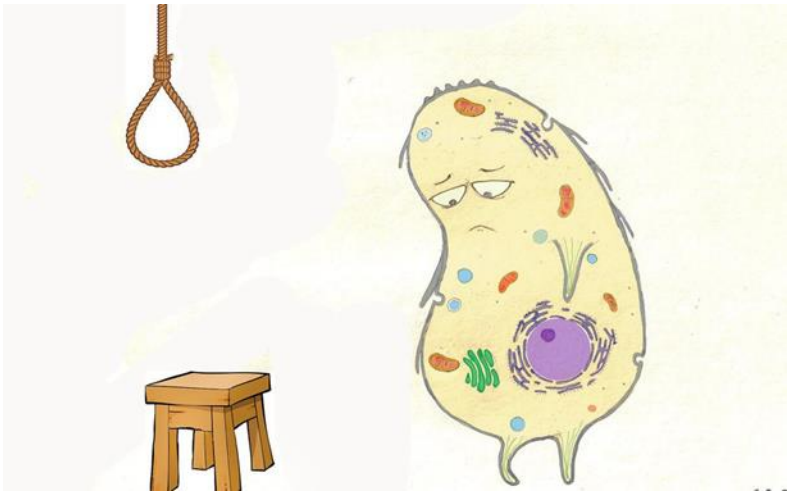
APOPTOSIS

Introduction

- Apoptosis can be defined as a pathway of cell death that induced by tightly regulated intracellular program.
- Its an energy dependent biochemical mechanism.

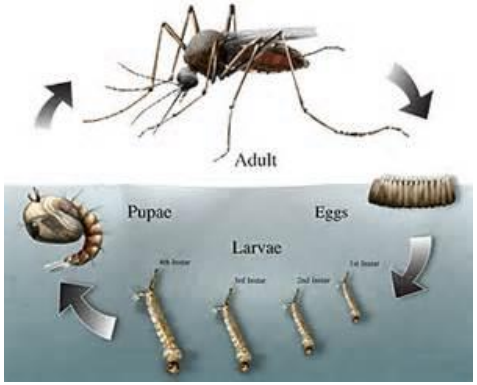


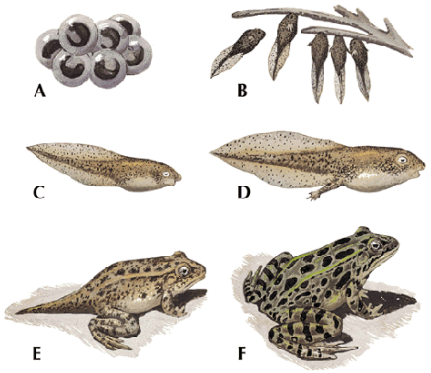
WHERE can APOPTOSIS be ENCOUNTERED ?

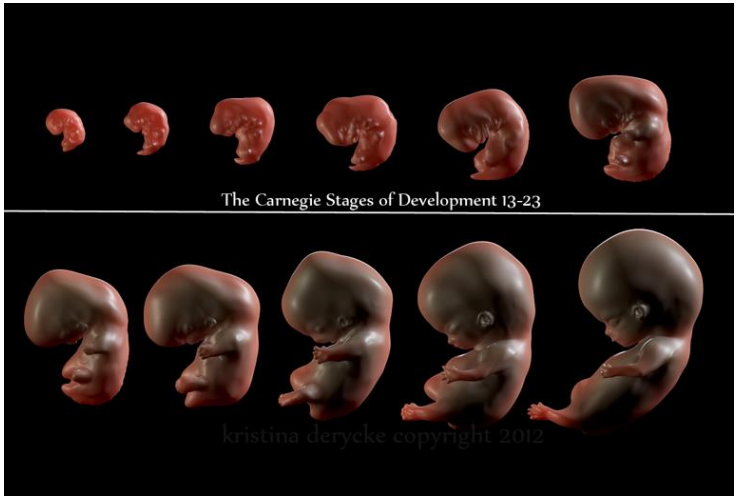
... Growth of Embrio
... Tissue Homeostasis
... Immunology
... Chronic viral diseases
... Neurodegenerative diseases
... Insuline-dependent Diabetes
... Development and Treatment of Malignancies

Importance of Apoptosis

Apoptosis is a necessary part of normal developmental process, specifically helps in proper development of organs, pattern formation and digitation.







