Lesión, muerte celular y envejecimiento

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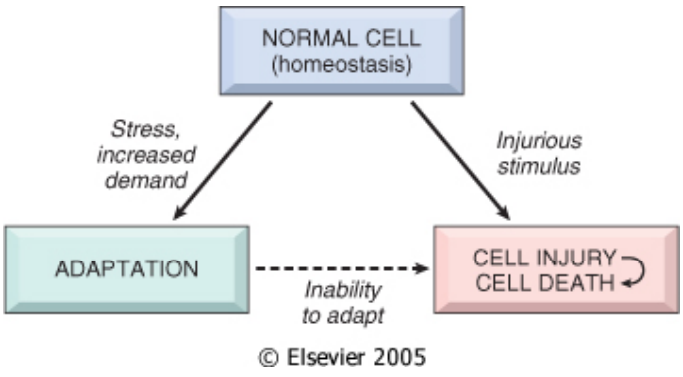
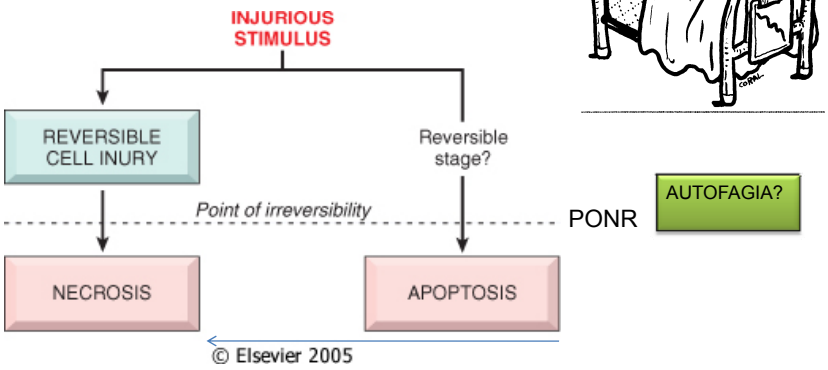
Estímulo:
•Persistencia
•Intensidad



Lesión celular



- De no ser por los mecanismos de muerte celular, tendríamos 16 kms de intestino, y 2 toneladas de médula ósea y linfonodos.
- Por lo tanto, la muerte ayuda a mantener la homeostasis de las poblaciones.

Causas de lesión celular

Isquemia Hipoxia/anoxia	Radicales libres	Trastornos genéticos
Agentes físicos	Agentes químicos y fármacos	Agentes infecciosos
Reacciones inmunológicas	Desequilibrios nutricionales	Endocrinas

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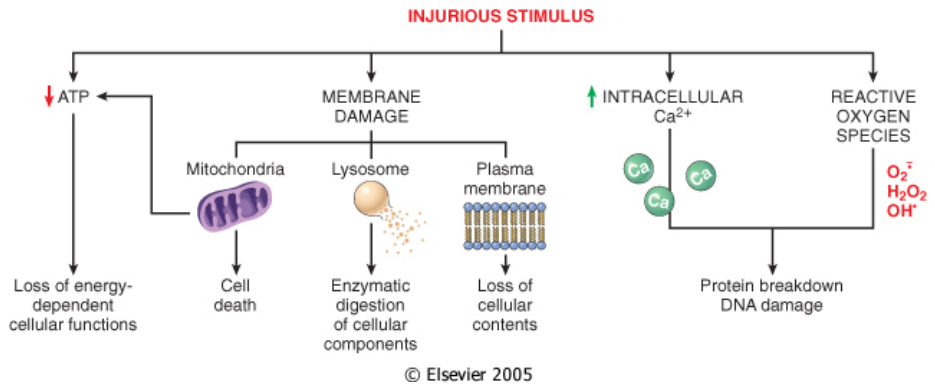
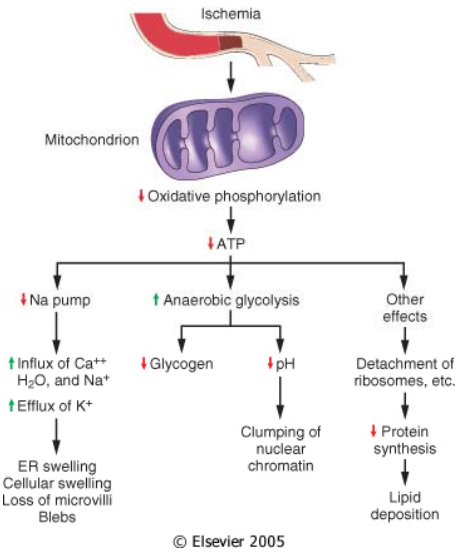
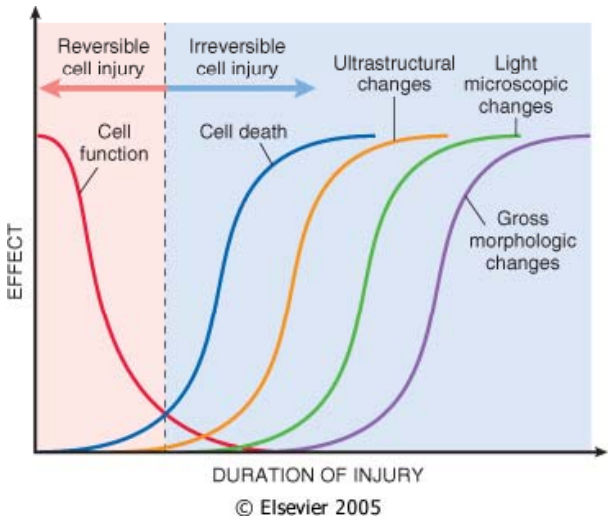
Sistemas celulares vulnerables a la noxa:



Lesión celular isquémica

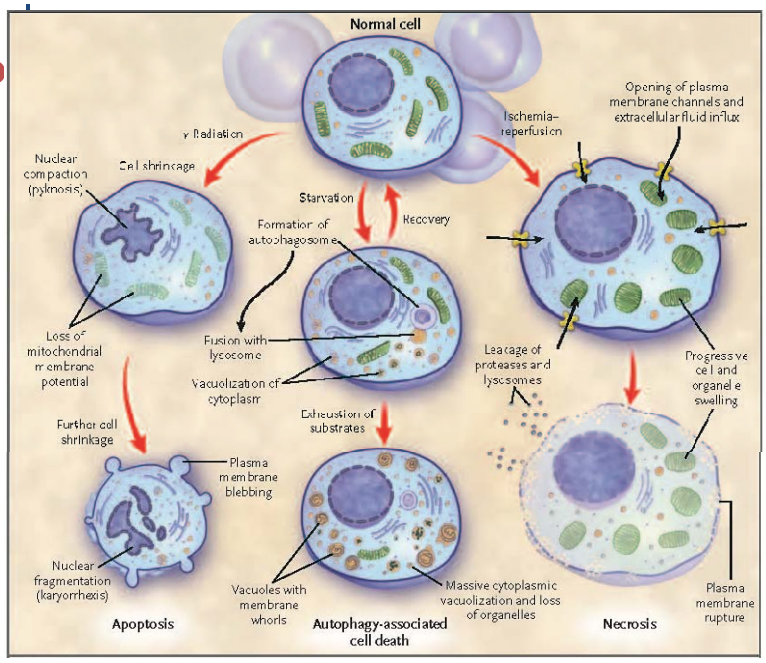


Cambios asociados a injuria

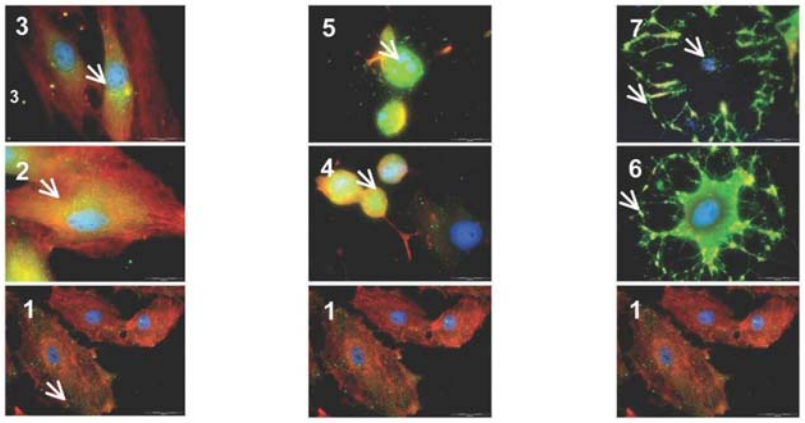


Patronesn morfológico de muerte:

Autofagia	Necrosis	Apoptosis
Acúmulo de vacuolas	Tumefacción y destrucción de membranas	Contracción celular
		Condensación cromatina



Autofagia, necrosis y apoptosis



Causas: Apoptosis v/s necrosis v/s autofagia

- Membrana plasmática
- ATP
- Tipo y duración noxa
- Capacidad metabólica

Autofagia

- De Duve
- Self-eating
- 32 genes en levadura, altamente conservados entre especies
- Degradación lproteolítica de componentes citosólicos en lisosoma

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Autofagia: La muerte puede esperar

Generación de energía y metabolitos

Digestión de organelos y macromoléculas redundantes o dañados

Causas:

- Deprivación ATP
- Deprivación GF
- Estrés oxidativo

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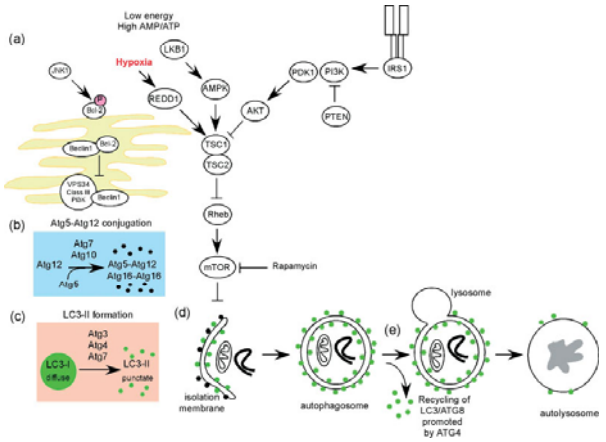
Autofagia (macroautofagia)



Glick, D, Barth S, Macleod F, J Pathol 2010

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Table 1. Autophagy-deficient mouse models and human diseases linked to defects in specific autophagy genes

Autophagy gene and function (human/mouse)	Human disease linked to mutation/inactivation	Mouse model phenotype	References
ATG16L/Atg16L Atg16L complexes with conjugated Atg5–Atg12 to promote expansion and curvature of the nascent phagophore	*T300A* mutation in *ATG16L* linked to Crohn's disease, discovered by GWAS	Loss of Atg16L1 inhibits autophagy in Paneth cells, reducing secretion of granules of antimicrobial peptides that influence intestinal microbiota and causing increased inflammation	32–35
BECN1/Becn1 Beclin1 regulates the kinase activity of Vps34 at the ER; complex includes regulatory components UVRAG, Atg14L, Rubicon and Ambra	*BECN1* is mono-allelically deleted in breast, ovarian and prostate cancer	*Becn1*-null mice are embryonic lethal, showing a defect in cavitation of the blastocyst. *Becn1* heterozygotes are predisposed to lymphoma, hepatocellular carcinoma and other cancers	16,17
UVRAG/Uvrag UVRAG complexes with Beclin1 and Vps34 at the ER to promote autophagy	*UVRAG* is mono-allelically deleted in colon cancer	N/A	18
IRGM/Irgm Immunity-related GTPase stimulates autophagy and promotes clearance of pathogenic bacteria	Deletion of upstream regulatory sequences segregates with Crohn's disease and is associated with altered IRGM expression	N/A	36
CLN3/Cln3 Associated with Golgi, endosomes and lipid rafts and may play a role in transporting ceramide and other sphingolipids to lipid rafts	Accumulation of proteolipids in children with Batten disease leads to neurodegeneration and is due to inactivation of the *CLN3* gene, which promotes autophagosome fusion with the lysosome	Immature autophagosomes in tissues from mice with knock-in of mutant forms of *Cln3*	45
Parkin A E3 ubiquitin ligase that localizes to the mitochondria and is required for mitophagy	Parkinson's disease (PD) is associated with cell death of dopaminergic neurons and progressive loss of cognitive and motor function. Mutation of several genes are linked to PD, including Parkin	N/A	63,64
p62/SQSTM1 A multifunctional adaptor protein that promotes turnover of polyubiquitinated protein aggregates through interaction with LC3 at the autophagosome	p62 mutations are linked to Paget's disease in which increased bone turnover results in abnormal bone architecture. Associated with deregulated NF-κB signalling and reduced turnover of ubiquitinated proteins	*p62*-null mice are resistant to Ras-driven lung carcinogenesis. Loss of *p62* prevents accumulation of ubiquitin-positive protein aggregates in the liver and neurons of *Atg7*-deficient mice	39,49,50,52,53
Lamp2 A lysosomal membrane protein required for fusion of the autophagosome with the lysosome	Danon disease is an X-linked disease resulting in hypertrophic cardiomyopathy and accumulation of autophagosomes in the heart muscle	Increased autophagosome numbers in multiple tissues, cardiomyopathy, skeletal myopathy, periodontitis associated with inflammation due to defective clearance of intracellular pathogens	46

