

TP53 : Guardian of the genome

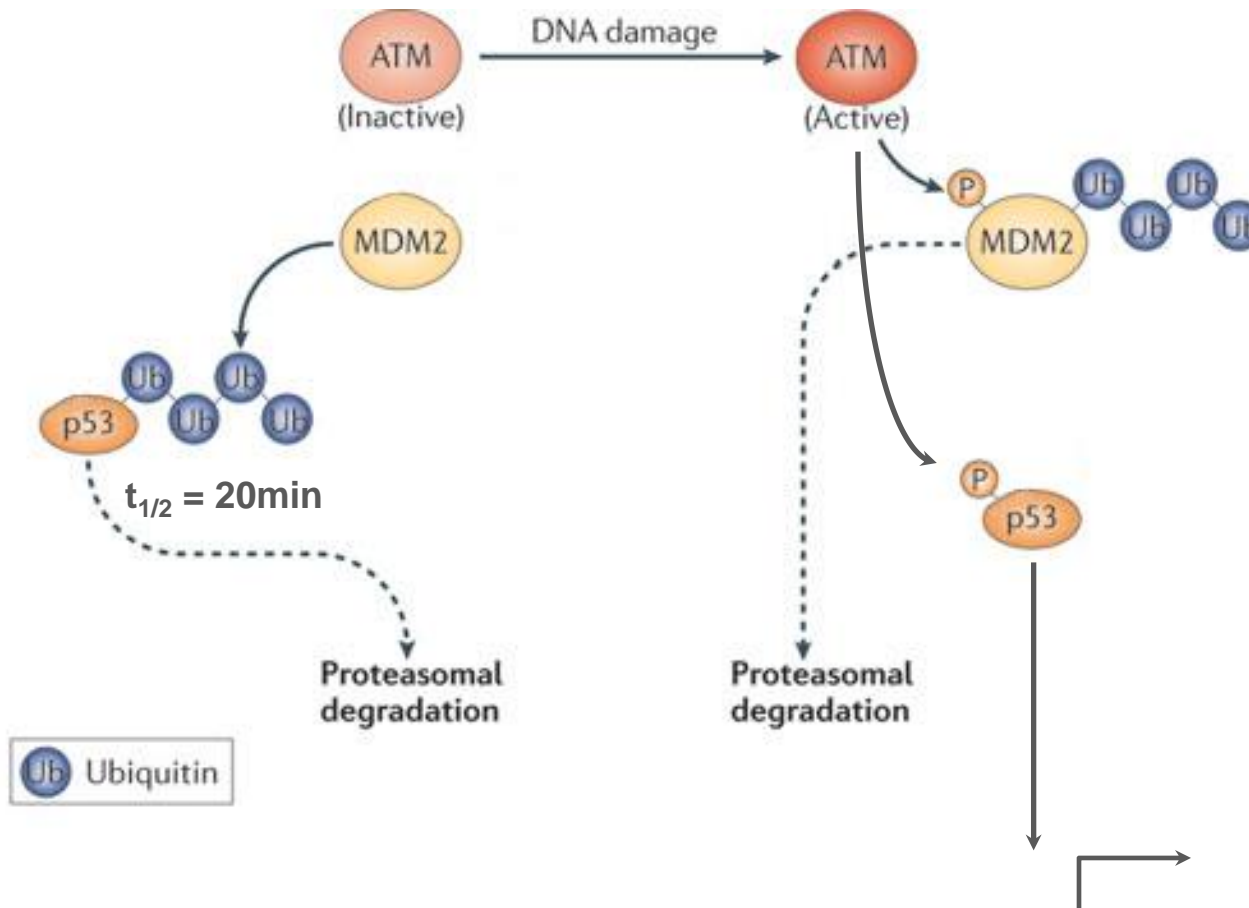
Li-Fraumeni syndrome

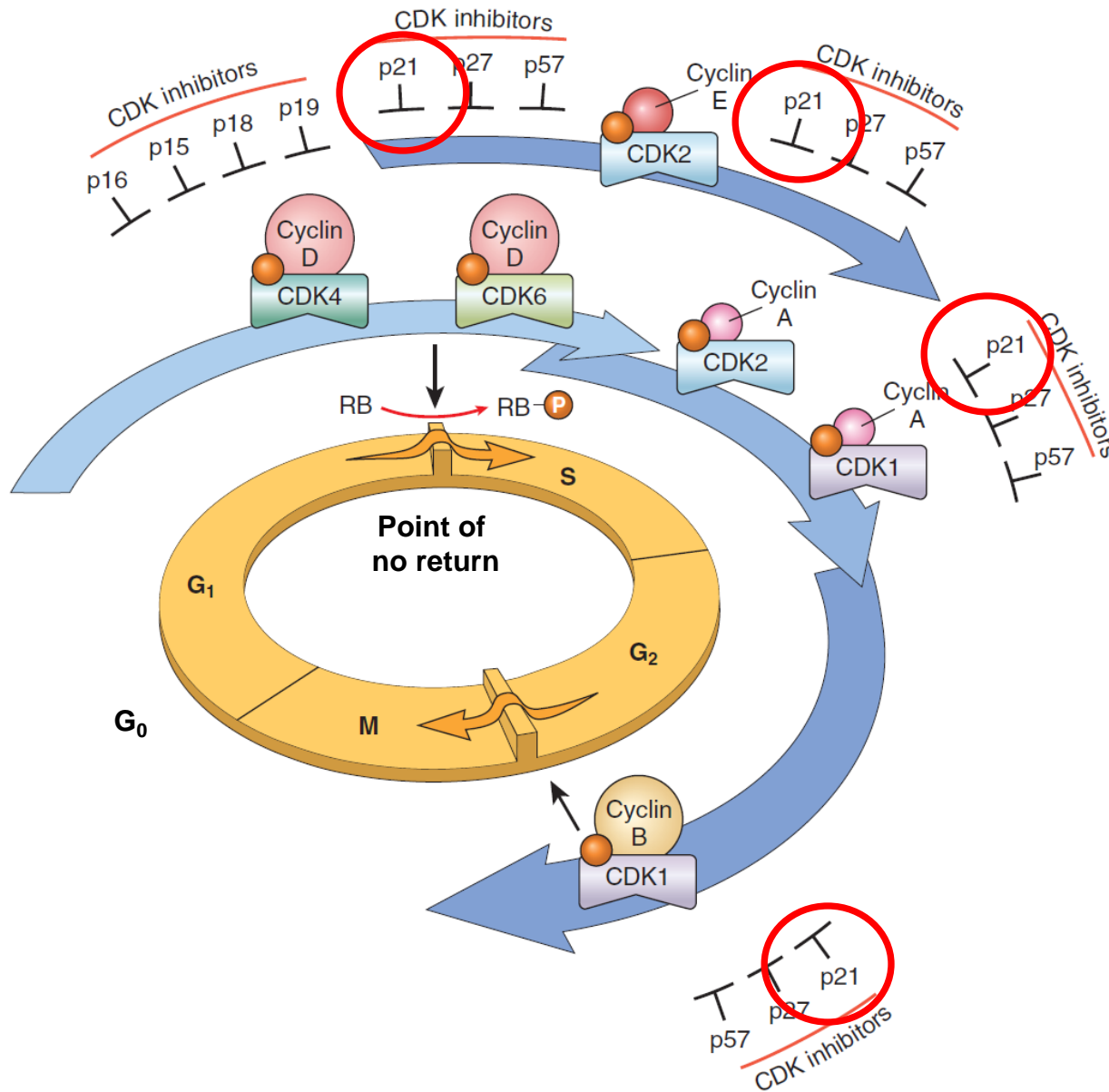
Tumor suppressor:

- Cell cycle arrest
temporary-quiescence
permanent-senescence
- Induce apoptosis

p53 senses:

