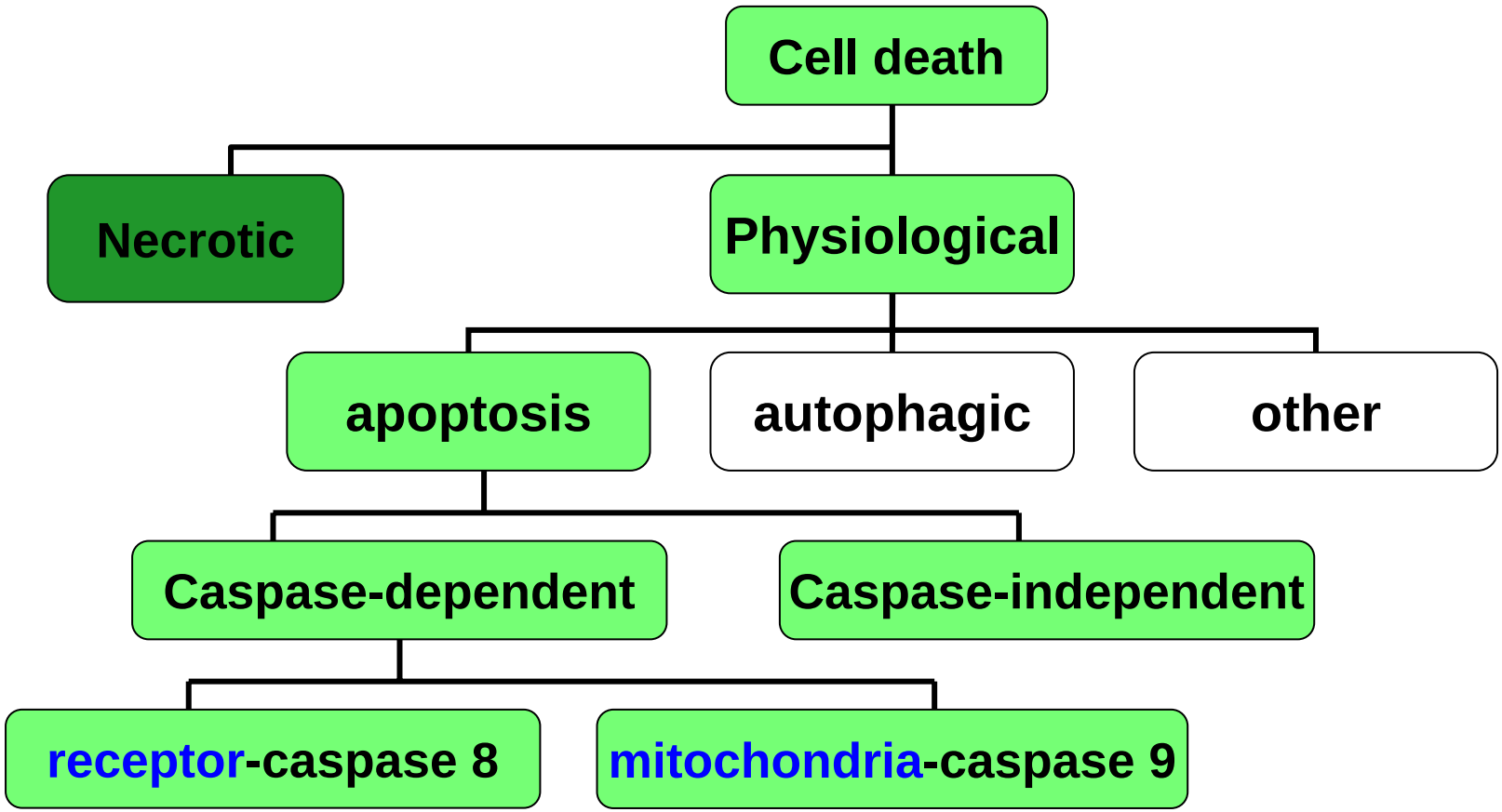
Cell death

Major types

Apoptosis: appropriate, programmed
Necrosis: inappropriate, accidental
Autophagy: self-digestion

Classification of cell death



APOPTOSIS

What is it?

Why is it important?

How is it controlled?

What is its role in age-related disease?

APOPTOSIS

Programmed cell death

Orderly cellular self destruction

Process: as crucial for survival of multi-cellular organisms as cell division

Forms of cell death

Necrosis	*Apoptosis*	*Mitotic catastrophe*
Passive	*Active*	*Passive*
Pathological	*Physiological or pathological*	*Pathological*
Swelling, lysis	*Condensation, cross-linking*	*Swelling, lysis*
Dissipates	*Phagocytosed*	*Dissipates*
Inflammation	*No inflammation*	*Inflammation*
Externally induced	*Internally or externally induced*	*Internally induced*

