Apoptosis

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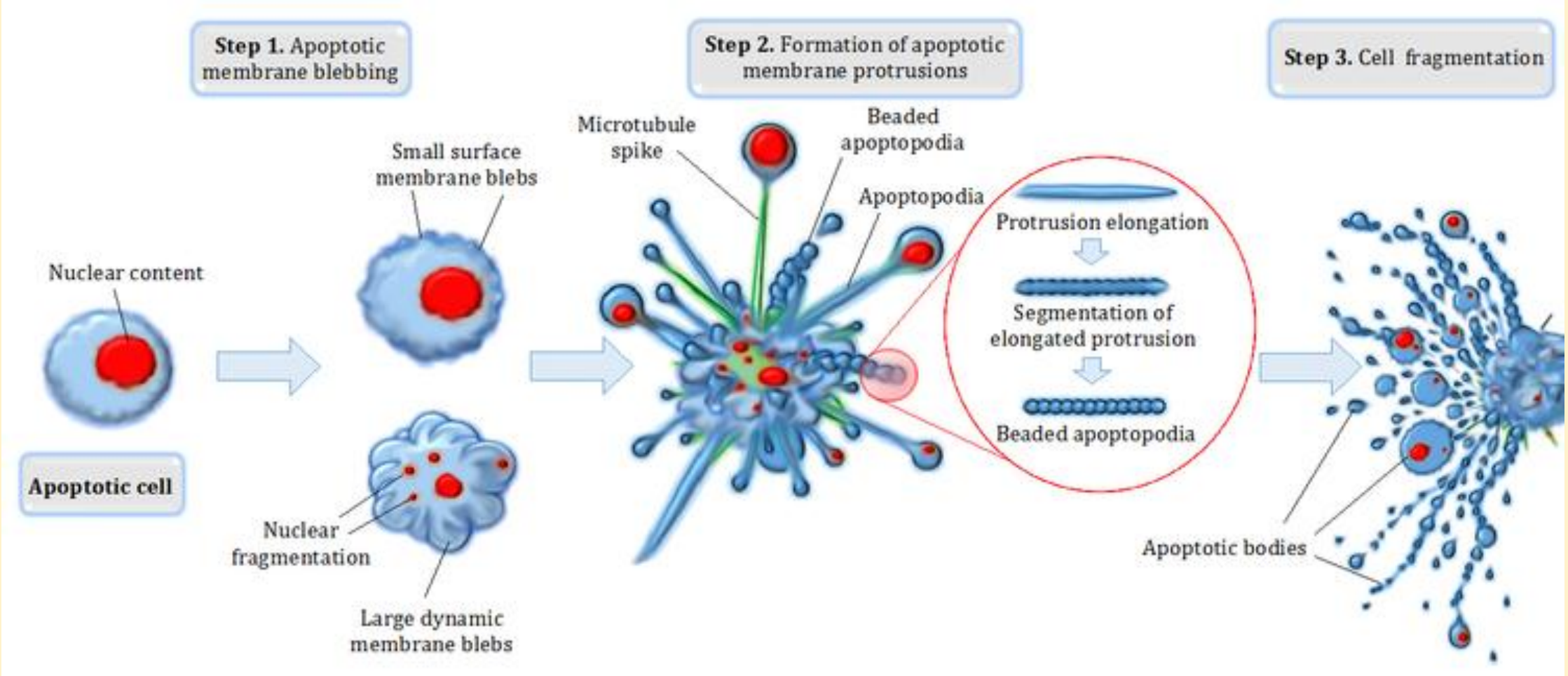
Introduction

