Apoptosis, necrosis and neurogenesis

Brain Tales

Anna Drabik

Homeostasis

The growth, development, and maintanence of multicellular organisms depend not only on the production of cells but also on mechanisms to destroy them

Cell life span

Only a few body parts last most of your lifetime

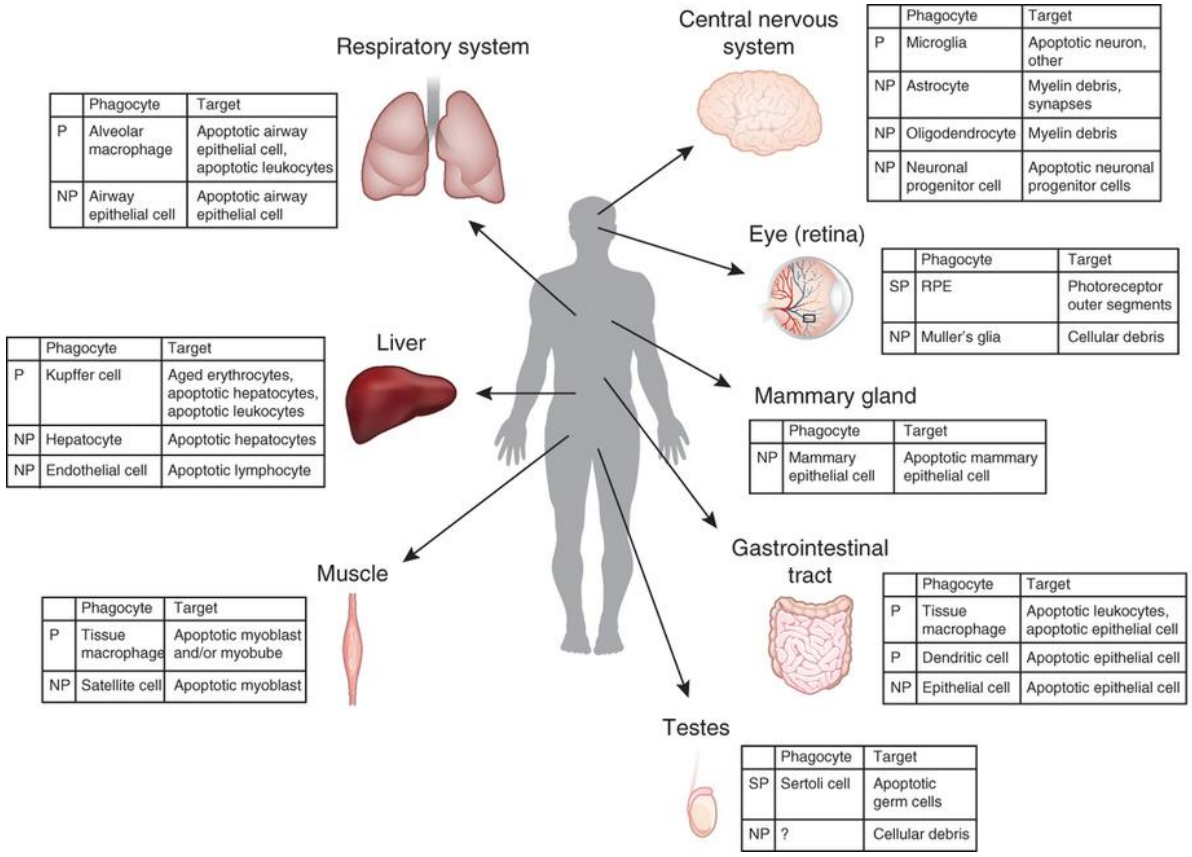
- neurons of the cerebral cortex
- inner lens cells of the eye
- muscle cells of the heart

Cells lining the acid filled stomach last only about 5 days.

The outer layer of skin is recycled about every two weeks.

An adult human liver replaces itself about once every year to year and a half.

The entire human skeleton is thought to be replaced every 10 years or so in adults.



	Phagocyte	Target
P	Alveolar macrophage	Apoptotic airway epithelial cell, apoptotic leukocytes
NP	Airway epithelial cell	Apoptotic airway epithelial cell

	Phagocyte	Target
P	Microglia	Apoptotic neuron, other
NP	Astrocyte	Myelin debris, synapses
NP	Oligodendrocyte	Myelin debris
NP	Neuronal progenitor cell	Apoptotic neuronal progenitor cells

	Phagocyte	Target
SP	RPE	Photoreceptor outer segments
NP	Muller's glia	Cellular debris

	Phagocyte	Target
P	Kupffer cell	Aged erythrocytes, apoptotic hepatocytes, apoptotic leukocytes
NP	Hepatocyte	Apoptotic hepatocytes
NP	Endothelial cell	Apoptotic lymphocyte

	Phagocyte	Target
NP	Mammary epithelial cell	Apoptotic mammary epithelial cell

	Phagocyte	Target
P	Tissue macrophage	Apoptotic myoblast and/or myobube
NP	Satellite cell	Apoptotic myoblast

	Phagocyte	Target
P	Tissue macrophage	Apoptotic leukocytes, apoptotic epithelial cell
P	Dendritic cell	Apoptotic epithelial cell
NP	Epithelial cell	Apoptotic epithelial cell

	Phagocyte	Target
SP	Sertoli cell	Apoptotic germ cells
NP	?	Cellular debris

Cell life span

Neutrophils can survive 3-4 days unless they digest bacteria. Then they die in about 12 hours.

Eosinophils live about 3 weeks.

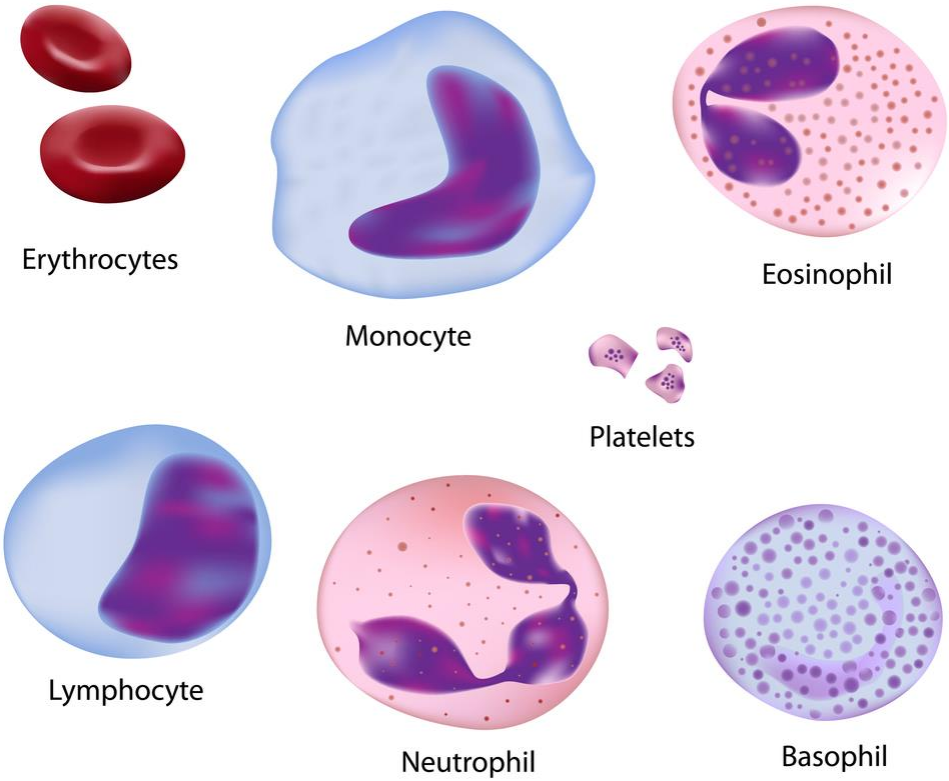
Basophils last about 3-10 days.

The life span of B lymphocytes that produce antibodies ranges from 4 days to 5 weeks.

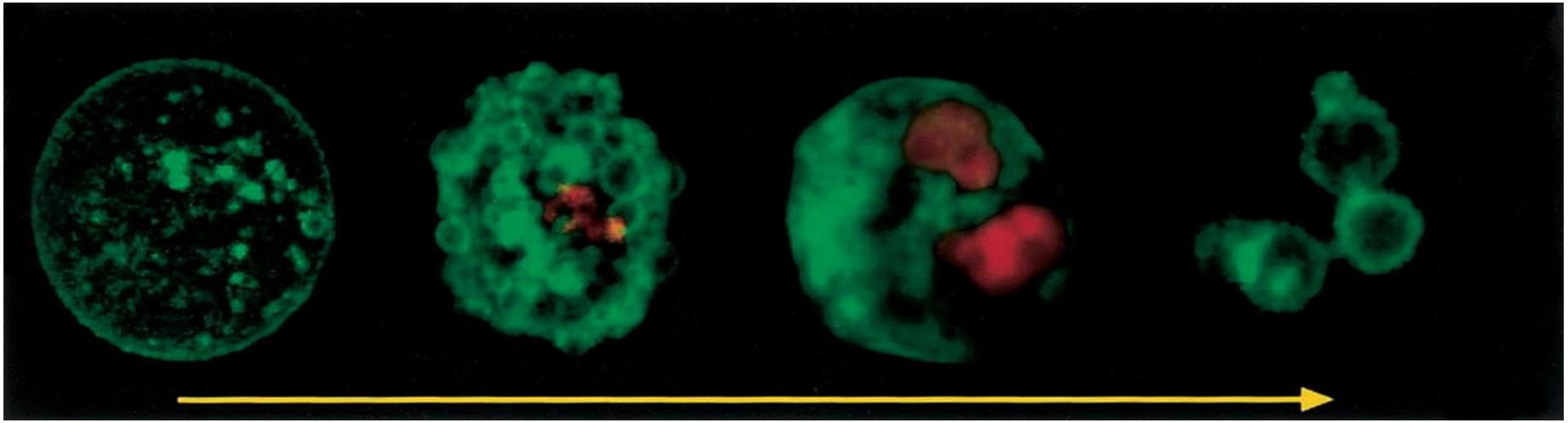
T lymphocytes can last either a day or two or for months depending upon their battle with foreign substances.

Monocytes and platelets interact in many settings such as inflammation and blood clotting and leave the circulation at random.

Erythrocytes, red blood cells, live 120 days.



Apoptosis



Programmed sequence of molecular events, in which the cell systematically destroys itself from whithin and is then eaten by other cells, leaving no trace

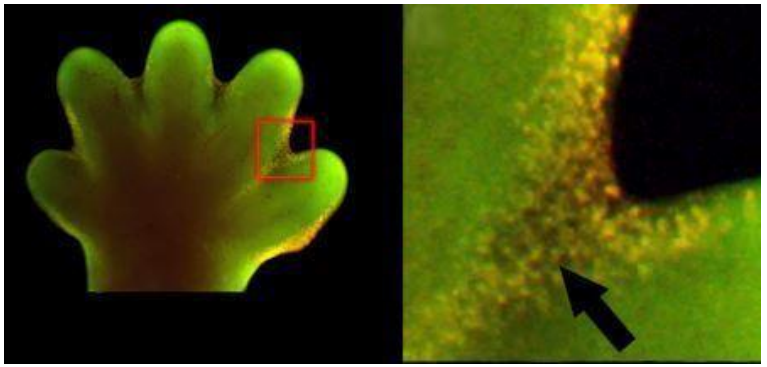
Apoptosis

- Cell die when they become damaged or infected
- They are removed before they threaten the health of the organism
- Undergo characteristic morphological changes (shrink, condense, cytoskeleton collapses)
- Neatly, rapidly cleared away
- Underestimated its extent

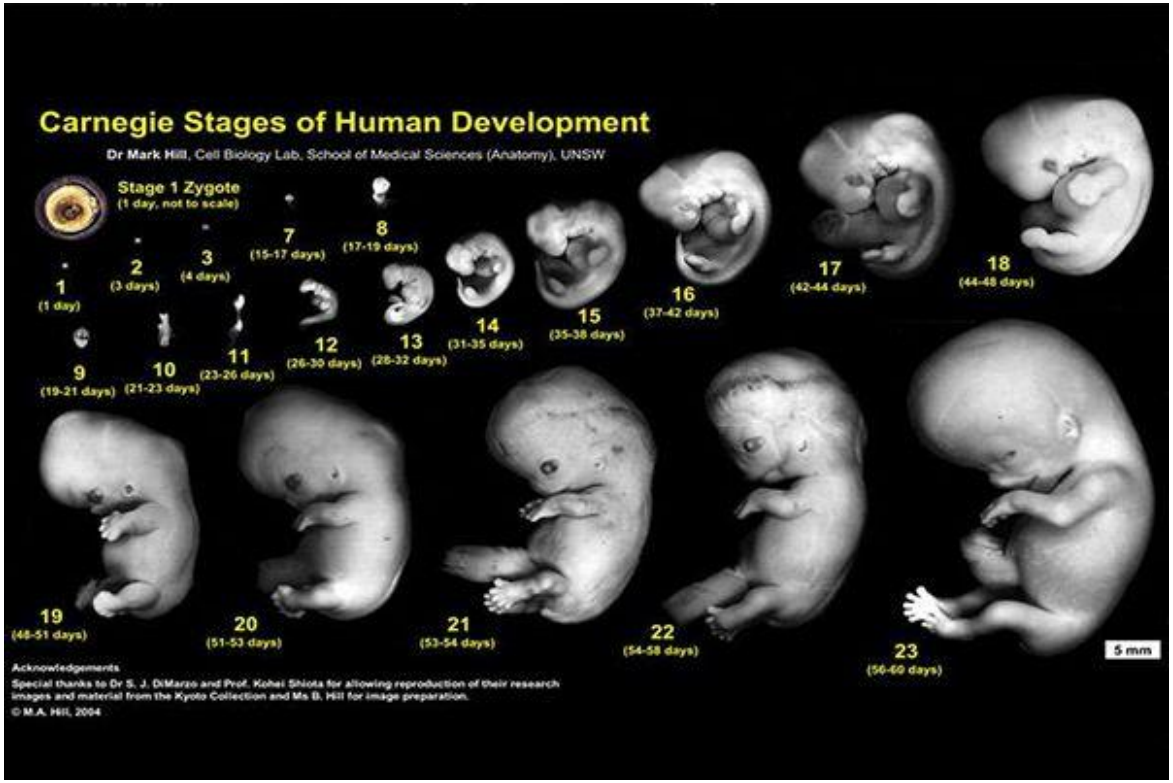
Apoptosis

Reasons of massive cell death?

- helps sculpt hands and feet during embryonic development
- no longer needed parts (tadpole-frog metamorphosis)
- quality control in development eliminating cells (misplaced, nonfunctional, potentially dnagerous; lymphocytes after destroy the microbes)



Apoptosis



Programmed cell death is a normal and necessary event of normal development.

During the development of the vertebrate nervous system, for example, ~50% of the neurons born die as part of the rewiring process.

The disappearance of the tadpole tail during metamorphosis and the formation of the fingers of the hand are classic examples of apoptotic processes.

Apoptosis

- Normal cells live on the edge, ready to kill itself in response to specific sets of signals.
- Cells can enter apoptosis as part of normal development or in response to viral infection, cellular stress, or DNA damage.
- The proteins that mediate the cell death response are also involved in destroying aberrant cells, such as cancer cells.
- Essentially all cancers accumulate mutations that inactivate their cell death pathway.
- This enables the cancer cell to replicate with increasingly aberrant DNA; in the presence of an intact apoptotic pathway such a cell would die apoptotically.
- Apoptotically dying cells activate a set of degradative enzymes, the caspases, that mediate the controlled disassembly and degradation of the cell.

– **Cancer cells**
  - Radiation and chemicals used in cancer therapy induce apoptosis in some types of cancer cells.