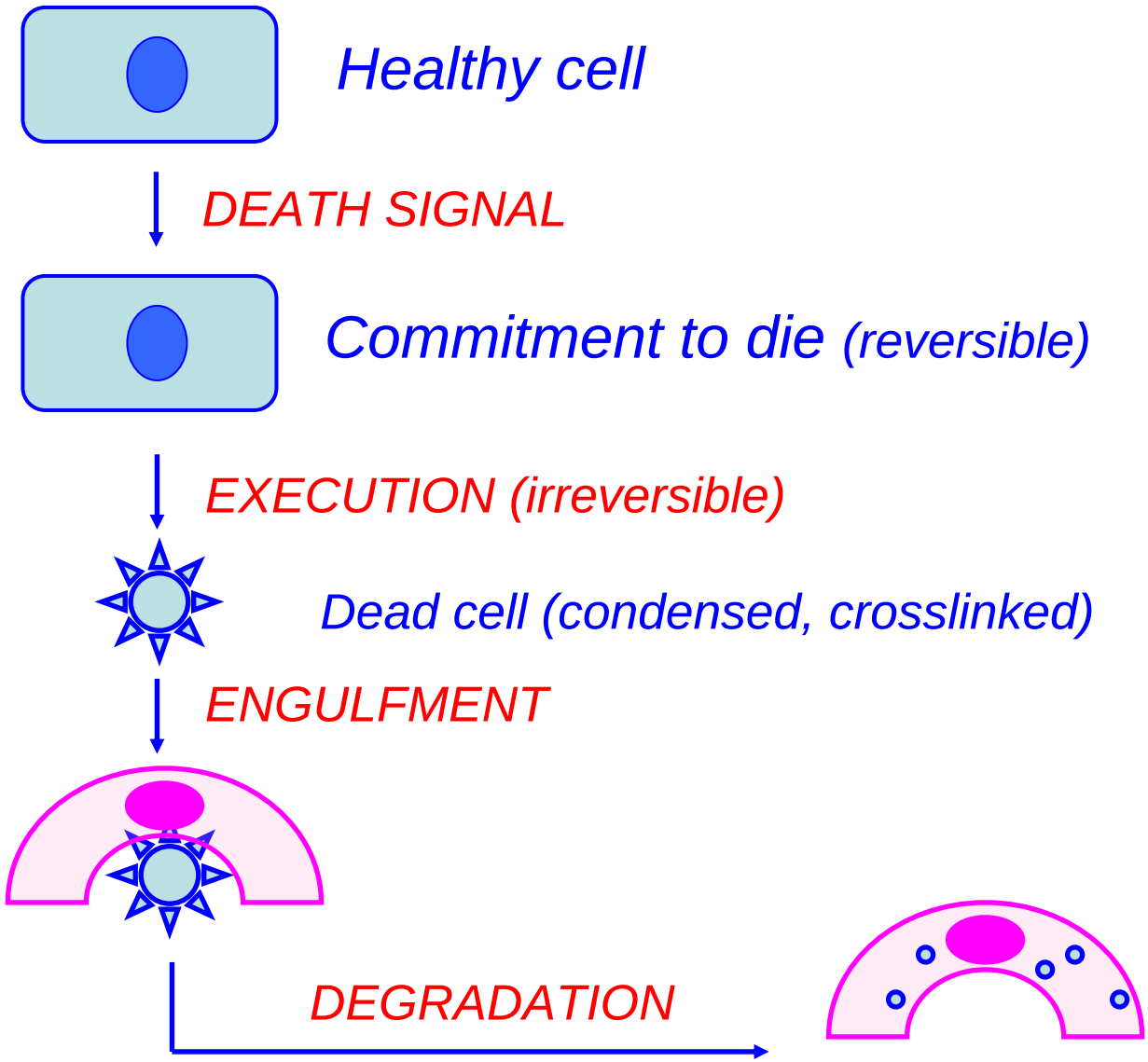
APOPTOSIS

Evolutionarily conserved

- *Occurs in all animals studies (plants too!)*

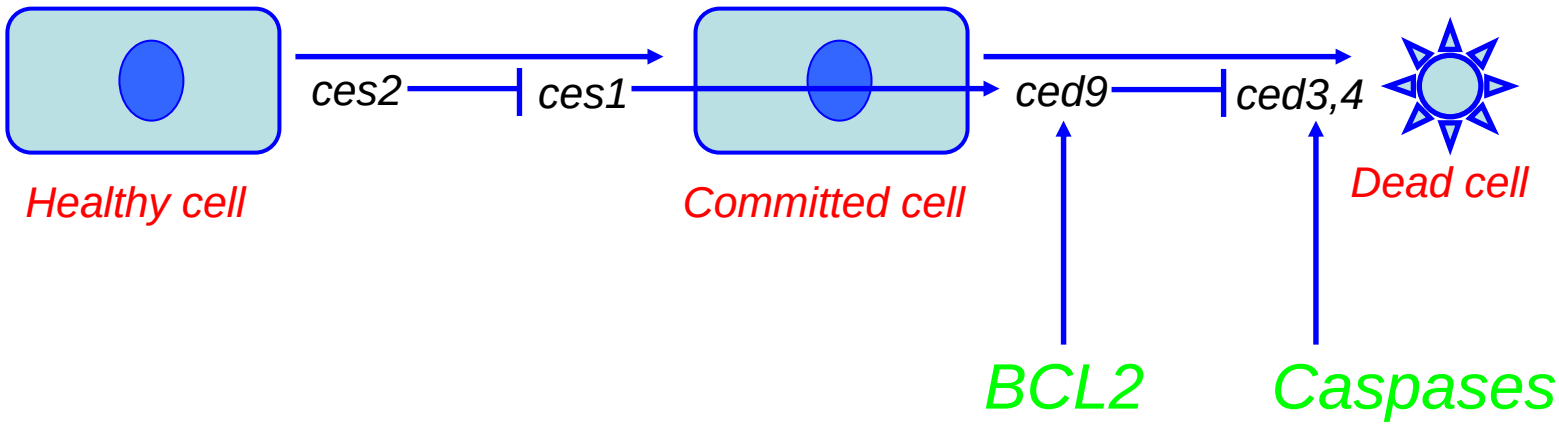
- *Stages and genes conserved from nematodes and flies to humans*