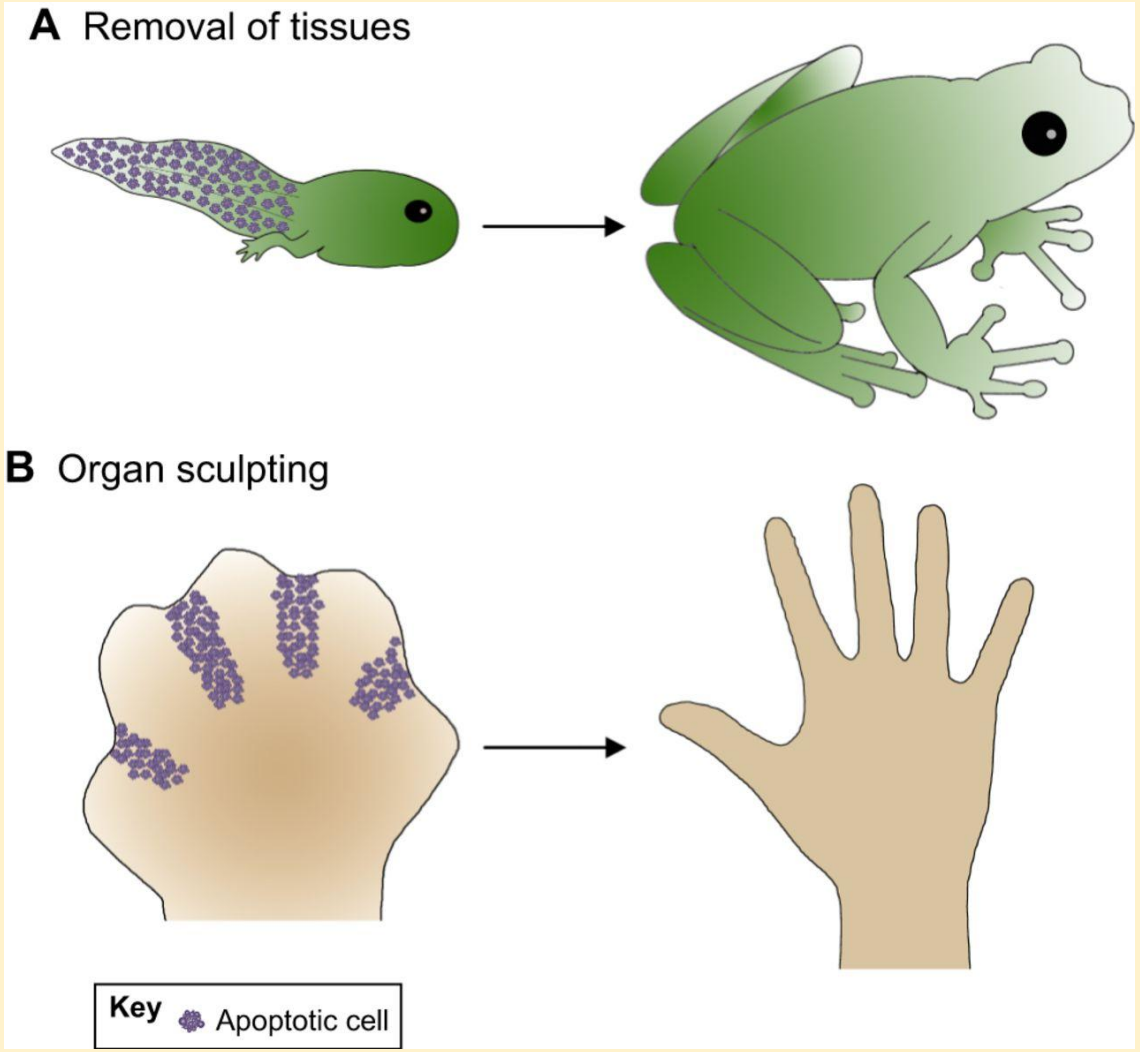
- **Apoptosis or Programmed Cell death** is a physiological process in which cell death is brought about through a regulated sequence of events. It allows for the programmed removal of specific cells, without harming nearby cells. Defects of this process play an important role in a variety of diseases.
- **Apoptosis Pathways :** Apoptosis can be initiated by one of two separate pathways; the **intrinsic or extrinsic pathway**. Both of these pathways end with a final common effector pathway, known as the execution phase.