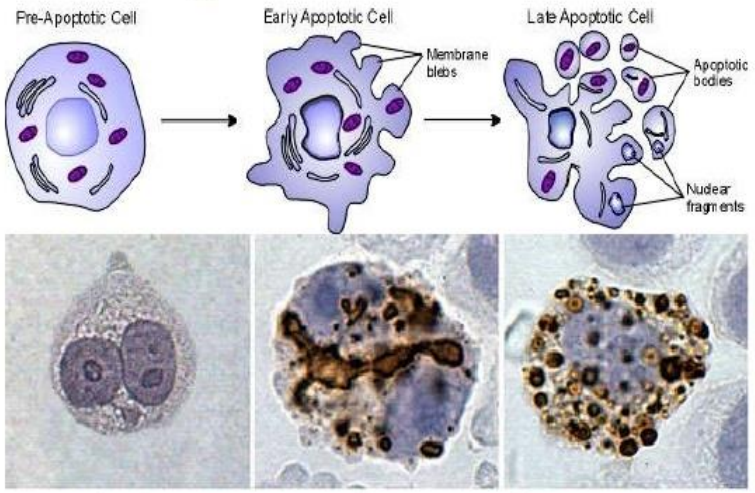
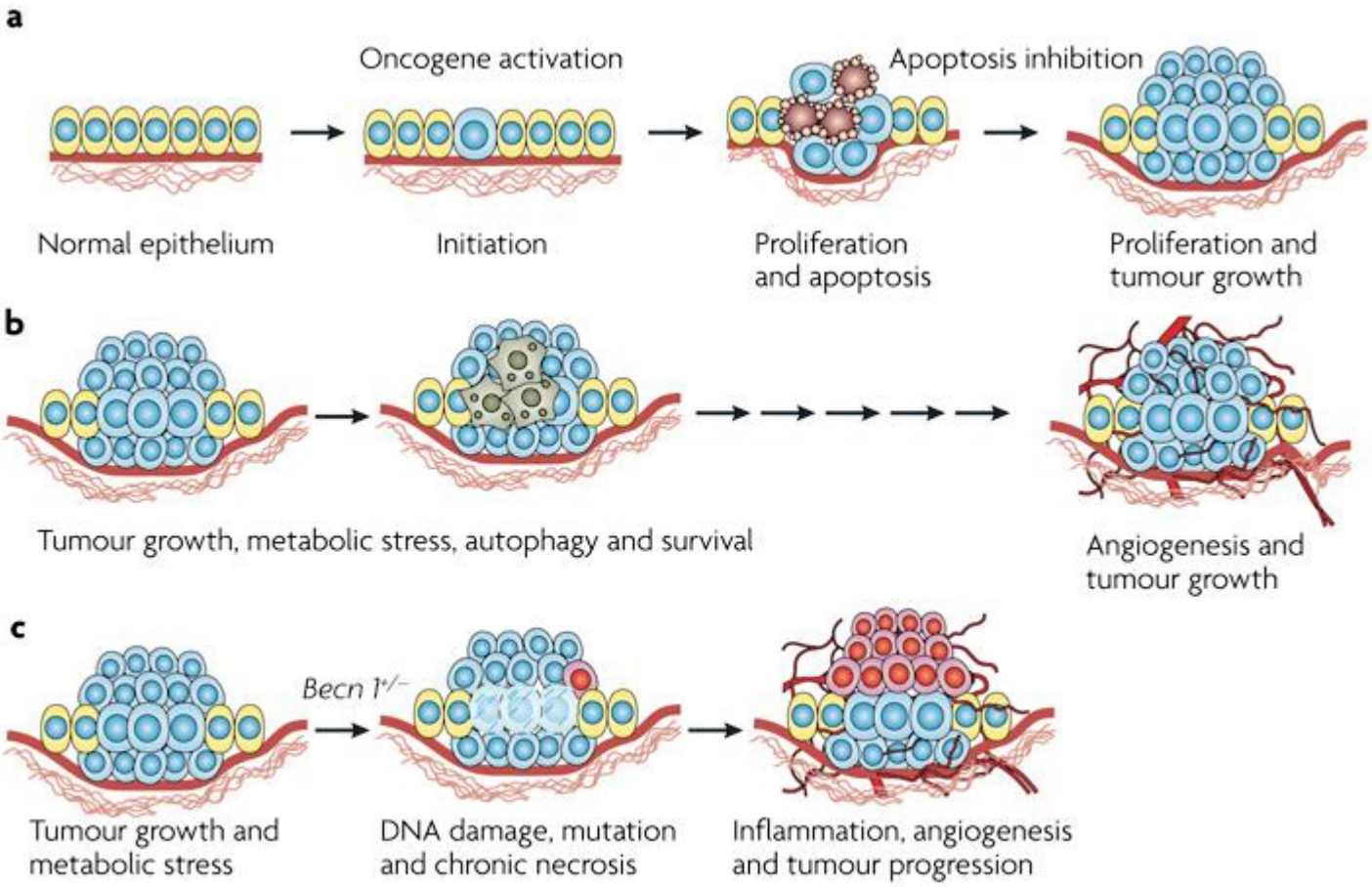
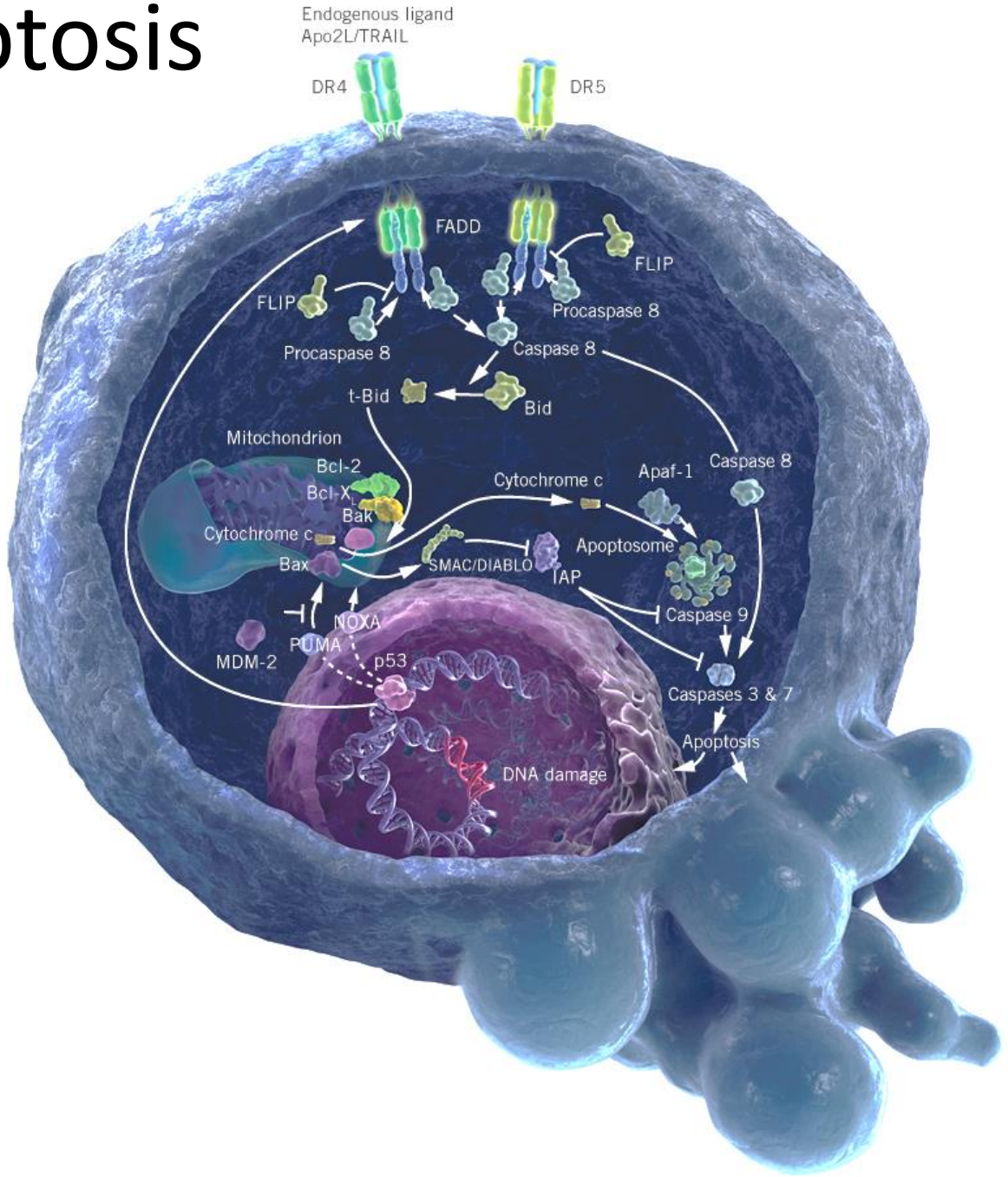


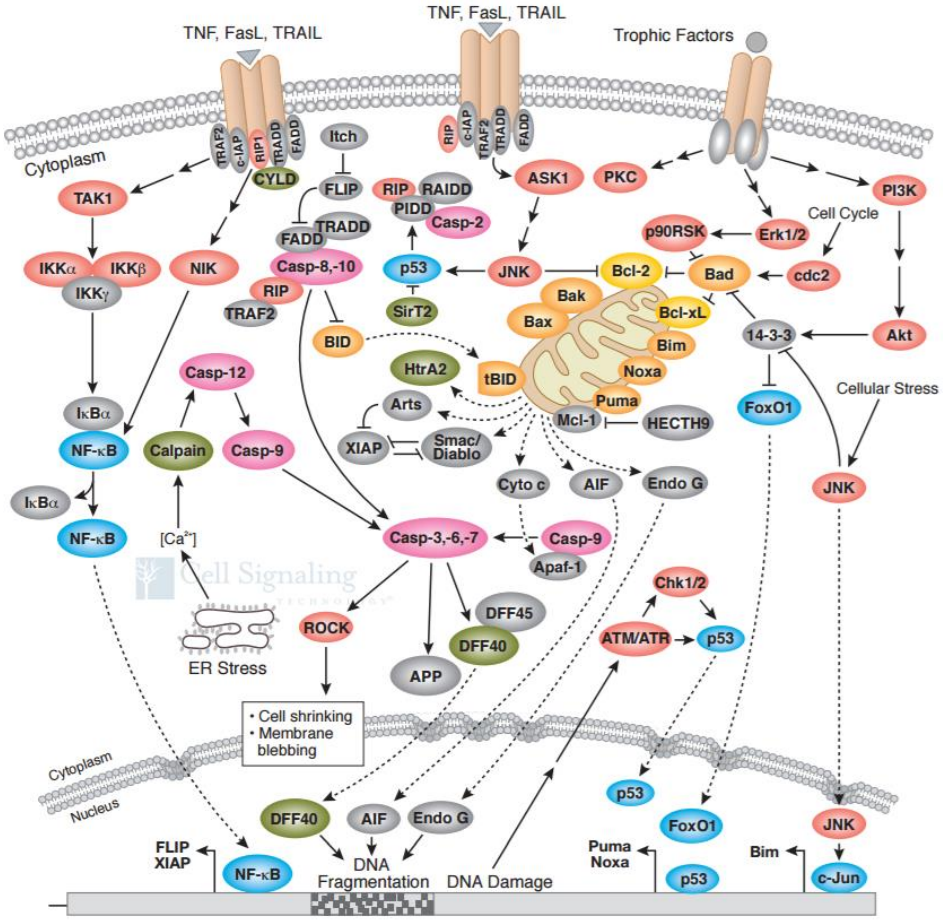
Fig. 1: SC-1 induced apoptosis in stomach carcinoma cells
Left: Before induction
Middle: 24h after induction
Right: 48h after induction


a
Oncogene activation
Apoptosis inhibition
Normal epithelium
Initiation
Proliferation and apoptosis
Proliferation and tumour growth
b
Tumour growth, metabolic stress, autophagy and survival
Angiogenesis and tumour growth
c
Becn 1+/−
Tumour growth and metabolic stress
DNA damage, mutation and chronic necrosis
Inflammation, angiogenesis and tumour progression

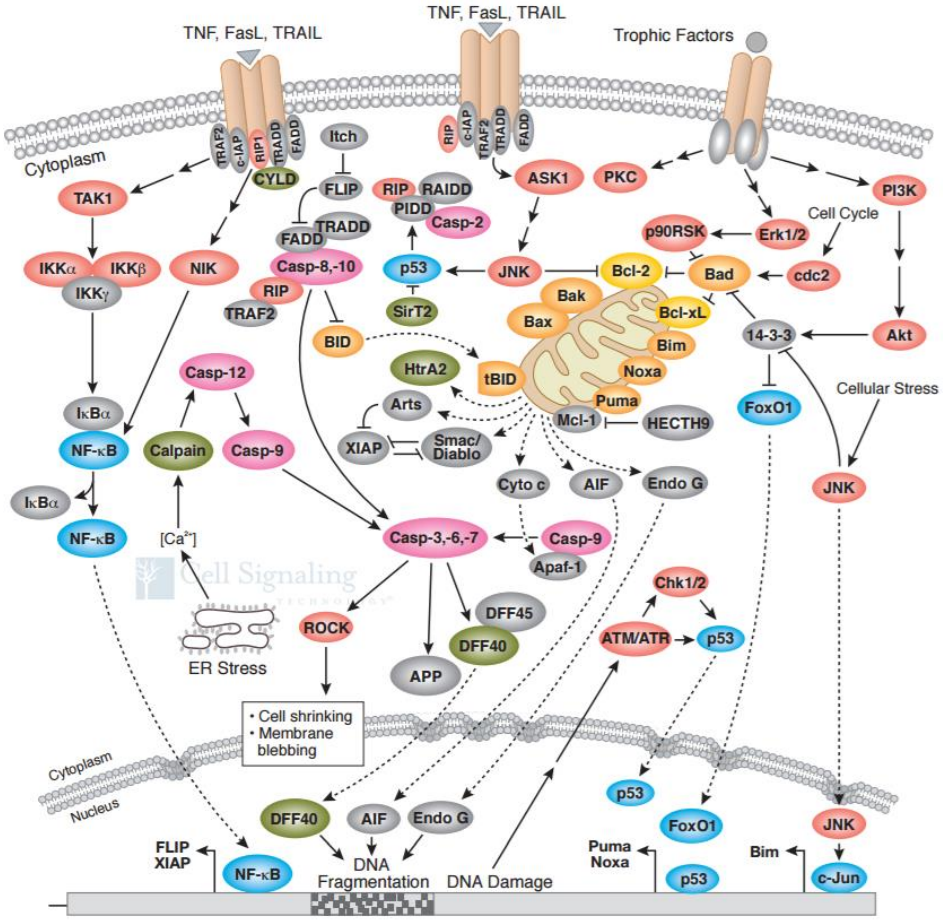
Apoptosis

- Death receptors
- Tumor necrosis factors
- Initiator caspases
- Executioner caspases
- Fas activation
- FLIP dimerization
- Cyt C; Apoptotic protease activating factor -1 (apoptosome)
- Bcl2 balance (conservative)
- Tumor suppressor p53
- Inhibitors of apoptosis IAP
- Phosphatydylserine

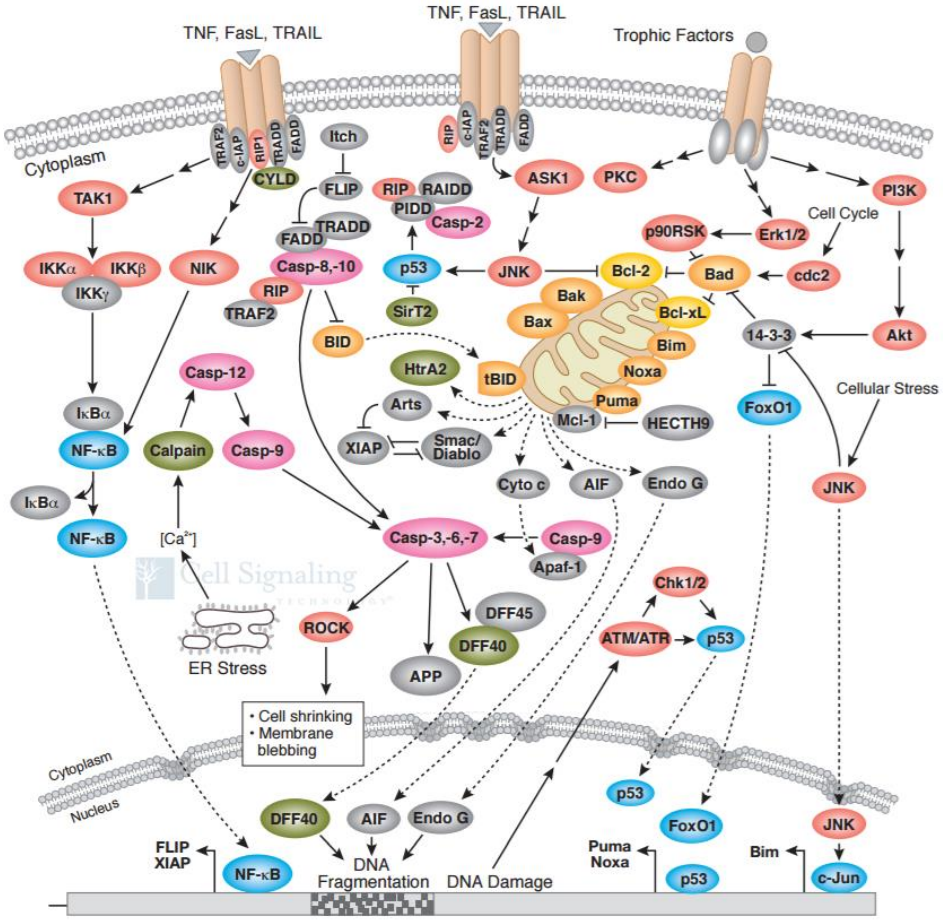




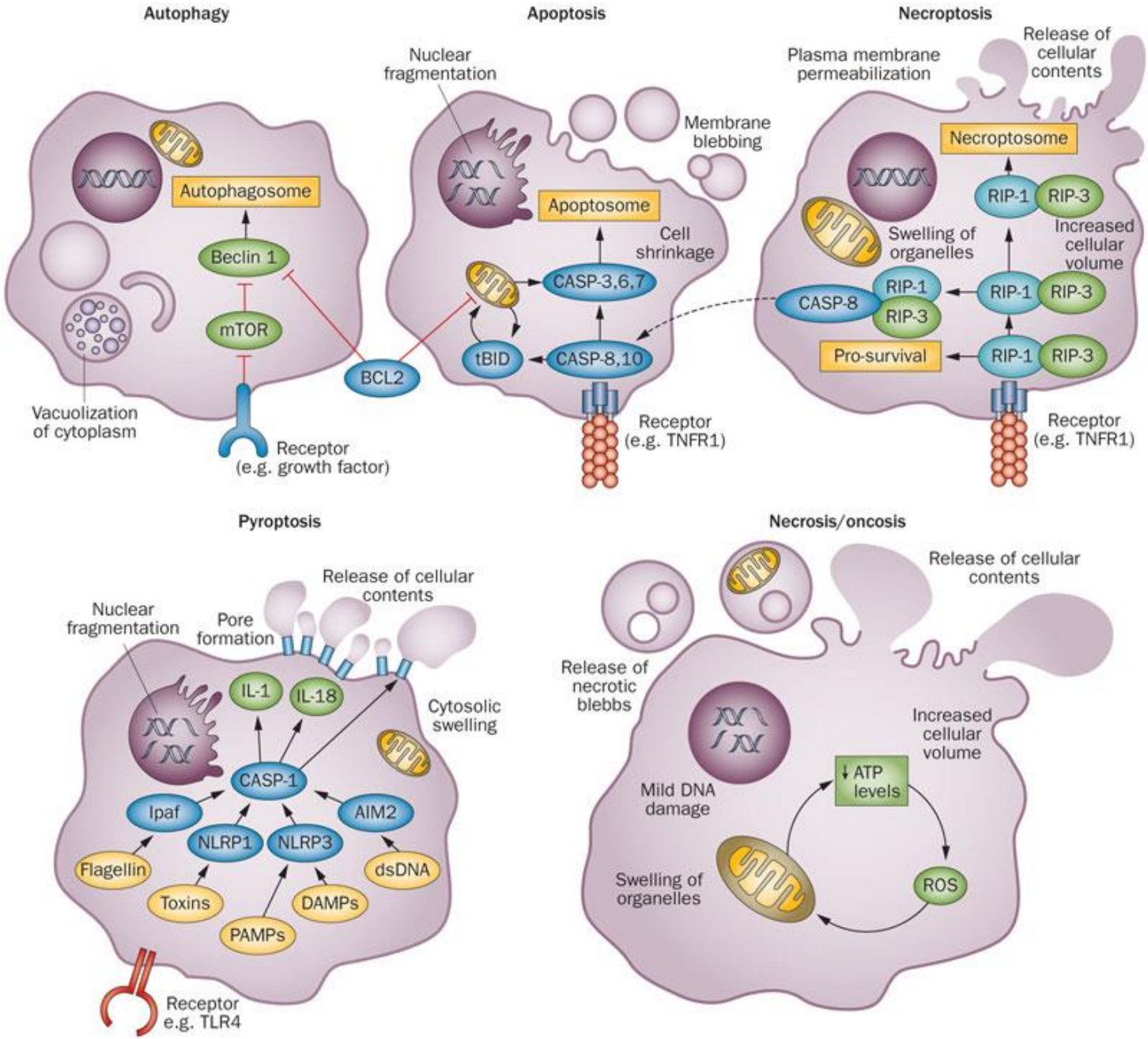
Caspases, a family of cysteine proteases, are the central regulators of apoptosis. Initiator caspases (including caspase-2, -8, -9, -10, -11, and -12) are closely coupled to pro-apoptotic signals. Once activated, these caspases cleave and activate downstream effector caspases (including caspase-3, -6, and -7), which in turn execute apoptosis by cleaving cellular proteins following specific Asp residues. Activation of Fas and TNFR by FasL and TNF, respectively, leads to the activation of caspase-8 and -10.