STAGES OF APOPTOSIS



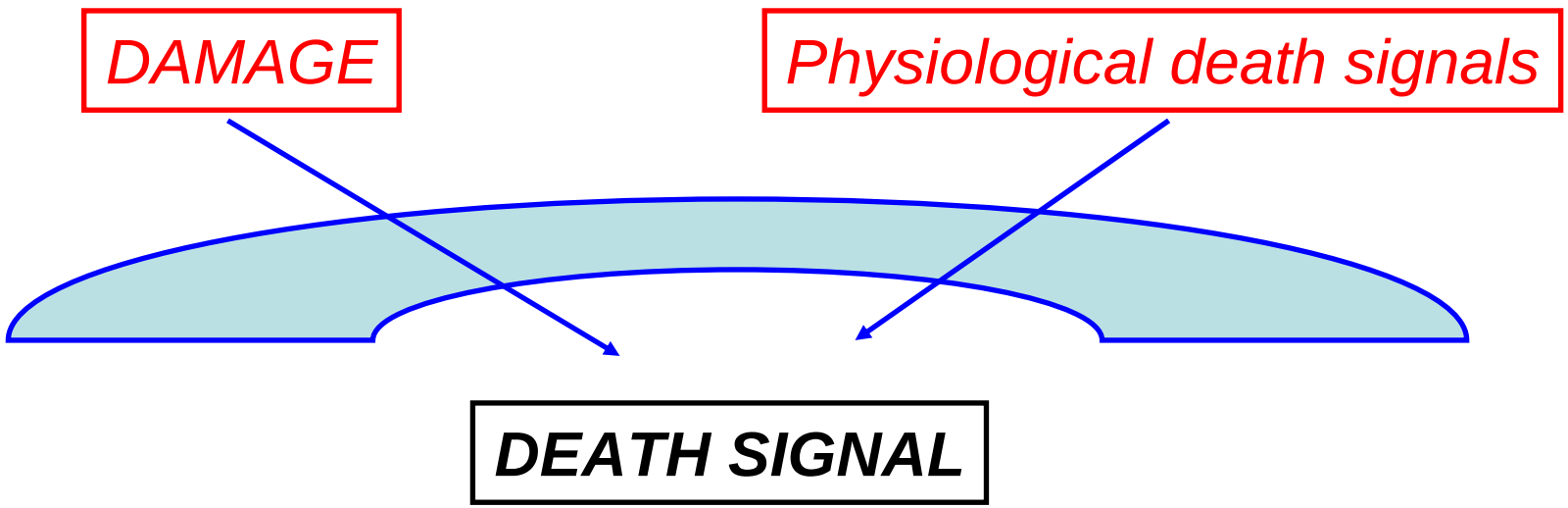
STAGES OF APOPTOSIS

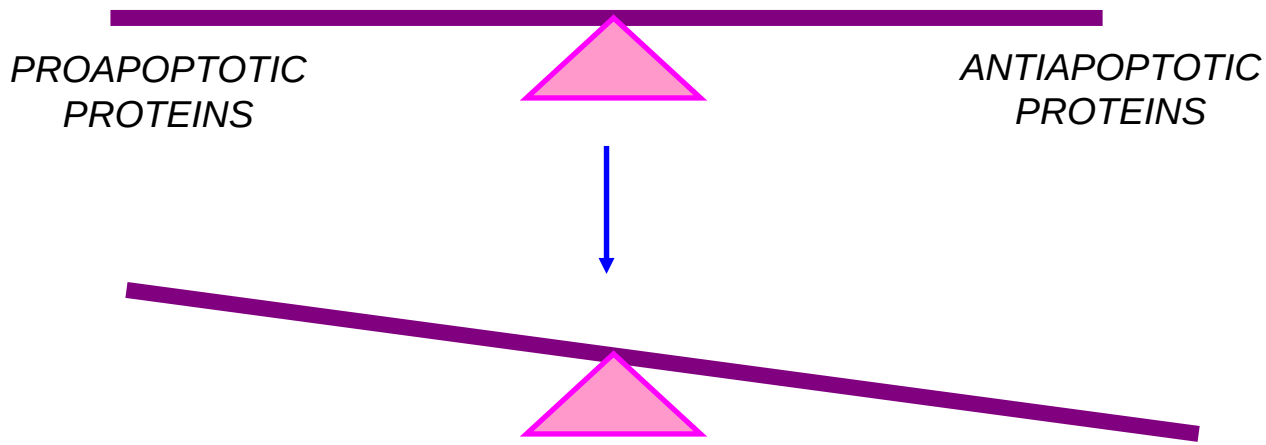
Genetically controlled: Caenorhabditis elegans
Soil nematode (worm)