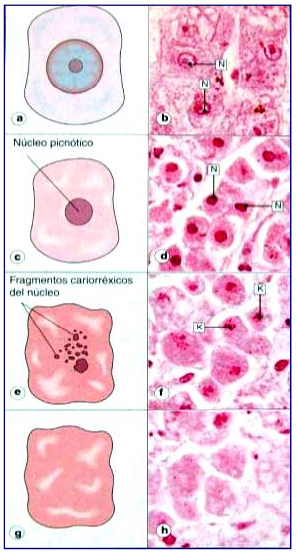
Lesión letal: Morfología

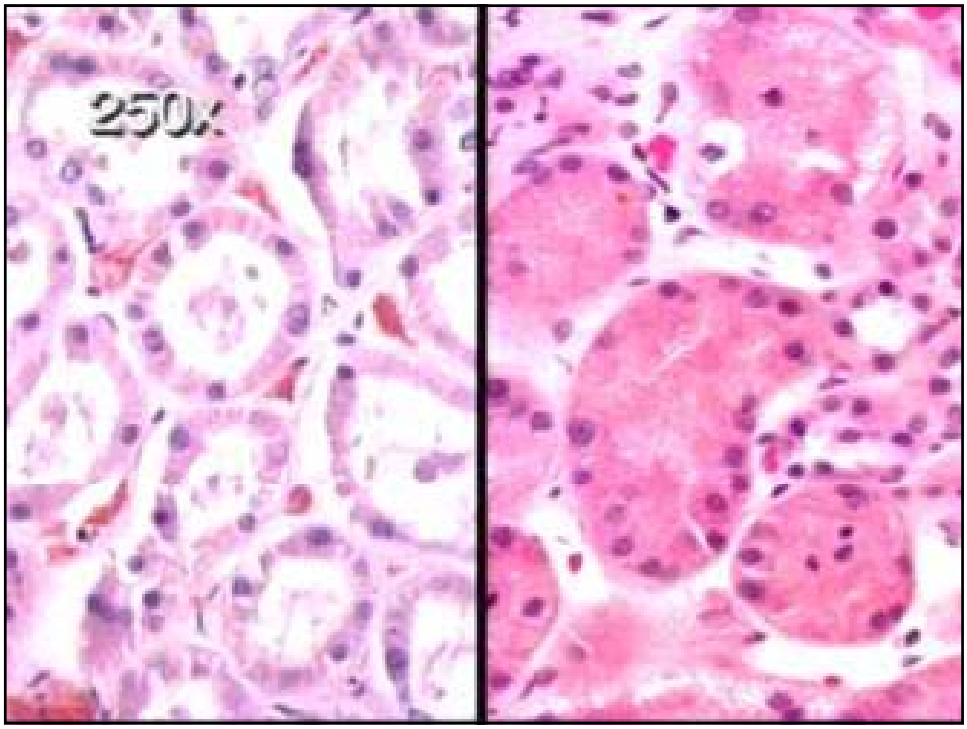
Núcleo

- Picnosis
- Constricción nuclear y aumento de la basofilia
- Cese de la transcripción

- Cariorrexis:
- Fragmentación del núcleo

- Cariolisis:
- Disolución del núcleo





Necrosis: Patrones

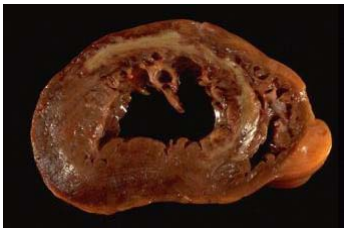
Cambios morfológicos que siguen a la muerte celular en el tejido vivo

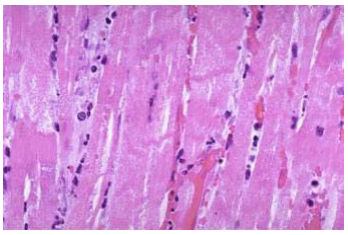
- Enzimas lisosómicas intracelulares
  - Autólisis o heterólisis
- Desnaturalización de las proteínas

Patrones de necrosis

Necrosis de coagulación

- Oclusión del riego arterial e isquemia tisular
- Tejido firme y pálido.
- Mantención de la arquitectura y siluetas celulares





Necrosis de coagulación

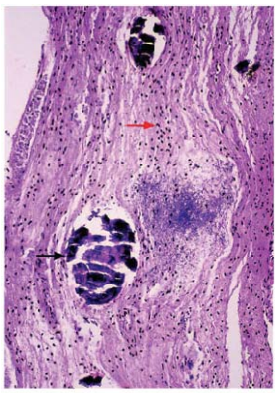


FIGURE 2- Pulp with partial necrosis, areas with preserved cell nuclei (red arrow) and calcification (black arrow) (H.E., original magnification 200X)

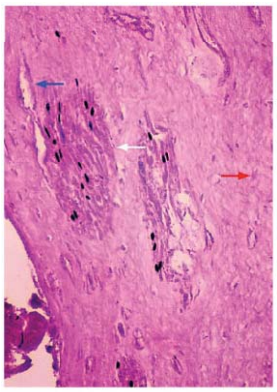
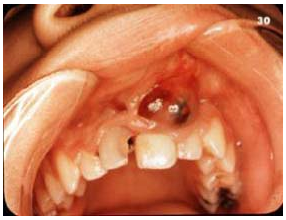


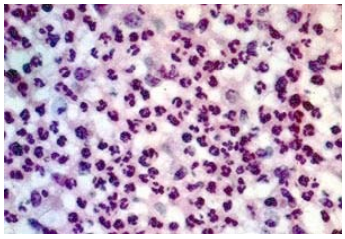
FIGURE 3- Pulp with complete necrosis, degeneration of blood vesses (blue arrow) cell nuclei (red arrow) and nerve bundles (white arrow) (H.E., orginal magnification 400X)

Patrones de necrosis

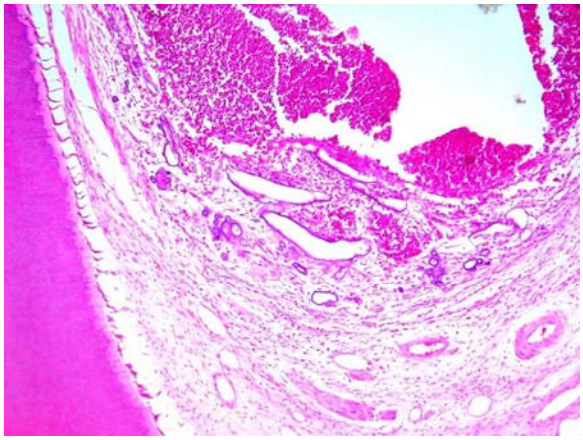
Necrosis por licuefacción

- Aspecto semilíquido a causa de las enzimas hidrolíticas
- Por bacterias piogénicas que atraen PMN





