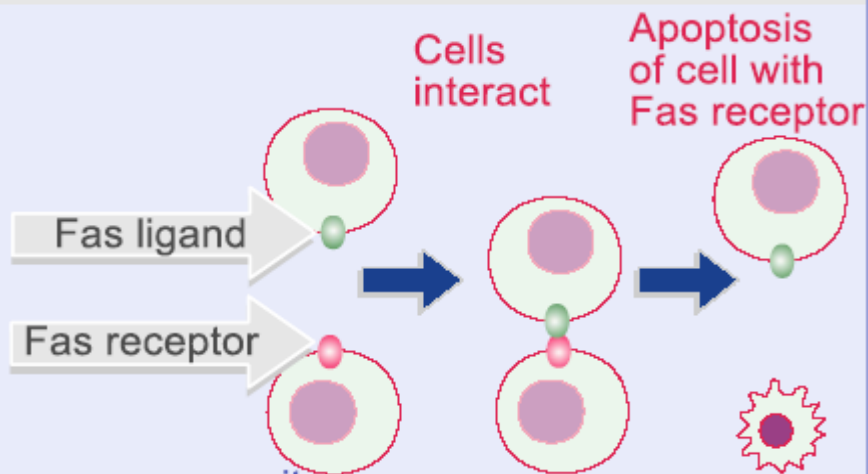
Molecular and cellular mechanisms of apoptosis

- Organelle dysfunction (mitochondria, ER)
- Death receptor activation (extrinsic)
- DNA damage
- Abnormal protein folding/accumulation

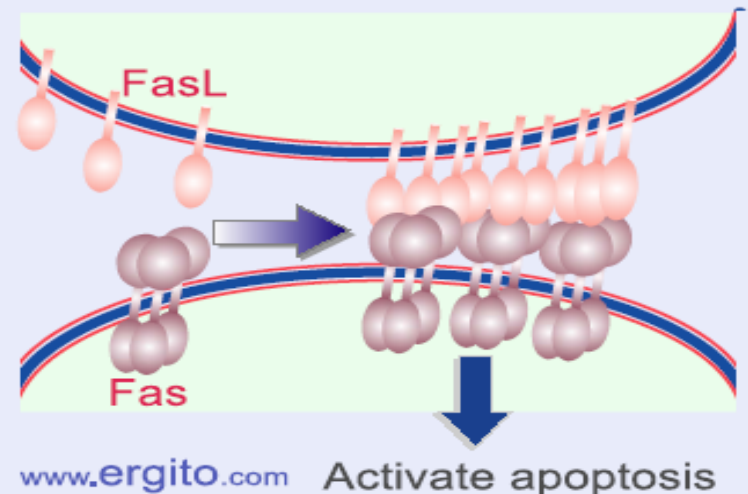
The Fas receptor is a major trigger for apoptosis

- The Fas receptor on a target cell is activated by interaction with the FasL protein on an activating cell plasma membrane.
- Fas is related to TNF receptor, and FasL is related to TNF.
- Fas is a trimer that aggregates upon interaction with FasL.
- Fas has an cytoplasmic domain called the "death domain" which is involved in protein-protein interactions.

Fas triggers apoptosis



Activated Fas trimers aggregate



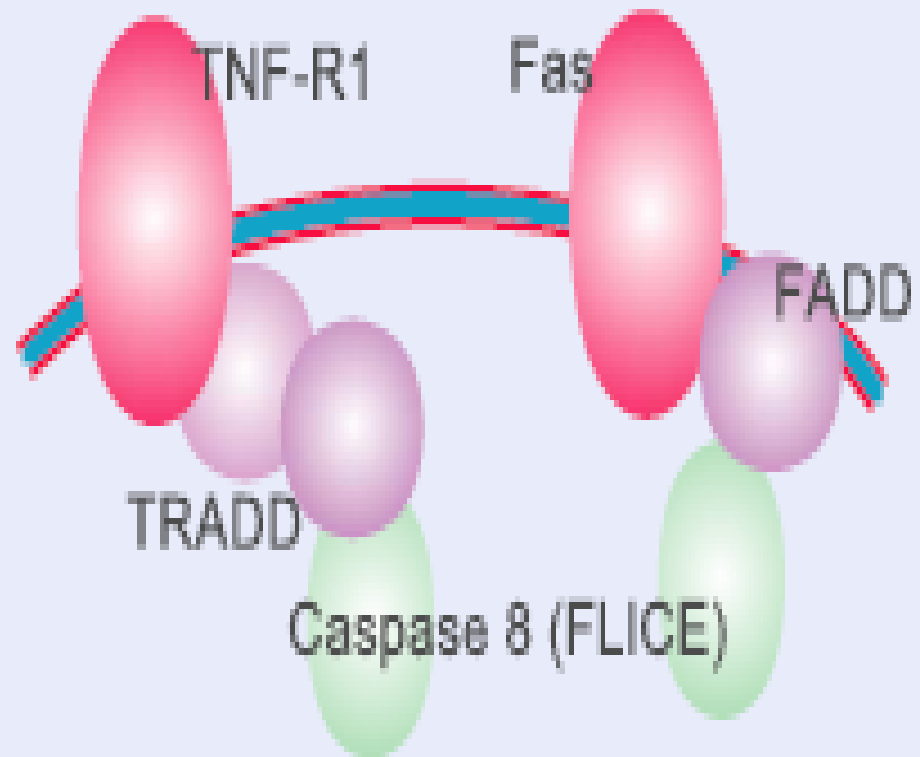
Apoptotic response is triggered by an ~80 amino acid intracellular domain near the C-terminus. This region is loosely conserved (~28%) between Fas and TNF-R1, and is called the **death domain**.