C. Elegans genes == mammalian genes

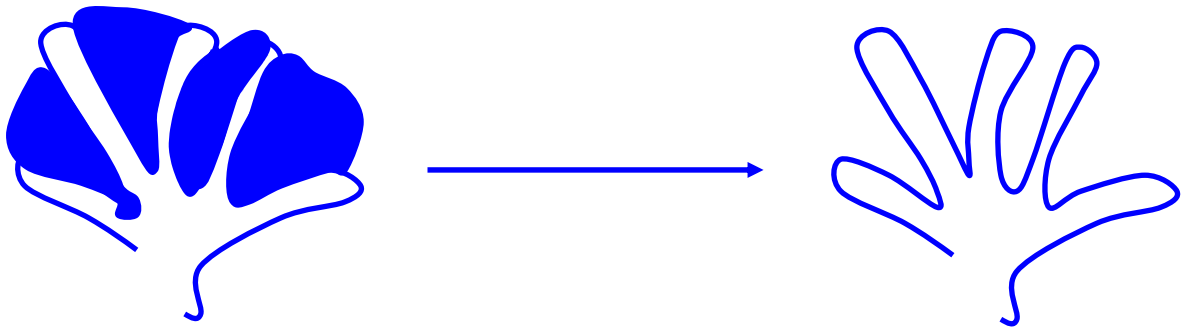
Cells are balanced between life and death



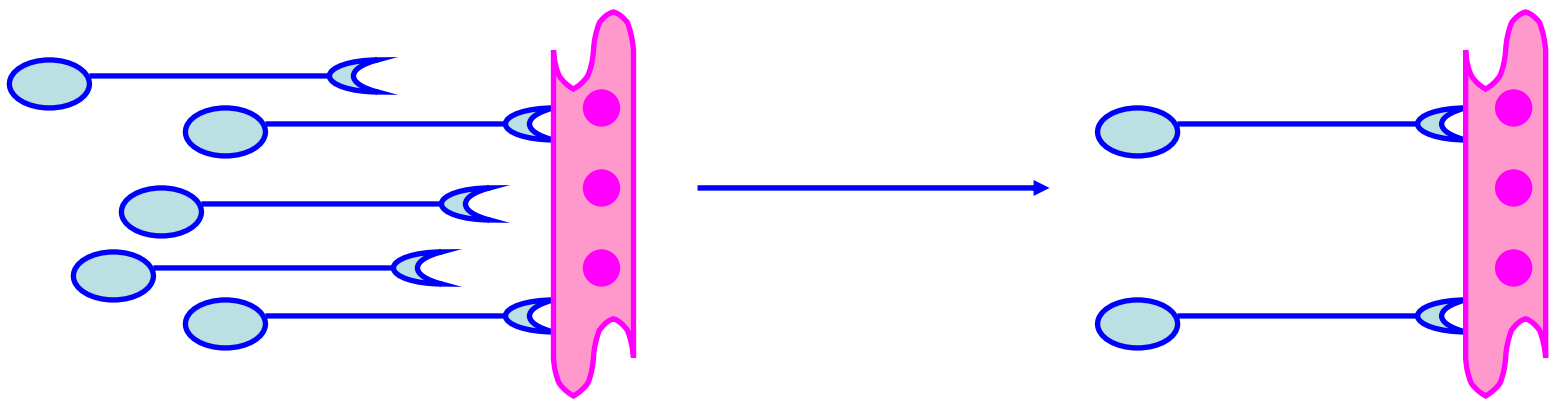


APOPTOSIS: important in embryogenesis

Morphogenesis (eliminates excess cells):