- Anoxia
- Abnormal oncoprotein activity (e.g. MYC/RAS)
- DNA damage

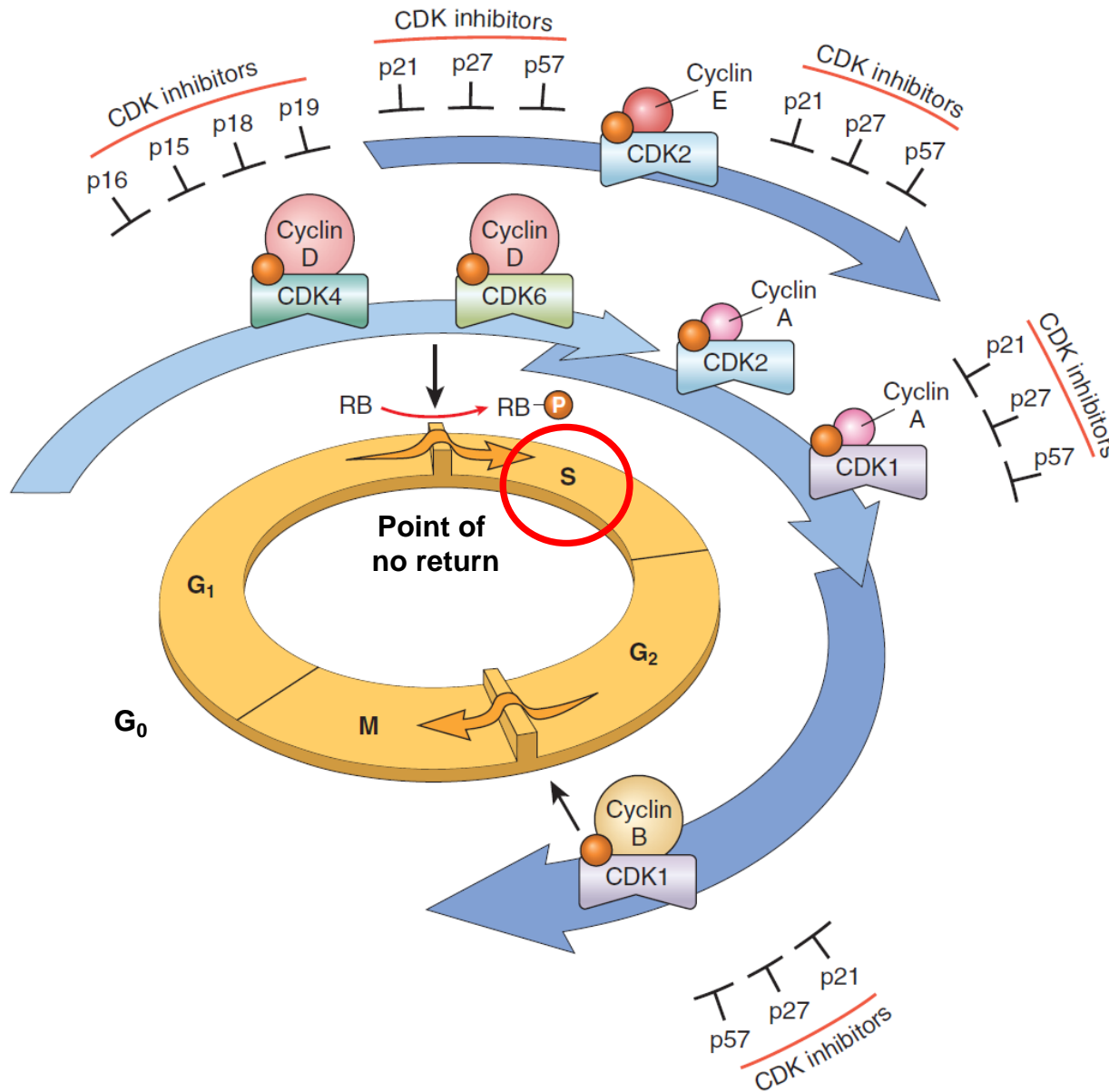




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Transcriptional targets:

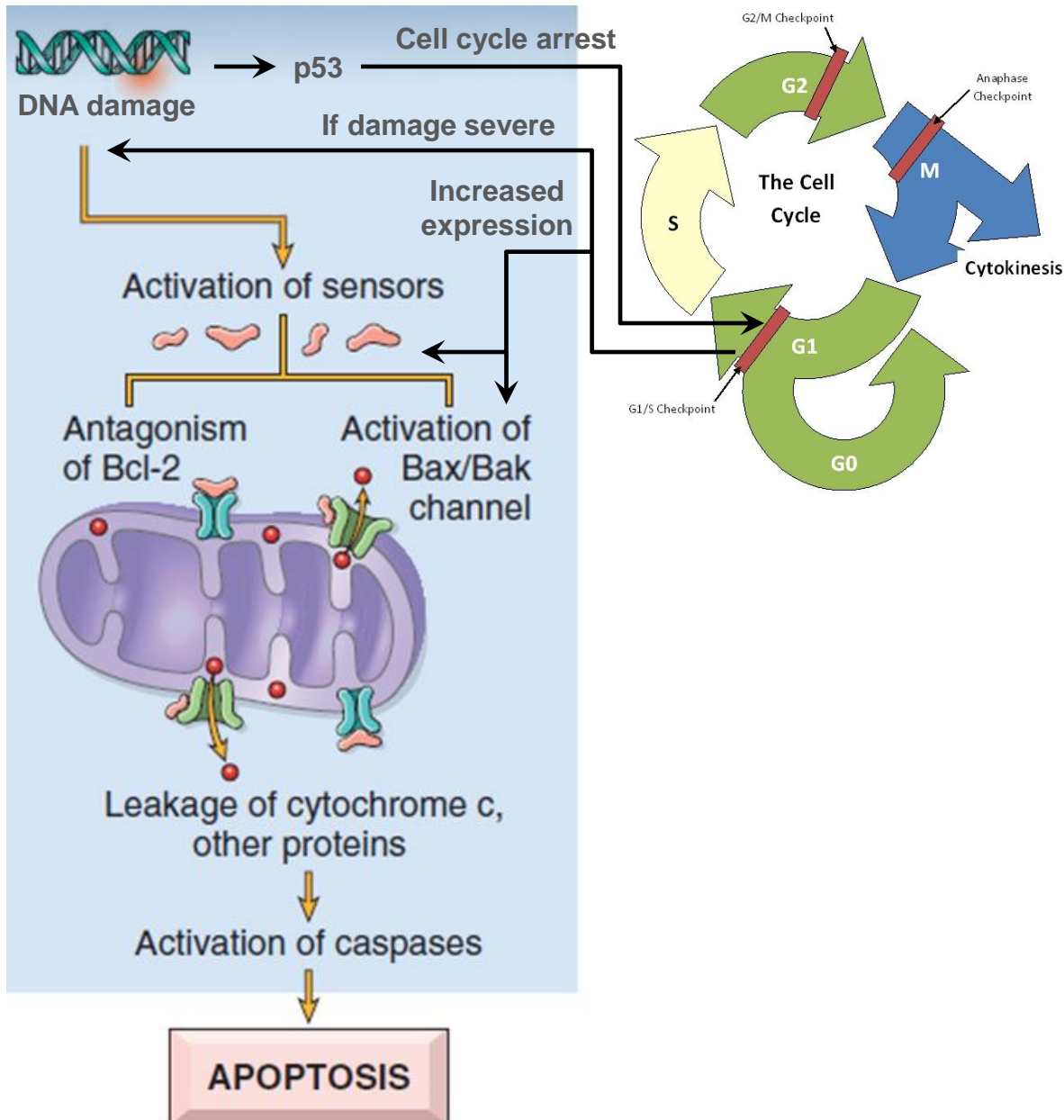
- **CDKN1A (p21)**
- *GADD45*: DNA repair
- *BAX*: Channel
- *PUMA*: Bcl-2 antagonist
- **miRNA**
 - ↓ Bcl-2
 - ↓ **Cyclins**
- *MDM2* (after repair)