The "classical" pathway for apoptosis

A ligand-receptor interaction triggers the release of cytochrome c from mitochondria.

Apoptosis uses several caspases

1 Receptor is activated



TNF receptor binds a protein called **TRADD**, which in turn binds a protein called **FADD**.

Fas receptor binds **FADD** directly.

In either case, **FADD** binds the protein **caspase-8** (also known as **FLICE**), which has a death domain as well as protease catalytic activity.

The activation of **caspase-8** activates a **common pathway** for apoptosis.

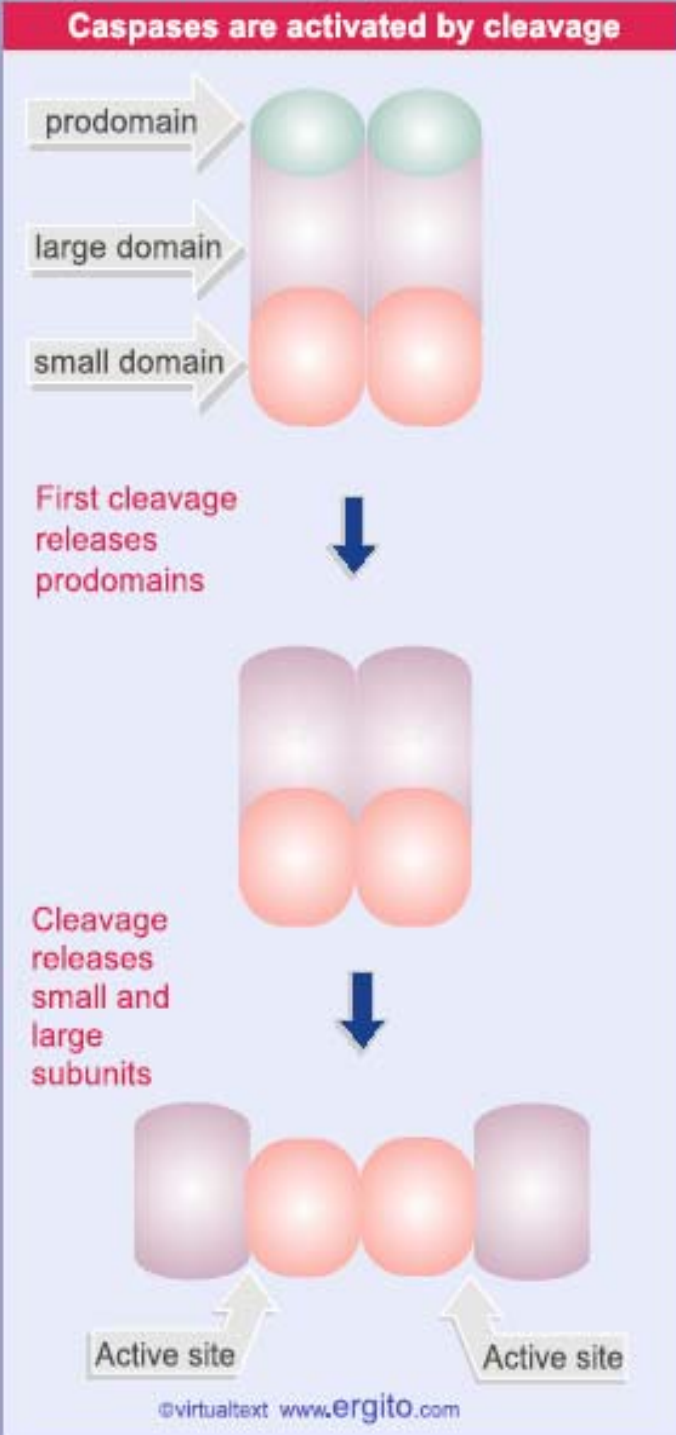
Caspases (cysteine aspartate proteases)

Caspases have a **catalytic cysteine**, and cleave their targets at an aspartate.