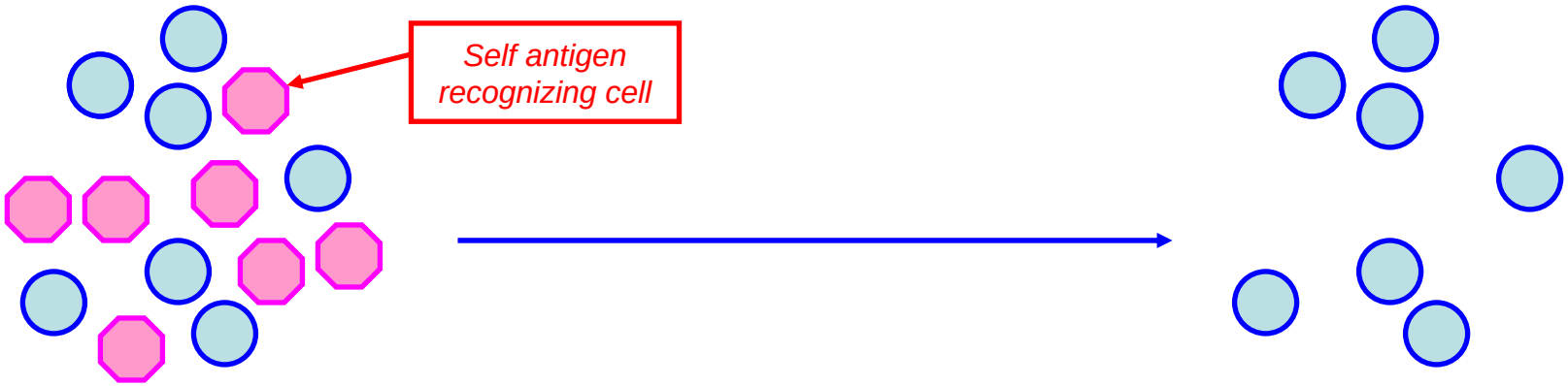


Selection (eliminates non-functional cells):

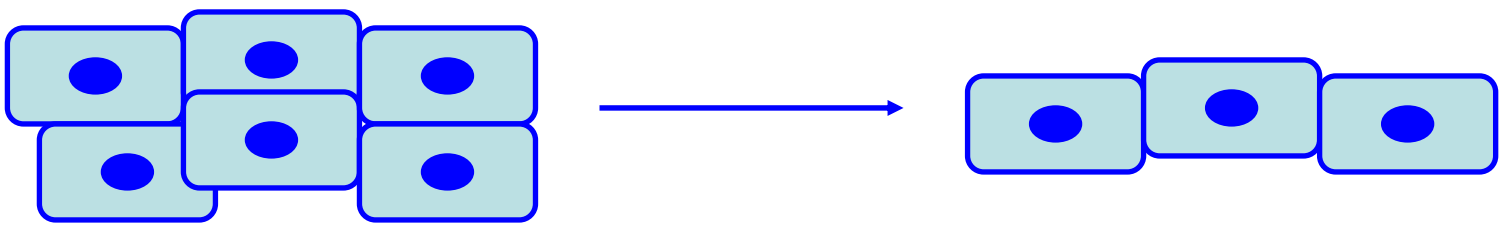


APOPTOSIS: important in embryogenesis

Immunity (eliminates dangerous cells):

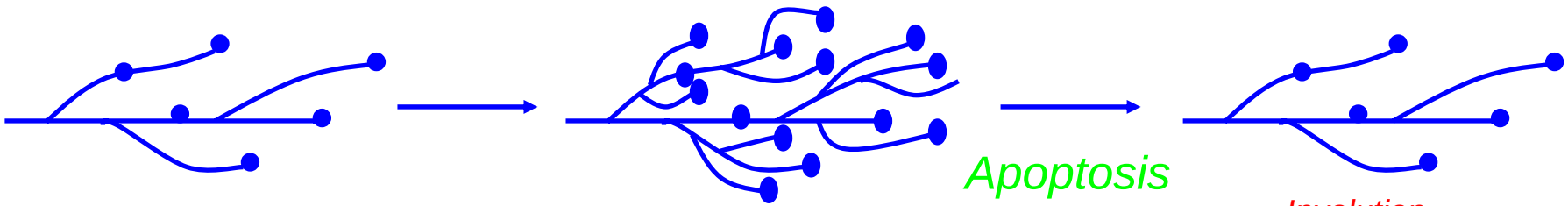


Organ size (eliminates excess cells):



APOPTOSIS: important in adults

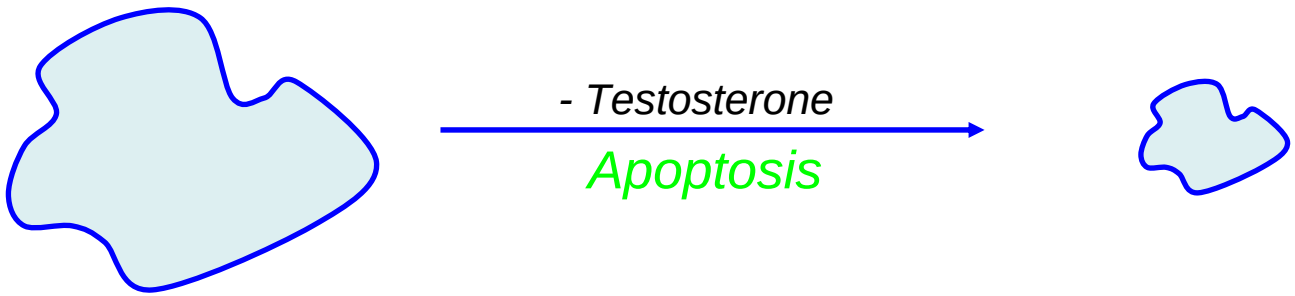
Tissue remodeling (eliminates cells no longer needed):