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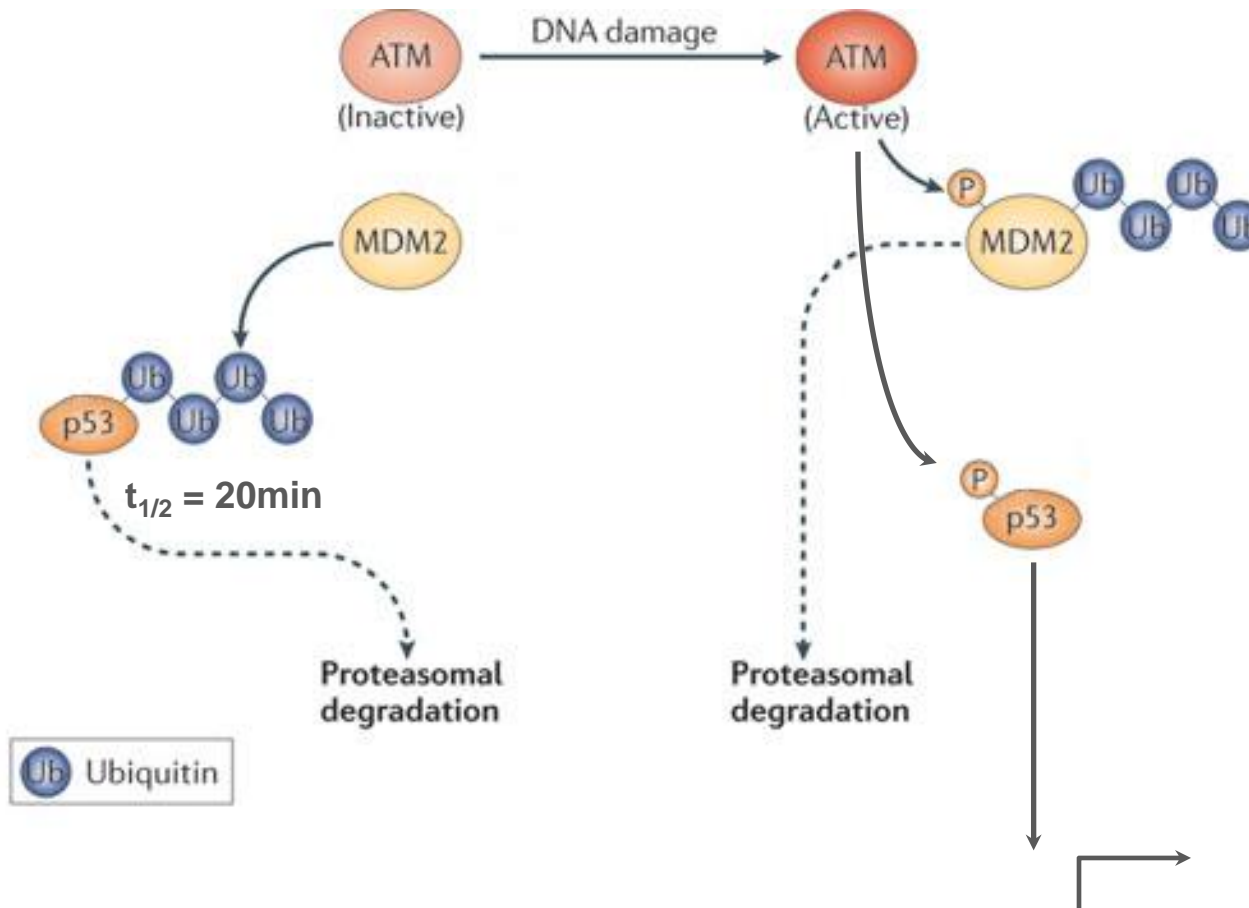
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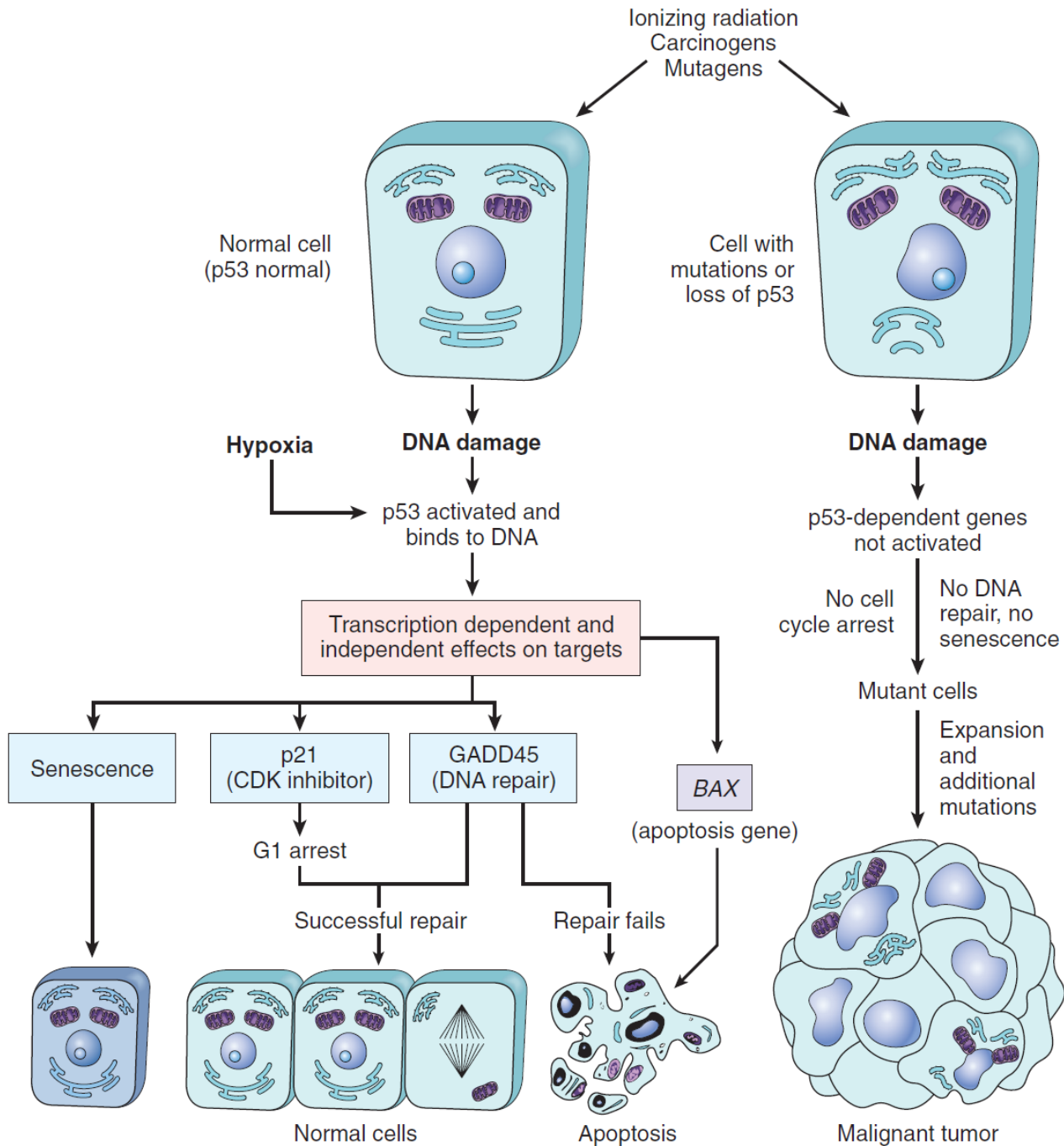
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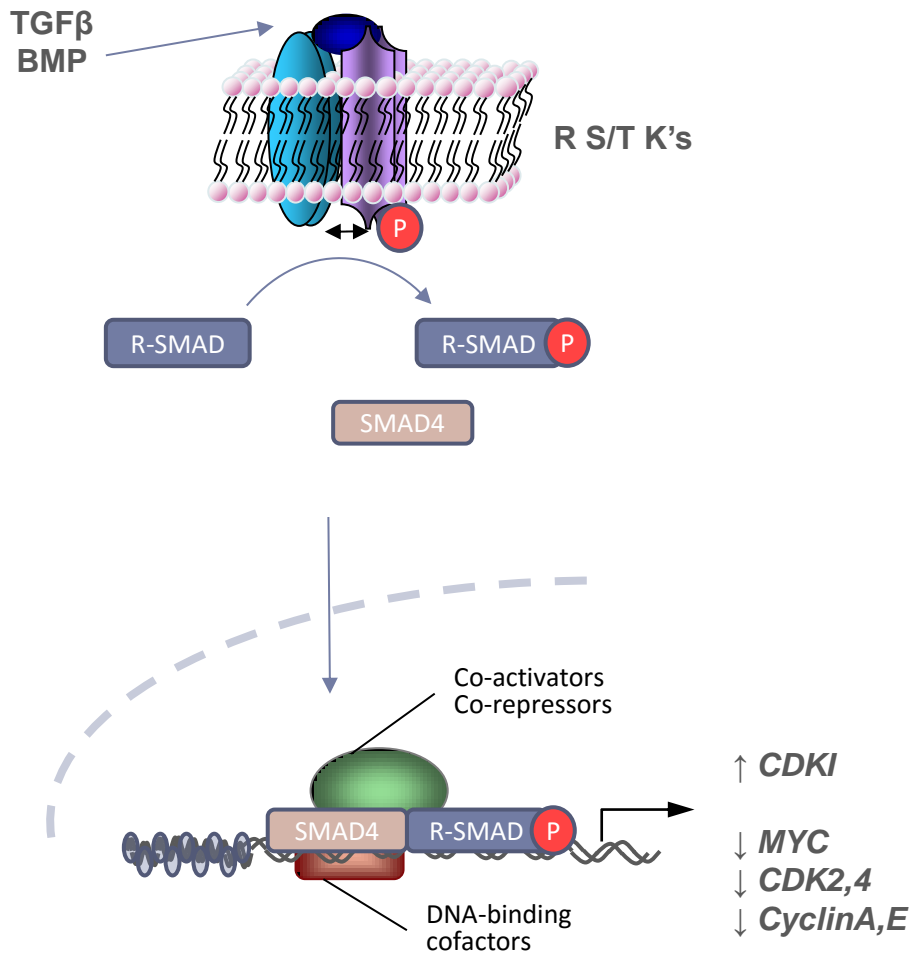
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Summary