Caspases fall into two groups. **The caspase-1 subfamily is involved in the response to inflammation.** **The caspase-3 subfamily (consisting of caspase 3 and caspases 6-10) is involved in apoptosis.**

All caspases are synthesized in the form of inactive procaspases.

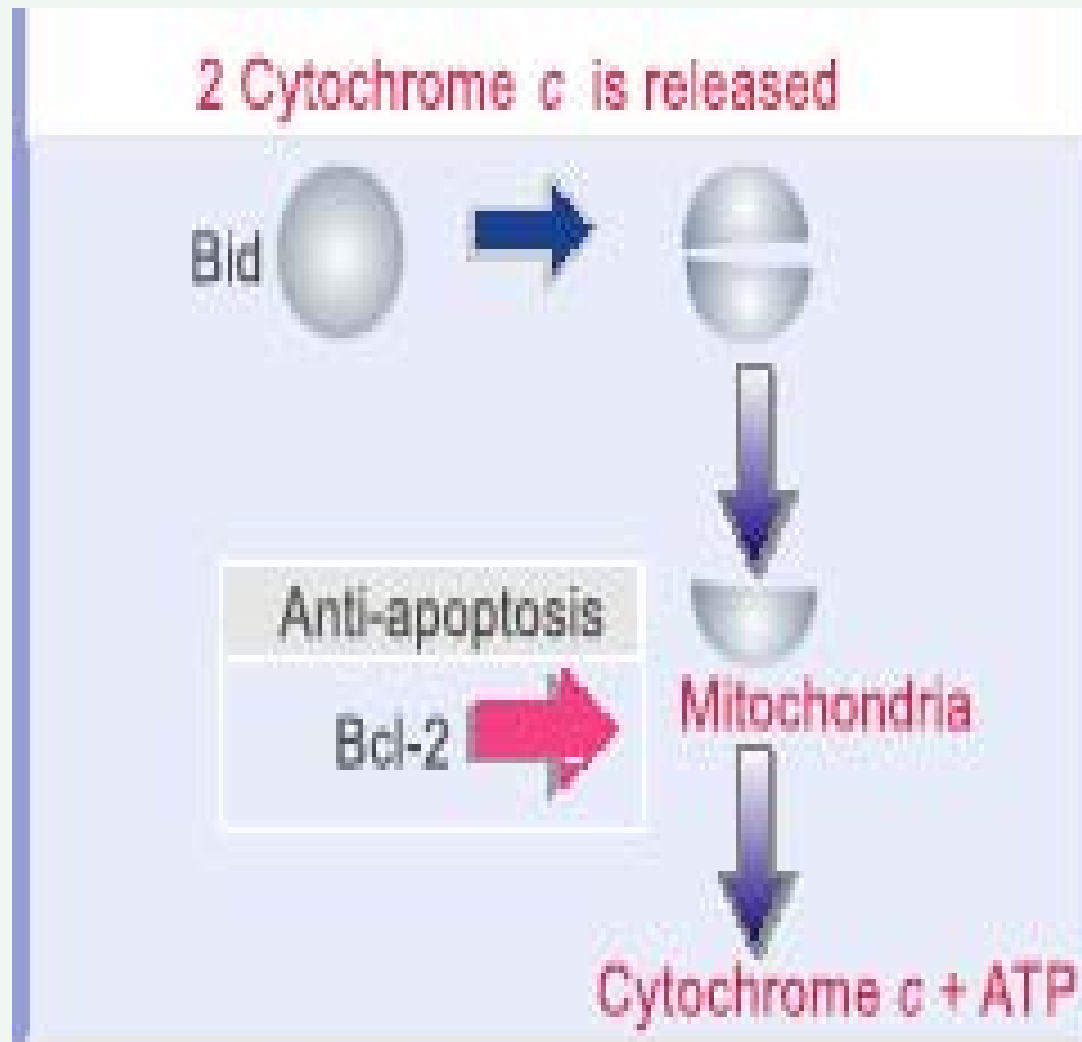
Dimerization causes an autocatalytic cleavage that activates the caspase



Caspase-8 cleaves Bid to release a C-terminal domain that translocates to the mitochondrion.

Bid is a member of the Bcl2 family and acts together with other members of the family to cause mitochondria to **release cytochrome c**.