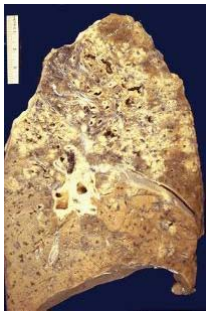
Absceso pulpar

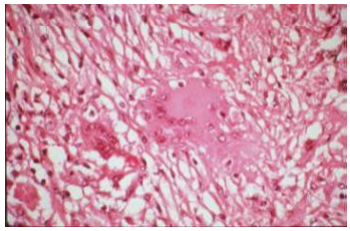


Patrones de necrosis

Necrosis por caseificación

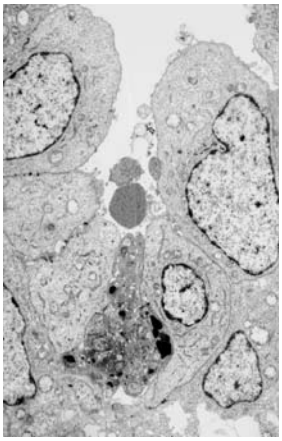
- TBC
- Tejido blanco y blando que recuerda queso
- Masa proteica amorfa, pérdida de la arquitectura tisular





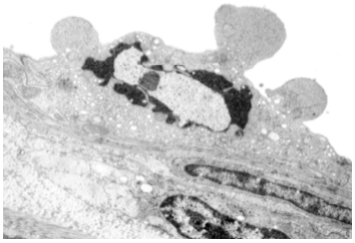
Apoptosis

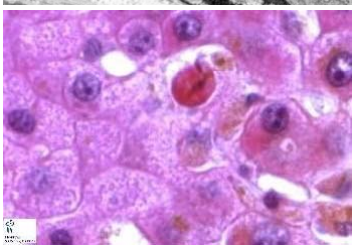
- Embriogénesis y desarrollo
- Homeostasis
- Envejecimiento
- Reacciones inmunitarias
- Lesión celular

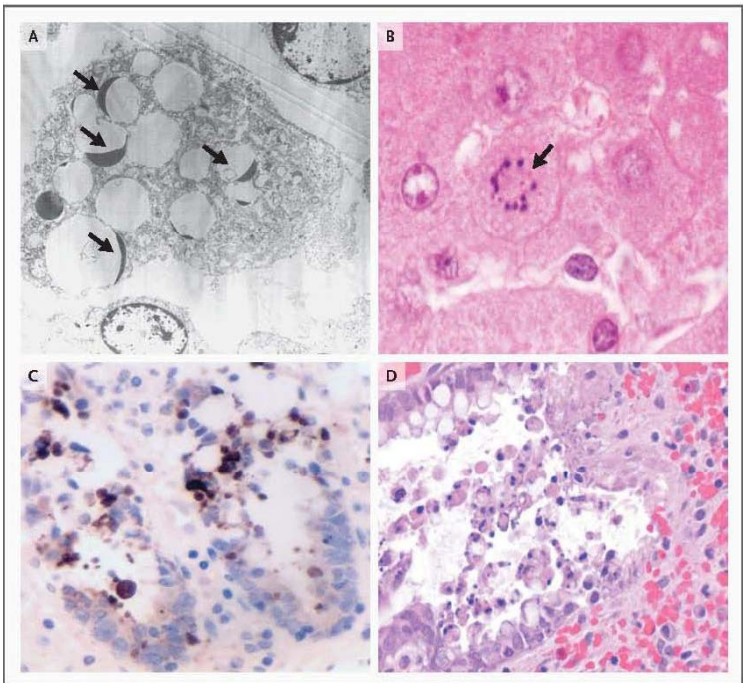


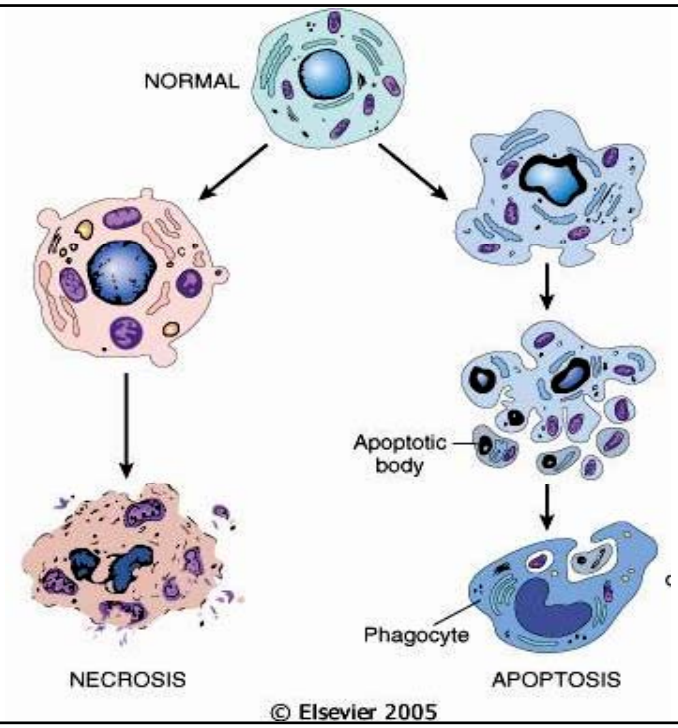
Morfología

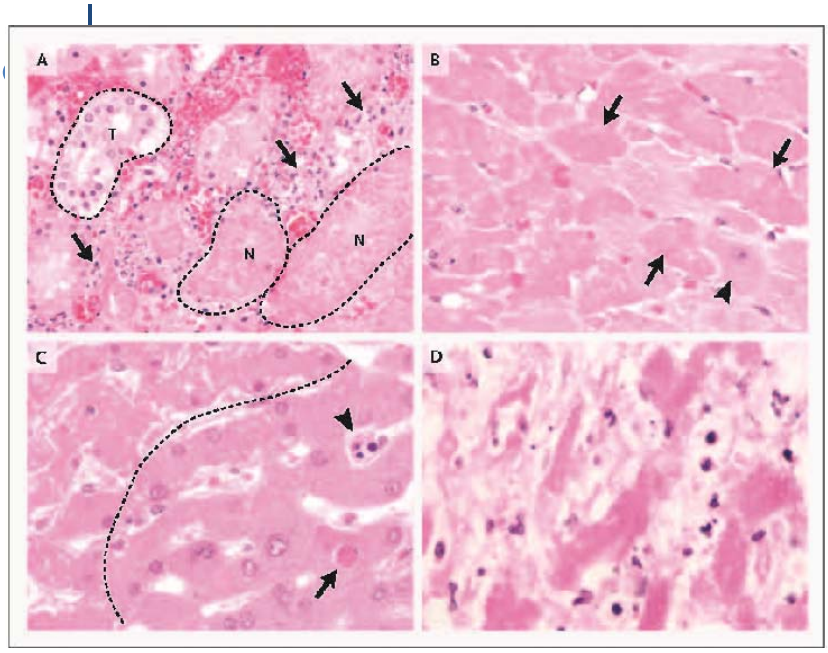
1. Células aisladas
2. Constricción celular
3. Eosinofilia
4. Condensación periférica de la cromatina
5. Cuerpos apoptóticos
6. Membranas intactas
7. Fagocitosis en ausencia de inflamación