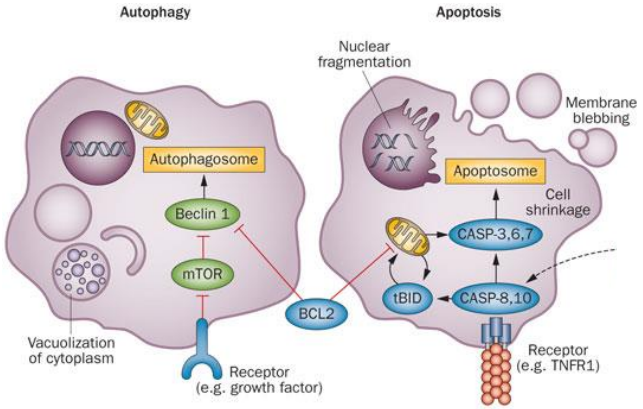
DNA damage induces the expression of PIDD, which binds to RAIDD and caspase-2 and leads to the activation of caspase-2. Cytochrome c released from damaged mitochondria is coupled to the activation of caspase-9. XIAP inhibits caspase-3, -7, and -9. Mitochondria release multiple pro-apoptotic molecules, such as Smac/Diablo, AIF, HtrA2, and Endo G, in addition to cytochrome c. Smac/Diablo binds to XIAP, preventing it from inhibiting caspases. Caspase-11 is induced and activated by pathological pro-inflammatory and pro-apoptotic stimuli and leads to the activation of caspase-1, thereby promoting inflammatory response and apoptosis by directly processing caspase-3.



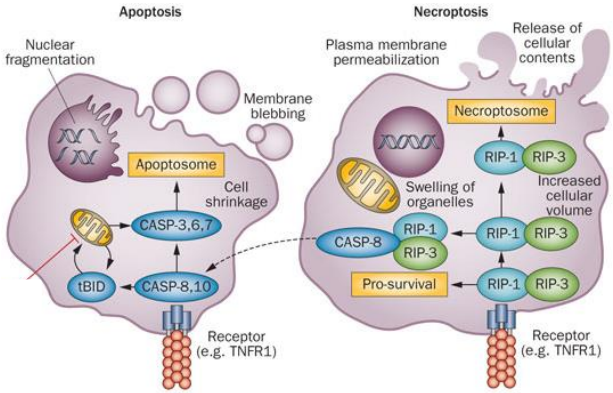
Caspase-12 and caspase-7 are activated under ER stress conditions. Anti-apoptotic ligands, including growth factors and cytokines, activate Akt and p90RSK. Akt inhibits Bad by direct phosphorylation and prevents the expression of Bim by phosphorylating and inhibiting the Forkhead family of transcription factors (FoxO). FoxO promotes apoptosis by upregulating pro-apoptotic molecules such as FasL and Bim.


Autophagy
Autophagosome
Beclin 1
mTOR
Vacuolization of cytoplasm
Receptor (e.g. growth factor)
BCL2
Apoptosis
Nuclear fragmentation
Membrane blebbing
Apoptosome
Cell shrinkage
CASP-3,6,7
tBID
CASP-8,10
Receptor (e.g. TNFR1)
Necroptosis
Plasma membrane permeabilization
Release of cellular contents
Necroptosome
RIP-1
RIP-3
Swelling of organelles
Increased cellular volume
CASP-8
Pro-survival
Receptor (e.g. TNFR1)
Pyroptosis
Release of cellular contents
Nuclear fragmentation
Pore formation
IL-1
IL-18
Cytosolic swelling
CASP-1
Ipaf
AIM2
NLRP1
NLRP3
Flagellin
dsDNA
Toxins
DAMPs
PAMPs
Receptor e.g. TLR4
Necrosis/oncosis
Release of cellular contents
Release of necrotic blebbs
Increased cellular volume
Mild DNA damage
↓ ATP levels
Swelling of organelles
ROS

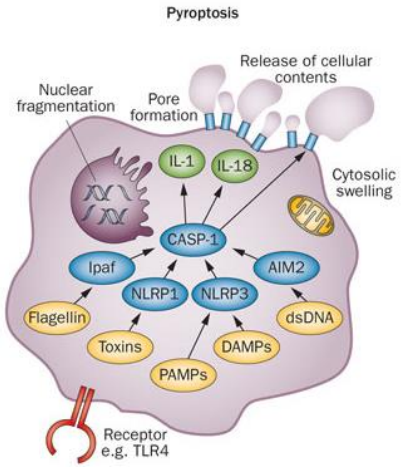
- Autophagocitosis; destructive mechanism that disassembles unnecesary or disfunctional cellular components



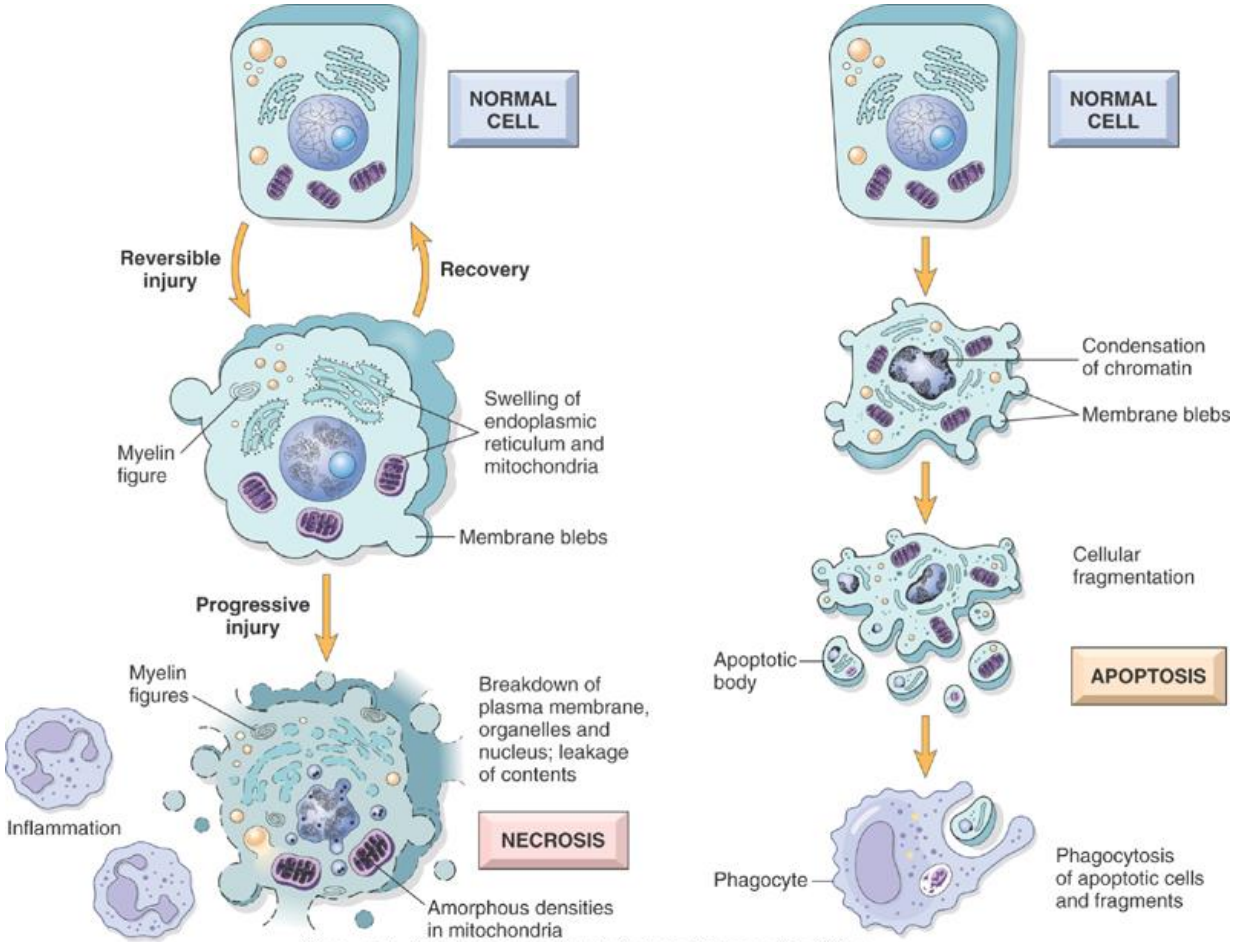
- Necroptosis; programmed cell death that is triggered by a specific regulatory signal from other cells



- Pyroptosis; programmed cell death associated with antimicrobial responses during inflammation



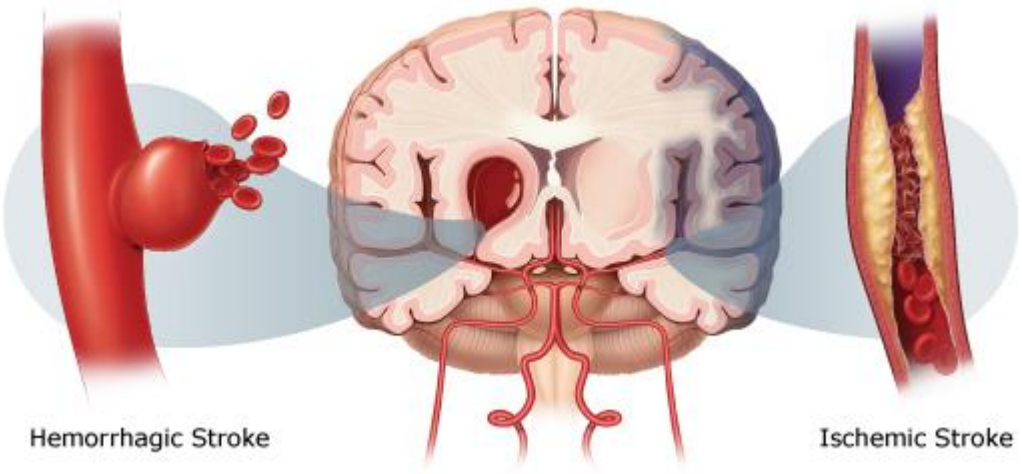
Necrosis



Cells die in response to an acute insult, such as trauma or a lack of blood supply.

Necrotic cell swell and burst, spilling their contents over their neighbors and eliciting the inflammatory response.

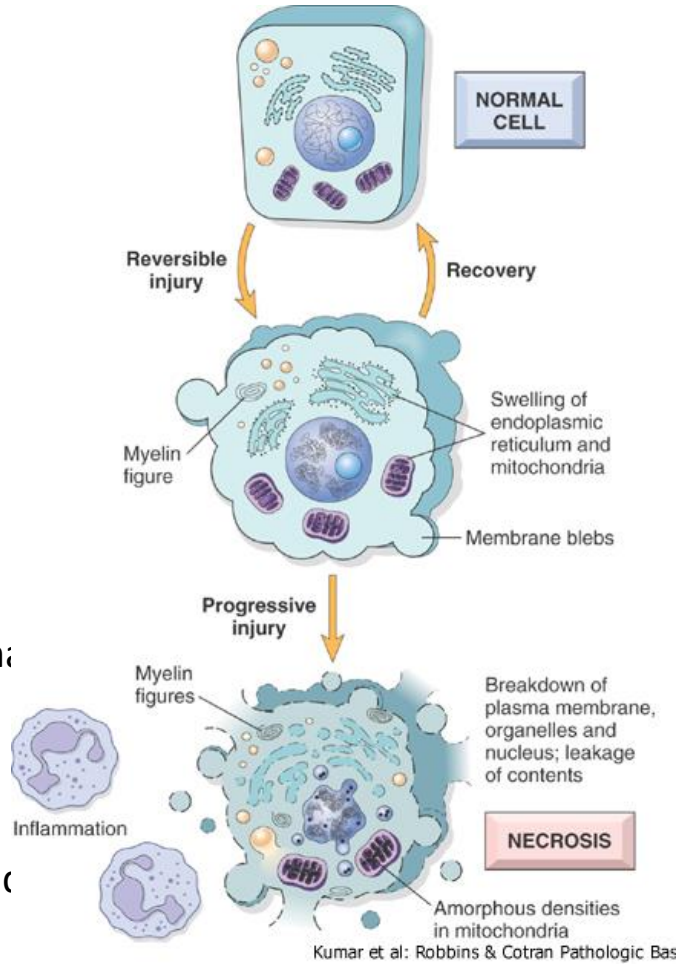
Necrosis



- Death due to unexpected and accidental cell damage.
- A number of toxic chemical or physical events can cause necrosis: toxins, radiation, heat, trauma, lack of oxygen due the blockage of blood flow, etc.
- Physical or chemical insults can lead to the lethal disruption of cell structure and activity.

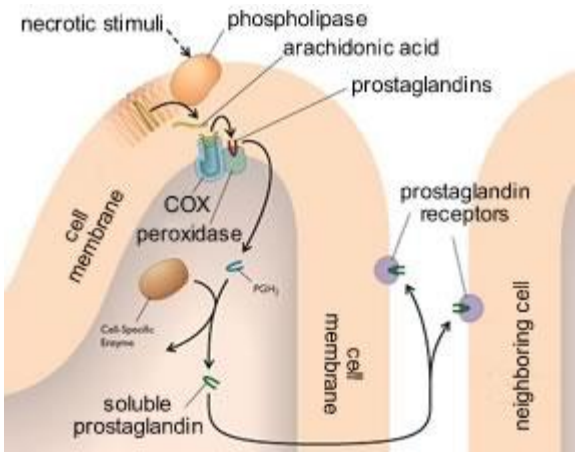
Necrosis

- As necrotic cells begin to die, they swell – holes appear in the plasma membrane and intracellular materials spill out into the surrounding environment.
- An important side-effect of these changes is the loss of the ability to regulate the intracellular environment.
- The normal intracellular concentration of Ca2+ is generally less that 10-7 M.
- The concentration of Ca2+ outside the cell is generally much higher, on the order of 10-3 M. There are also high levels of Ca2+ sequestered within mitochondria and other intracellular compartments.
- The low concentration of intracellular Ca2+ requires energy to maintain - Ca2+ must be pumped out of the cytoplasm.
- As the cell dies, its ability to maintain the integrity of the plasma membrane and to pump ions is lost.
- Ca2+ acts as an allosteric effector of many proteins, drastically altering their activity.
- Unregulated Ca2+ induces the generation of toxic chemicals and activates enzymes that lead to the degradation of cellular molecules.
- As the cell is disassembled, various breakdown products are produced and released into the neighborhood.



Necrosis/ Inflammation

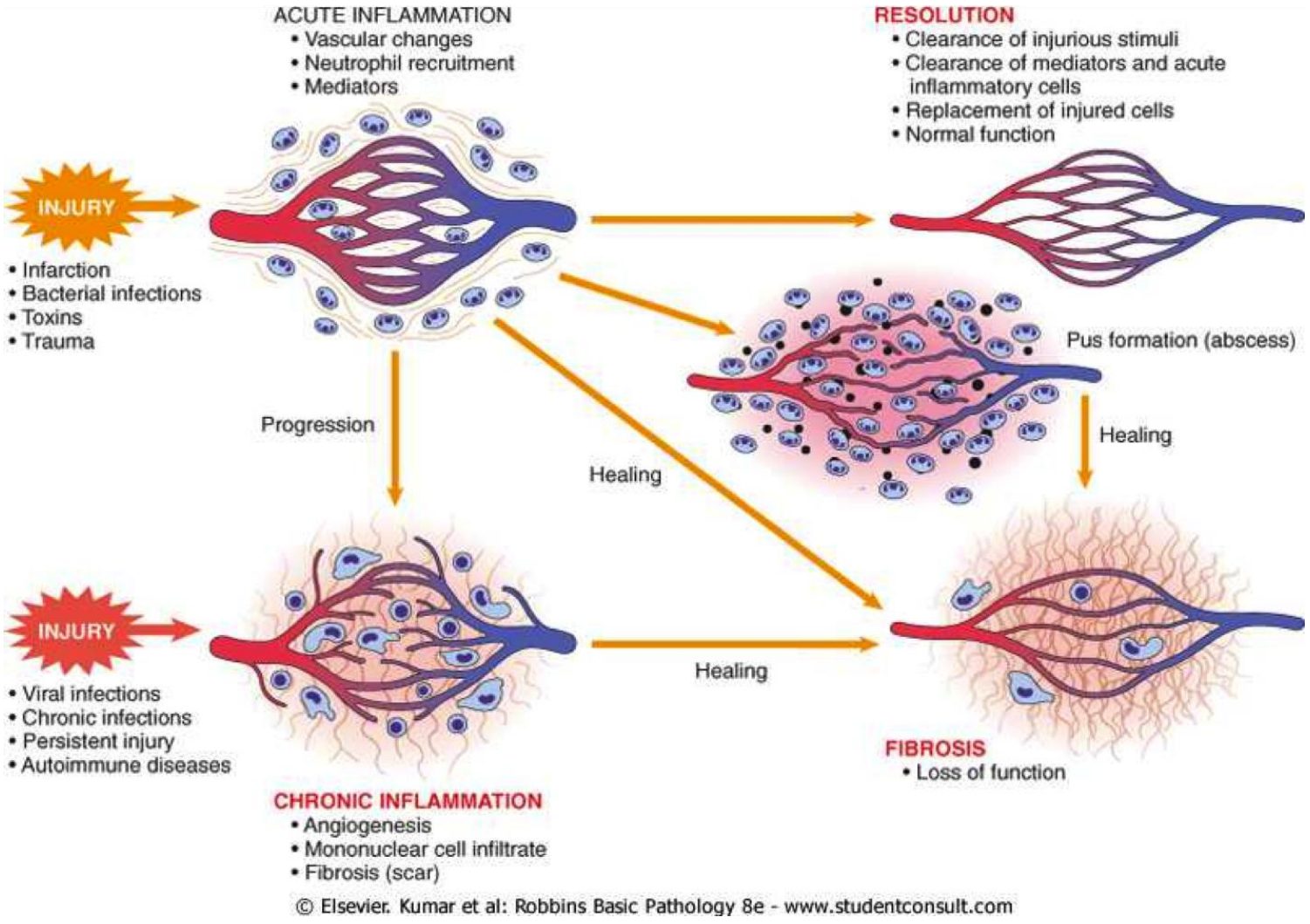
- The presence of Free Fatty Acids molecules is interpreted by neighboring cells as a sign of tissue damage. They react to defend themselves.
- The FFAs generated by damaged and dying cells are themselves substrates for enzymes, in particular the cyclooxygenases.
- These enzymes transform FFAs into prostaglandins and other molecules, known collectively as eicosanoids, which mediate inflammatory responses.
- A number of conditions are characterized by chronic inflammation, for example rheumatoid arthritis.
- Aspirin and aspirin-derivatives preferentially inhibit COX1; other drugs, such as indomethacin and rofecoxib (vioxx) are specific for COX2.