Virgin mammary gland

Late pregnancy, lactation

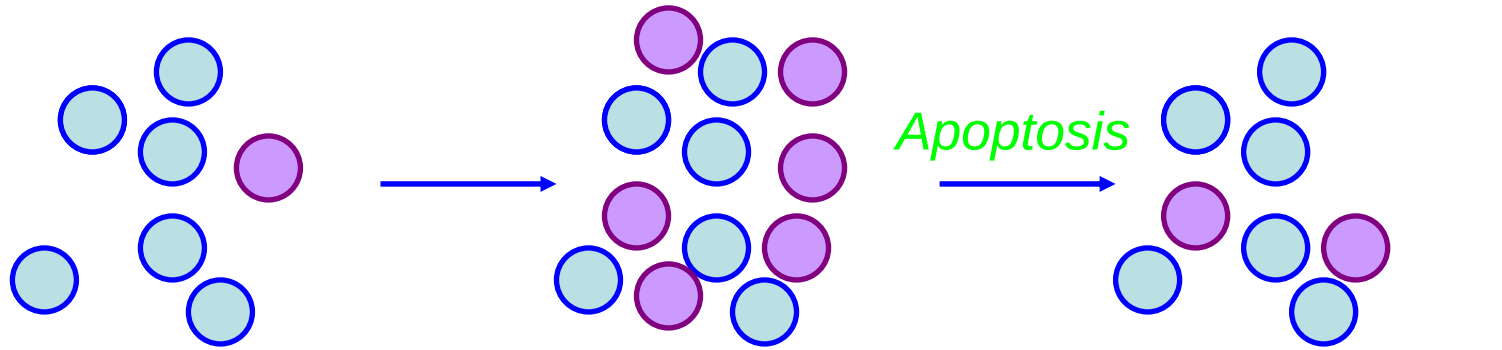
Involution
(non-pregnant, non-lactating)



Prostate gland

APOPTOSIS: important in adults

Tissue remodeling (eliminates cells no longer needed):

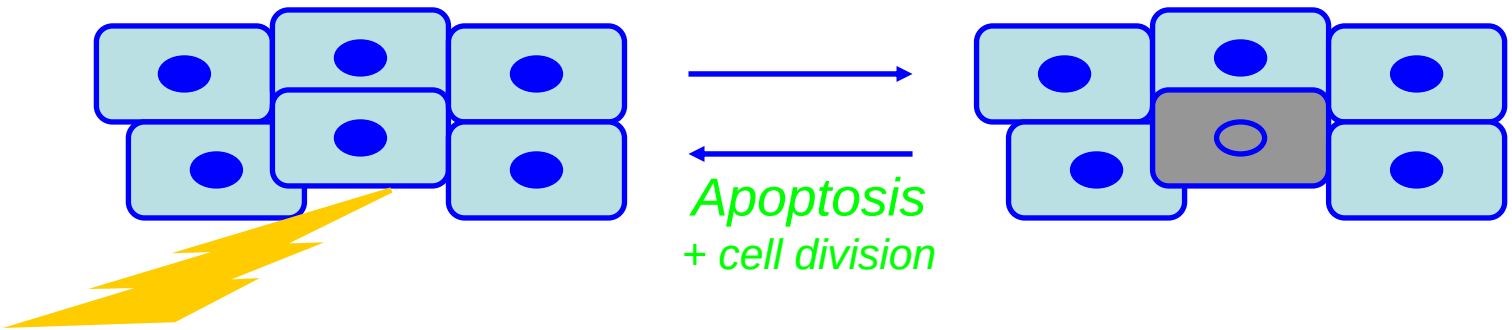


Steroid immunosuppressants: kill lymphocytes by apoptosis

Lymphocytes poised to die by apoptosis

APOPTOSIS: important in adults

Maintains organ size and function:



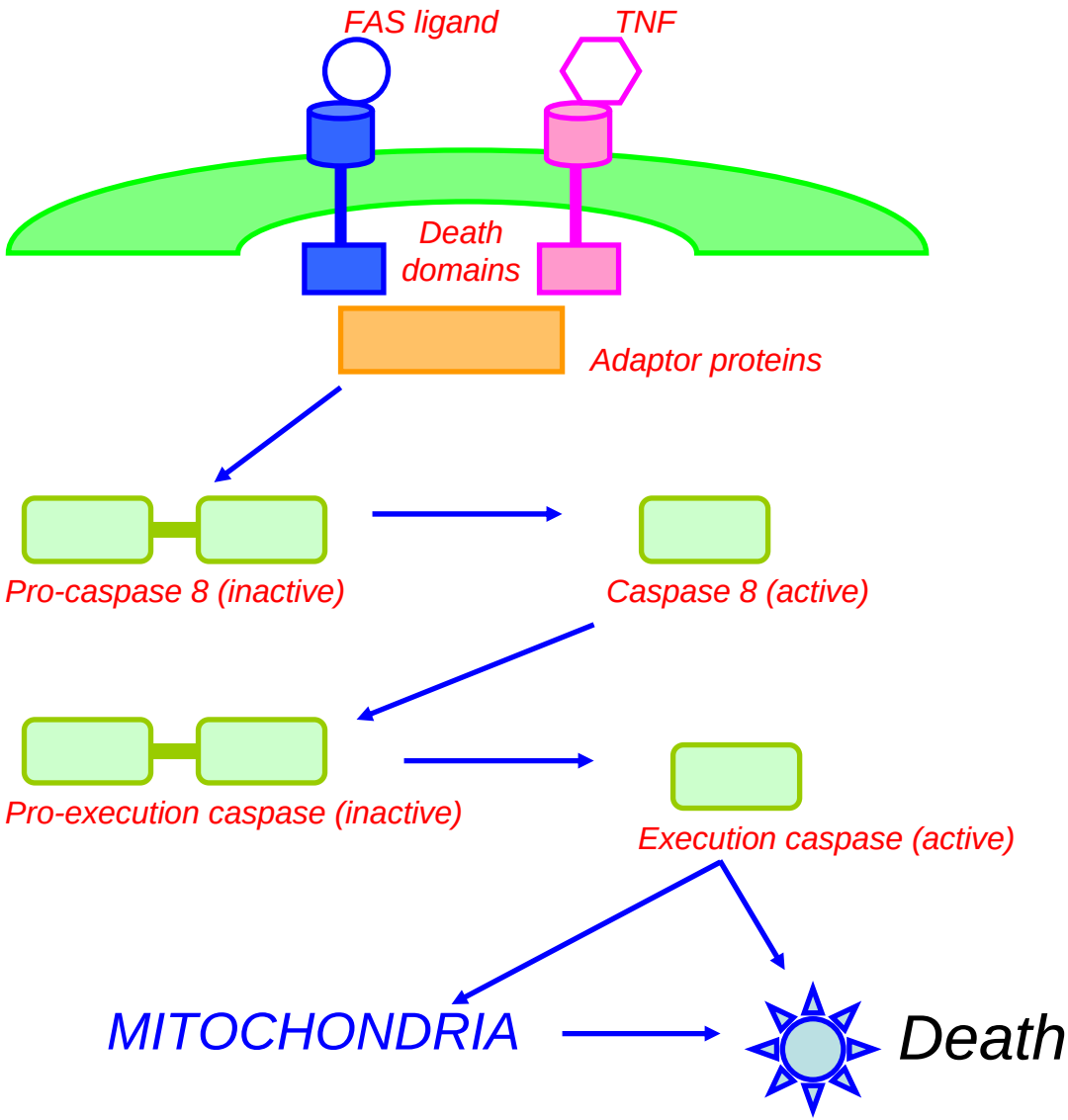
Cells lost by apoptosis are replaced by cell division

(remember limited replicative potential of cells)

APOPTOSIS: control

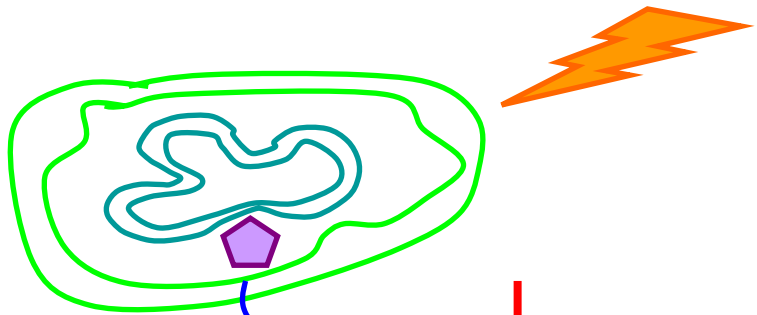
Receptor pathway (extrinsic, physiological):

Death receptors:
(FAS, TNF-R, etc)



APOPTOSIS: control

Intrinsic pathway (damage):



Mitochondria

Cytochrome c release

Pro-caspase 9 cleavage

Pro-execution caspase (3) cleavage

Caspase (3) cleavage of cellular proteins,
Nuclease activation,
Etc.