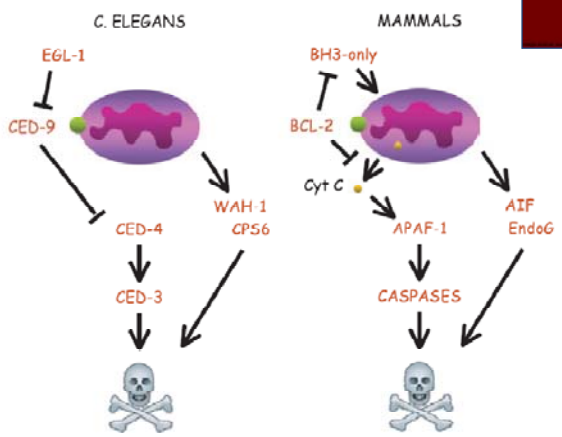



A
B
C
D


NORMAL
Apoptotic body
Phagocyte
NECROSIS
APOPTOSIS
© Elsevier 2005

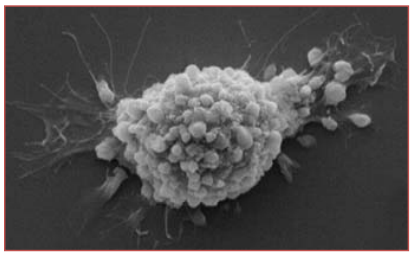


Apoptosis: Aspectos bioquímicos



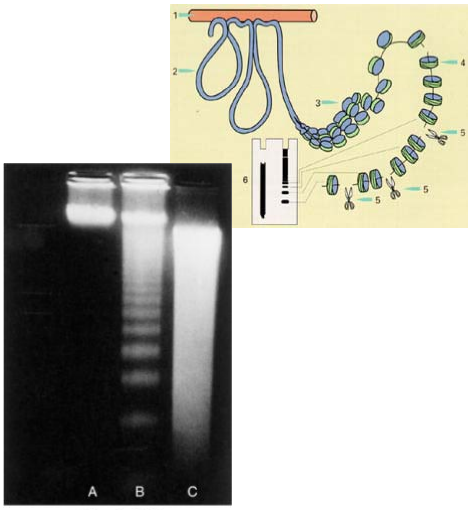
Características bioquímicas

Fragmentación de las proteínas y ADN:	• caspasas
Energía	• ATP
Reconocimiento fagocitario	• fosfatidilserina y trombospondina



Características bioquímicas

- Fragmentación internucleosomal del ADN
  - Endonucleasas dependientes da Ca^{2+} y Mg^{2+}



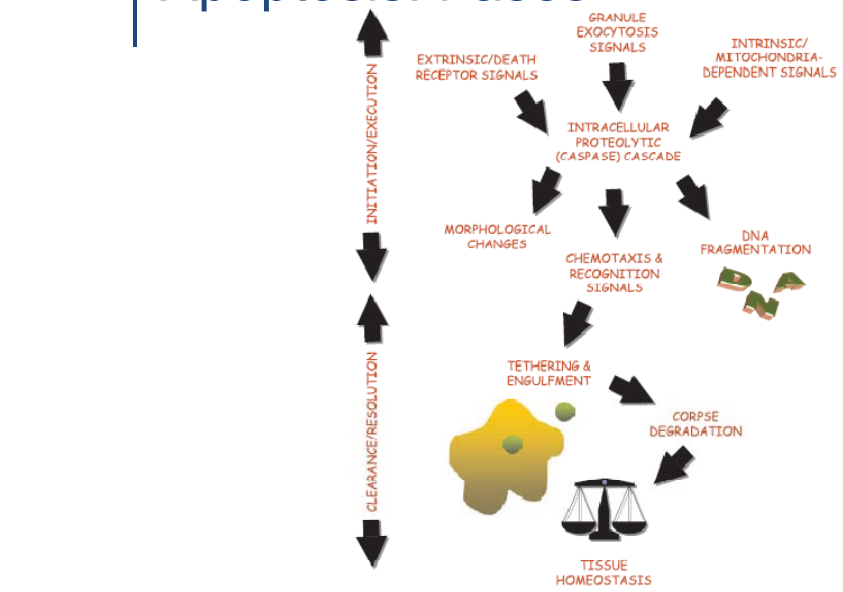
Apoptosis vs necrosis

Table II. Fundamental differences between apoptosis and necrosis

	Necrosis	*Apoptosis*
Etiology	Acute cell injury due to extracellular stimuli	Various intracellular or extarcellular stimuli
Character	Pathologic	Physiologic or pathologic
Distribution	Groups of cells or patches of tissues	Widely scattered isolated cells
Energy requirement	Passive process (ATP-independent)	Active process (ATP-dependent)
Morphologic features	Swelling of the cytoplasm	Shrinkage of the cytoplasm
	Cell membrane lysis with loss of cell contents and organelles	Externalization of phosphatidylserine and cell membrane blebbing with formation of membrane-surrounded apoptotic bodies, which encompass cytoplasm and organelles
	Random DNA fragmentation	Chromatin condensation and DNA fragmentation into oligosomal fragments with "DNA ladder" formation
Reaction of the surrounding tissues	Inflammation	Phagocytosis without inflammatory reaction

