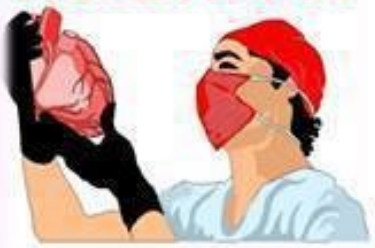
PATHOLOGY



Medical Committee
The University of Jordan

☐ SHEET

■ SIIDE

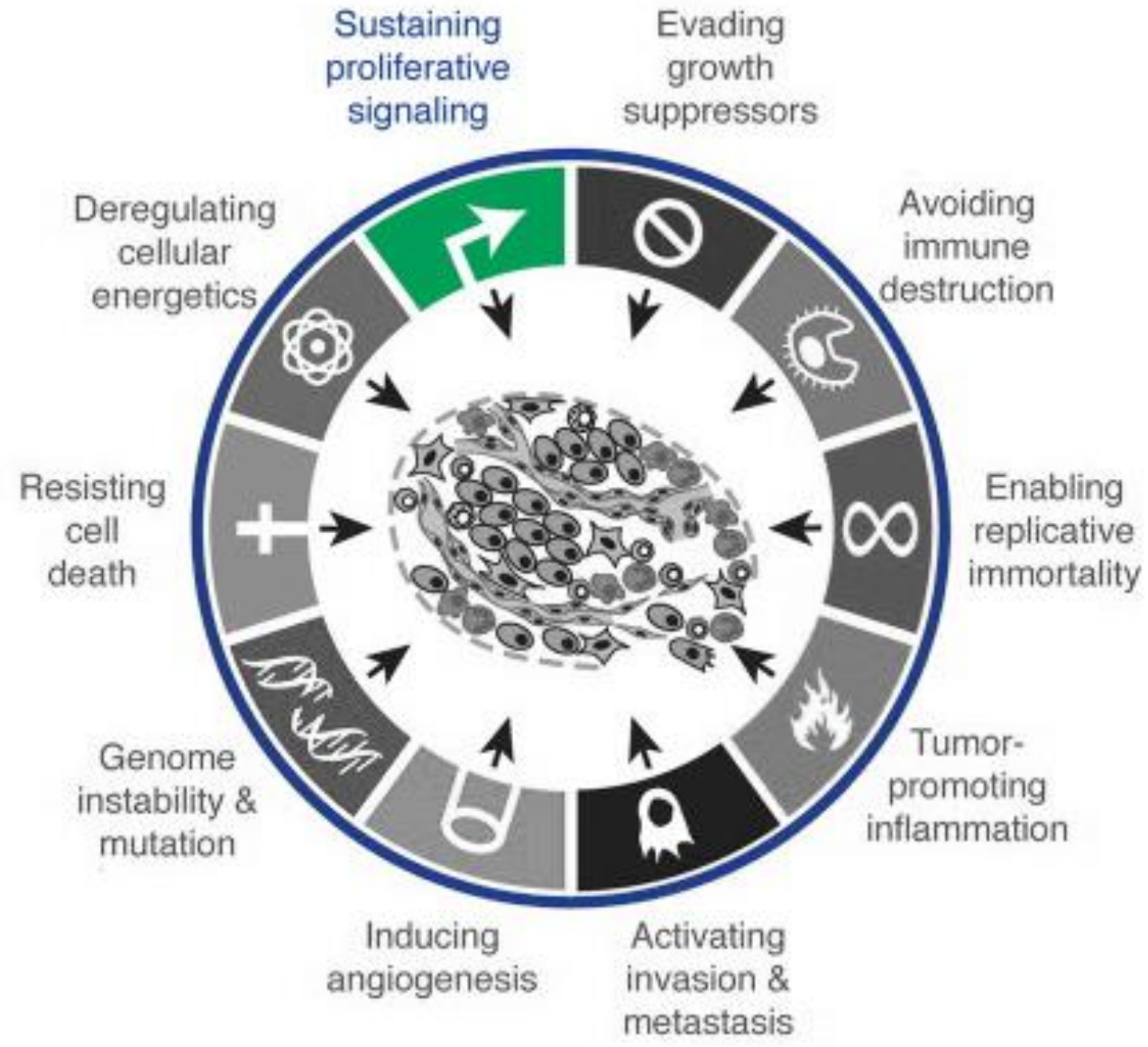
Slide : 17- Neoplasia

Doctor: Dr. Mazen

Designed by: Majida Al-Foqara'