TGFβ pathway signalling

Potent inhibitor of proliferation

Type II receptor mutations:

- Colon
- Stomach
- Endometrium

SMAD4 mutations:

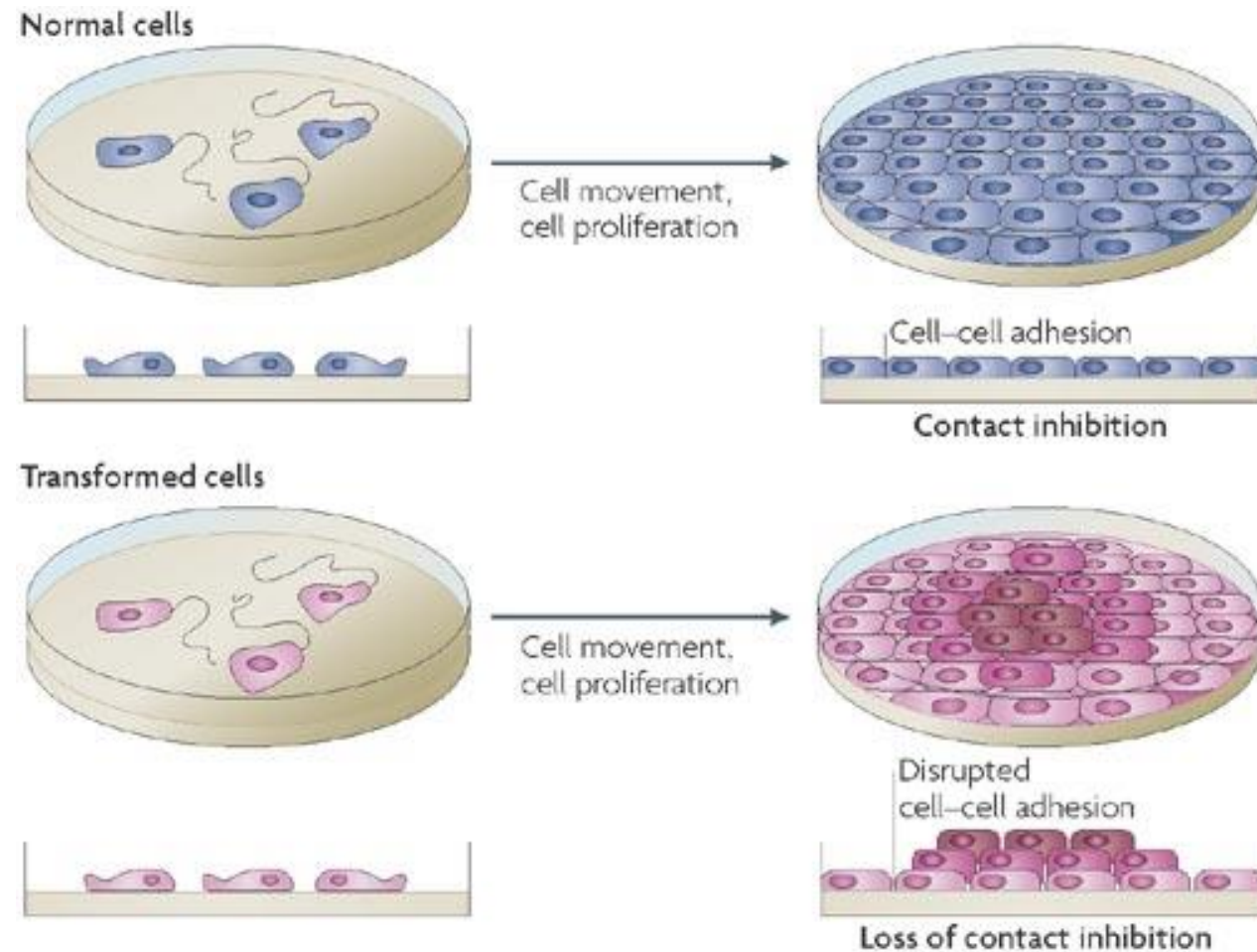
- Pancreas

Immune evasion,
Angiogenesis, EMT

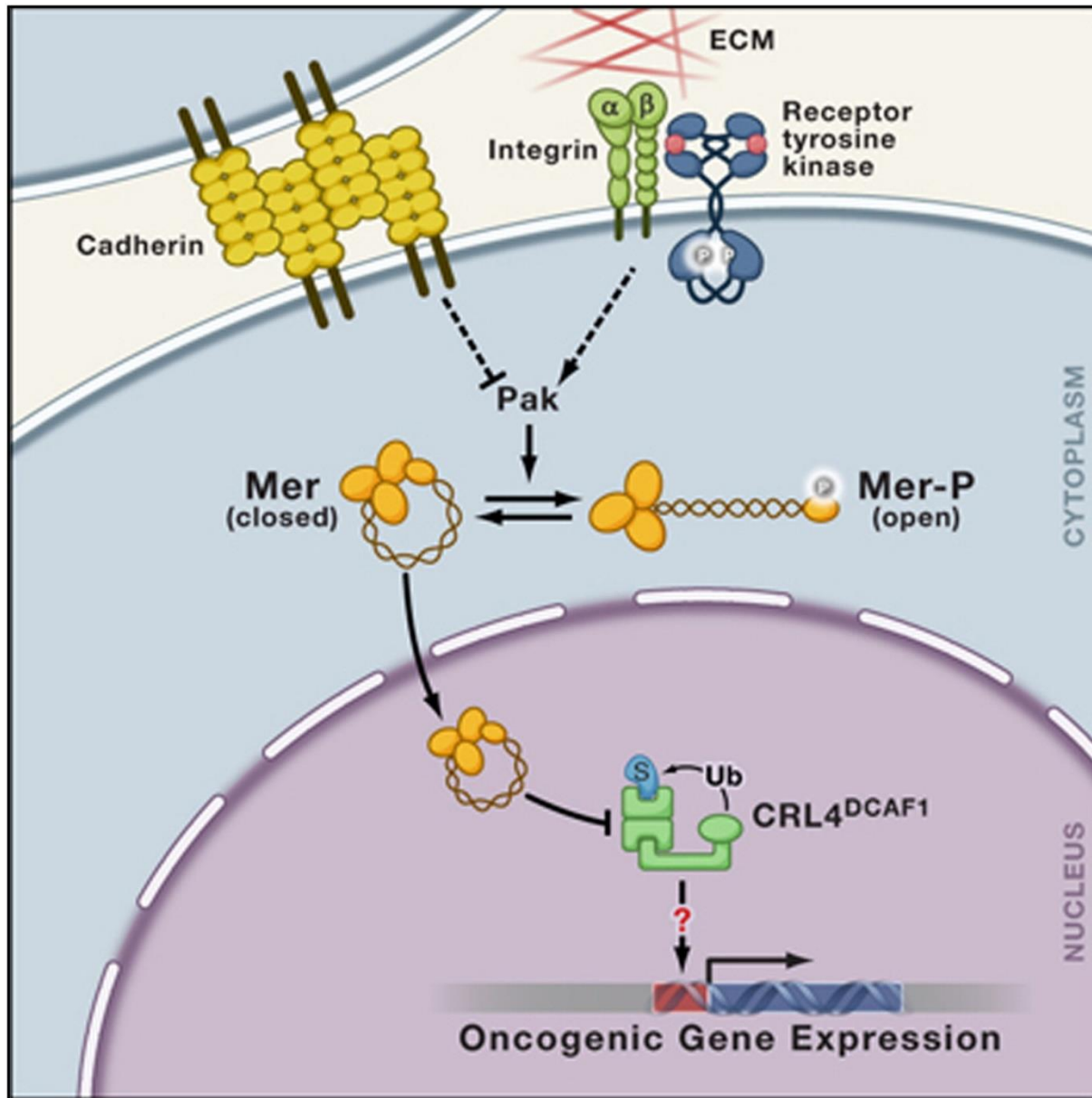
Contact Inhibition, NF2, and APC

Not fully understood

E-Cadherin homodimeric interaction



Nature Reviews | Molecular Cell Biology



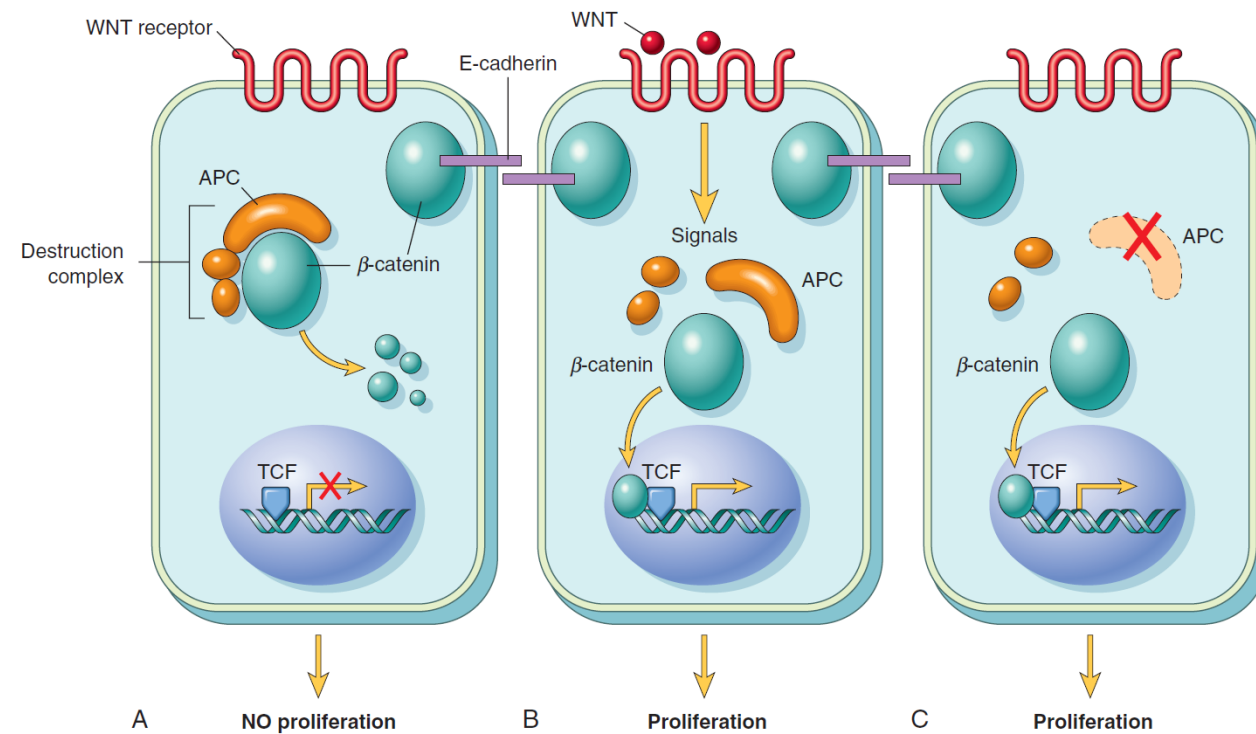