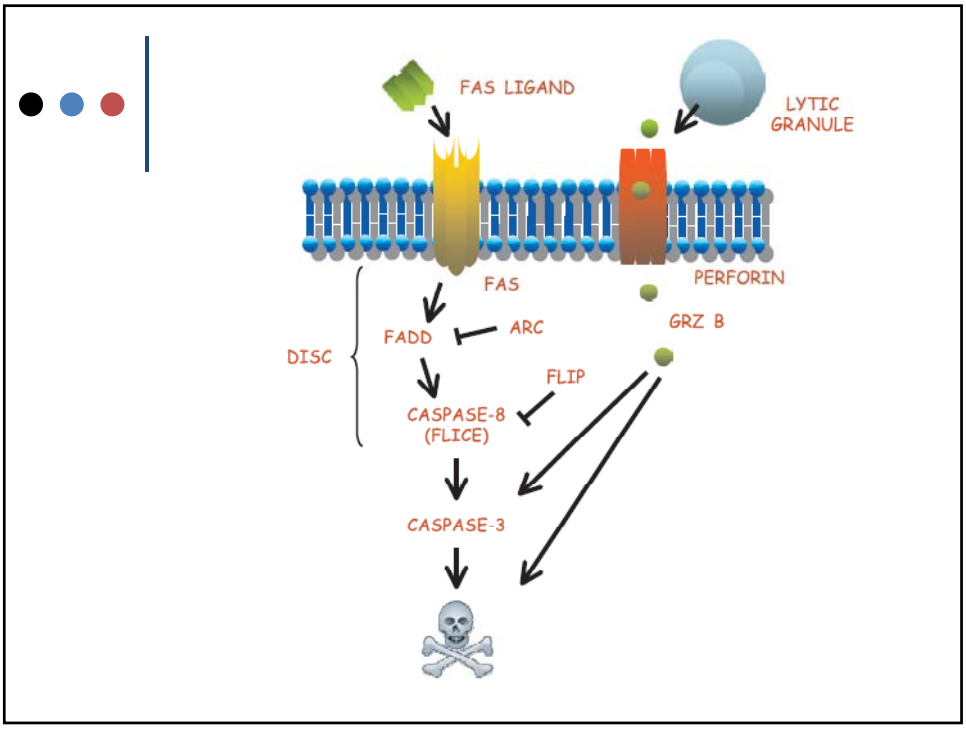
De qué depende el patrón de muerte?

Apoptosis: Fases

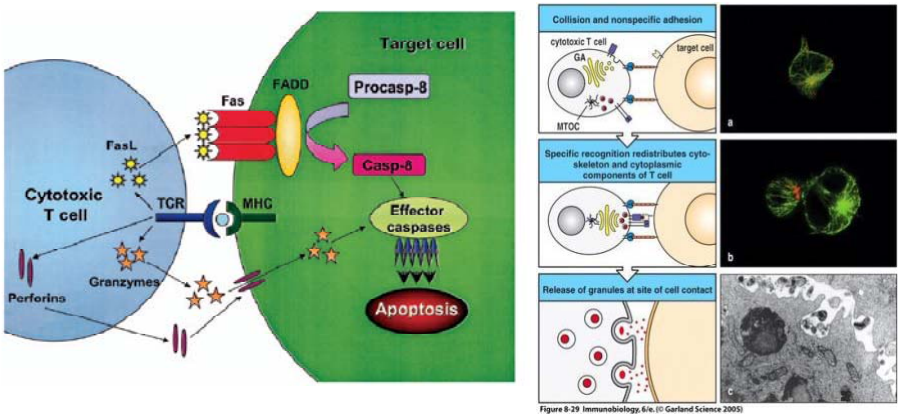


Apoptosis: Vía extrínseca

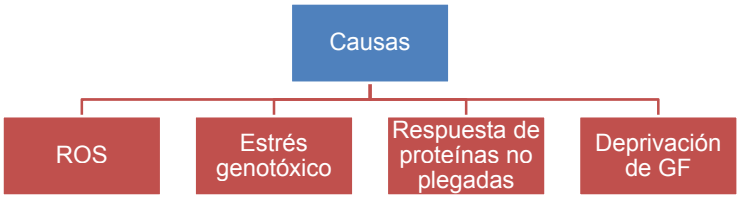
- Inmunológica
- Ligandos y receptores de muerte
- Superfamilia TNF-α
- DISC
- Caspasa-8