Source: Google Images

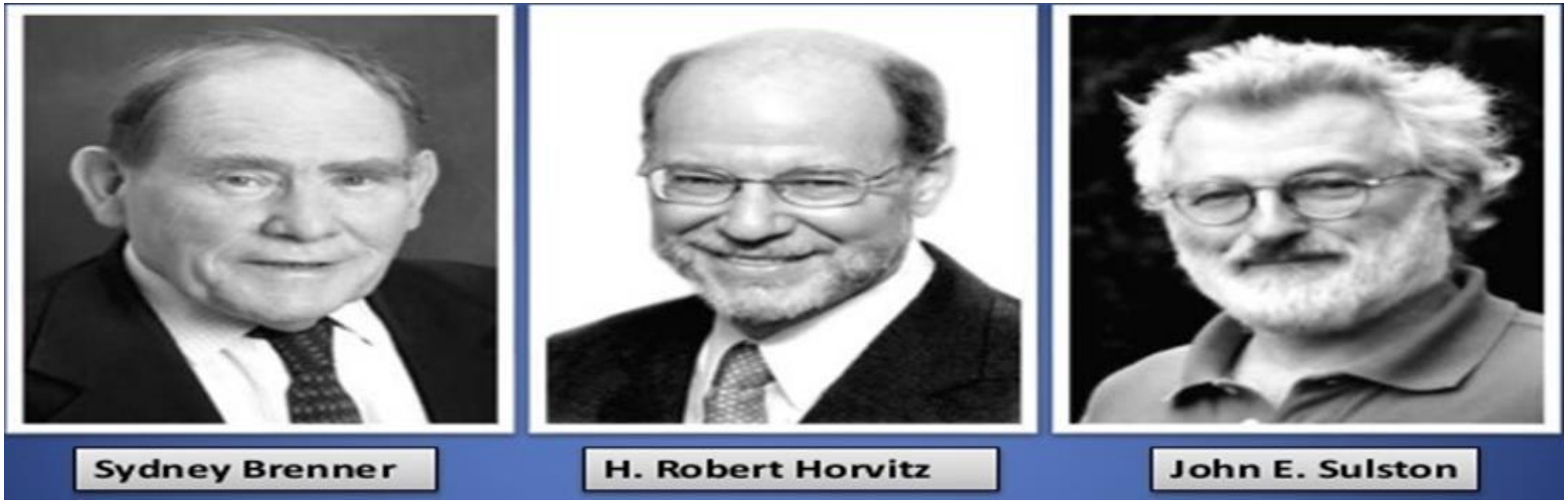
Apoptosis: Historical perspective

1842 Carl Vogt: Principle of apoptosis

1885 Walther Flemming: Process of programmed cell death

1965 John Foxton Ross Kerr : distinguish apoptosis from traumatic cell death by electron microscopy

2002 **Nobel Prize in medicine**



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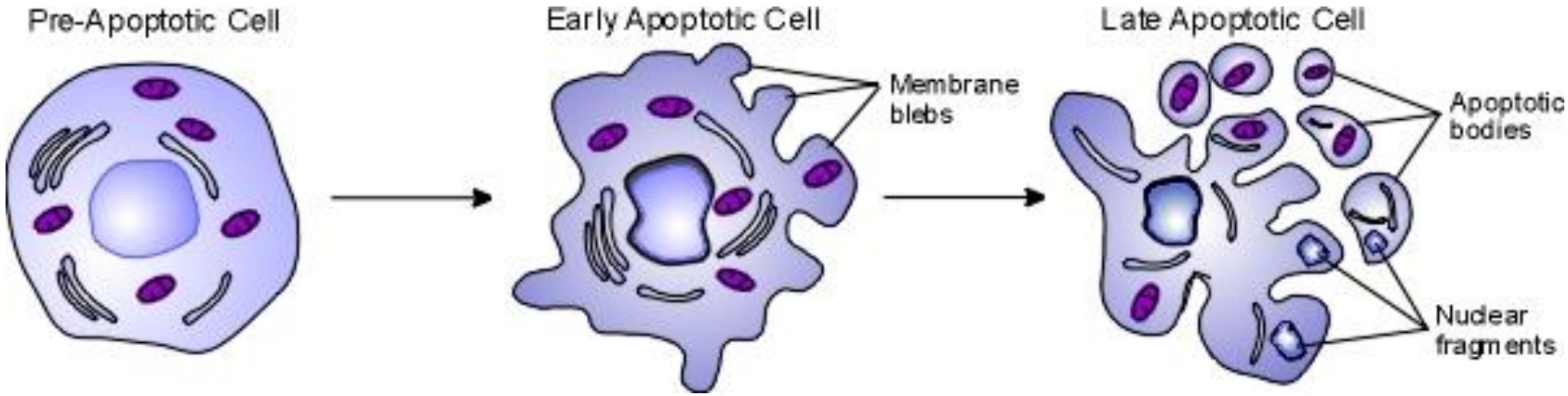
Phenotype of Cellular Apoptosis

- Membrane blebbing but no loss of integrity
- Aggregation of chromatin at the nuclear membrane.
- Begins with shrinkage of cytoplasm and condensation of nucleus.
- Ends with fragmentation of cell into apoptotic bodies



Source: http://www.utm.utoronto.ca/

Biochemical markers of Apoptosis

1) **A number of activities take place**

- *Occupation of death receptors*
- *Dimerization of Bcl-2 family members*
- *Release of cytochrome c*
- *Activation of caspases*
- *Activation of DNAse*