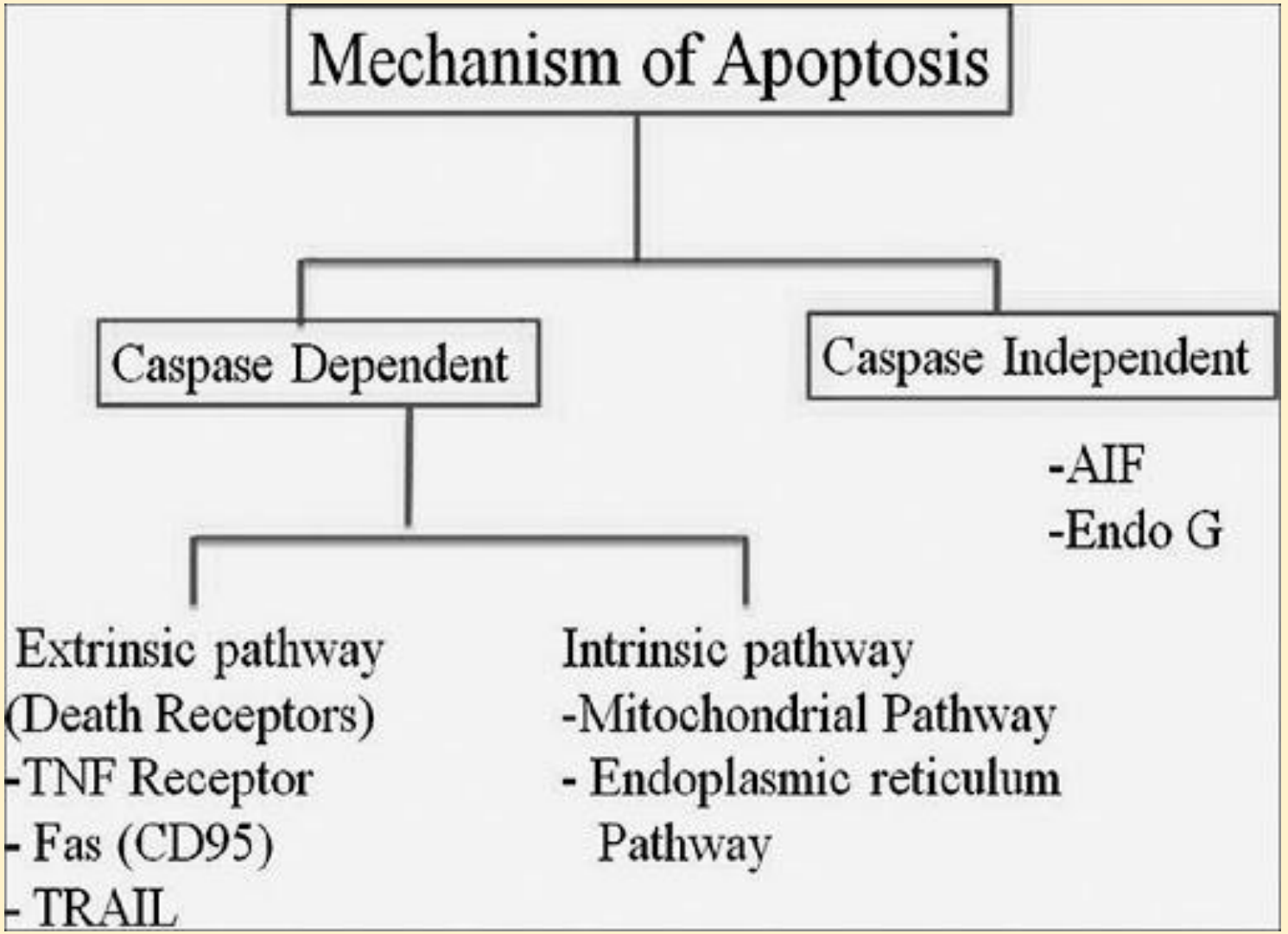
Biochemical events lead to characteristic cell changes (morphology) and death. These changes include