Contact Inhibition, NF2, and APC

Neurofibromin-2 (merlin)

NF2 homozygous loss = neurofibromatosis type 2:

noncancerous tumors in the nervous system (e.g. acoustic neuromas)





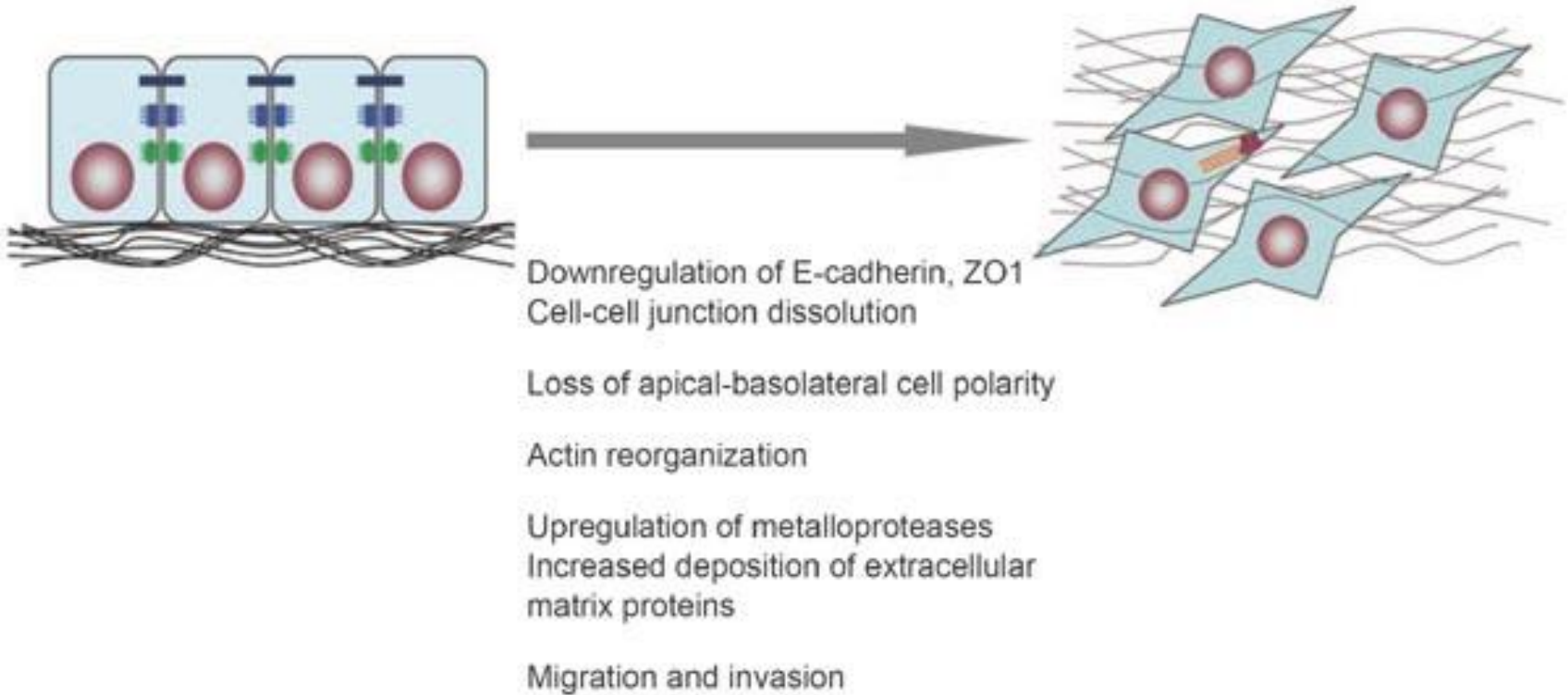
Contact Inhibition, NF2, and APC

adenomatous polyposis coli

β -catenin targets:

- growth-promoting genes
Cyclin D1
MYC
- Transcriptional regulators
TWIST
SLUG/SNAIL
↓
↓ E-cadherin expression →
↓ Contact inhibition
Role in **EMT**