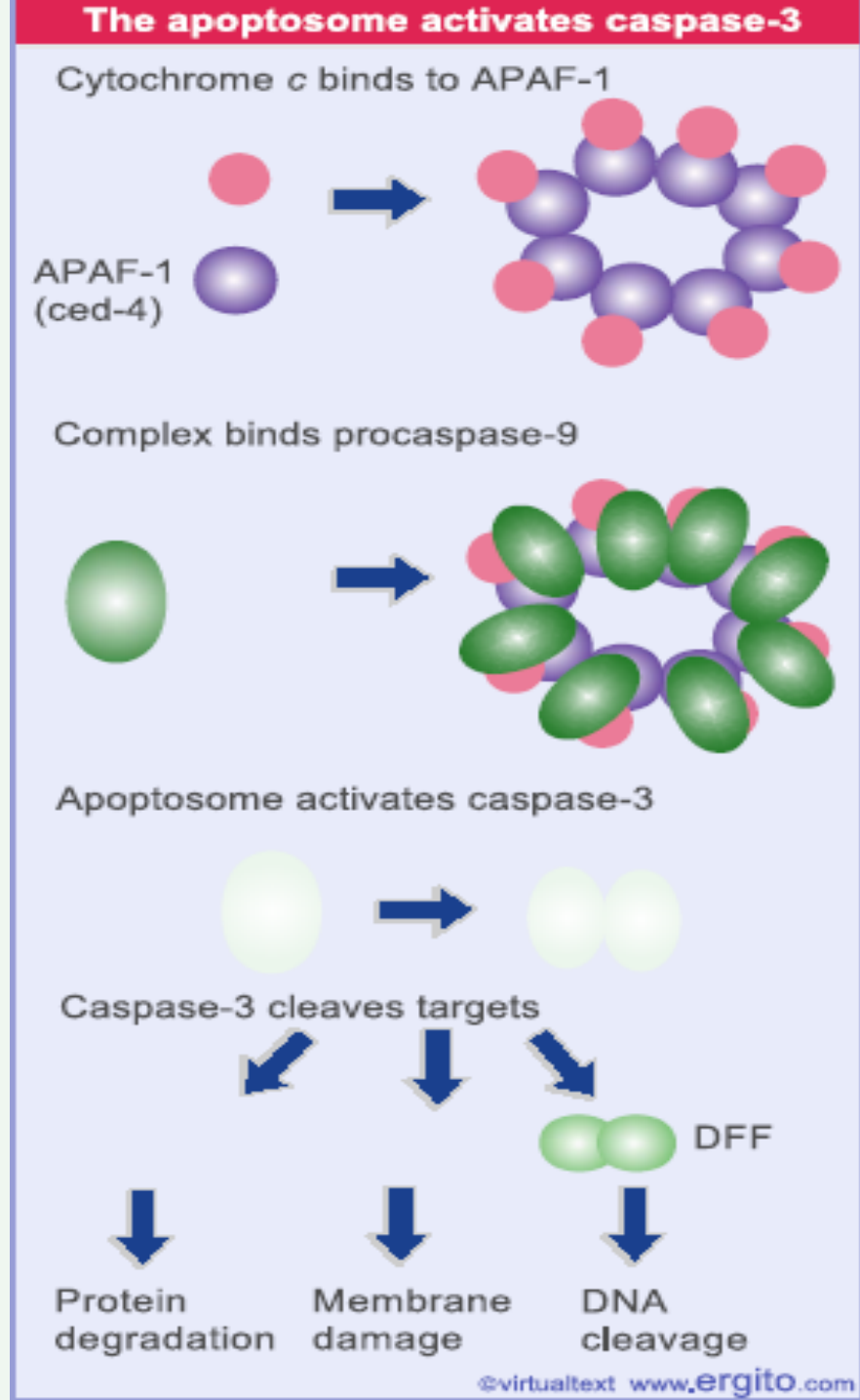
Some members of the family, including **Bcl2**, **inhibit the release of cytochrome c**.



The release of cytochrome c is a crucial control point in the pathway.

Cytochrome c causes Apaf-1 to aggregate with procaspase-9 to form the apoptosome, which then activates caspase-9 by autocleavage.

Caspase-9 cleaves caspase-3 and other caspases to trigger the effector phase of apoptosis, when cellular structures are destroyed.



Necrosis- triggers

- **Acute energy depletion**

- ischemia, glutamate receptor overactivation, hypoglycemia

- **Trauma**

- **Harsh environments**

- strong detergents, acids, oxidants, heat, cold, excessive mechanical strain)

- **Excessive accumulation of ROS**

- **Extensive DNA damage**

Necrosis- mechanisms

- **Perturbation of ion homeostasis**

- Ca^{++} , Na^+ , Mg^{++} , Zn^{++}
- Acidosis
- Animal models- “degenerins” (ion channels)

- **Protein degradation**

- Lysosomes
- Cathepsins
- Hydrolases
- Calpains
- Caspases?

Thank you