Hallmarks of Cancer
Growth


Sustaining proliferative signaling
Evading growth suppressors
Avoiding immune destruction
Enabling replicative immortality
Tumor-promoting inflammation
Activating invasion & metastasis
Inducing angiogenesis
Genome instability & mutation
Resisting cell death
Deregulating cellular energetics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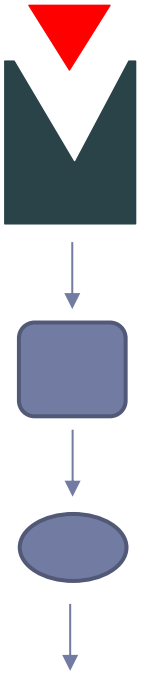
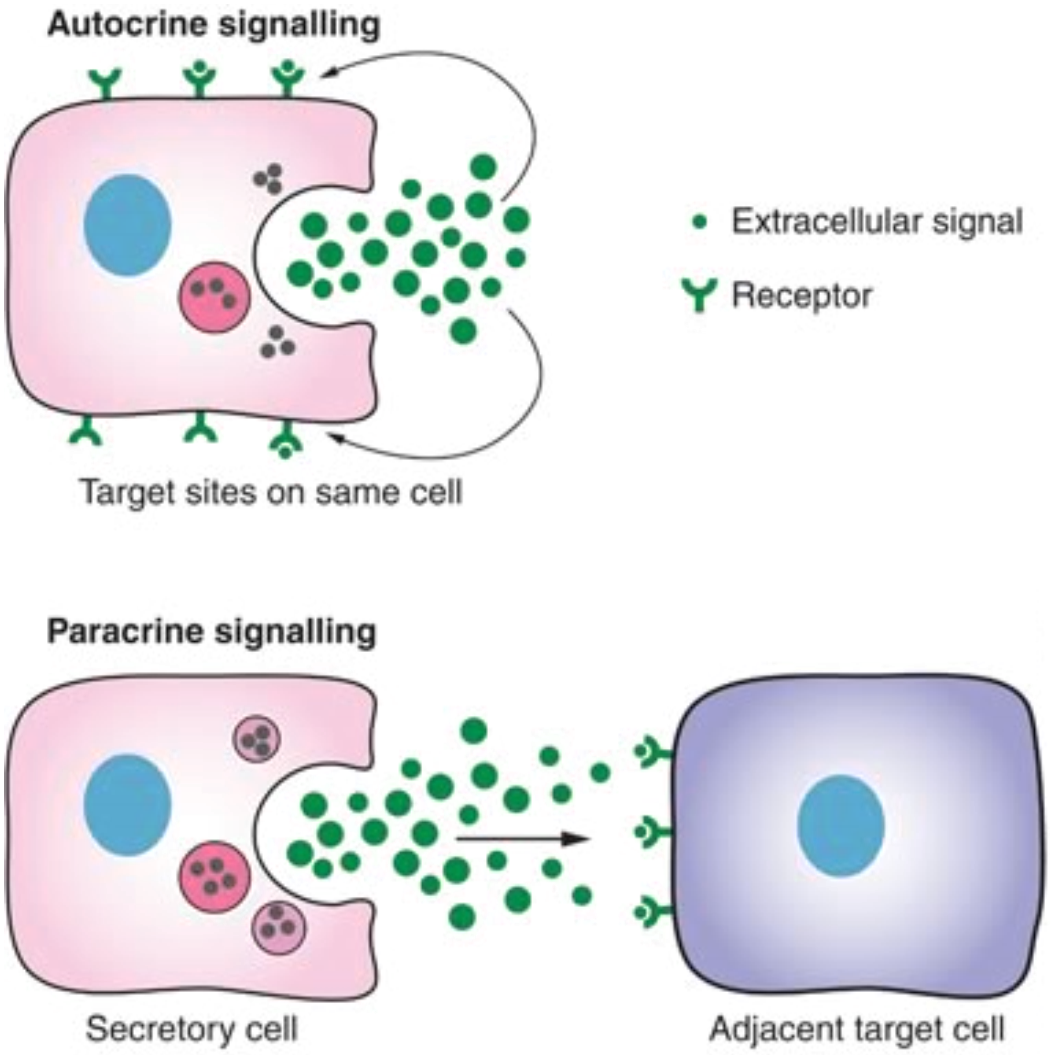