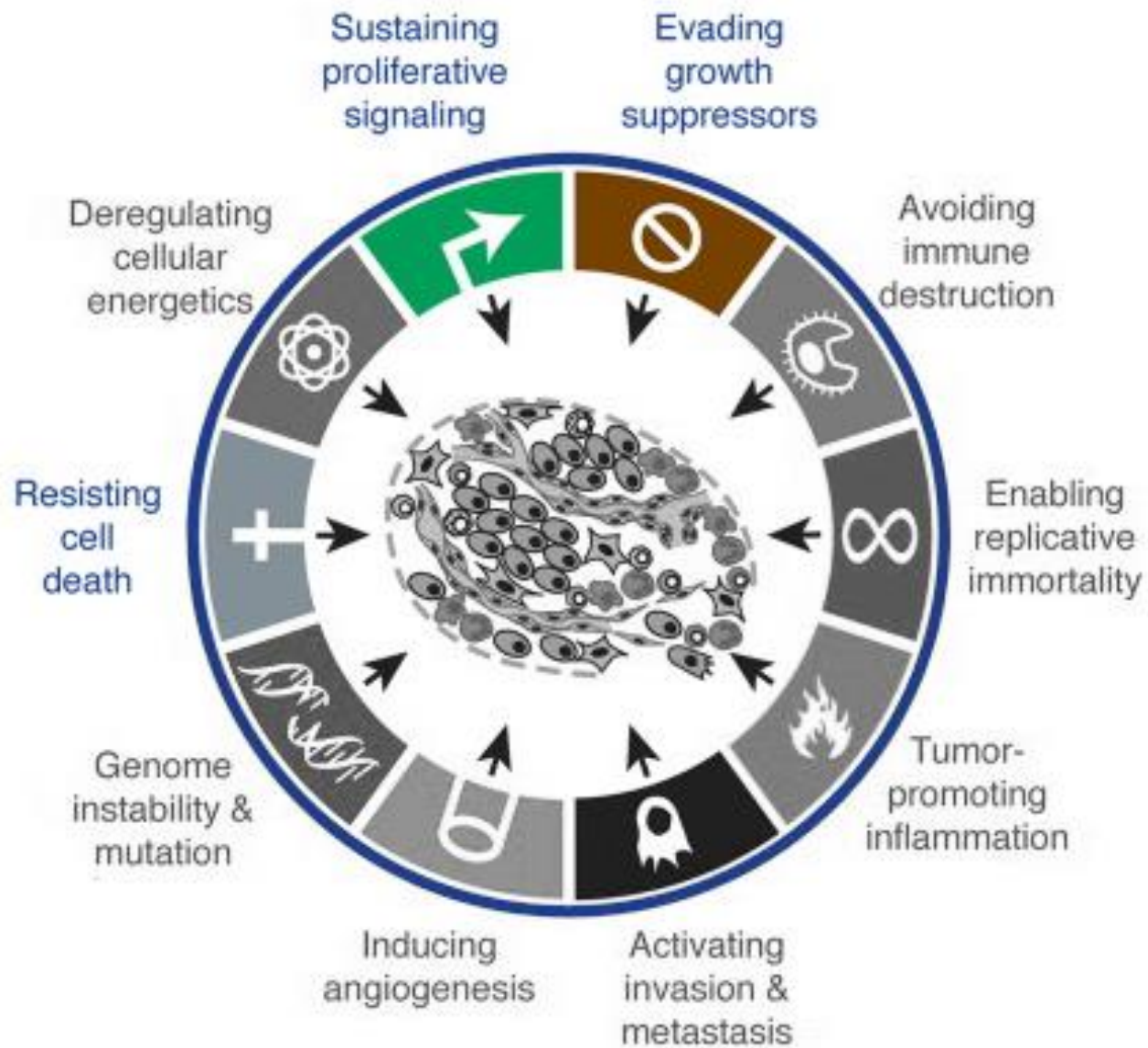
EMT





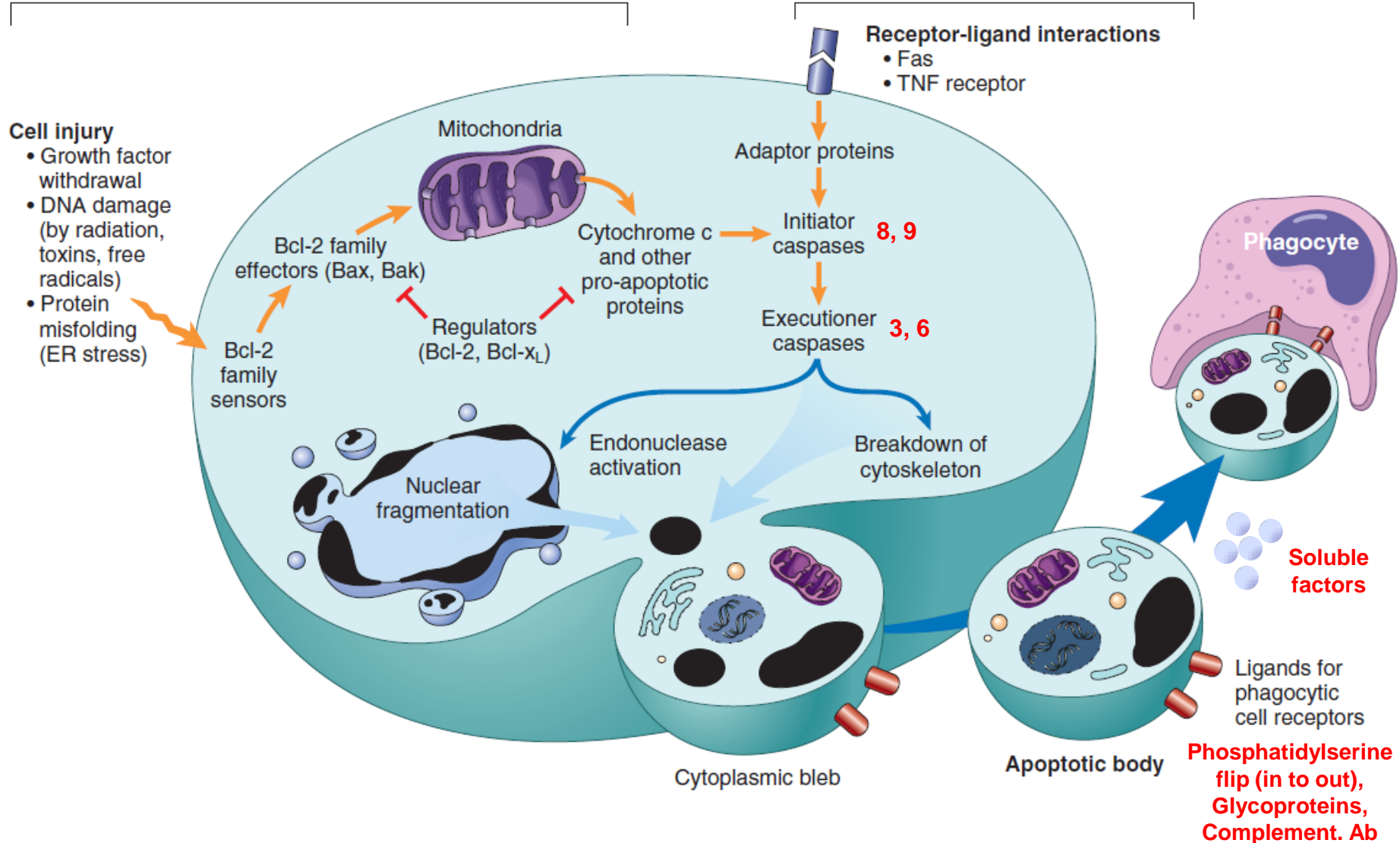
Hallmarks of Cancer

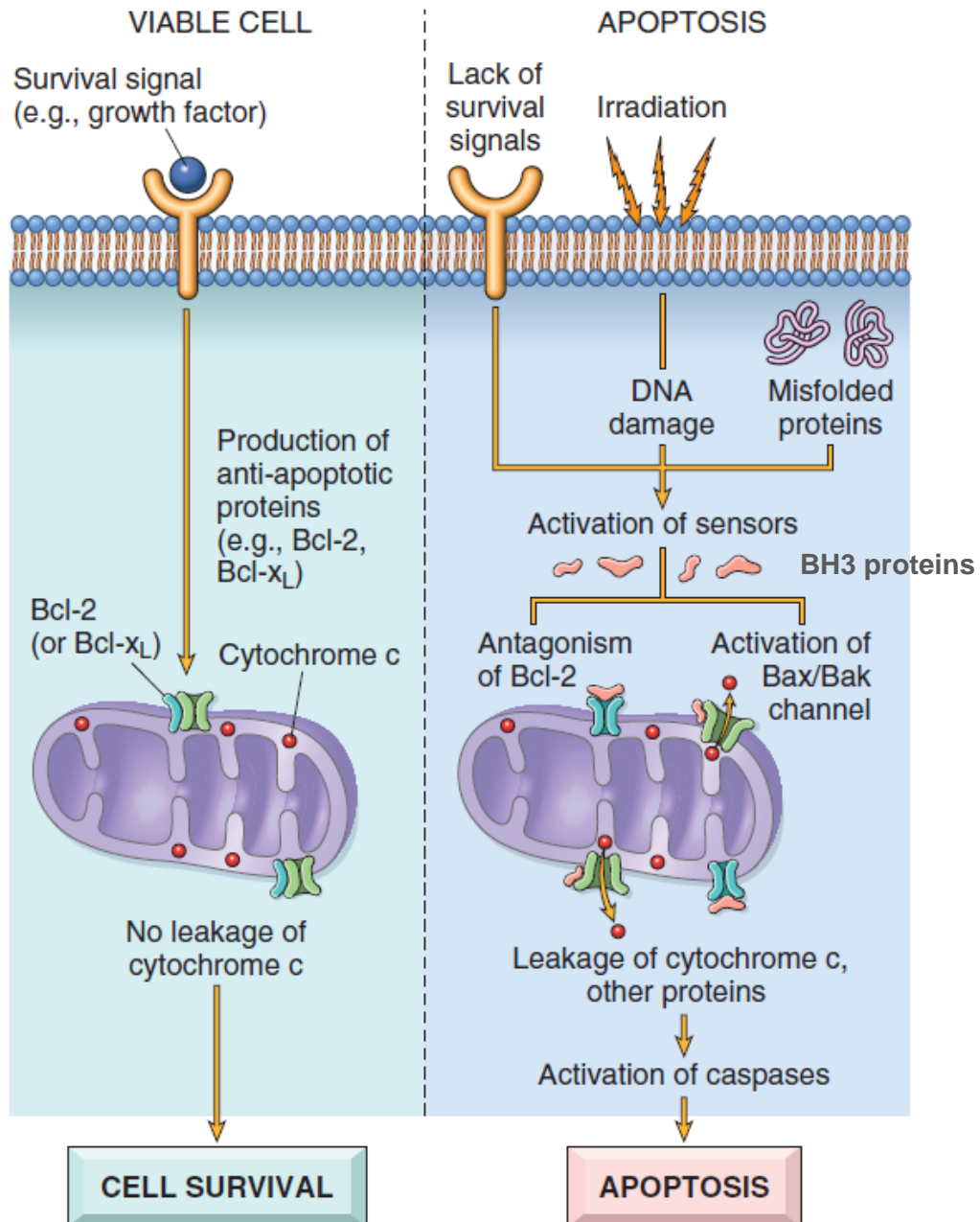
Evasion of Cell Death



MITOCHONDRIAL (INTRINSIC) PATHWAY

DEATH RECEPTOR (EXTRINSIC) PATHWAY





Mitochondrial (intrinsic)