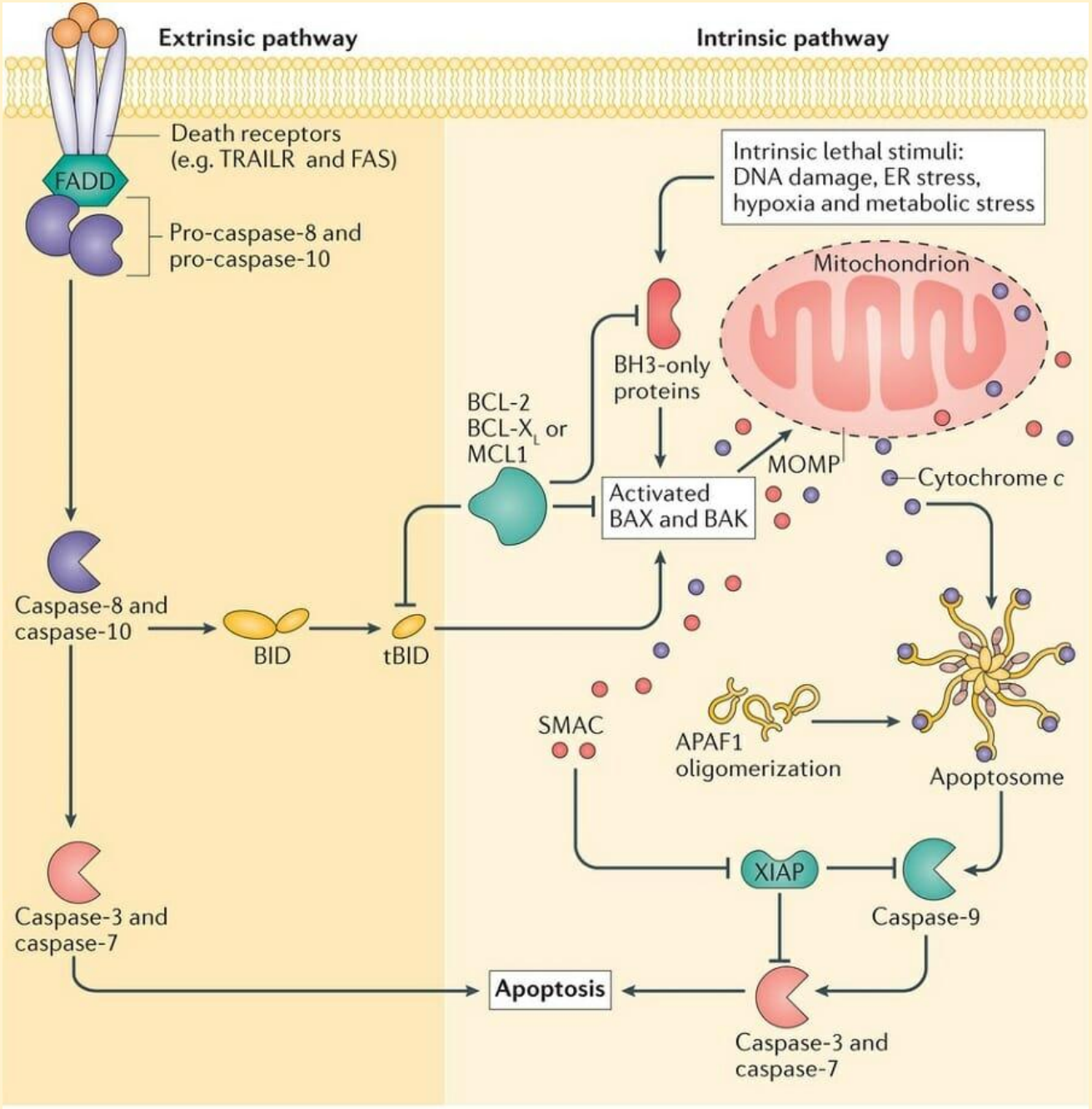
- Blebbing,
- Cell shrinkage,
- Nuclear fragmentation,
- Chromatin condensation,
- Chromosomal DNA fragmentation, and
- Global mRNA decay.

The average adult human loses between 50 and 70 billion cells each day due to apoptosis. For an average human child between the ages of 8 and 14, approximately 20–30 billion cells die per day