Cell signalling

1. Growth factor binding
2. Transient activation of the growth factor receptor
3. Signal transduction
4. Transcription regulation
5. Cell cycle entry & progression

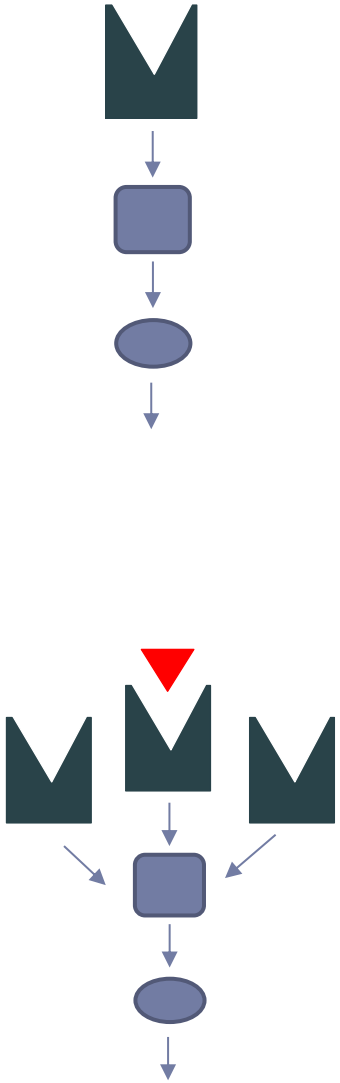


Growth factors

Typically paracrine
Subverted by abnormal stromal interaction

Autocrine = +ve feedback loop

e.g. Glioblastoma - PDGF
Sarcomas - TGFα



Receptors

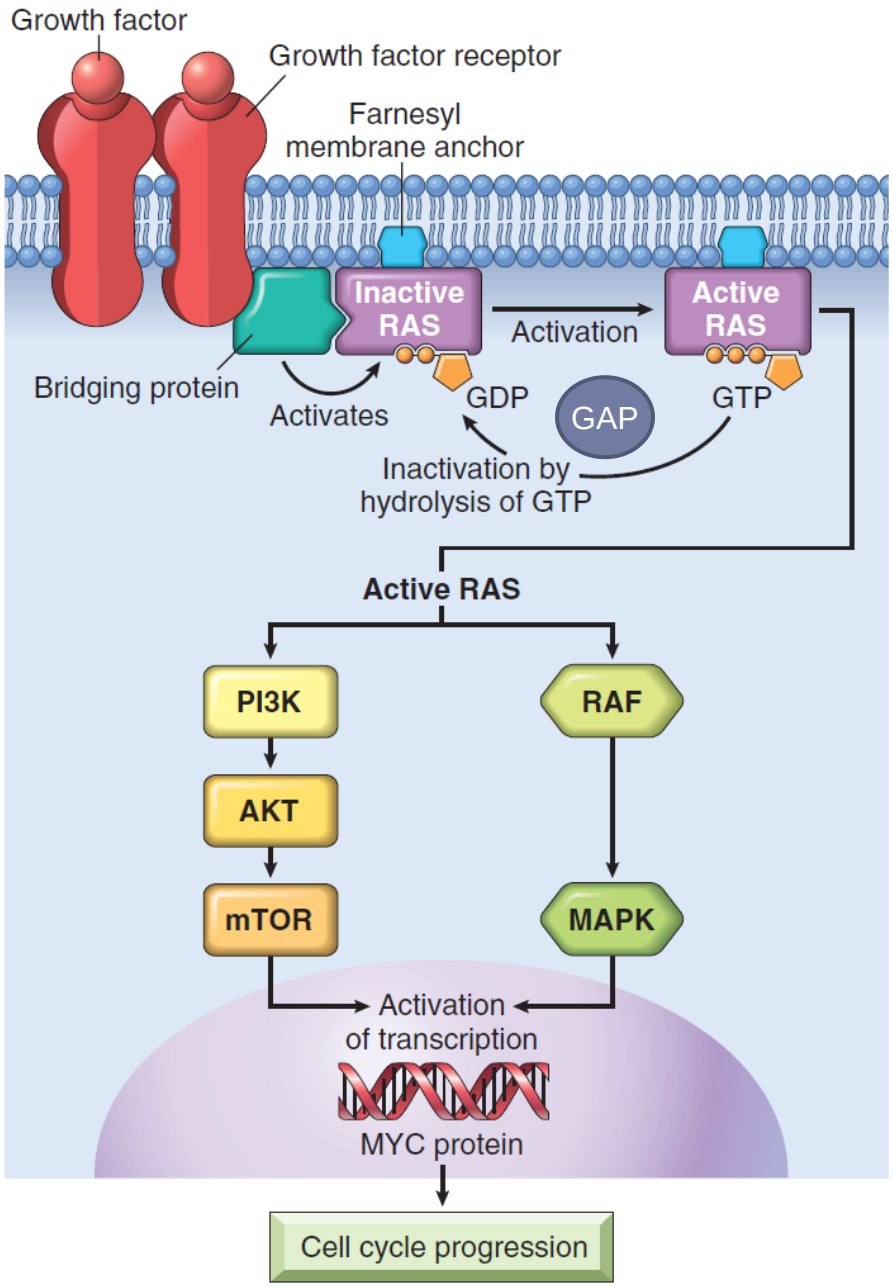
Receptor mutations leading to constitutive activation