Mitochondrial permeability is key

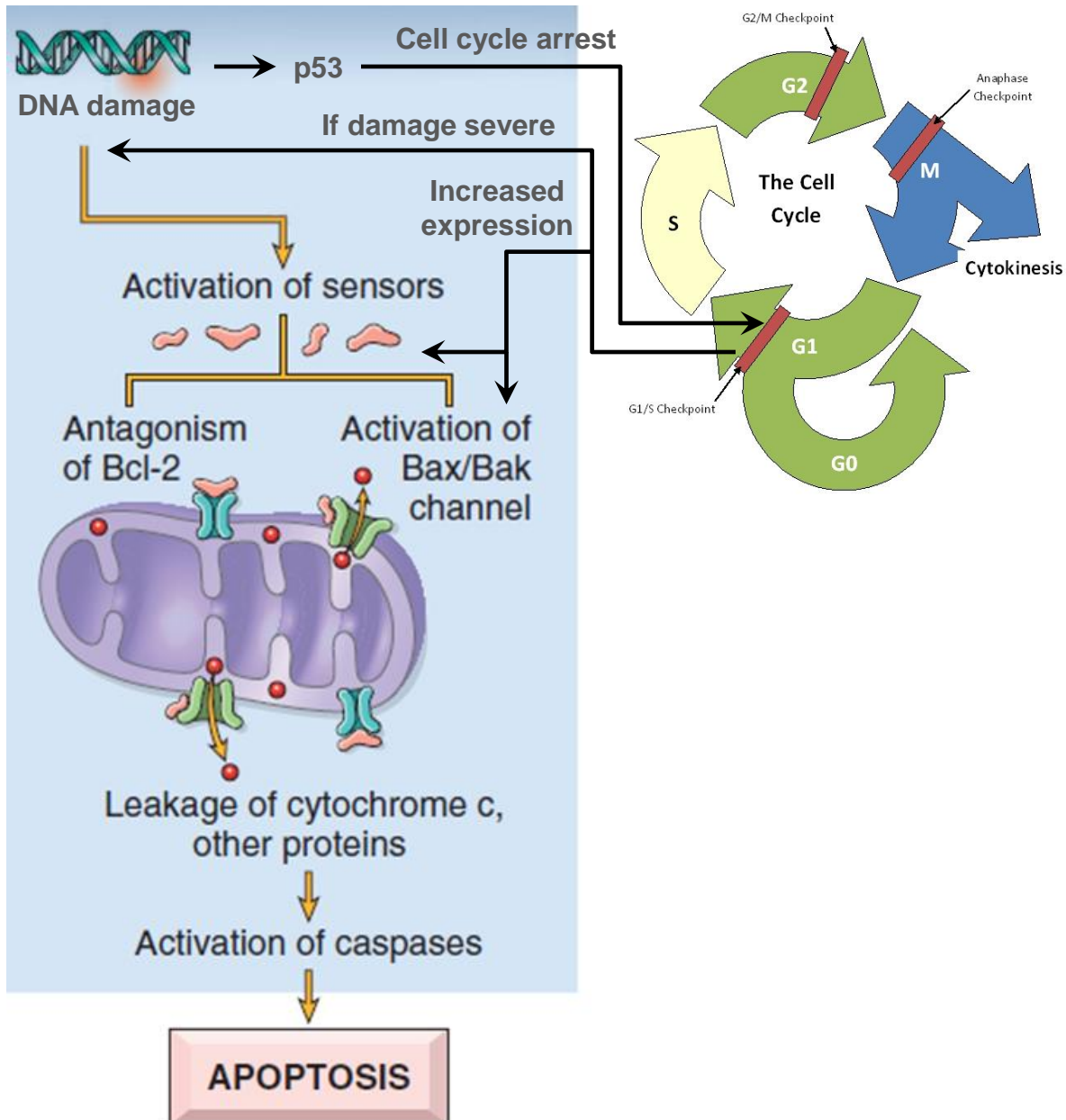
controlled > 20 proteins

Cytochrome c + cofactors, activates caspase-9

Anti-apoptotic proteins are inhibited

Bcl-2 & Bcl-x_L levels are reduced

Responsible for apoptosis in most situations

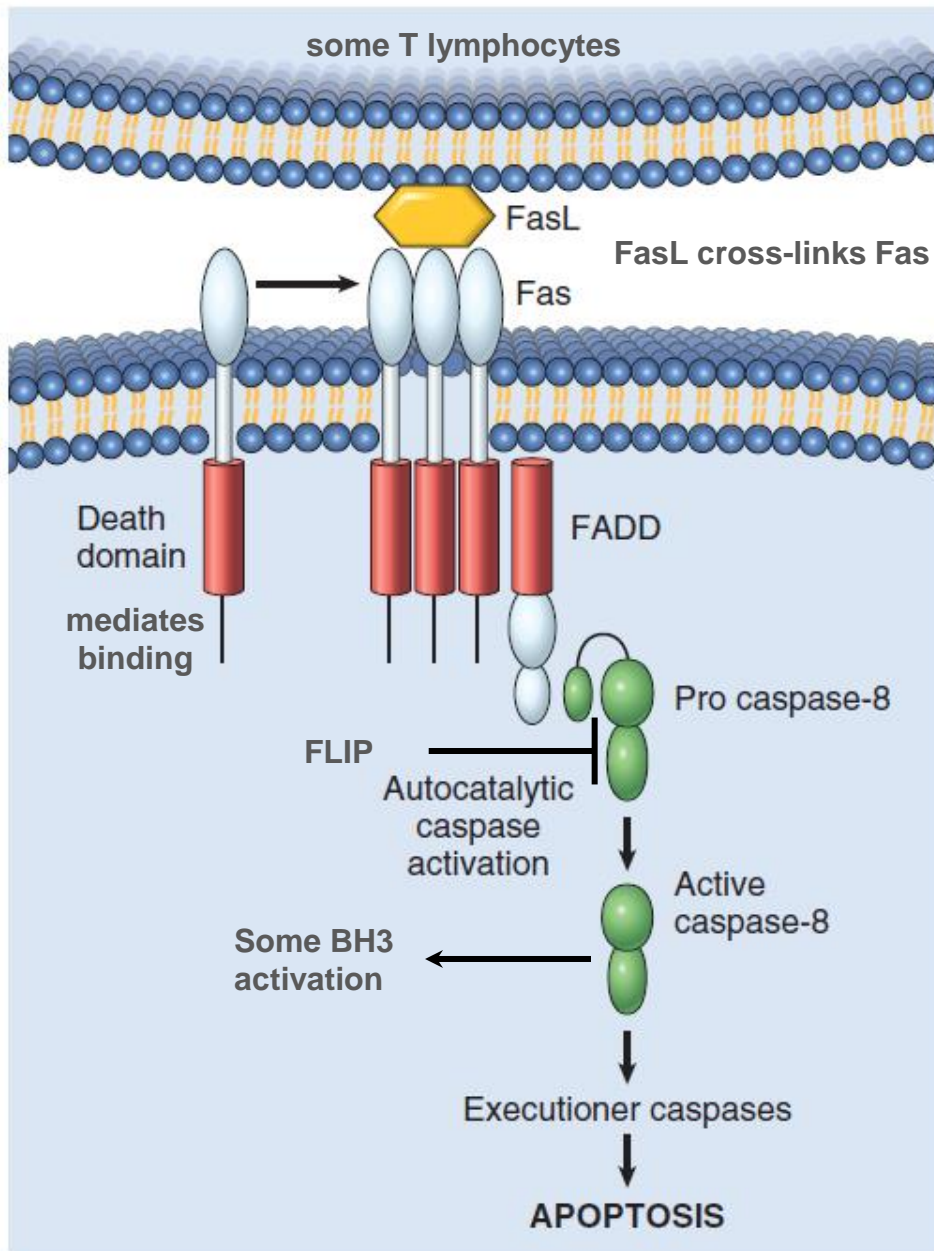


DNA damage

p53 accumulation

G1 arrest

p53 absence/mutation in certain cancers



Death receptor (extrinsic)

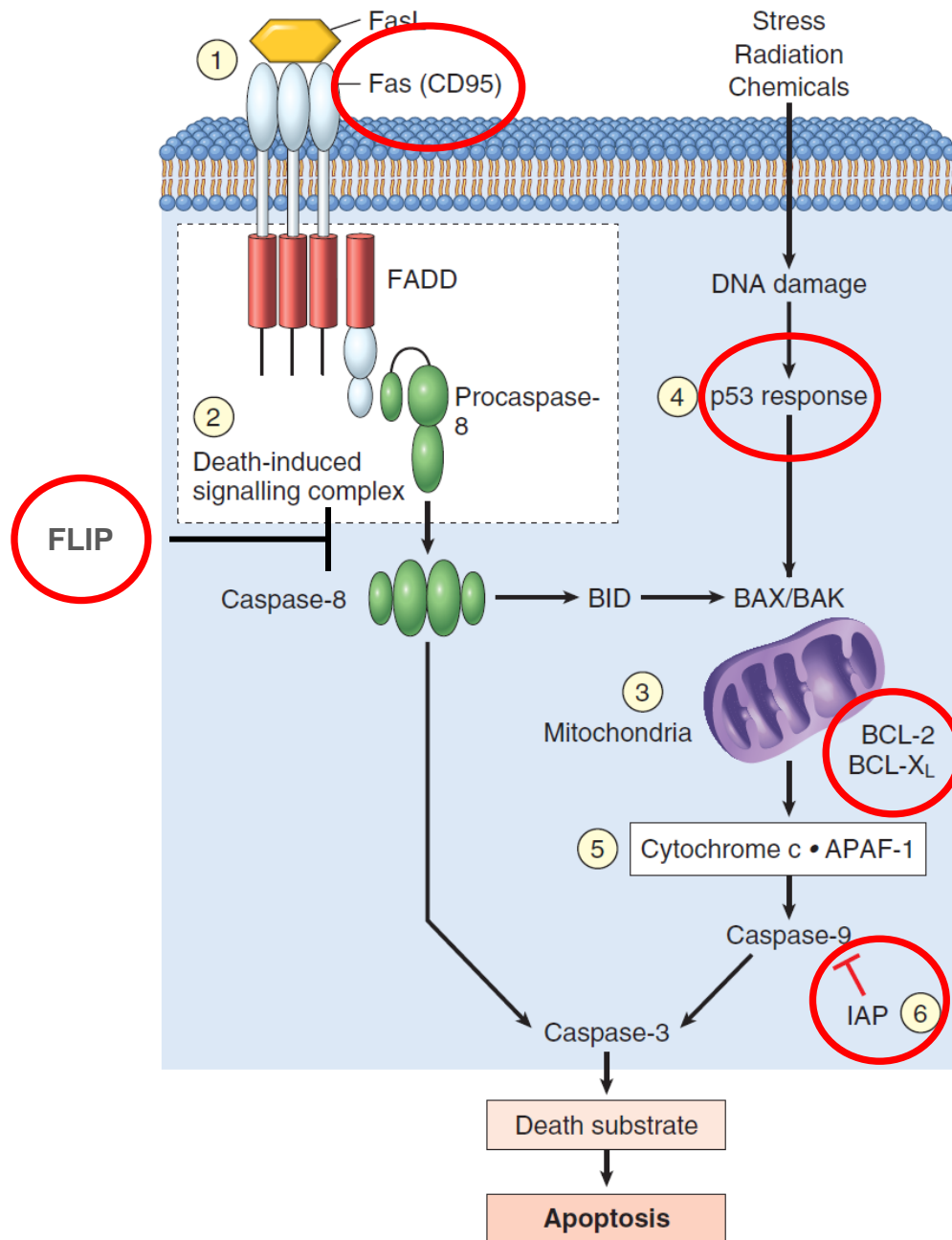
TNF receptor family

Responsible for apoptosis of self-reactive lymphocytes and target cells of some cytotoxic T lymphocytes

Fas or FasL mutations result in autoimmune diseases