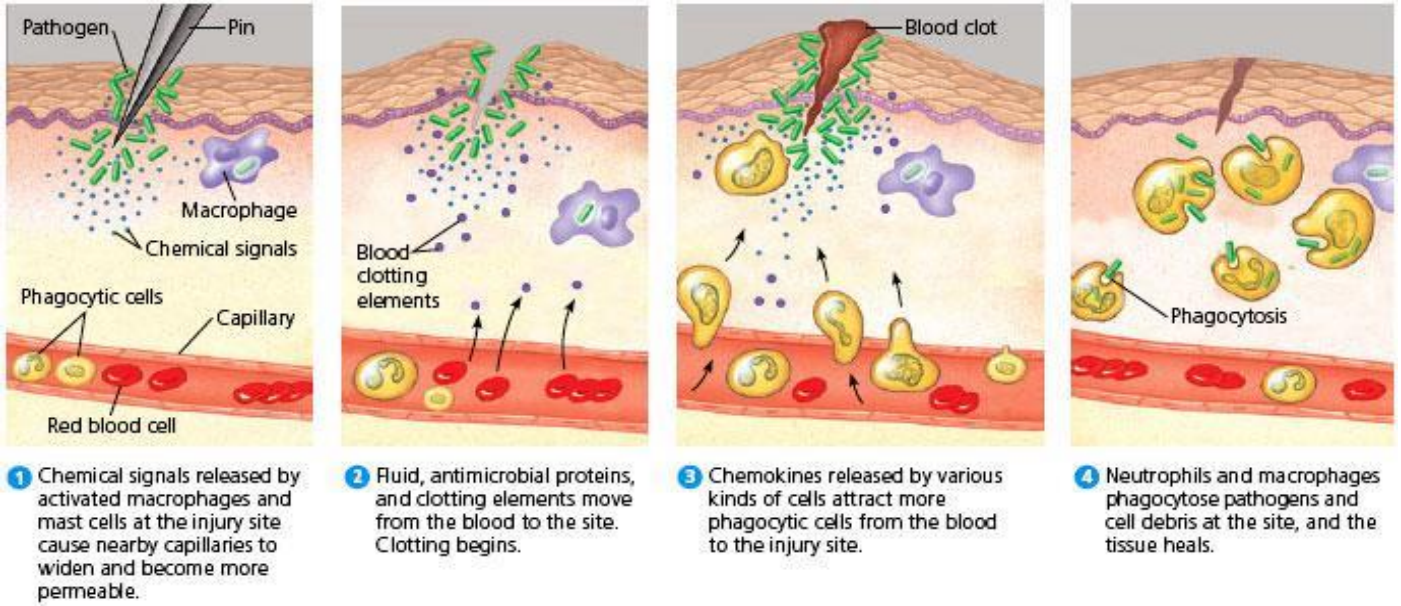
Inflammation

- Inflammation is part of the body's immune response.
- Acute inflammation - starts rapidly (rapid onset) and quickly becomes severe.
- Chronic inflammation - this means long-term inflammation, which can last for several months and even years.
- Our infections, wounds and any damage to tissue would never heal without inflammation - tissue would become more and more damaged and the body, or any organism, would eventually perish.
- Chronic inflammation can eventually cause several diseases and conditions, including some cancers, rheumatoid arthritis, atherosclerosis, periodontitis, and hay fever.

Inflammation

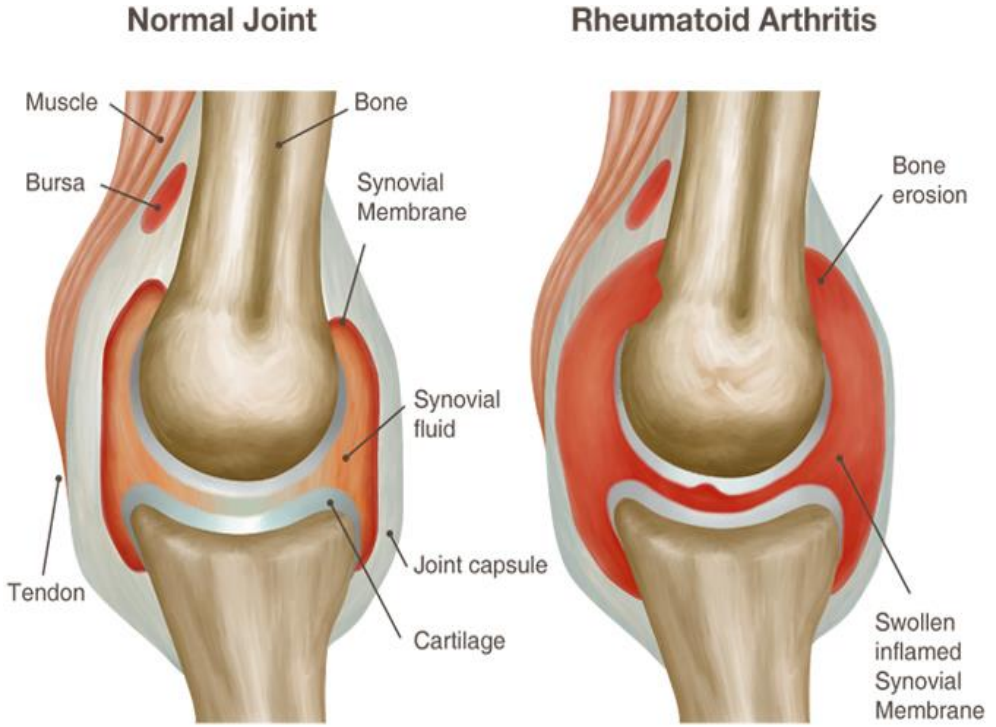


Acute Inflammation



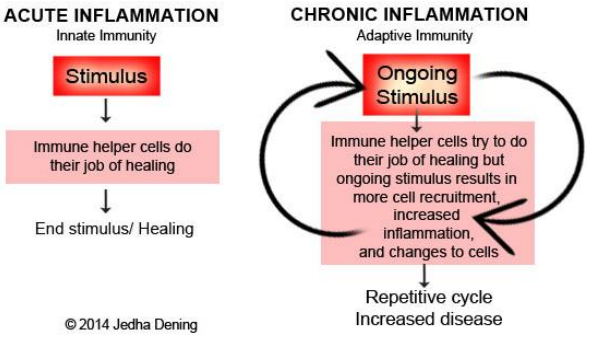
- Starts rapidly (rapid onset) and quickly becomes severe. Signs and symptoms are only present for a few days, but in some cases may persist for a few weeks.
- Examples of diseases, conditions, and situations which can result in acute inflammation include:
- Acute bronchitis
- Sore throat from a cold or flu
- A scratch/cut on the skin

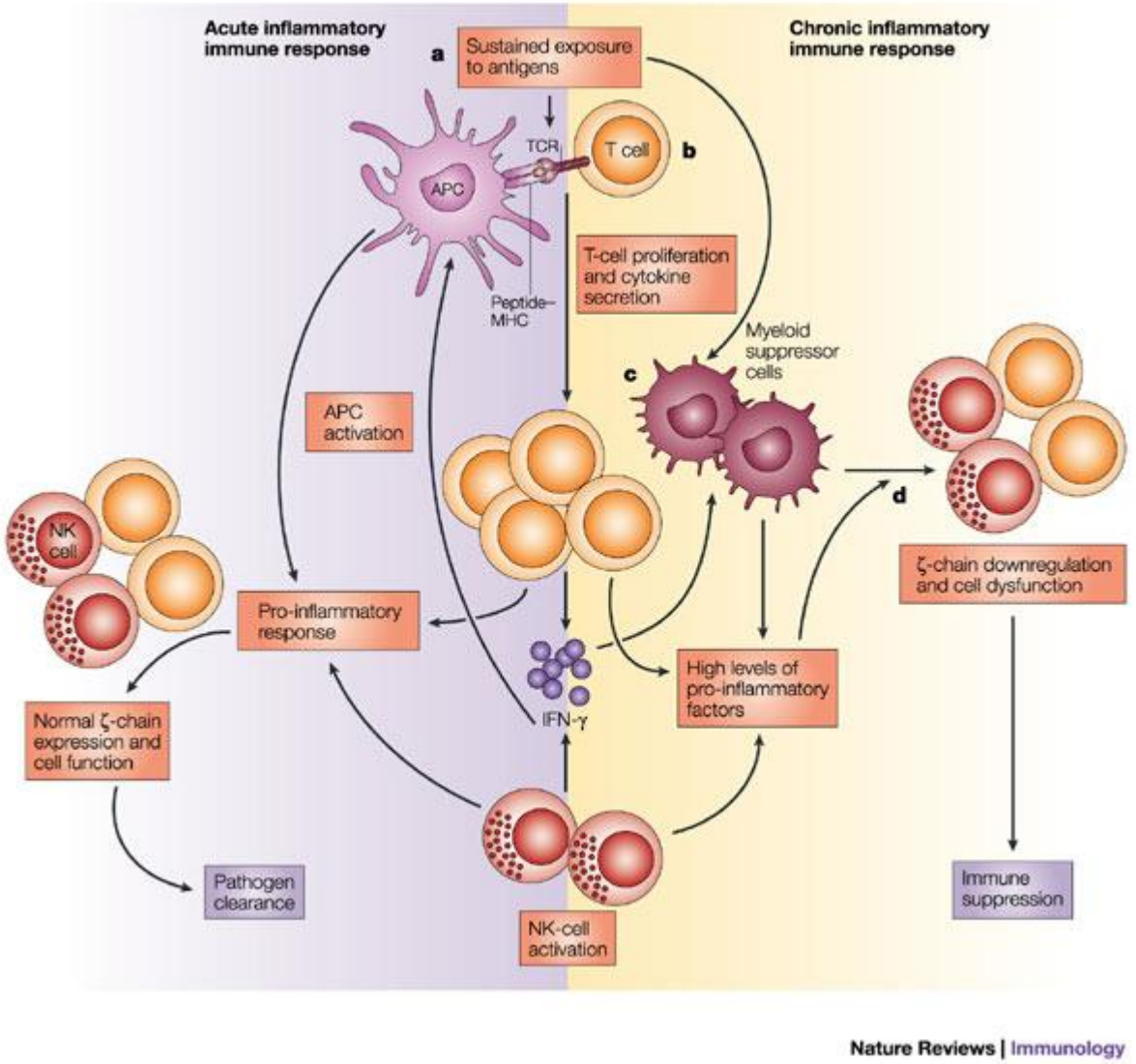
Chronic Inflammation



- Long-term inflammation, which can last for several months and even years.
- Failure to eliminate whatever was causing an acute inflammation
- An autoimmune response to a self antigen - the immune system attacks healthy tissue, mistaking it (them) for harmful pathogens
- A chronic irritant of low intensity that persists.

Inflammation





Foods For Arthritis & Inflammatory Pain

Cherries
Contain anthocyanocides which help lower uric acids levels reducing pain

Ginger
Ginger contains gingerols which are potent anti-inflammatory compounds.
Eat more fresh ginger, or drink ginger root tea.

Pineapple
Contains Bromelain which is an effective anti-inflammatory

Tumeric
Contain cucumin which is an anti-oxidant & anti-inflammatory.

Raw Apple Cider Vinegar
Contains helpful anti-inflammatory properties.
1 Tbsp in 6-8 ounces of water, or use as part of a salad dressing.

Omega 3's
Contain anthocyanocides which help lower uric acids levels reducing pain. Eat more chia, fish, hemp, and flax seeds.

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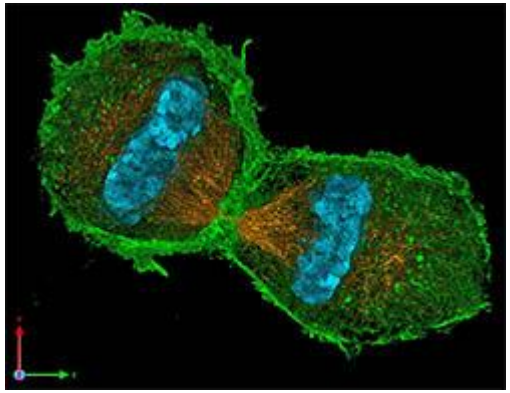
* *Avoid * *

Sugar Foods
Leads to increased AGES (toxins causing inflammation), which results in more aches and pains

Omega 6 oils
High intake of omega 6 increases inflammation in the body. Replace foods containing omega -6s with healthier omega 3 foods.

Fried Foods
Overcooked food or foods cooked at high temperatures incite the inflammatory response because they create AGES

Salt
For some people excess sodium consumption can inflame the joints. Less salt may help arthritis symptoms.

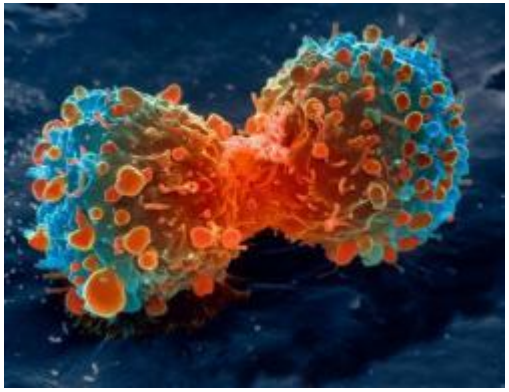


Cell division

Cells divide for many reasons:

- cells divide to replace old, dead, or damaged cells
- divide so living things can grow

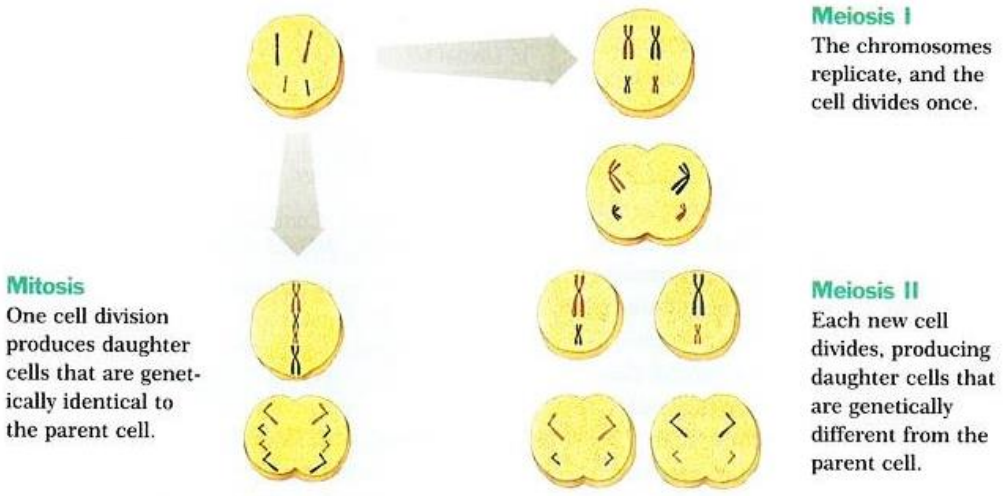
In human bodies, nearly two trillion cells divide every day



Cell division

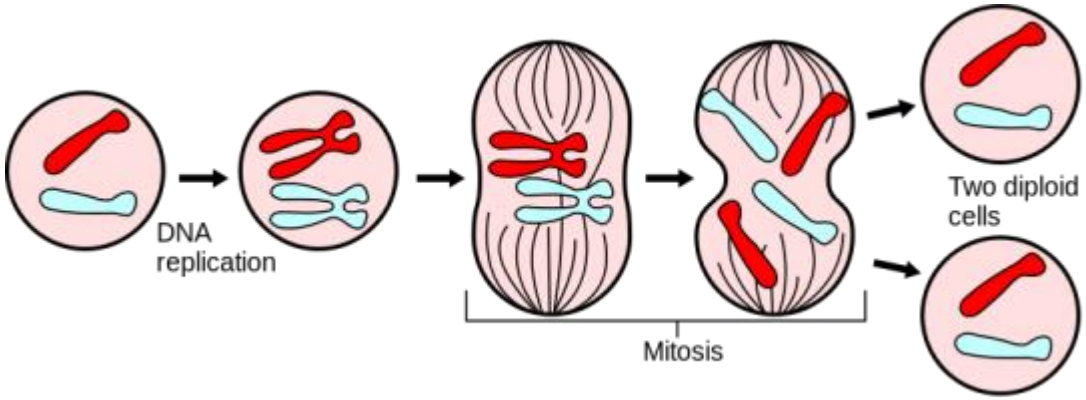
Depending on the type of cell, there are two ways cells divide mitosis and meiosis.