e.g. EGFR mutations in colon/lung cancer

Receptor over-expression

e.g. EGFR Lung SCC
HER2/NEU breast

e.g. EGF
PDGF



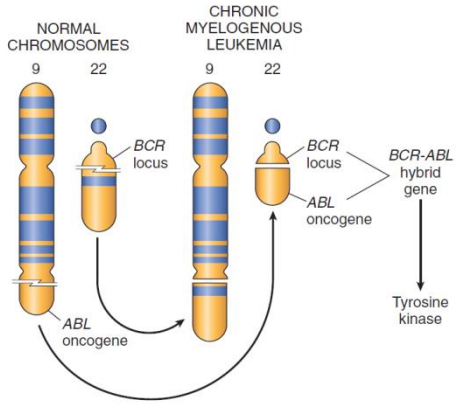
Signal transducers

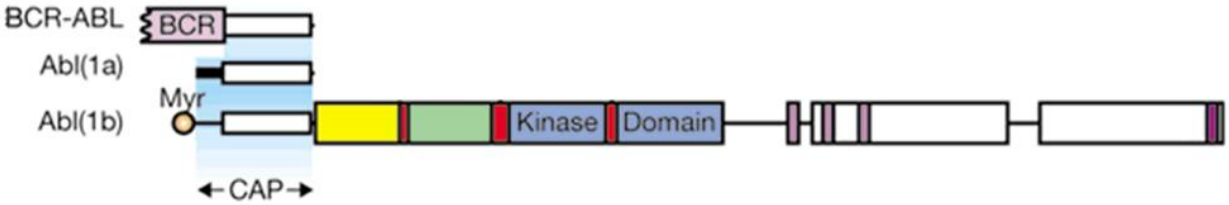
RAS

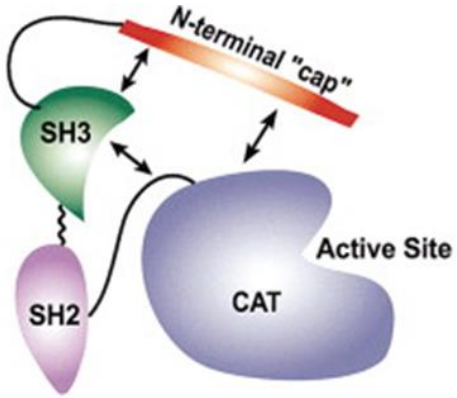
Small G protein

Most commonly mutated proto-oncogene in human tumors

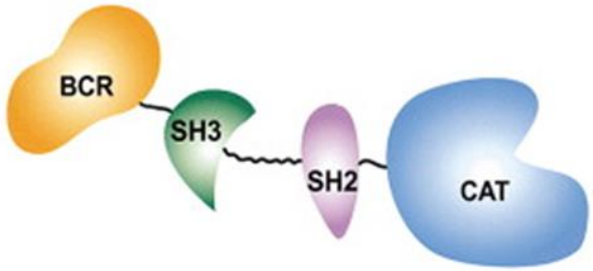
Point mutations within the GTP-binding pocket or in the enzymatic region essential for GTP hydrolysis.