Caspase-8 may cleave and activate Bid a "BH3 sensor" activating the mitochondrial pathway

Some viruses produce homologues of FLIP



Apoptosis abnormalities

Bcl-2 over-expression:

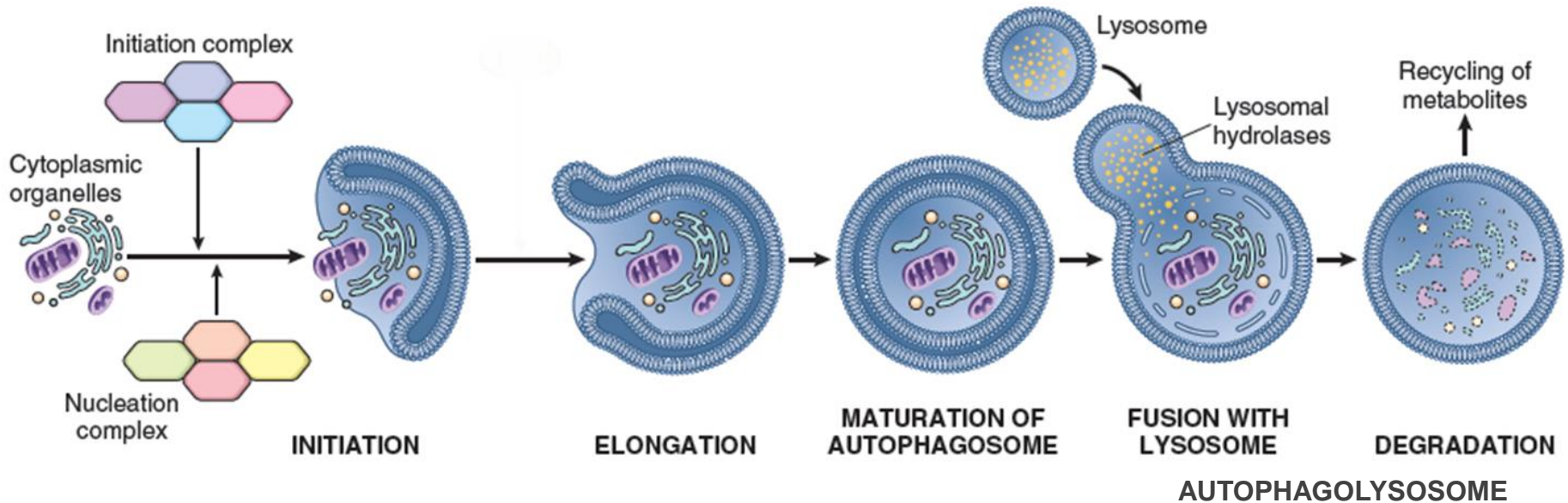
- Follicular B cell lymphoma (85%)
- t(14;18)
- Indolent growth

Reduced CD95 levels

FLIP over-expression

IAP over-expression

Greek: auto, *self*; phagy, *eating*



- ▶ Survival mechanism/nutrient deprivation
- ▶ Organelle turnover
- ▶ Has a role in cancer (anti or pro depending on internal/external factors)
- ▶ Regulatory overlap with apoptosis
- ▶ BH3 sensor Beclin-1 can induce apoptosis or autophagy