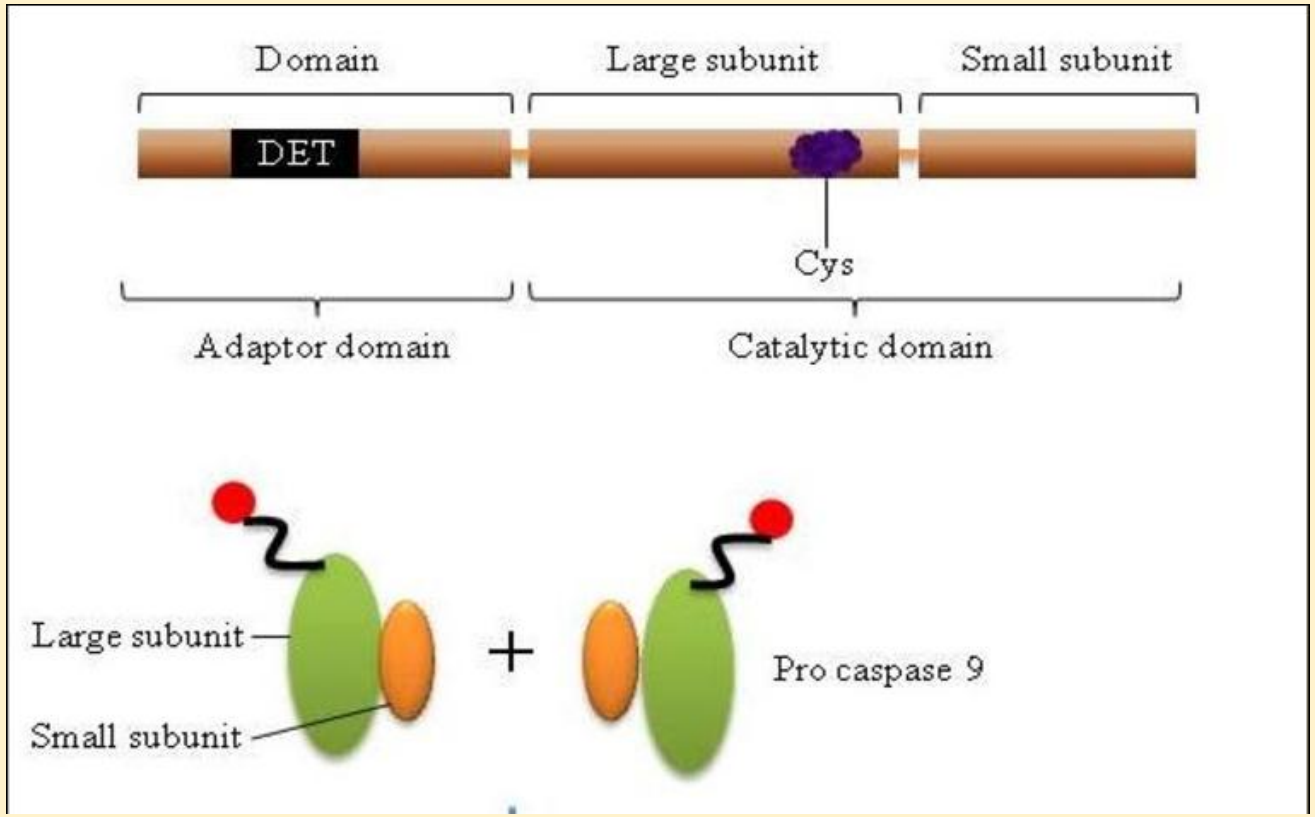

Step 1. Apoptotic membrane blebbing
Step 2. Formation of apoptotic membrane protrusions
Step 3. Cell fragmentation
Nuclear content
Apoptotic cell
Small surface membrane blebs
Nuclear fragmentation
Large dynamic membrane blebs
Microtubule spike
Beaded apoptopodia
Apoptopodia
Protrusion elongation
Segmentation of elongated protrusion
Beaded apoptopodia
Apoptotic bodies

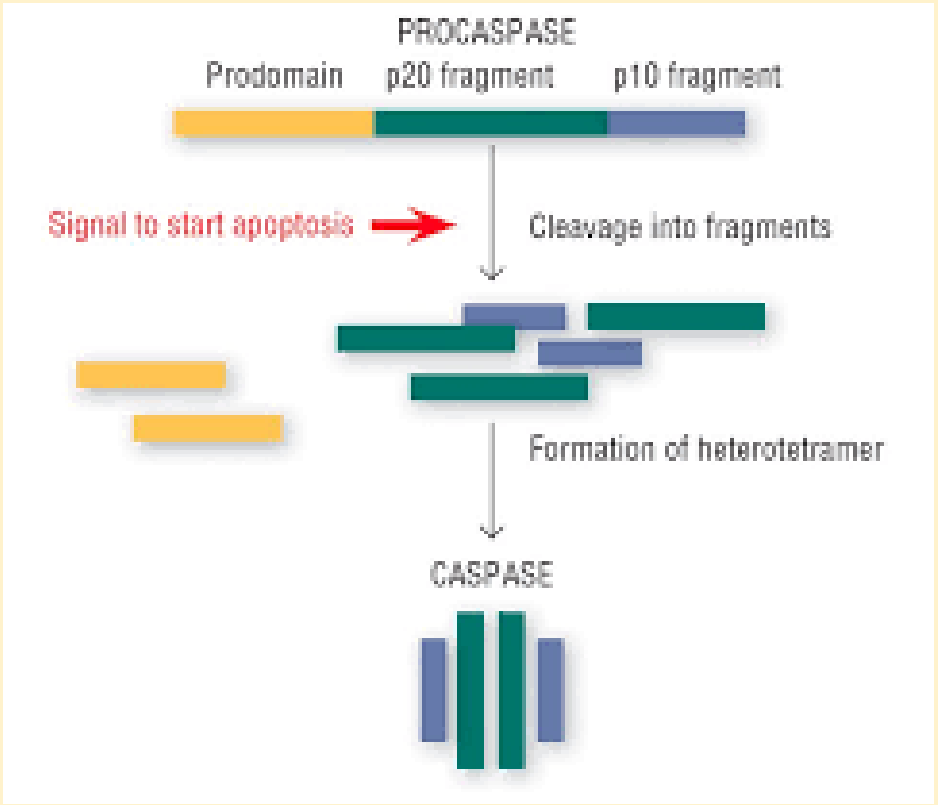

A Removal of tissues
B Organ sculpting
Key
Apoptotic cell


Mechanism of Apoptosis
Caspase Dependent
Caspase Independent
-AIF
-Endo G
Extrinsic pathway
(Death Receptors)
-TNF Receptor
- Fas (CD95)
- TRAIL
Intrinsic pathway
-Mitochondrial Pathway
- Endoplasmic reticulum
Pathway