Apoptosis: Vía de los gránulos líticos

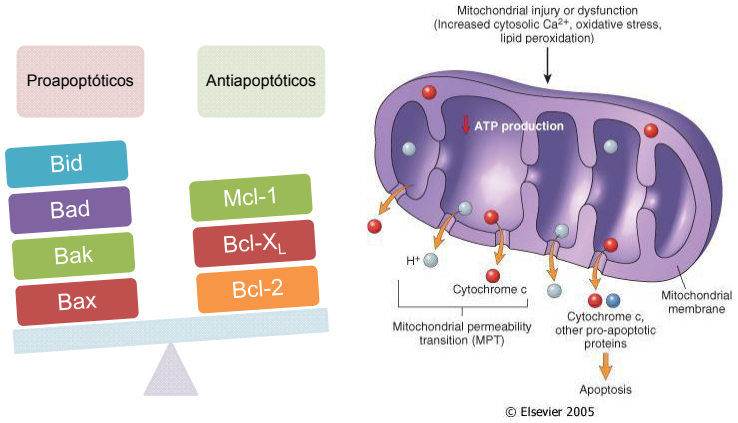


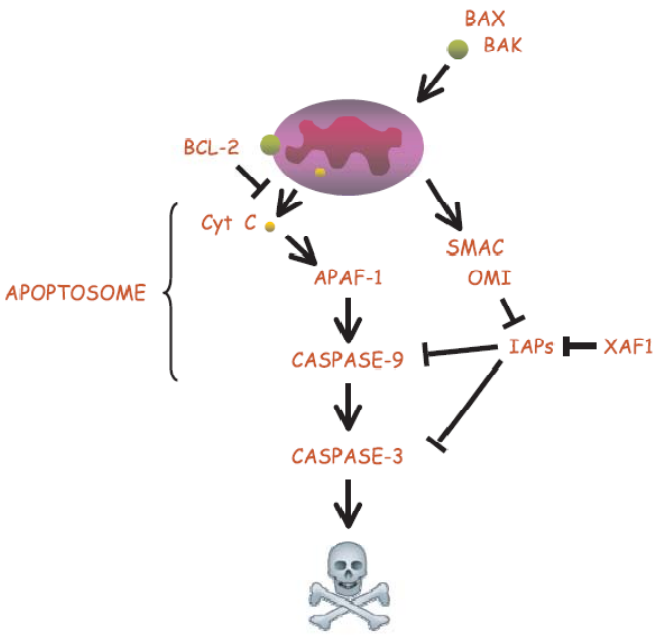
Apoptosis vía intrínseca



Apoptosis: Vía intrínseca

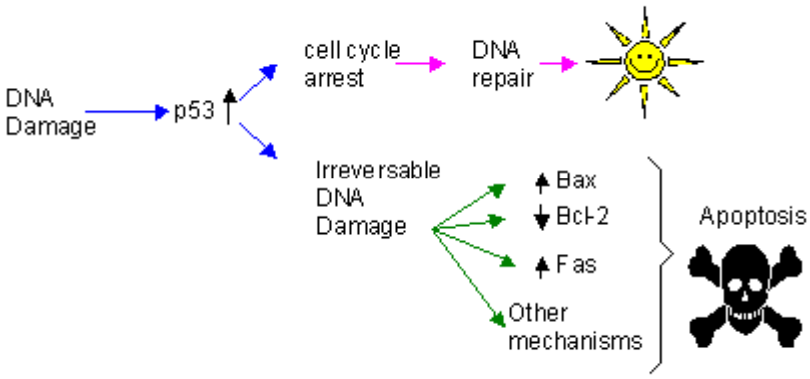
Vía intrínseca: Reguladores bcl

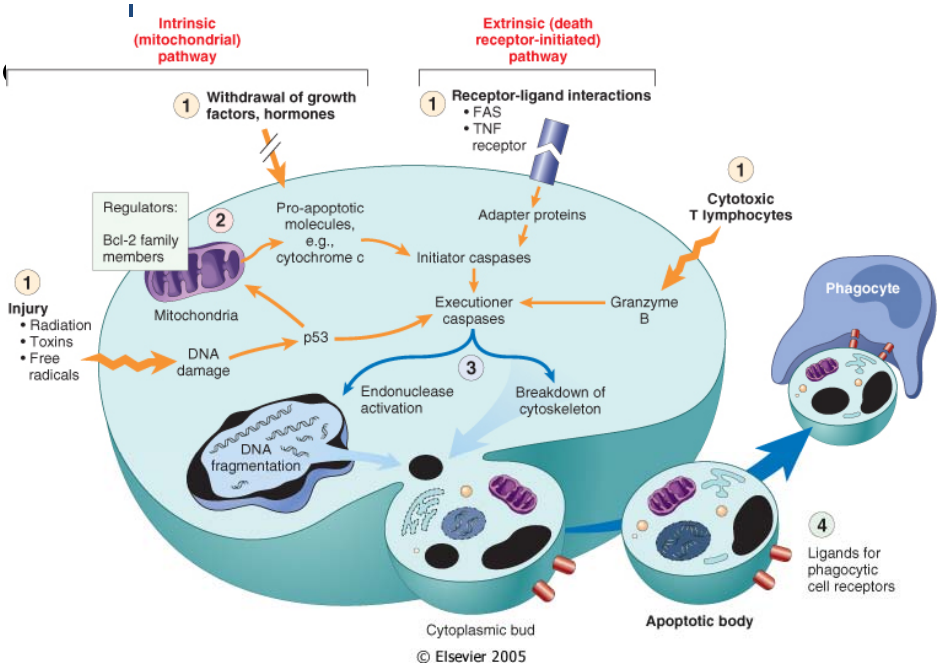




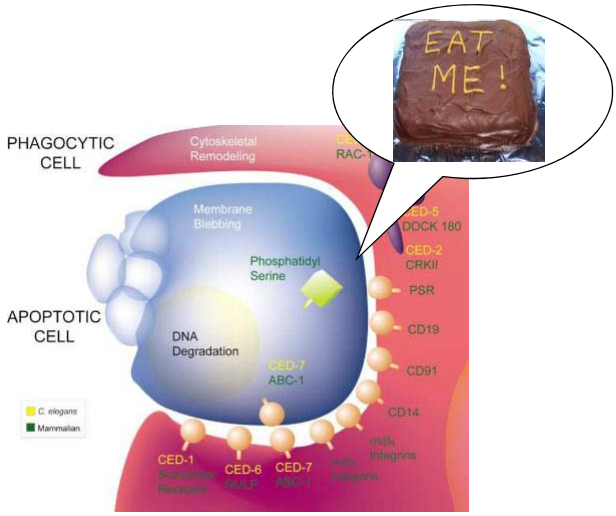
•P53

Estrés genotóxico
Hipoxia





Fases: 2. Eliminación de células muertas



Apoptosis en enfermedad

> 50% enfermedades s/tto. adecuado

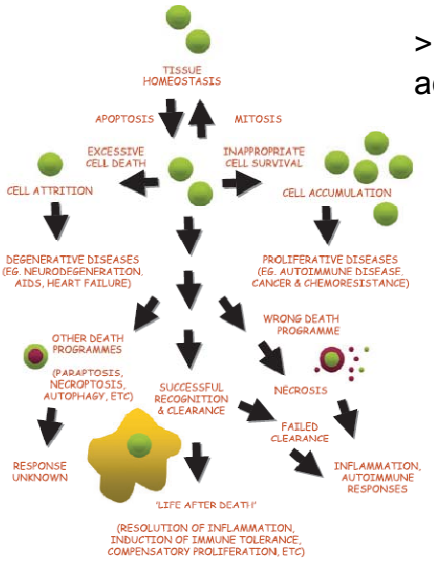
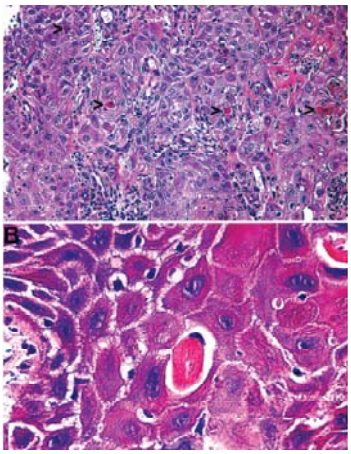
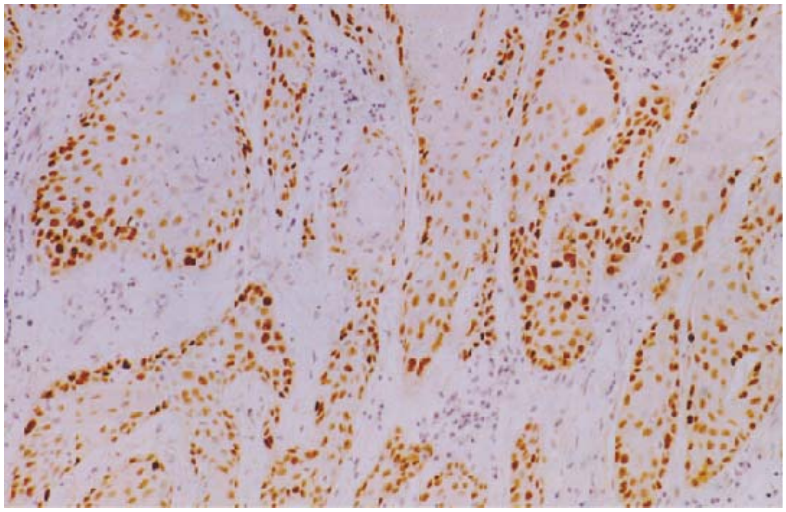


Fig. 5 Role of apoptosis in disease. Apoptosis is required for the maintenance of tissue homeostasis. Disruption of apoptosis, or interference with the engulfment of apoptotic cell corpses, can contribute to the pathogenesis of several of the most common human diseases, as discussed in the present review. Other forms of cell death may also occur, but these pathways have not been well described to date.