INACTIVE C-ABL



ACTIVE BCR-ABL

Signal transducers

ABL

Non-receptor associated tyrosine kinase (TK)

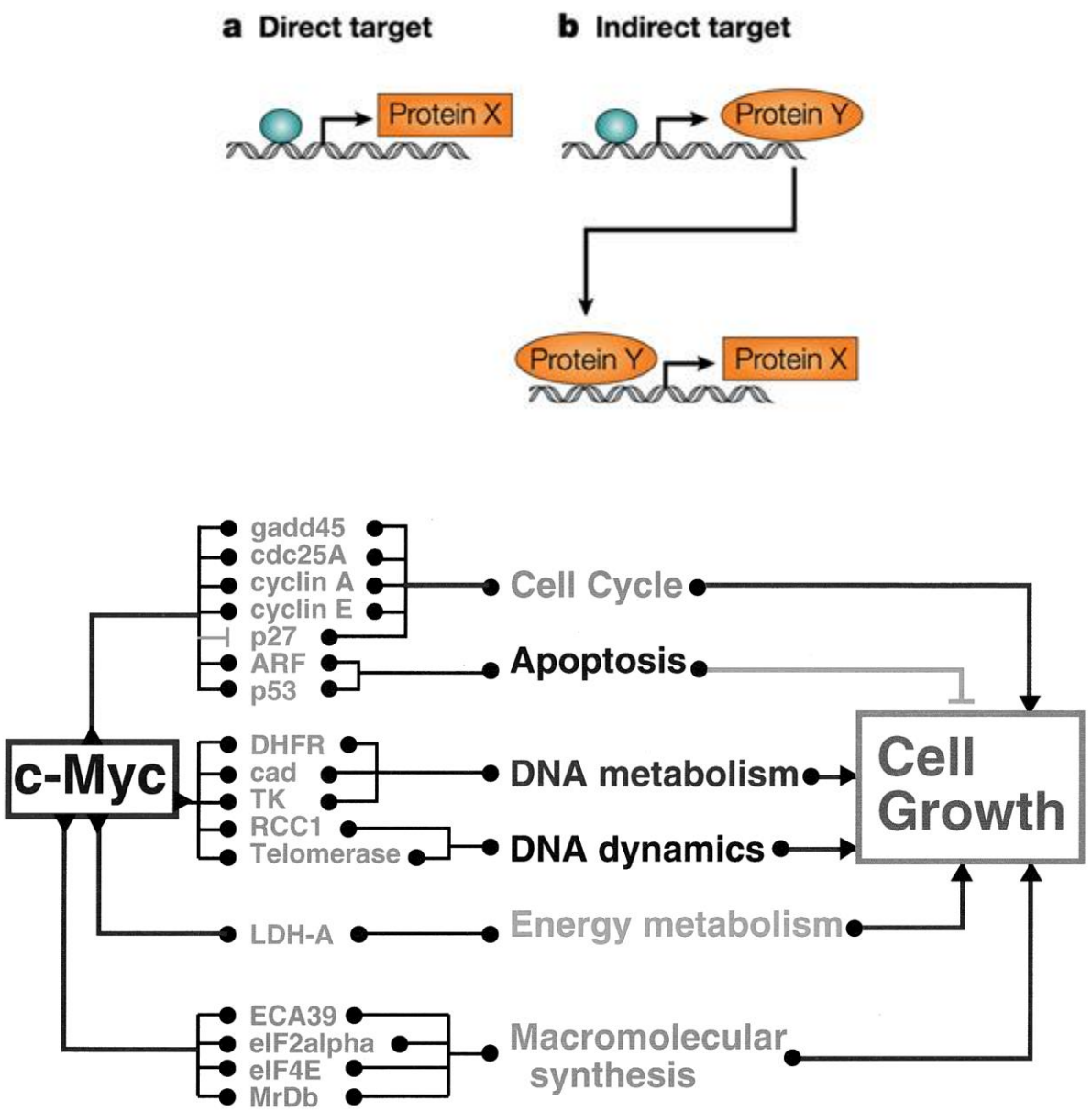
Internal ABL regulatory mechanism disrupted