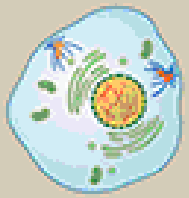
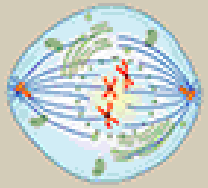
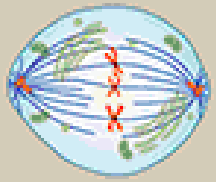
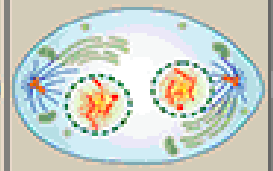
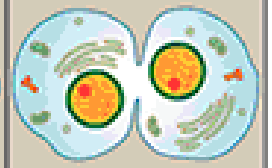
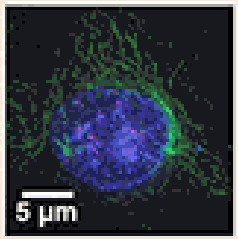
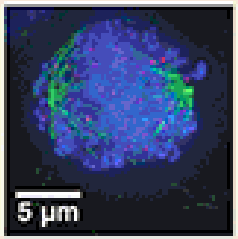
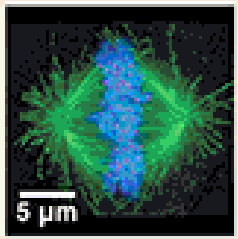
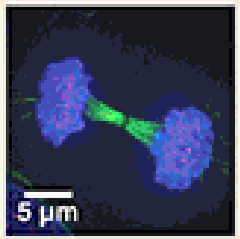
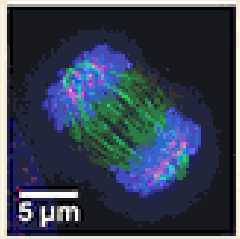
Mitosis is a single cell divides into two cells that are replicas of each other and have the same number of chromosomes. This type of cell division is good for basic growth, repair, and maintenance.



Meiosis a cell divides into two cells that have half the number of chromosomes. Reducing the number of chromosomes by half is important for sexual reproduction and provides for genetic diversity.

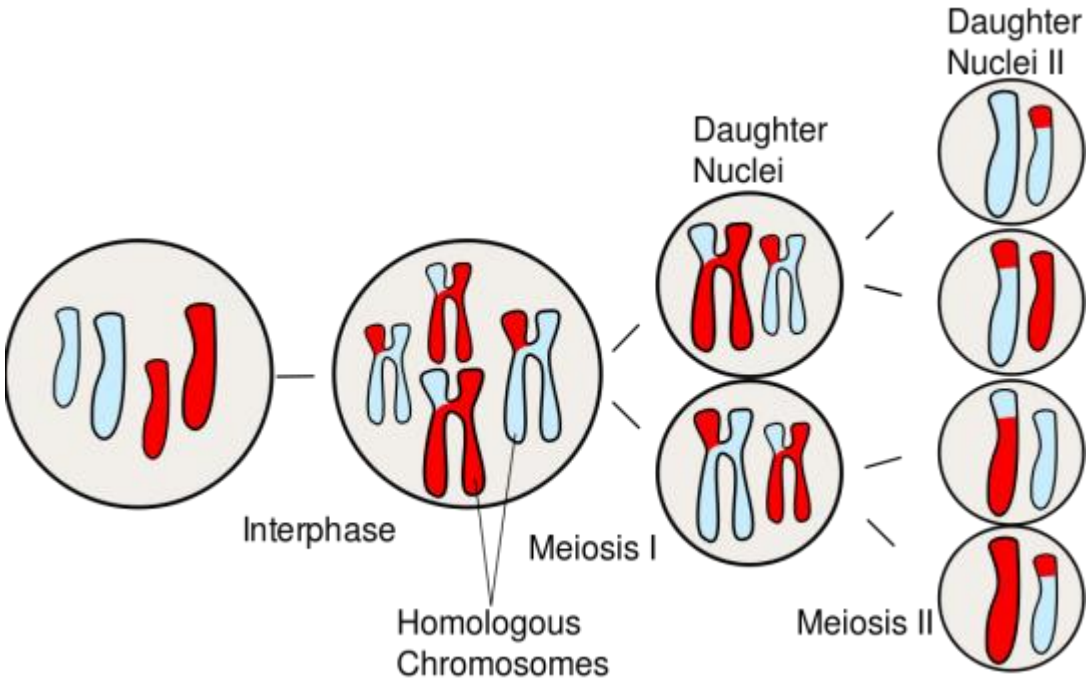
Mitosis



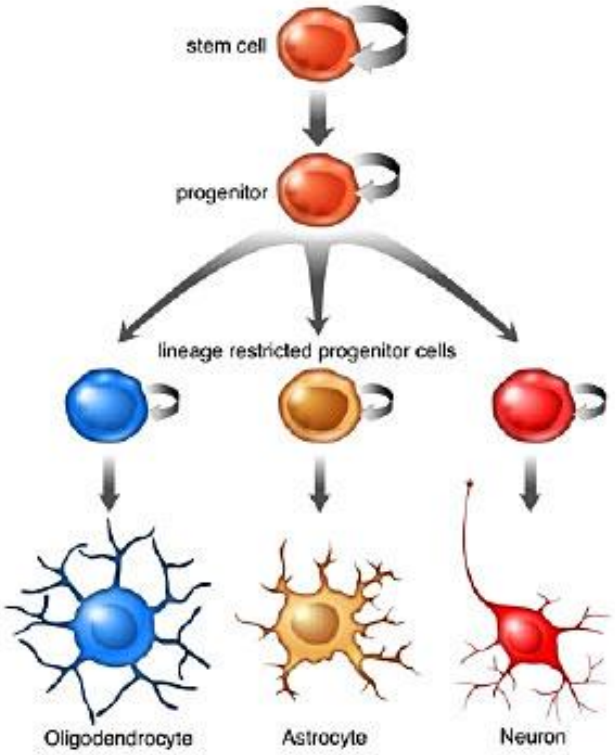
Prophase	Prometaphase	Metaphase	Anaphase	Telophase	Cytokinesis
					
• Chromosomes condense and become visible • Spindle fibers emerge from the centrosomes • Nuclear envelope breaks down • Centrosomes move toward opposite poles	• Chromosomes continue to condense • Kinetochores appear at the centromeres • Mitotic spindle microtubules attach to kinetochores	• Chromosomes are lined up at the metaphase plate • Each sister chromatid is attached to a spindle fiber originating from opposite poles	• Centromeres split in two • Sister chromatids (now called chromosomes) are pulled toward opposite poles • Certain spindle fibers begin to elongate the cell	• Chromosomes arrive at opposite poles and begin to decondense • Nuclear envelope material surrounds each set of chromosomes • The mitotic spindle breaks down • Spindle fibers continue to push poles apart	• Animal cells: a cleavage furrow separates the daughter cells • Plant cells: a cell plate, the precursor to a new cell wall, separates the daughter cells
					

MITOSIS

Meiosis

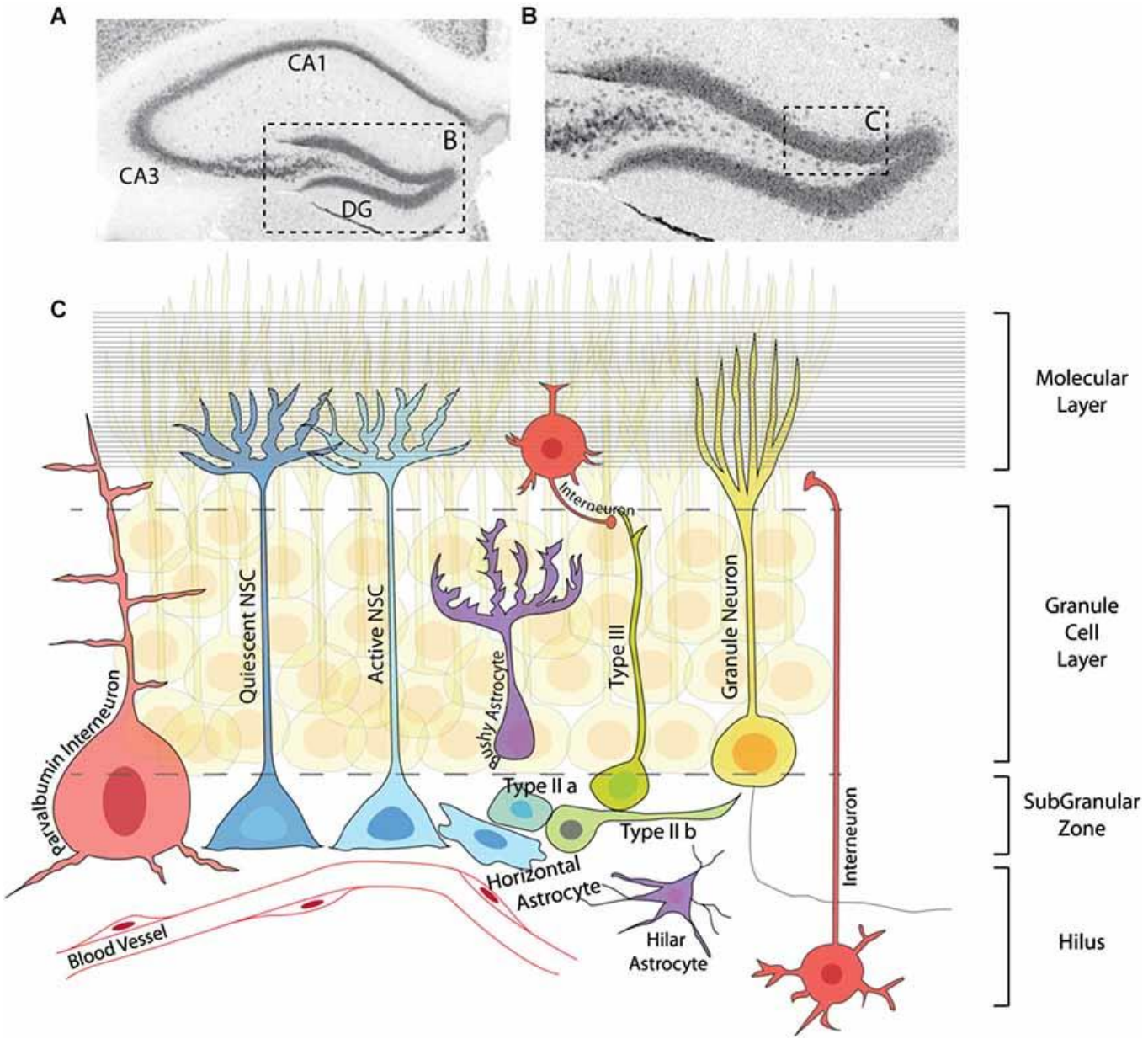

Daughter
Nuclei II
Daughter
Nuclei
Interphase
Meiosis I
Homologous
Chromosomes
Meiosis II