2) **Translocation of phosphatidylserine**

3) **ATP-dependency**

4) **Internucleosomal DNA fragmentation (ladder pattern)**

5) **No inflammation**

The intrinsic apoptotic pathway

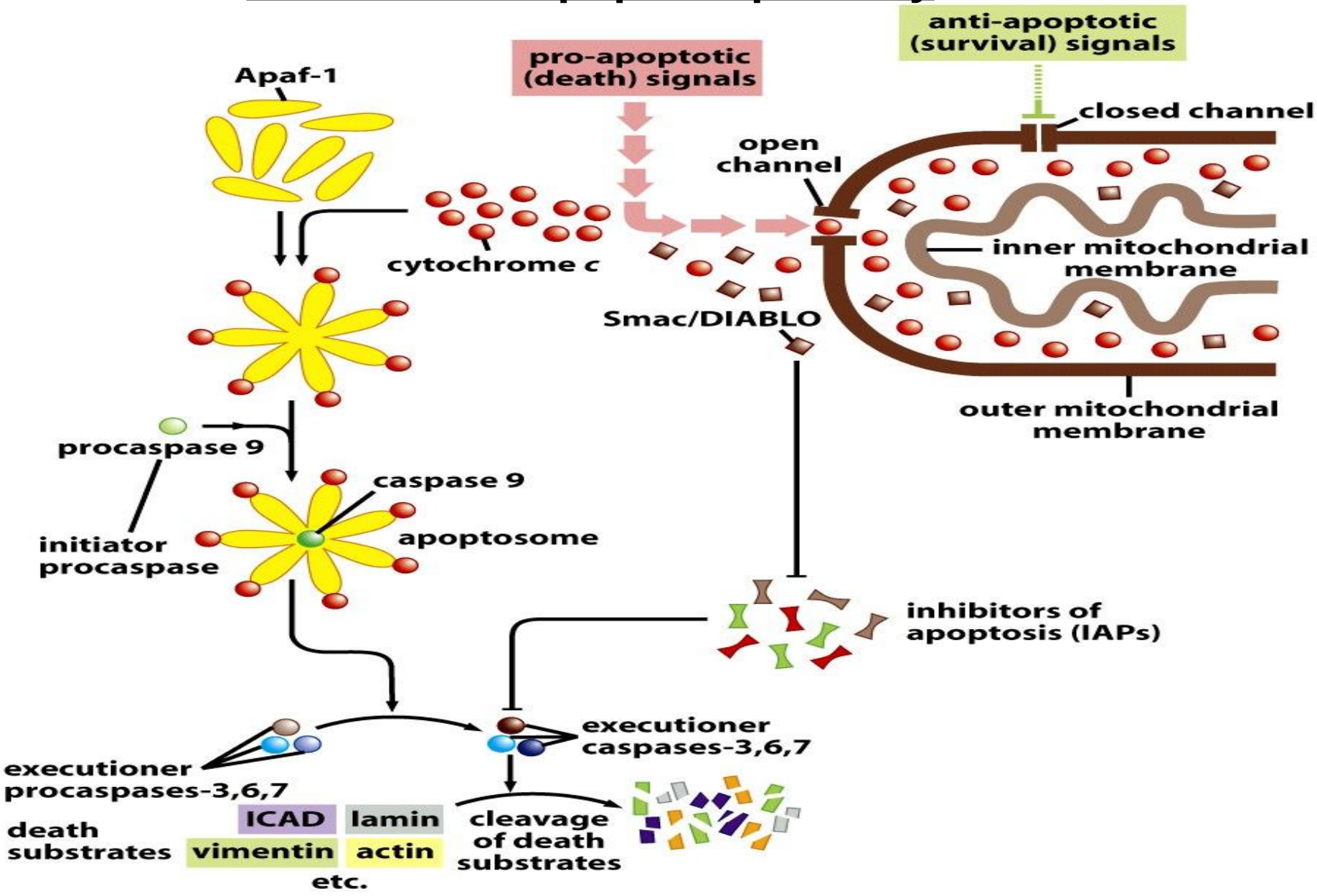
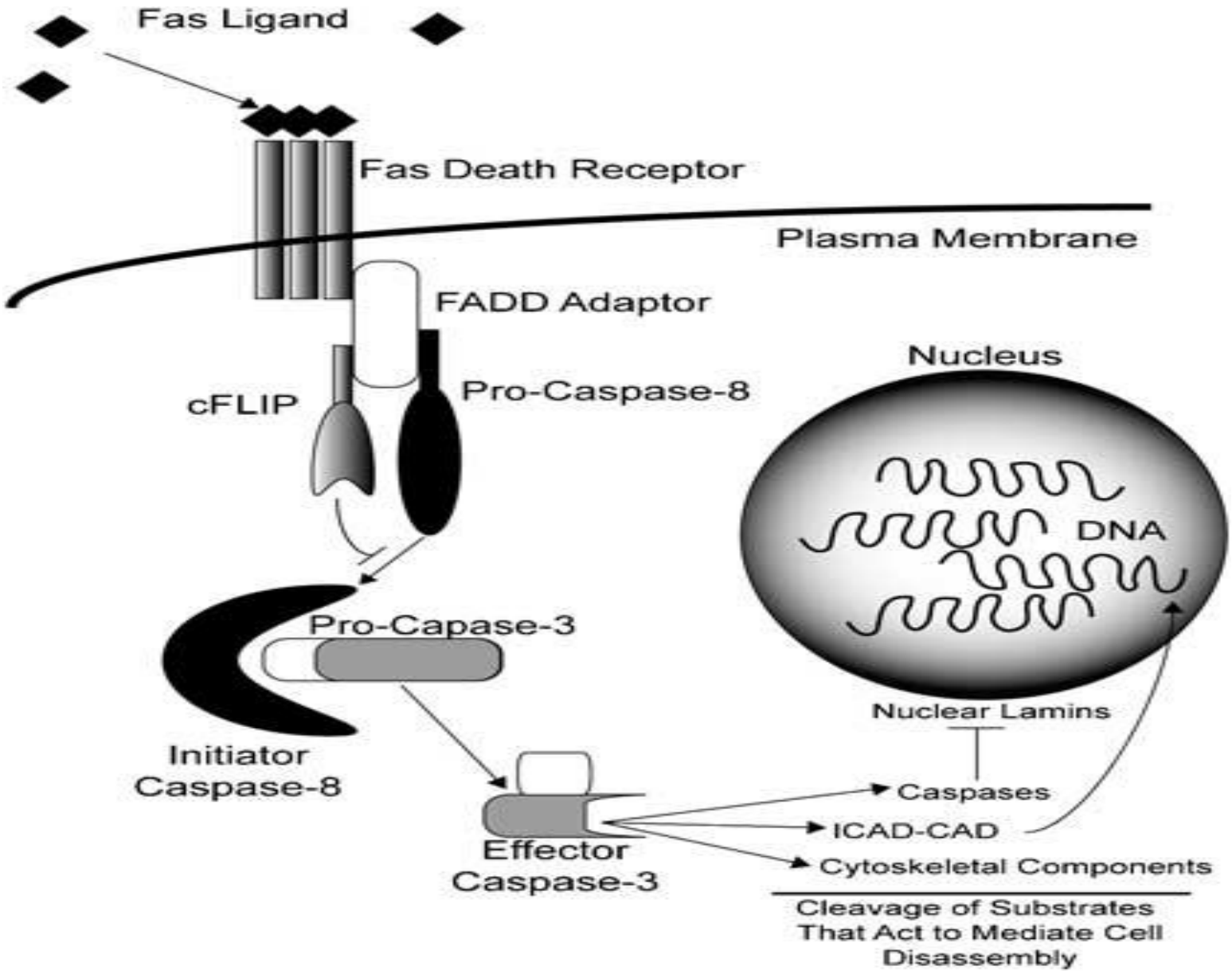