Extrinsic pathway
Intrinsic pathway
Death receptors
(e.g. TRAILR and FAS)
FADD
Pro-caspase-8 and
pro-caspase-10
Intrinsic lethal stimuli:
DNA damage, ER stress,
hypoxia and metabolic stress
Mitochondrion
BH3-only
proteins
BCL-2
BCL-X$_L$ or
MCL1
MOMP
Cytochrome c
Activated
BAX and BAK
Caspase-8 and
caspase-10
BID
tBID
SMAC
APAF1
oligomerization
Apoptosome
XIAP
Caspase-9
Caspase-3 and
caspase-7
Apoptosis
Caspase-3 and
caspase-7

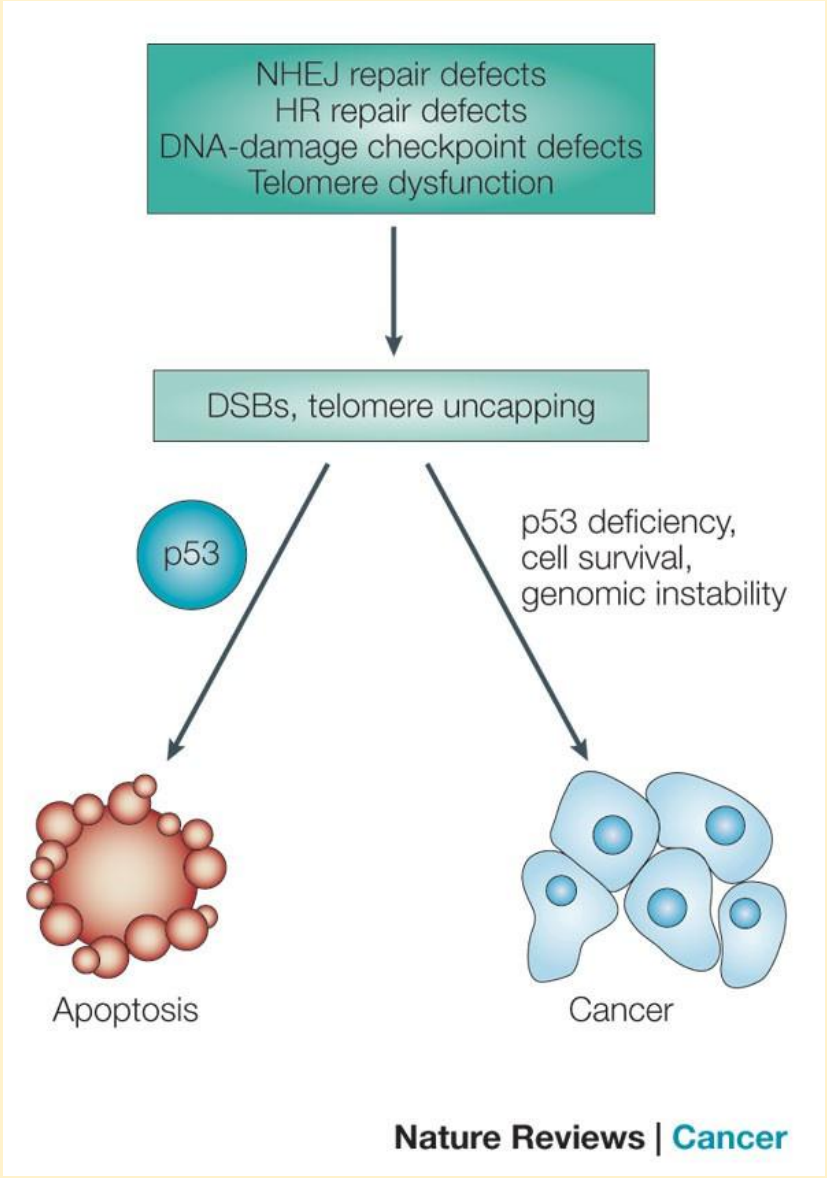
Caspase Activation





CASPASES

- Cysteine-dependent aspartate-secific proteases
- Play a central role in transduction of apoptopic signals
- Highly conserved proteins
- Intiator Caspases
  - Activates by binding to specific oligomeric adaptor protein
- Effector Caspases
  - Activated by active initiator caspases through proteolytic cleavage
  - Degrade intracellular proteins to carry out cell death program


NHEJ repair defects
HR repair defects
DNA-damage checkpoint defects
Telomere dysfunction
DSBs, telomere uncapping
p53
p53 deficiency,
cell survival,
genomic instability
Apoptosis
Cancer
Nature Reviews | Cancer