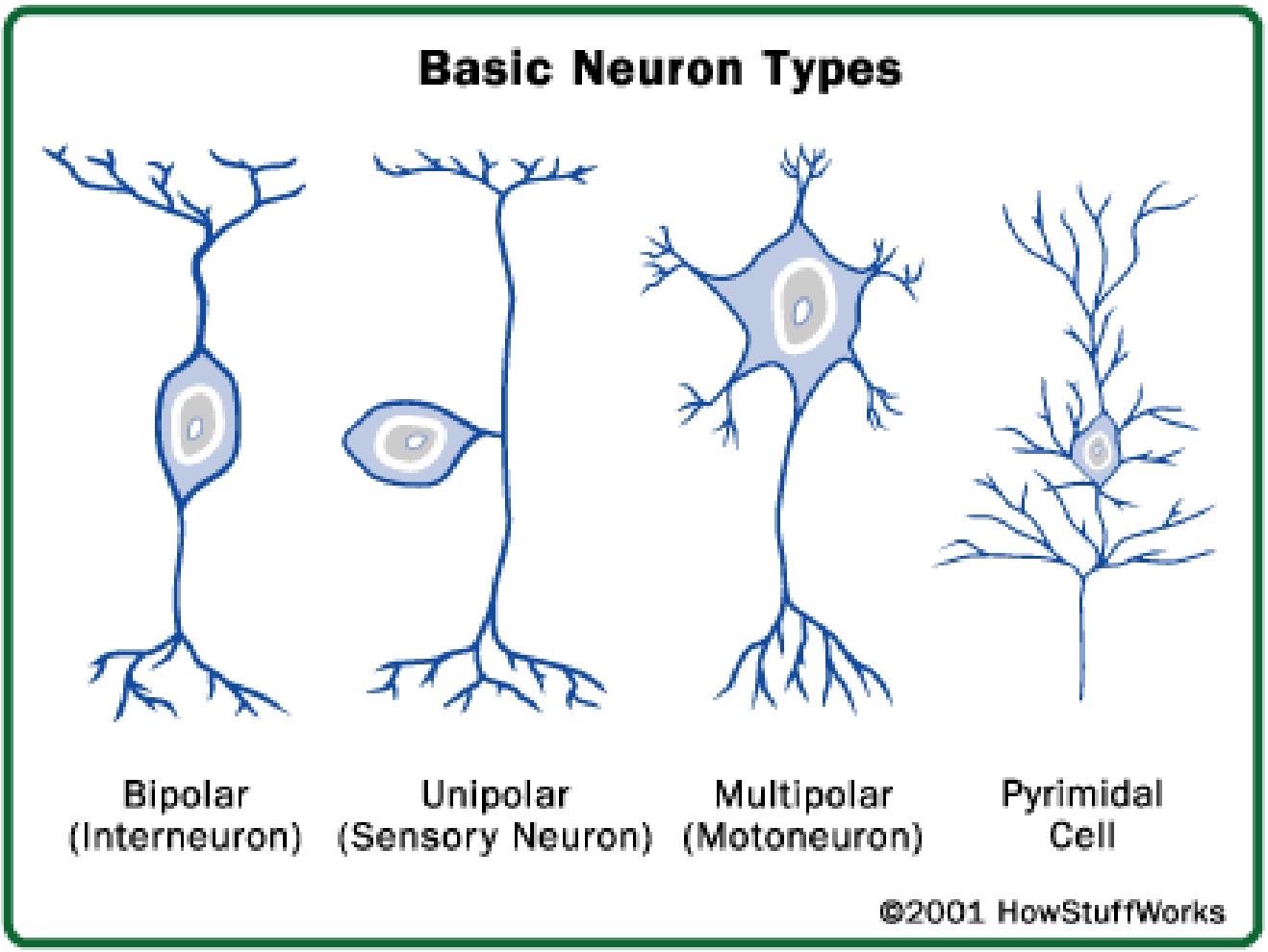
Neurogenesis

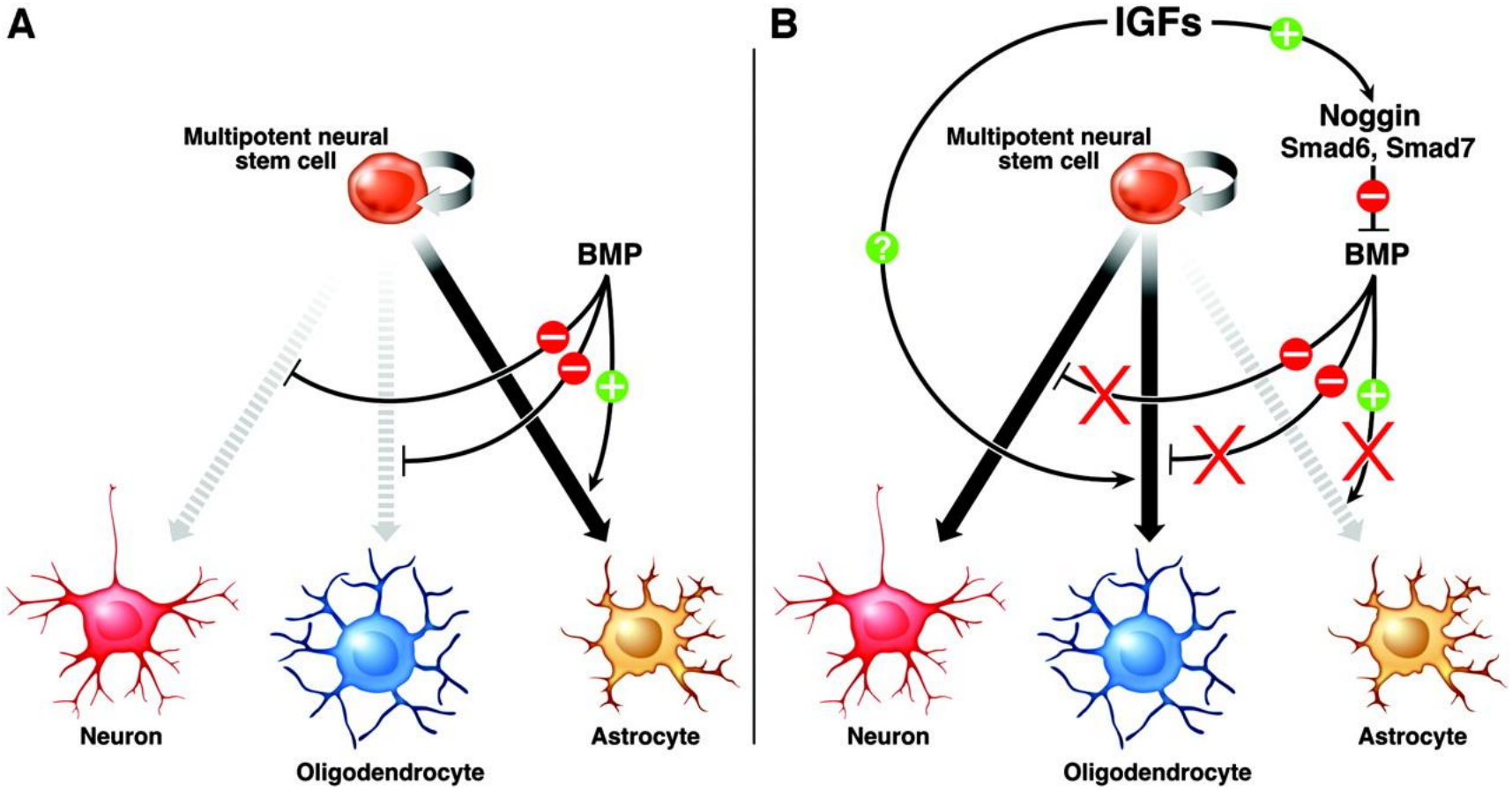


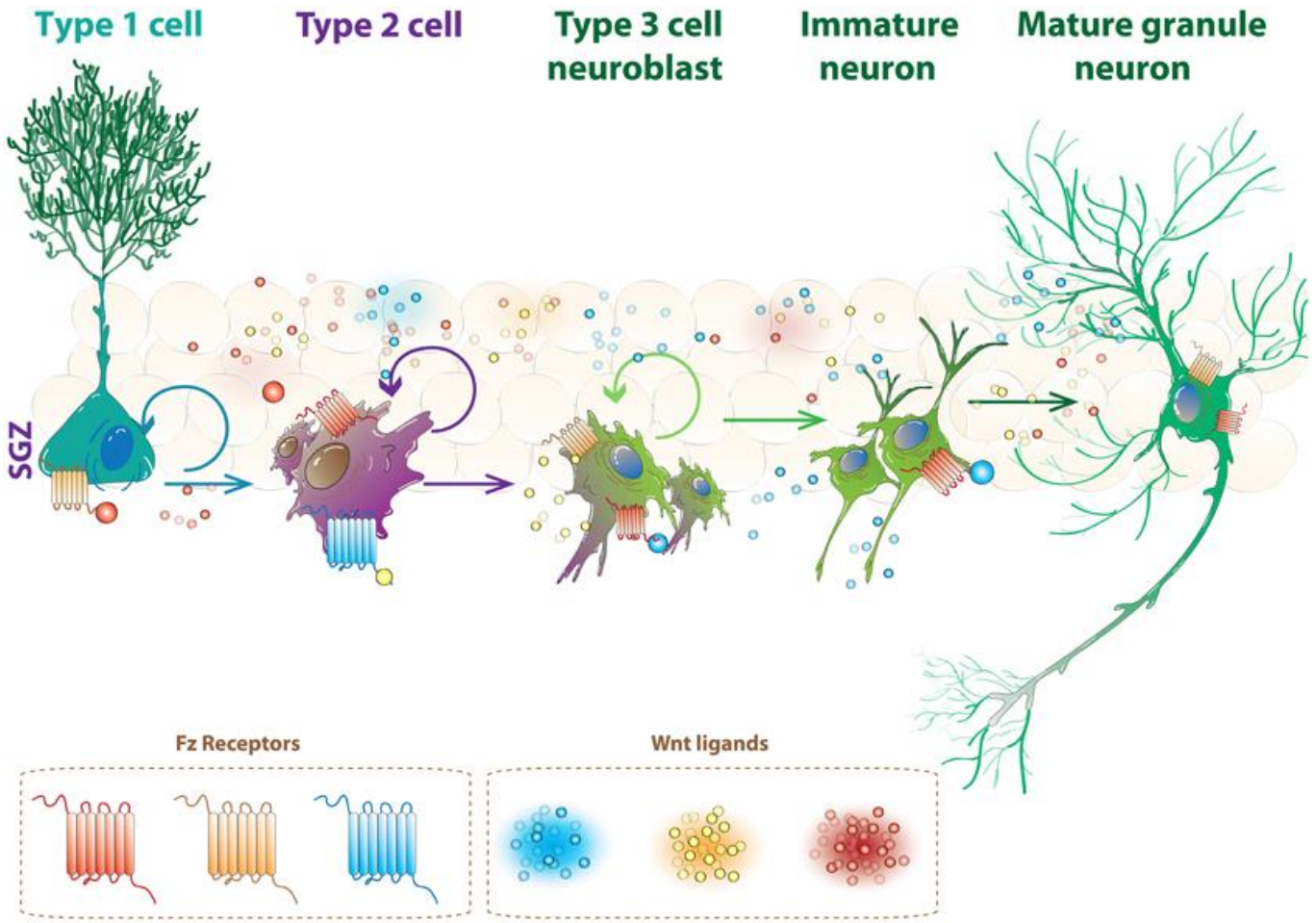
Proliferation and differentation of CNS cells

Nobel prize Robert Horovitz 2002

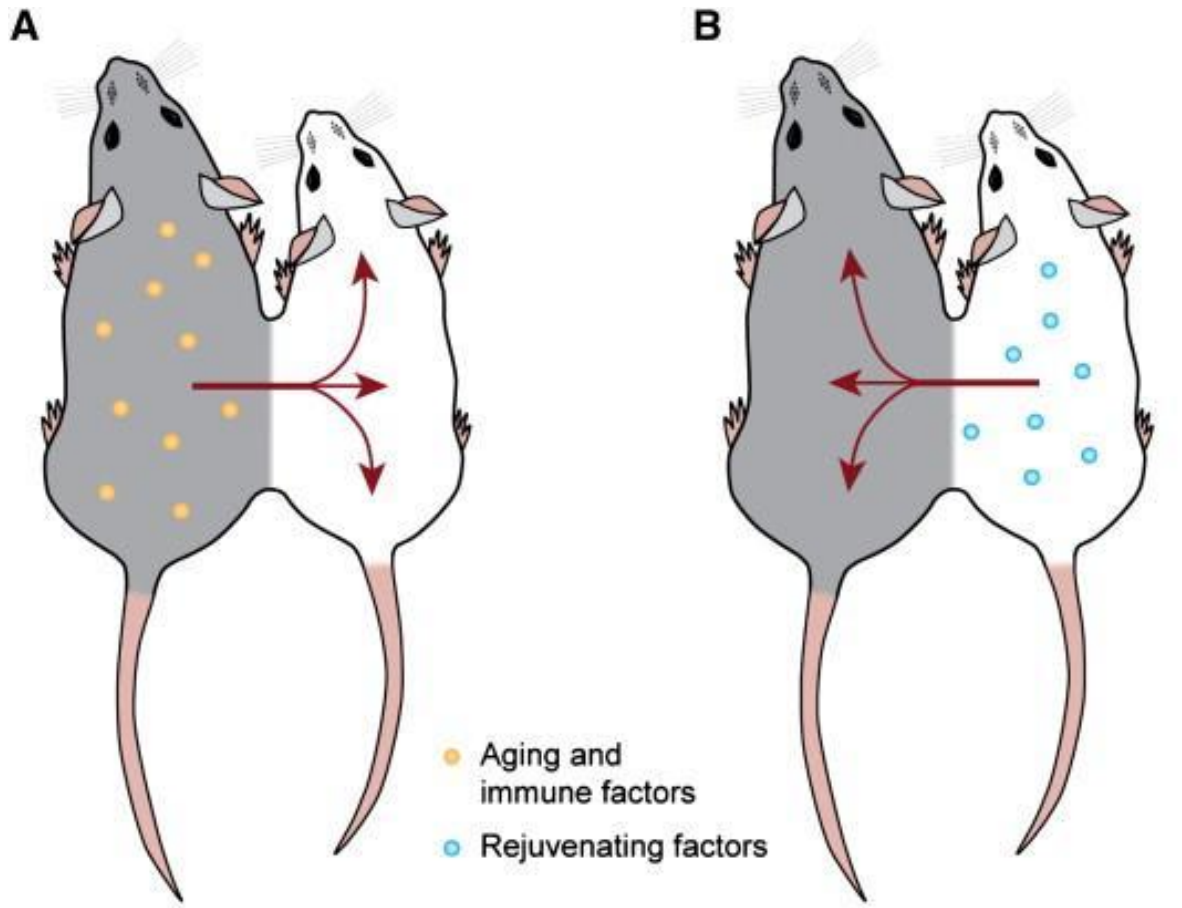

A
CA1
CA3
B
DG
B
C
C
Molecular Layer
Granule Cell Layer
SubGranular Zone
Hilus
Interneuron
Quiescent NSC
Active NSC
Bushy Astrocyte
Type III
Granule Neuron
Parvalbumin Interneuron
Type II a
Type II b
Horizontal Astrocyte
Hilar Astrocyte
Interneuron
Blood Vessel


Basic Neuron Types
Bipolar (Interneuron)
Unipolar (Sensory Neuron)
Multipolar (Motoneuron)
Pyrimidal Cell
©2001 HowStuffWorks


A
Multipotent neural stem cell
BMP
Neuron
Oligodendrocyte
Astrocyte
B
IGFs
Noggin
Smad6, Smad7
Multipotent neural stem cell
BMP
?
Neuron
Oligodendrocyte
Astrocyte



Bone marrow cell synthesize brain-derived neurotrophic factor and nerve growth factor reduce apoptotic cell death, enhance endogenous neurogenesis, and improve neurological recovery



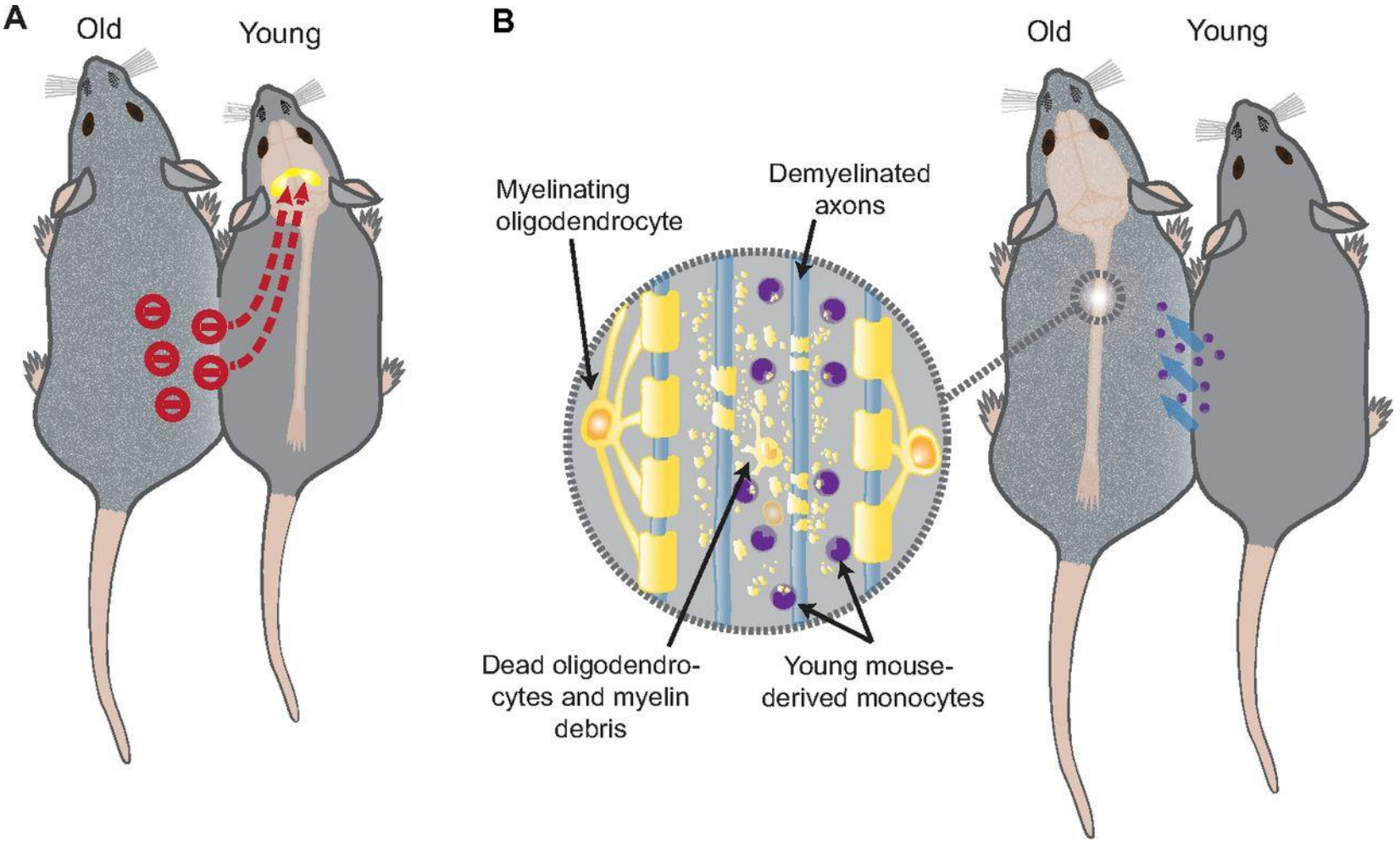
Aging

- Decreased neurogenesis
- Impaired synaptic plasticity
- Impaired cognition

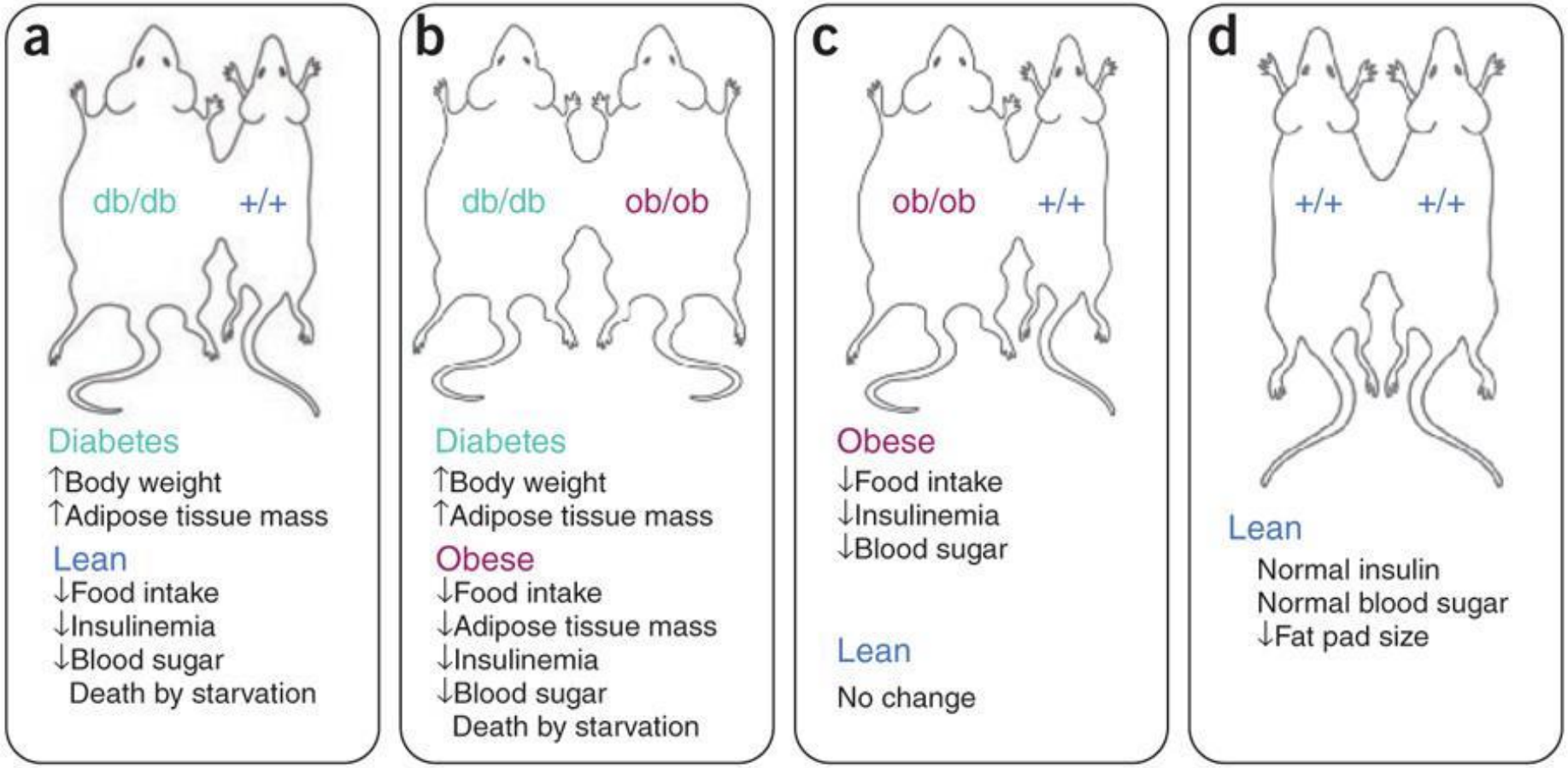
Rejuvenation

- Increased neurogenesis
- Unknown effect on synaptic plasticity?
- Unknown effect on cognition?