Figure 9-29 The Biology of Cancer (© Garland Science 2007)

Death receptor- mediated apoptosis



Regulators of apoptosis

Inhibitors of Apoptosis

Physiologic inhibitors
1. Growth factors
2. Extracellular matrix
3. CD40 ligand
4. Neutral amino acids
5. Zinc
6. Estrogen
7. Androgens

Viral genes
1. Adenovirus *E1B*
2. Baculovirus *p35*
3. Baculovirus *IAP*
4. Cowpox virus *crmA*
5. Epstein-Barr virus *BHRF1, LMP-1*
6. African swine fever virus *LMW5-HL*
7. Herpesvirus γ1 34.5

Pharmacological agents
1. Calpain inhibitors
2. Cysteine protease inhibitors
3. Tumor promoters
   - PMA
   - Phenobarbital
   - α-Hexachlorocyclohexane

Inducers of Apoptosis

Physiologic activators
1. TNF family
   - Fas ligand
   - TNF
2. Transforming growth factor β
3. Neurotransmitters
   - Glutamate
   - Dopamine
   - *N*-methyl-D-aspartate
4. Growth factor withdrawal
5. Loss of matrix attachment
6. Calcium
7. Glucocorticoids

Damage-related inducers
1. Heat shock
2. Viral infection
3. Bacterial toxins
4. Oncogenes
   - *myc, rel, E1A*
5. Tumor suppressors
   - p53
6. Cytolytic T cells
7. Oxidants
8. Free radicals
9. Nutrient deprivation—antimetabolites

Therapy-associated agents
1. Chemotherapeutic drugs
   - Cisplatin, doxorubicin, bleomycin, cytosine arabinoside, nitrogen mustard, methotrexate, vincristine
2. Gamma radiation
3. UV radiation

Toxins
1. Ethanol
2. β-amyloid peptide

Fig. 2. A partial list of the agents that have been reported to induce or inhibit apoptosis.