Death

BAX
BAK
BOK
BCL-Xs
BAD
BID
B IK
BIM
NIP3
BNIP3

BCL-2
BCL-XL
BCL-W
MCL1
BFL1
DIVA
NR-13
Several viral proteins

APOPTOSIS: control

Physiological receptor pathway

Intrinsic damage pathway

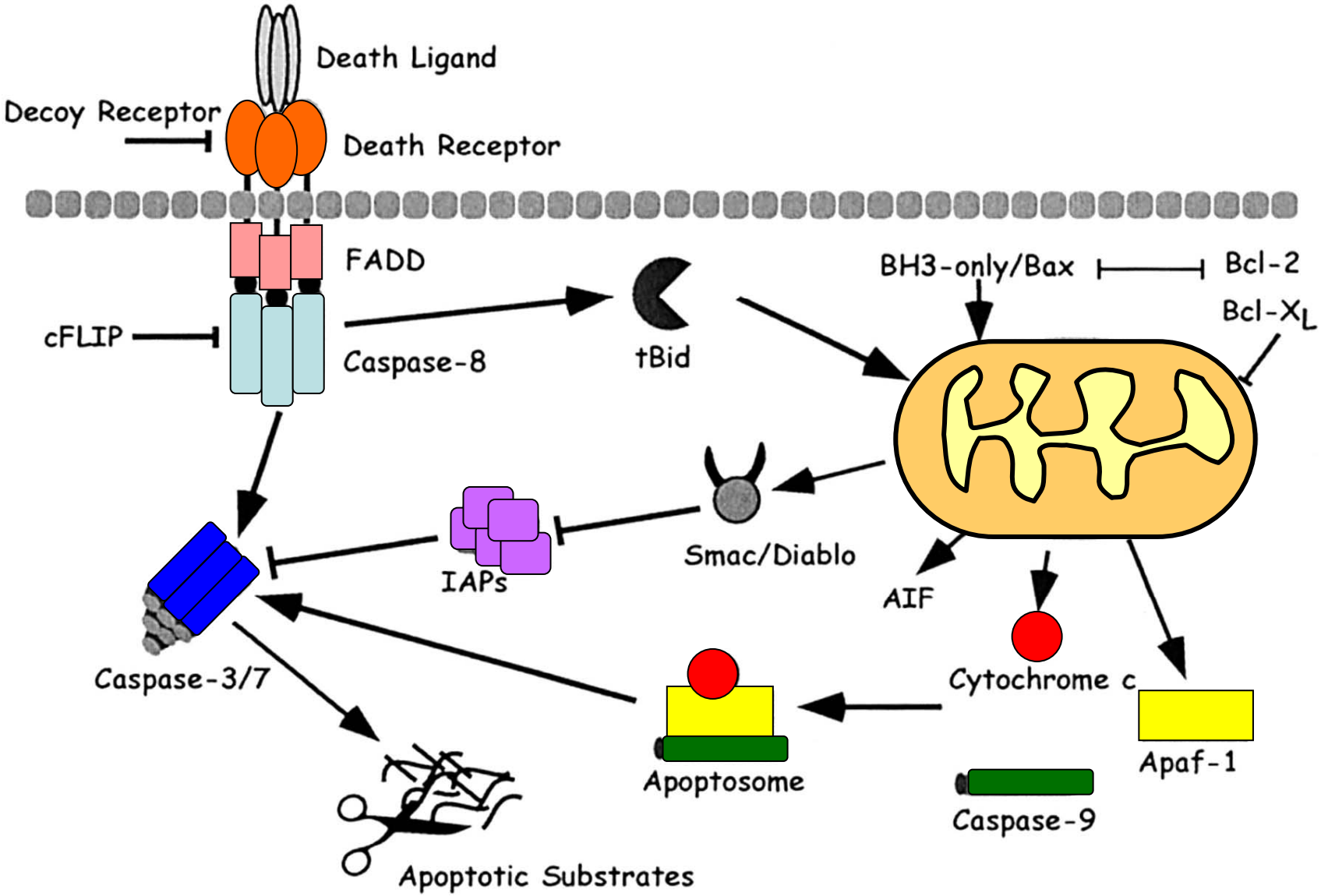
MITOCHONDRIAL SIGNALS

Caspase cleavage cascade

Orderly cleavage of proteins and DNA

CROSSLINKING OF CELL CORPSES; ENGULFMENT (no inflammation)

Induction and Regulation of Apoptosis



APOPTOSIS: Role in Disease

TOO MUCH: *Tissue atrophy*

Neurodegeneration
Thin skin
etc

TOO LITTLE: *Hyperplasia*

Cancer
Atherosclerosis
etc

APOPTOSIS: Role in Disease

Neurodegeneration

Neurons are post-mitotic (cannot replace themselves)

Neuronal death caused by loss of proper connections,
loss of proper growth factors (e.g. NGF),
damage (especially oxidative damage)

Neuronal dysfunction or damage results in loss of synapses
(synaptosis; reversible)
apopsosis (irreversible)

PARKINSON'S DISEASE
ALZHEIMER'S DISEASE
HUNTINGTON'S DISEASE etc.

APOPTOSIS: Role in Disease

Cancer

Apoptosis eliminates damaged cells
(damage => mutations => cancer

Tumor suppressor p53 controls senescence
and apoptosis responses to damage

Most cancer cells defective in apoptotic response

High levels of anti-apoptotic proteins
or
Low levels of pro-apoptotic proteins
===> CANCER

APOPTOSIS: Role in Disease

AGING

Aging --> both too much and too little apoptosis (evidence for both)

Too much (accumulated oxidative damage?) ---> tissue degeneration

Too little (defective sensors, signals? ---> dysfunctional cells accumulate hyperplasia (precancerous lesions)