Heterochronic parabiosis provides insights into ageing and stem cell function

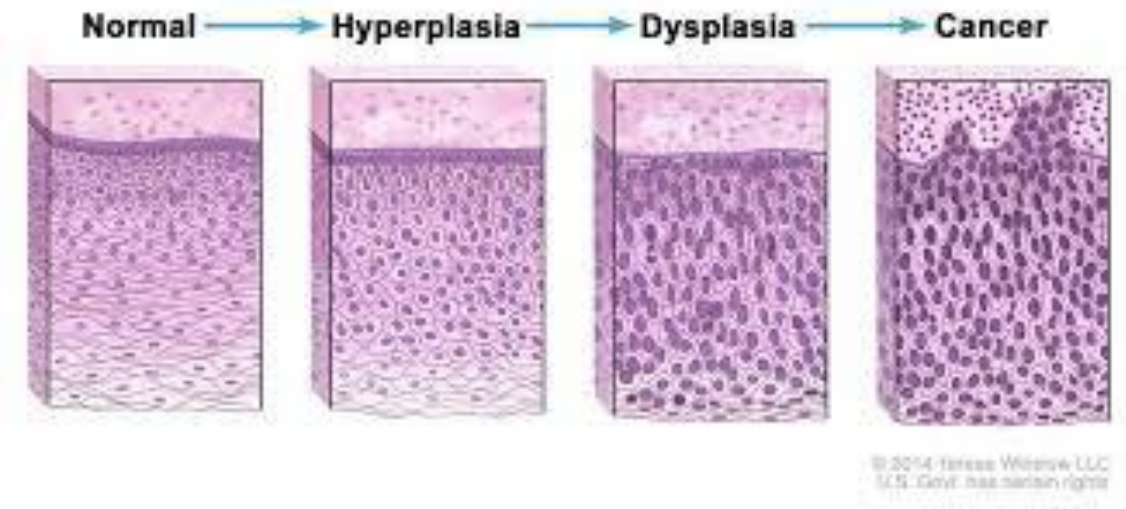


Peter van Wijngaarden, and Robin J. M. Franklin
Development 2013;140:2562-2575



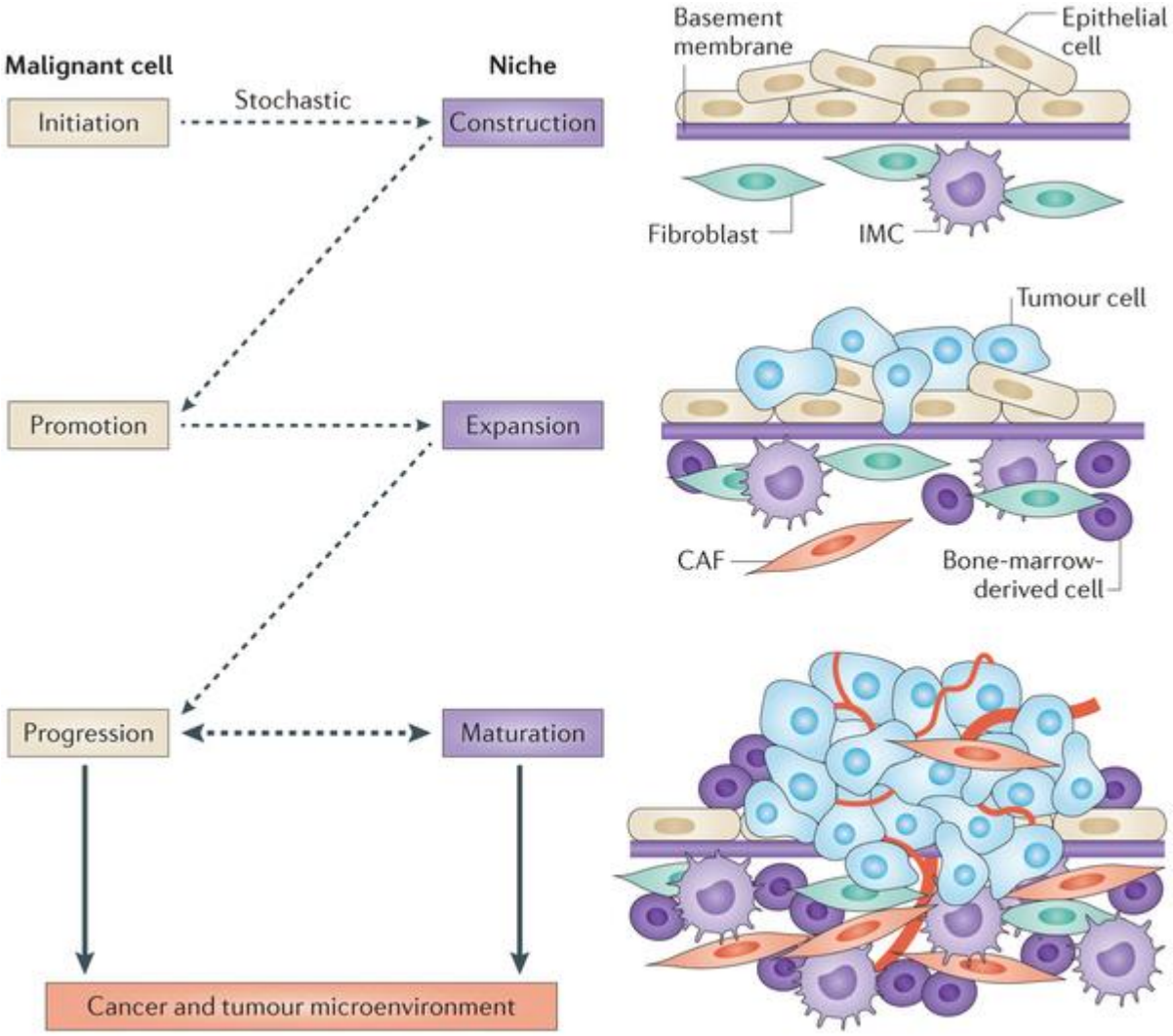
DL Coleman; Nature Medicine 16, 1097–1099 (2010)
doi:10.1038/nm1010-1097

Cancer

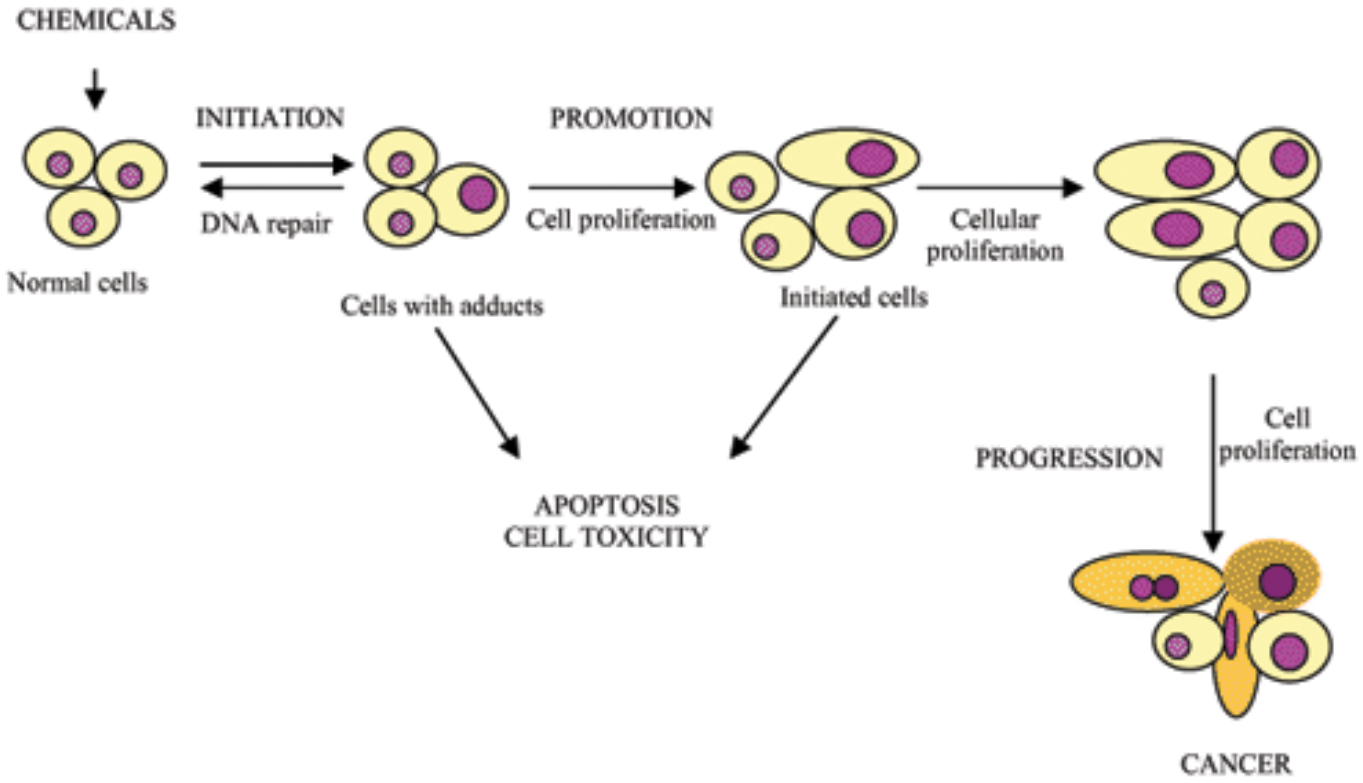


- 20% mortality
- Cancerous cells break the most basic rules of cell behavior (cell signaling, cycle, growth, apoptosis, tissue architecture)
- Collaborative assemblies

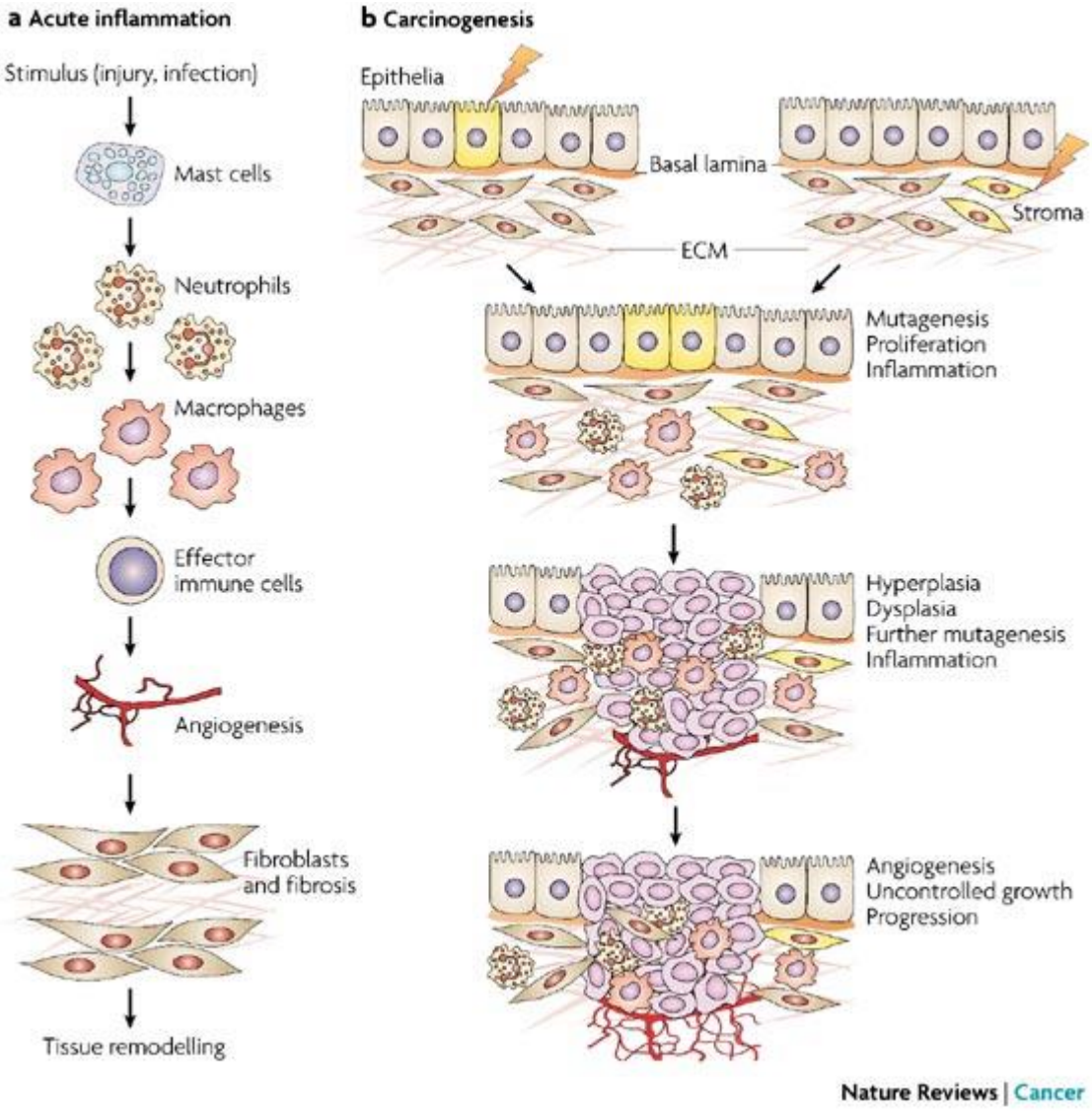
Cancer


Malignant cell
Niche
Initiation
Stochastic
Construction
Promotion
Expansion
Progression
Maturation
Cancer and tumour microenvironment
Basement membrane
Epithelial cell
Fibroblast
IMC
Tumour cell
CAF
Bone-marrow-derived cell
Nature Reviews | Cancer

Cancer

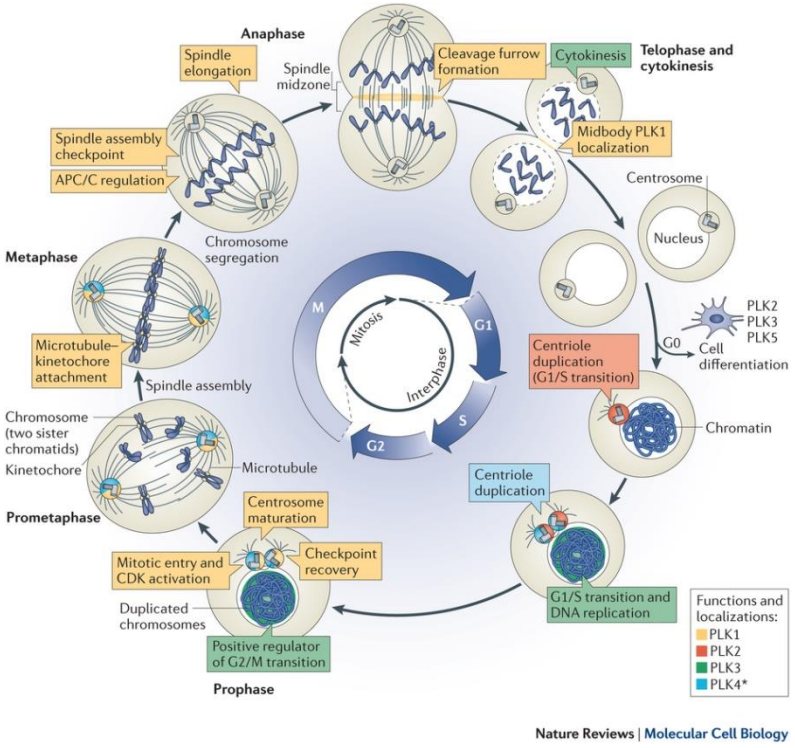

CHEMICALS
INITIATION
DNA repair
PROMOTION
Cell proliferation
Cellular proliferation
Normal cells
Cells with adducts
Initiated cells
APOPTOSIS
CELL TOXICITY
PROGRESSION
Cell proliferation
CANCER

Cancer

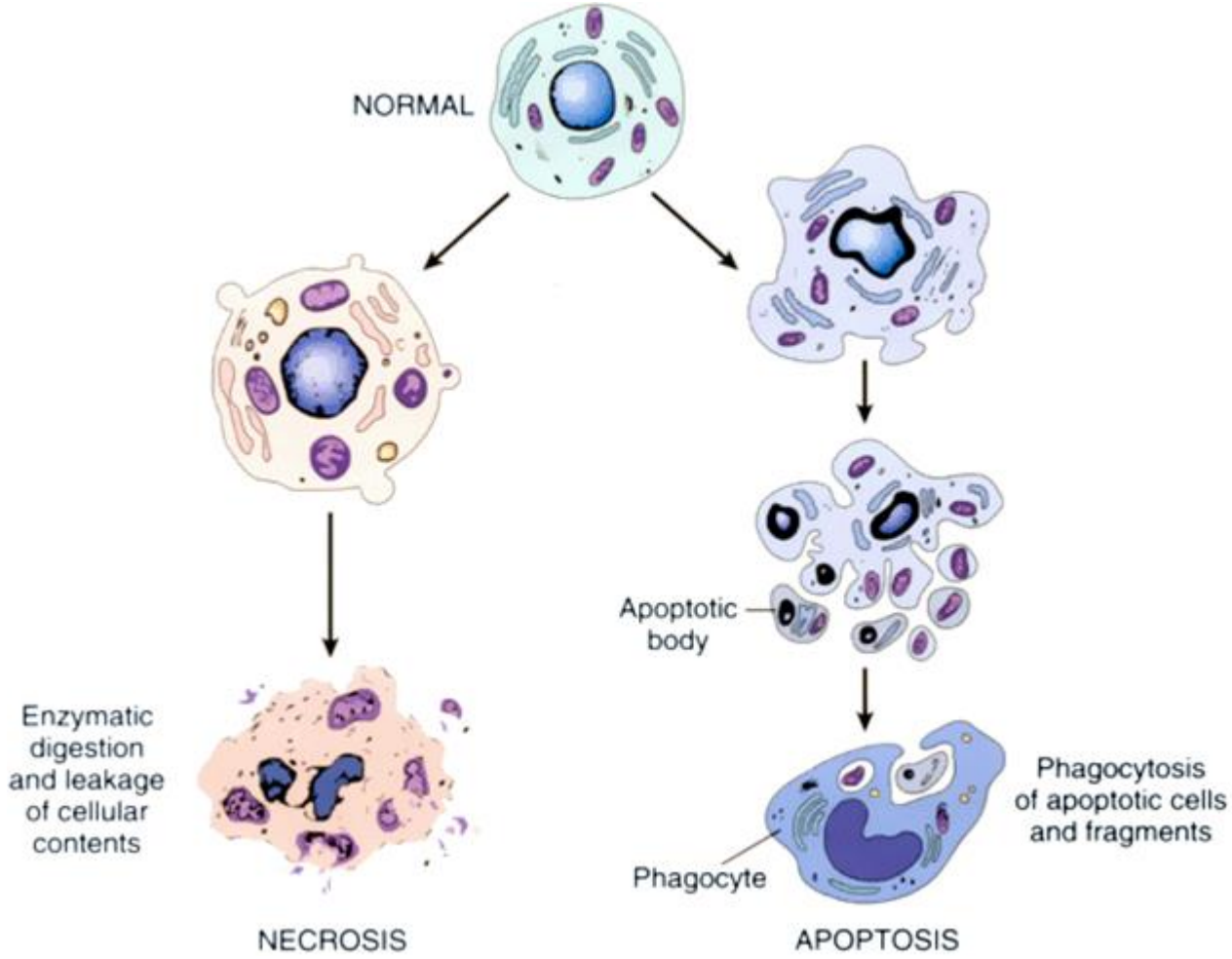

a Acute inflammation
Stimulus (injury, infection)
Mast cells
Neutrophils
Macrophages
Effector immune cells
Angiogenesis
Fibroblasts and fibrosis
Tissue remodelling
b Carcinogenesis
Epithelia
Basal lamina
Stroma
ECM
Mutagenesis
Proliferation
Inflammation
Hyperplasia
Dysplasia
Further mutagenesis
Inflammation
Angiogenesis
Uncontrolled growth
Progression
Nature Reviews | Cancer