Constitutive TK activity

Downstream RAS pathway activation

Oncogene addiction

Imatinib (Gleevec)



Transcription factors

MYC

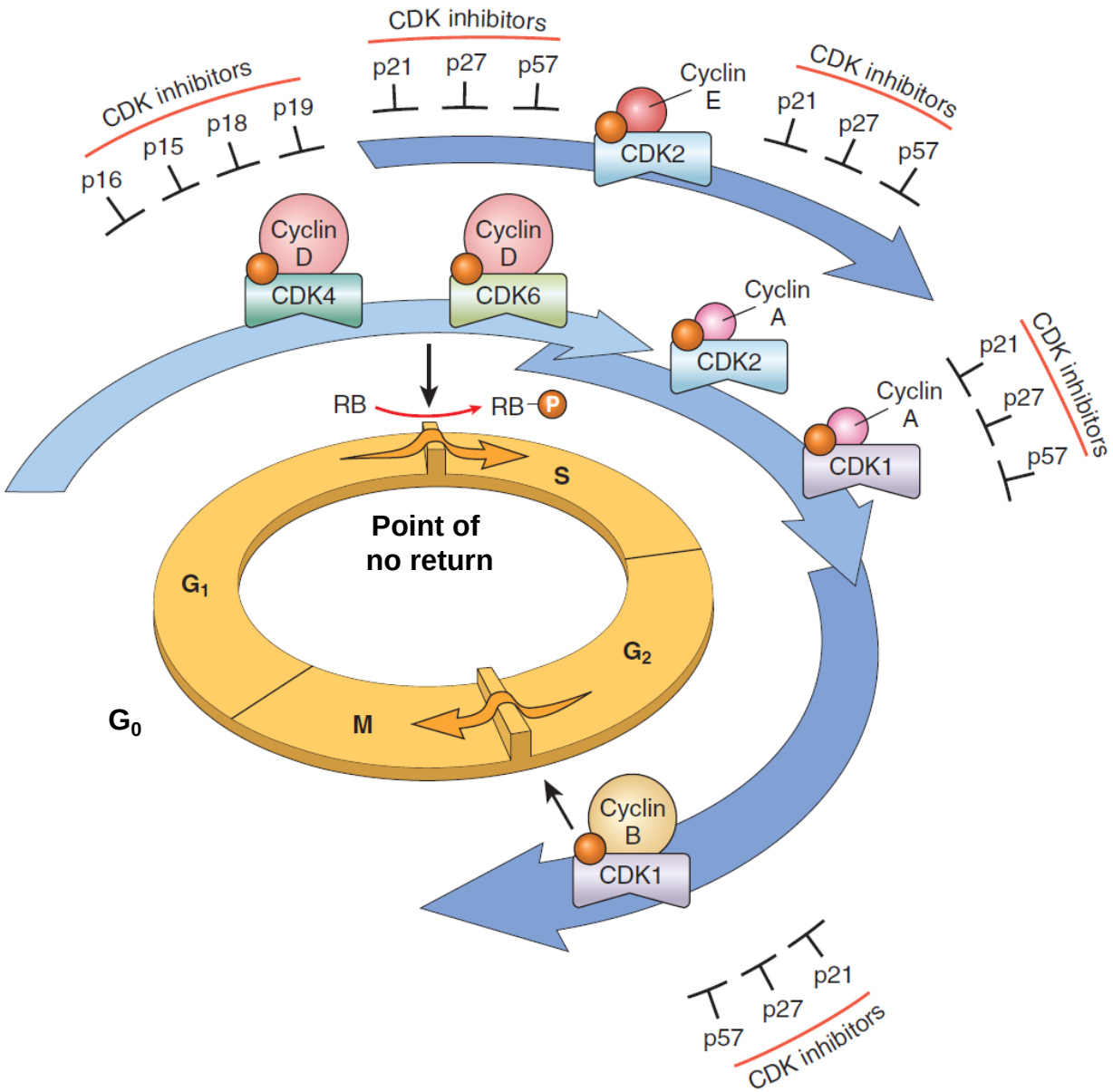
Activate/repress transcription

+CDK
-CDKI

t(8;14) *MYC* in Burkitt lymphoma