Comparison between two forms of cell death, apoptosis and necrosis

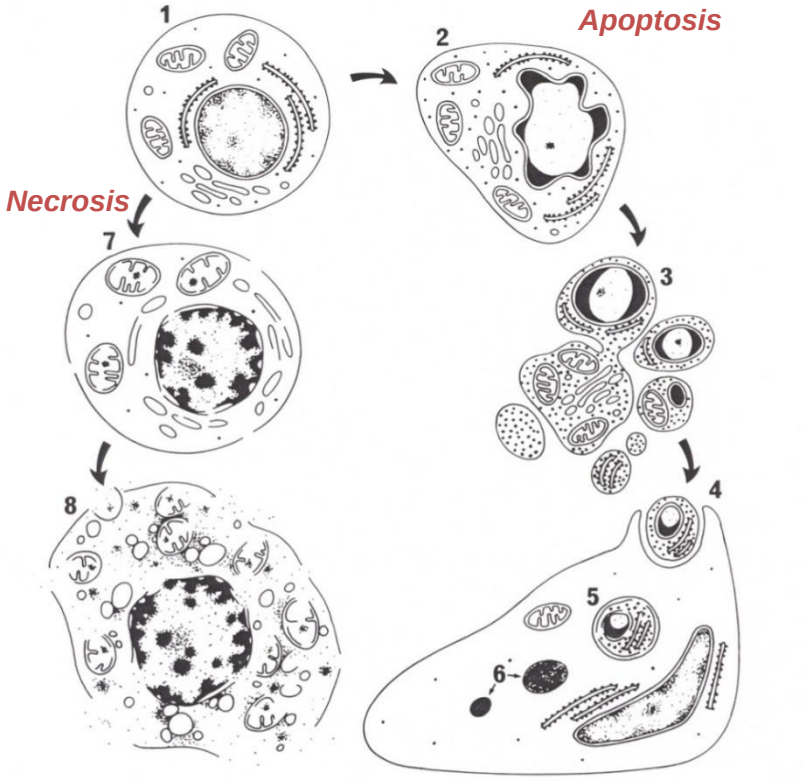


Fig. 1 Sequence of ultrastructural changes in apoptosis (2–6) and necrosis (7 and 8). A normal cell is shown in stylized form at 1. Early apoptosis (2) is characterized by compaction and segregation of chromatin in sharply circumscribed masses that abut on the inner surface of the nuclear envelope, convolution of the nuclear outline, condensation of the cytoplasm with preservation of the integrity of organelles, and the beginning of convolution of the cell surface. In the next phase (3), the nucleus fragments and further condensation of the cytoplasm is associated with extensive cell surface protrusion, followed by separation of the surface protuberances to produce membrane-bounded apoptotic bodies of varying size and composition. These bodies are phagocytosed (4) by nearby cells and are degraded by lysosomal enzymes (5), being rapidly reduced to nondescript residues within telolysosomes (6). In the irreversibly injured cell, the onset of necrosis (7) is manifest as irregular clumping of chromatin without radical change in its distribution, gross swelling of mitochondria with the appearance of flocculent densities in their matrices, dissolution of ribosomes, and focal rupture of membranes. At a more advanced stage of this process (8), all cellular components disintegrate. In tissues, the overall configuration of the cell is reasonably maintained until it is removed by mononuclear phagocytes, but in cell cultures dissolution eventually ensues.

Table 9.3 Apoptosis versus necrosis

	Apoptosis	Necrosis
Provoking stimuli		
	programmed tissue remodeling	metabolic stresses
	maintenance of cell pool size	absence of nutrients
	genomic damage	changes in pH, temperature
	metabolic derangement	hypoxia, anoxia
	hypoxia	
	imbalances in signaling pathways	
Morphological changes		
Affected cells	individual cells	groups of cells
Cell volume	decreased	increased
Chromatin	condensed	fragmented
Lysosomes	unaffected	abnormal
Mitochondria	morphologically normal initially	morphologically aberrant
Inflammatory response	none	marked
Cell fate	apoptotic bodies consumed by neighboring cells	lysis
Molecular changes		
Gene activity	required for program	not needed
Chromosomal DNA	cleaved at specific sites	random cleavage
Intracellular calcium	increased	unaffected
Ion pumps	continue to function	lost

Adapted from R.J.B. King, Cancer Biology, 2nd ed. Harlow, UK: Pearson Education, 2000.

Table 9-3 The Biology of Cancer (© Garland Science 2007)

Apoptosis: Role in Diseases