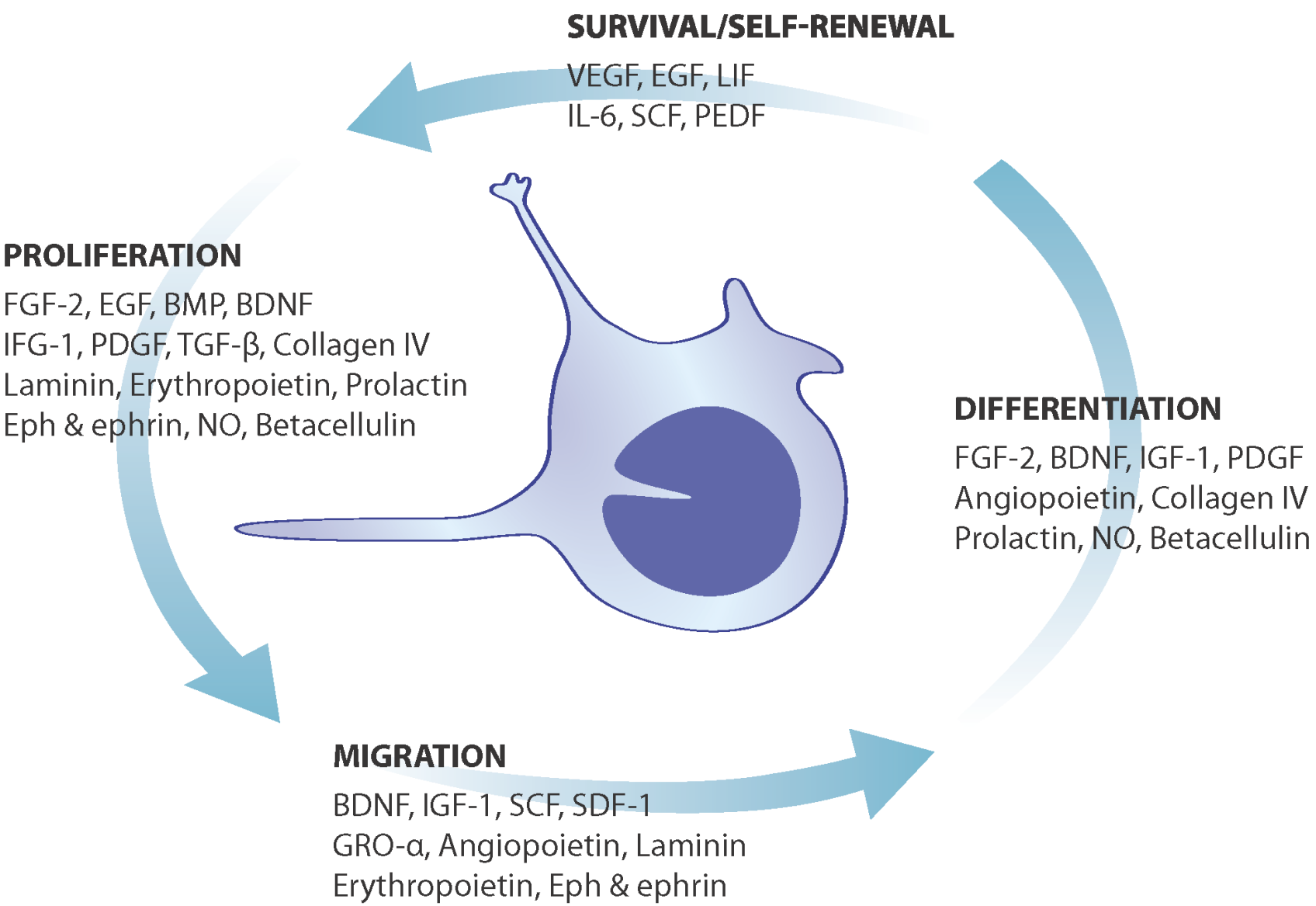
Multicellular collaboration

Cells send, receive, interpret, and elaborate set of signals (social controls)

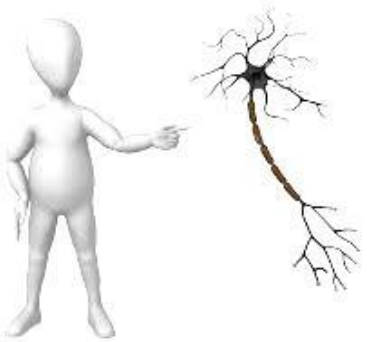


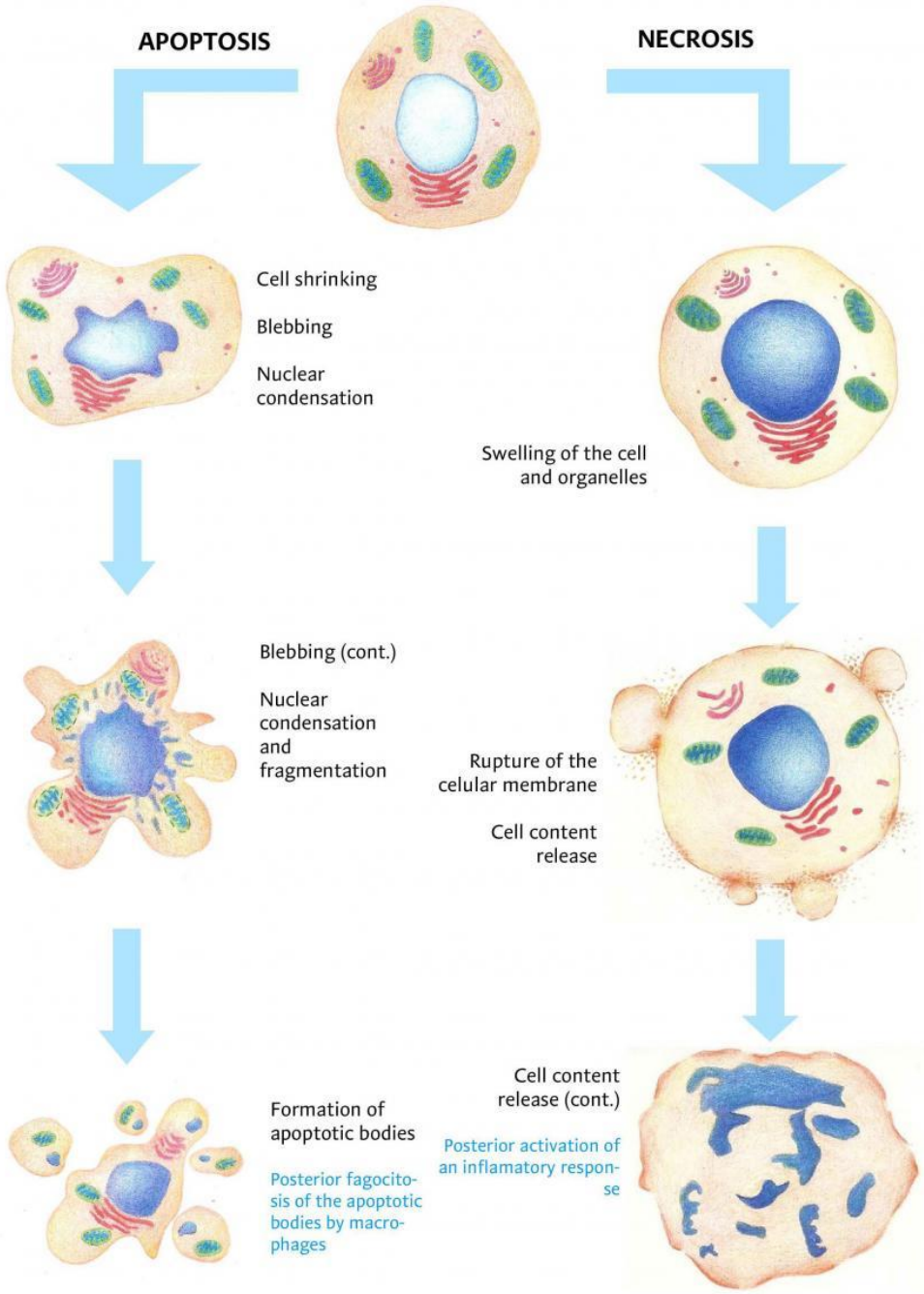
Cell behaves in a responsible manner
(resting, growing, dividing, differentiating or dying)
as needed for the good of the organism

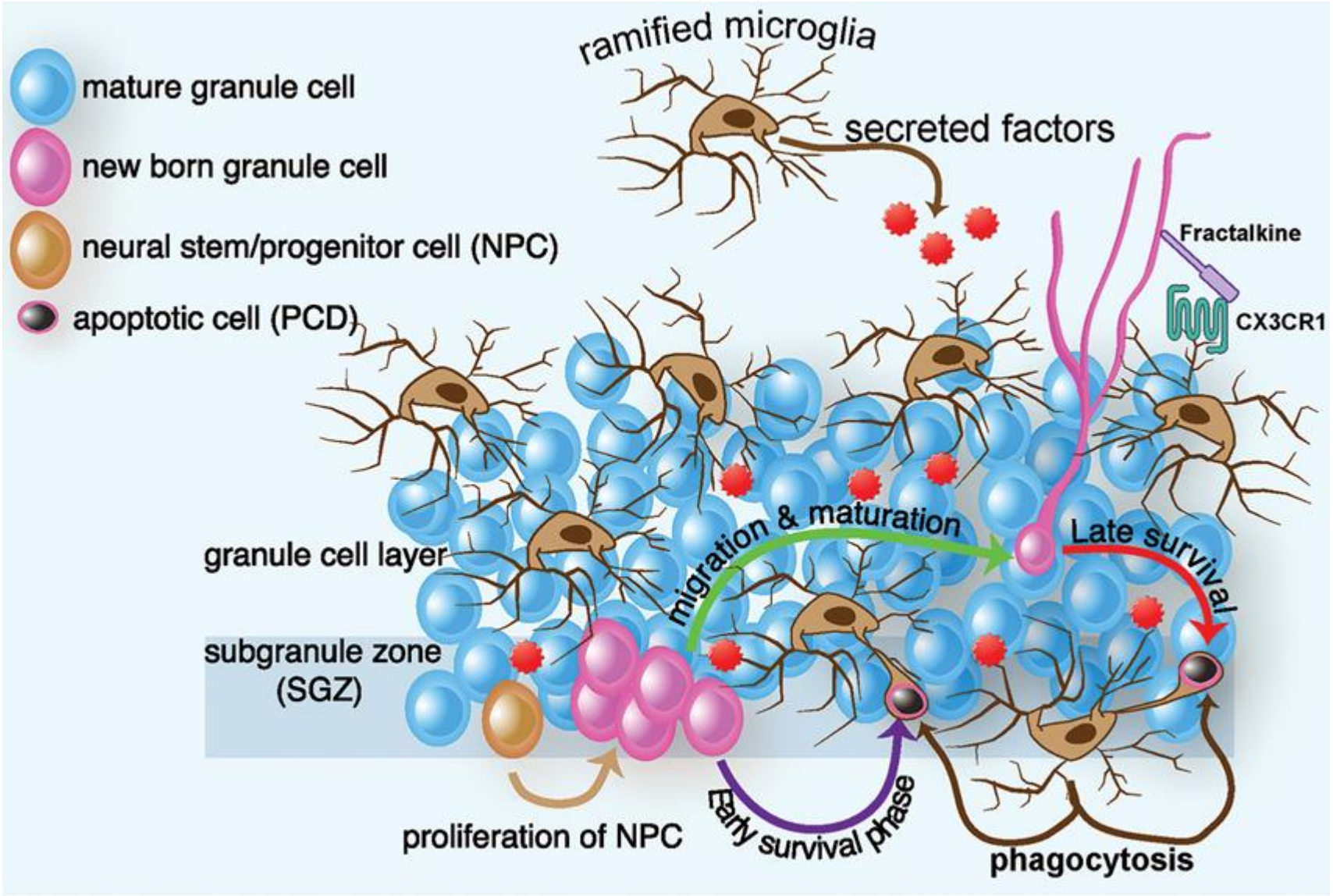

NORMAL
Enzymatic digestion and leakage of cellular contents
Apoptotic body
Phagocytosis of apoptotic cells and fragments
Phagocyte
NECROSIS
APOPTOSIS

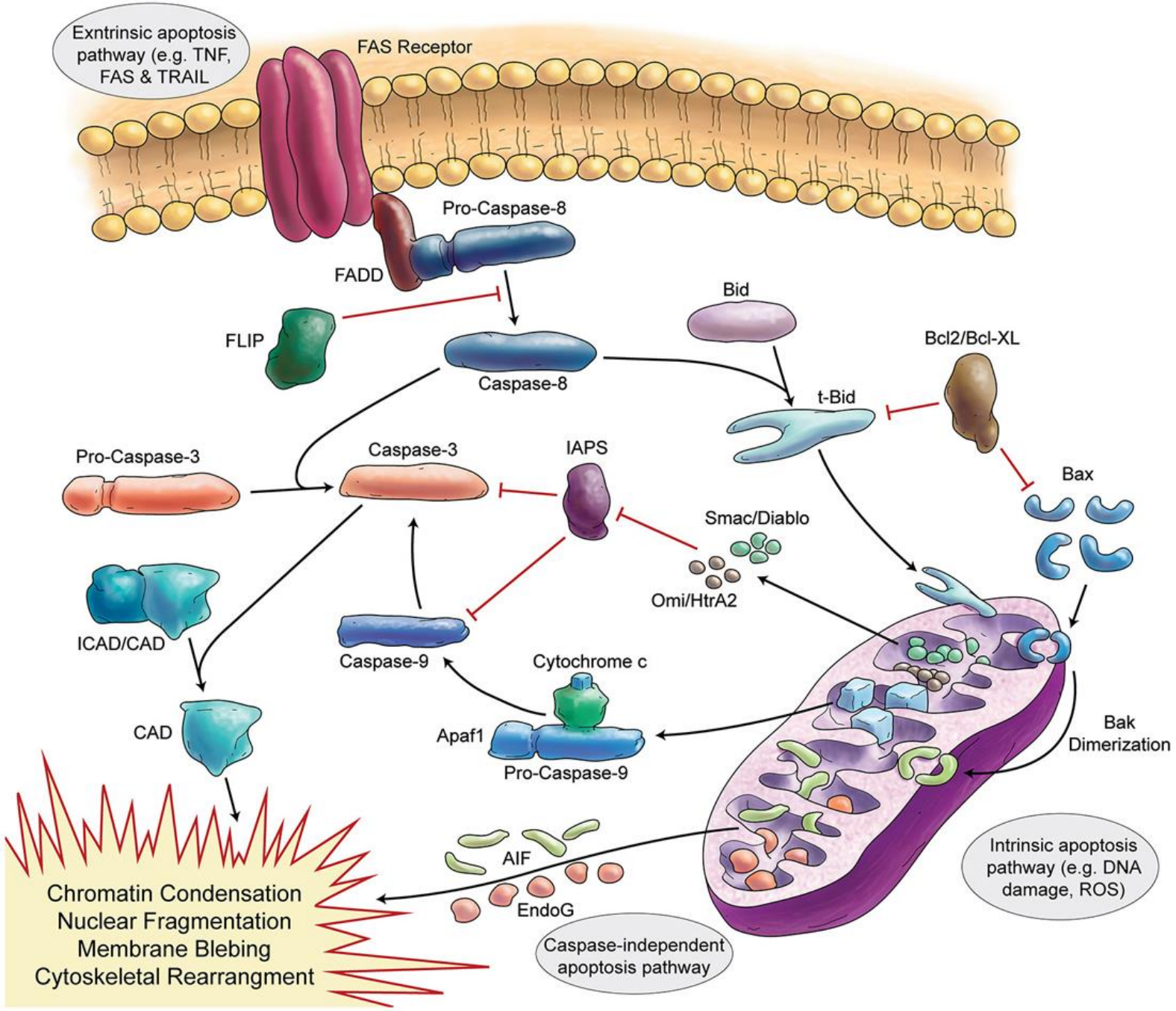

SURVIVAL/SELF-RENEWAL
VEGF, EGF, LIF
IL-6, SCF, PEDF
PROLIFERATION
FGF-2, EGF, BMP, BDNF
IFG-1, PDGF, TGF-β, Collagen IV
Laminin, Erythropoietin, Prolactin
Eph & ephrin, NO, Betacellulin
DIFFERENTIATION
FGF-2, BDNF, IGF-1, PDGF
Angiopoietin, Collagen IV
Prolactin, NO, Betacellulin
MIGRATION
BDNF, IGF-1, SCF, SDF-1
GRO-α, Angiopoietin, Laminin
Erythropoietin, Eph & ephrin

Thank you ☺




APOPTOSIS
NECROSIS
Cell shrinking
Blebbing
Nuclear condensation
Swelling of the cell and organelles
Blebbing (cont.)
Nuclear condensation and fragmentation
Rupture of the celular membrane
Cell content release
Formation of apoptotic bodies
Posterior fagocitosis of the apoptotic bodies by macrophages
Cell content release (cont.)
Posterior activation of an inflamatory response


mature granule cell
new born granule cell
neural stem/progenitor cell (NPC)
apoptotic cell (PCD)
ramified microglia
secreted factors
Fractalkine
CX3CR1
granule cell layer
subgranule zone
(SGZ)
migration & maturation
Late survival
proliferation of NPC
Early survival phase
phagocytosis


Exntrinsic apoptosis pathway (e.g. TNF, FAS & TRAIL
FAS Receptor
Pro-Caspase-8
FADD
FLIP
Caspase-8
Bid
t-Bid
Bcl2/Bcl-XL
Bax
Pro-Caspase-3
Caspase-3
IAPS
Smac/Diablo
Omi/HtrA2
ICAD/CAD
Caspase-9
Cytochrome c
Apaf1
Pro-Caspase-9
CAD
Bak Dimerization
AIF
EndoG
Chromatin Condensation
Nuclear Fragmentation
Membrane Blebing
Cytoskeletal Rearrangment
Caspase-independent apoptosis pathway
Intrinsic apoptosis pathway (e.g. DNA damage, ROS)