Apoptosis y cáncer

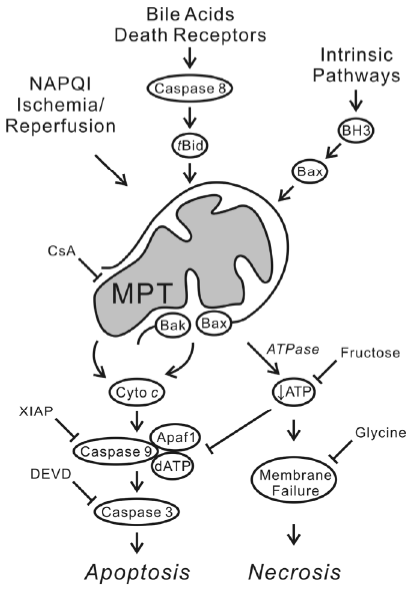
- >50% neoplasias
- >bcl-2, >p53 (TP53)
- Cá lengua: bcl-2/bax
- > agentes quimioterapéuticos inducen apoptosis

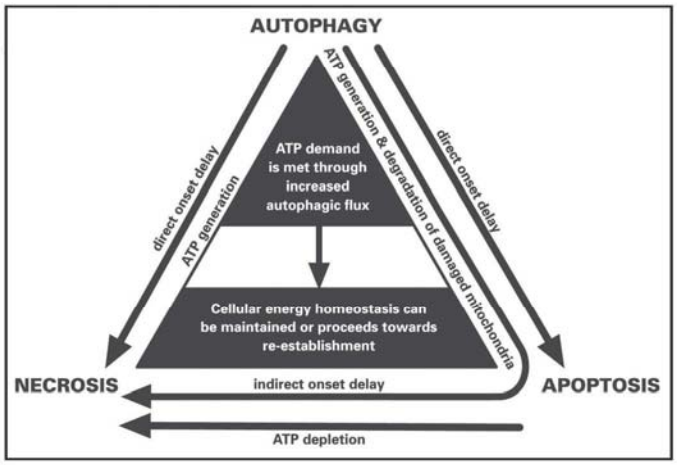




Overexpression of p53 in a well-differentiated SCC: magnification ´ 40.

Necroapoptosis





Envejecimiento

"Aging seems to be the only available way to live a long life."

– Daniel Francois Esprit Auber (3)

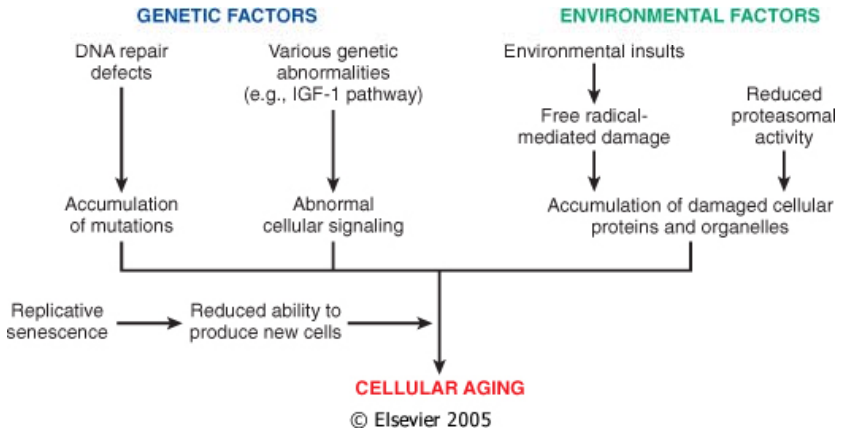
TABLE 1

Characteristics of Aging

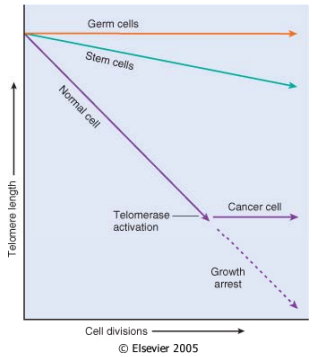
1. Increased mortality with age after maturation.
2. Changes in biochemical composition in tissues with age.
3. Progressive decrease in physiological capacity with age.
4. Reduced ability to respond adaptively to environmental stimuli with age.
5. Increased susceptibility and vulnerability to disease.

BIOLOGY OF AGING—TROEN

Envejecimiento celular



Senescencia celular



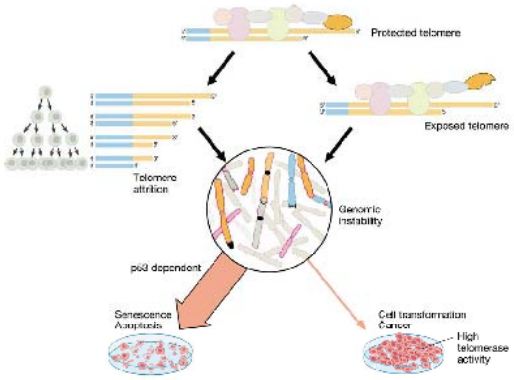


Figure 5. Schematic model of how short or unprotected telomere ends cause genomic instability followed by cell proliferation arrest and cell death. Sometimes the genetic changes allows escape from this response and instead lead to cell transformation and cancer.

Elizabeth Blackburn: Nobel prize in medicine 2009

Envejecimiento

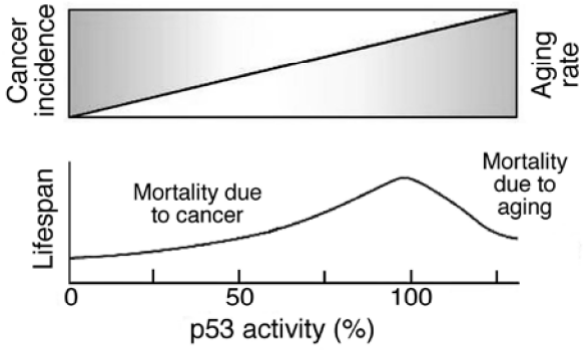


Fig. 5. Balancing cancer and aging. Adapted with permission from: Ferbeyre G, Lowe SW. The price of tumour suppression? Nature 2002; 415:26–27 (reference 201).

EL FIN

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