Procaspases Are Activated by Binding to Adaptor Proteins

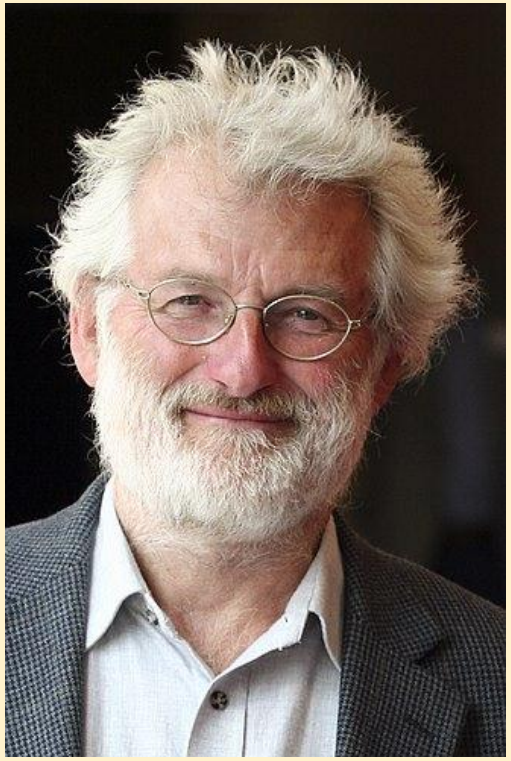
- All nucleated animal cells contain the seeds of their own destruction, in the form of various inactive procaspases that lie waiting for a signal to destroy the cell. It is therefore not surprising that caspase activity is tightly regulated inside the cell to ensure that the death program is held in check until needed.
- How are procaspases activated to initiate the caspase cascade? A general principle is that the activation is triggered by adaptor proteins that bring multiple copies of specific procaspases, known as *initiator procaspases,* close together in a complex or aggregate. In some cases, the initiator procaspases have a small amount of protease activity, and forcing them together into a complex causes them to cleave each other, triggering their mutual activation. In other cases, the aggregation is thought to cause a conformational change that activates the procaspase. Within moments, the activated caspase at the top of the cascade cleaves downstream procaspases to amplify the death signal and spread it throughout the cell (see Figure).

- **Extrinsic Pathway**: Procaspase activation can be triggered from outside the cell by the activation of *death receptors* on the cell surface. Killer lymphocytes, for example, can induce apoptosis by producing a protein called **Fas ligand**, which binds to the death receptor protein **Fas** on the surface of the target cell. The clustered Fas proteins then recruit intracellular adaptor proteins that bind and aggregate procaspase-8 molecules, which cleave and activate one another. The activated caspase-8 molecules then activate downstream procaspases to induce apoptosis (Figure). Some stressed or damaged cells kill themselves by producing both the Fas ligand and the Fas protein, thereby triggering an intracellular caspase cascade.
- **Intrinsic Pathway**: When cells are damaged or stressed, they can also kill themselves by triggering procaspase aggregation and activation from within the cell. In the best understood pathway, mitochondria are induced to release the electron carrier protein *cytochrome c* (see Figure) into the cytosol, where it binds and activates an adaptor protein called **Apaf-1** (Figure). This mitochondrial pathway of procaspase activation is recruited in most forms of apoptosis to initiate or to accelerate and amplify the caspase cascade. DNA damage, for example, as discussed earlier, can trigger apoptosis. This response usually requires p53, which can activate the transcription of genes that encode proteins that promote the release of cytochrome *c* from mitochondria. These proteins belong to the Bcl-2 family.

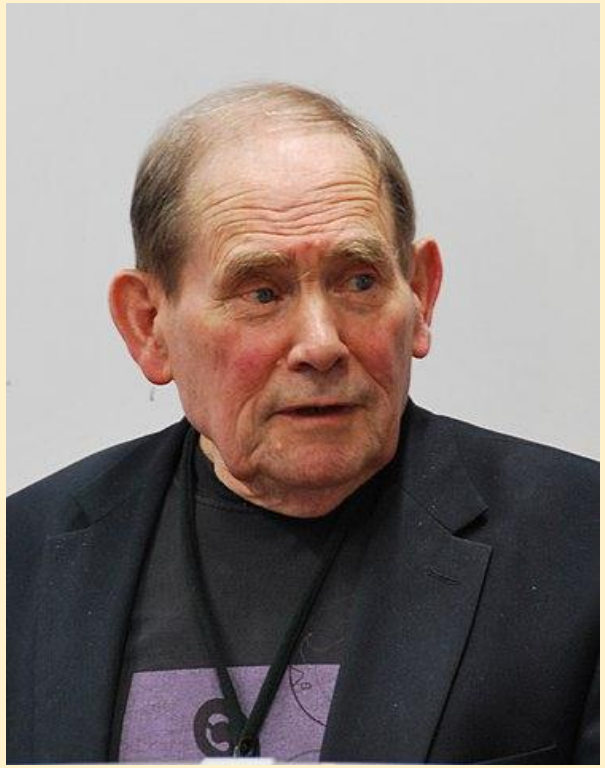
Summary

- In multicellular organisms, cells that are no longer needed or are a threat to the organism are destroyed by a tightly regulated cell suicide process known as programmed cell death, or apoptosis.
- Apoptosis is mediated by proteolytic enzymes called caspases, which trigger cell death by cleaving specific proteins in the cytoplasm and nucleus.
- Caspases exist in all cells as inactive precursors, or procaspases, which are usually activated by cleavage by other caspases, producing a proteolytic caspase cascade.
- The activation process is initiated by either extracellular or intracellular death signals, which cause intracellular adaptor molecules to aggregate and activate procaspases.
- Caspase activation is regulated by members of the Bcl-2 and IAP protein families.

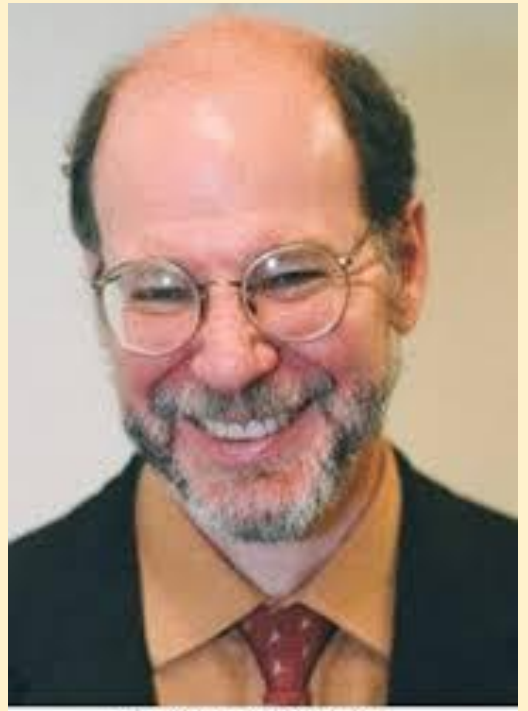
Nobel Prize in Physiology or Medicine (2002): Genetic regulation of organ development and programmed cell death.
Experimental material: roundworm *Caenorhabditis elegans*



John Sulston (1941-2018)



Sydney Brenner (1927-2019)



H. Robert Horvitz
(1947 -)

References:

- https://www.ncbi.nlm.nih.gov/books/NBK26873/
- https://biologydictionary.net/apoptosis/

Wong *Journal of Experimental & Clinical Cancer Research* 2011, **30**:87
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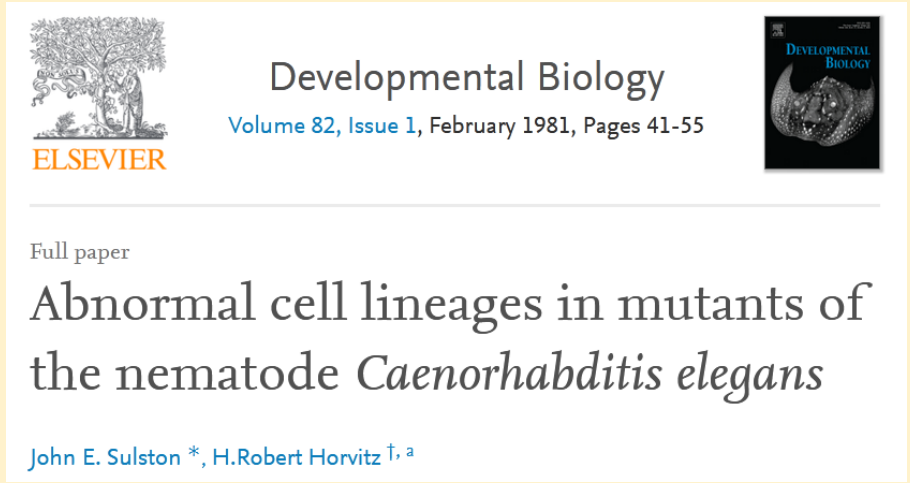

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John E. Sulston *, H.Robert Horvitz [†, a]