Amplification in breast, colon, & lung cancers

NMYC neuroblastoma
LMYC small cell lung cancer



Cyclins & CDKs

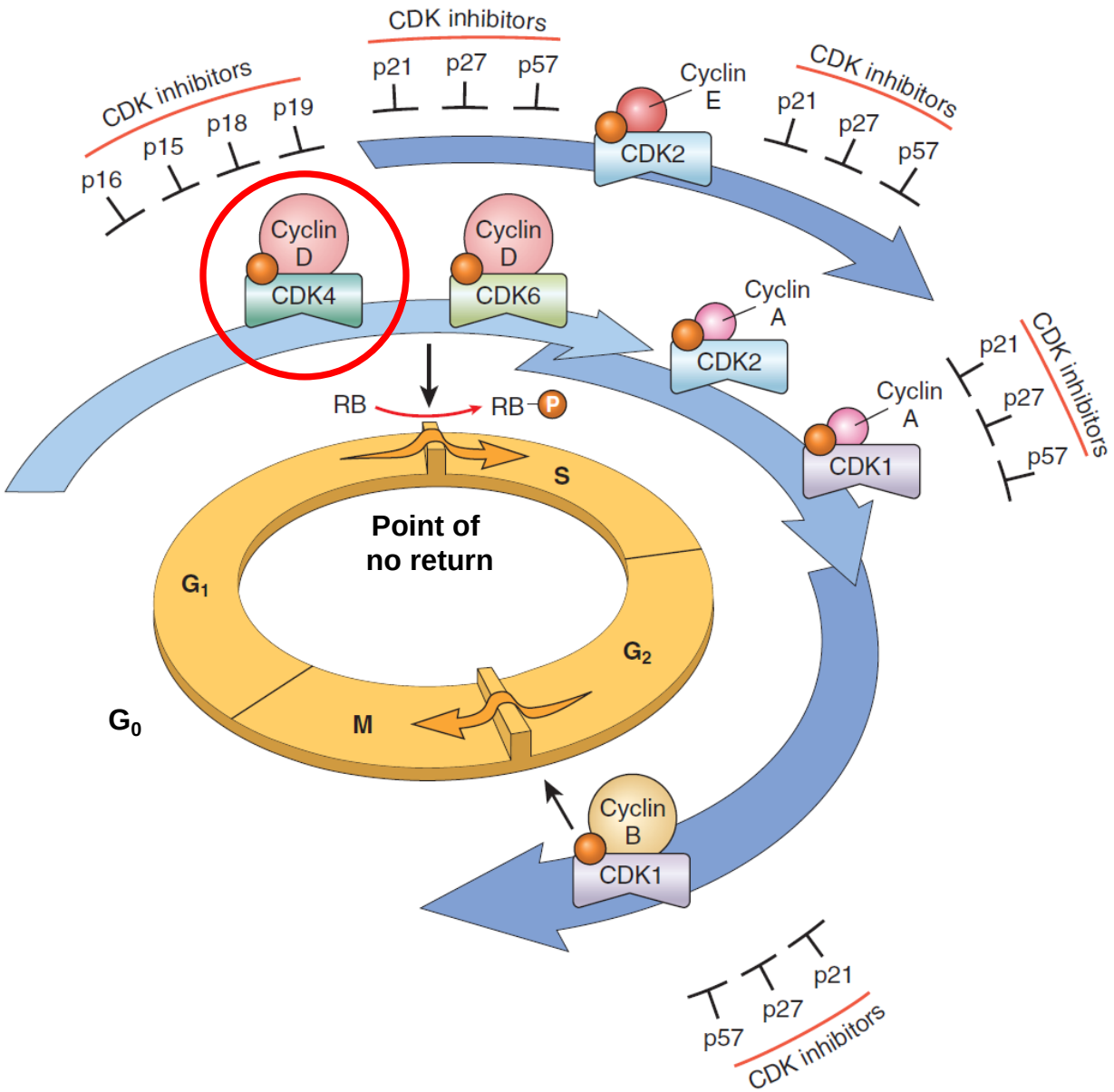
Quiescent cells G_0 induced to enter the cell cycle by GF & ECM integrin signalling

Cyclin+CDK=active CDK

Regulation by CDKI

Checkpoints:

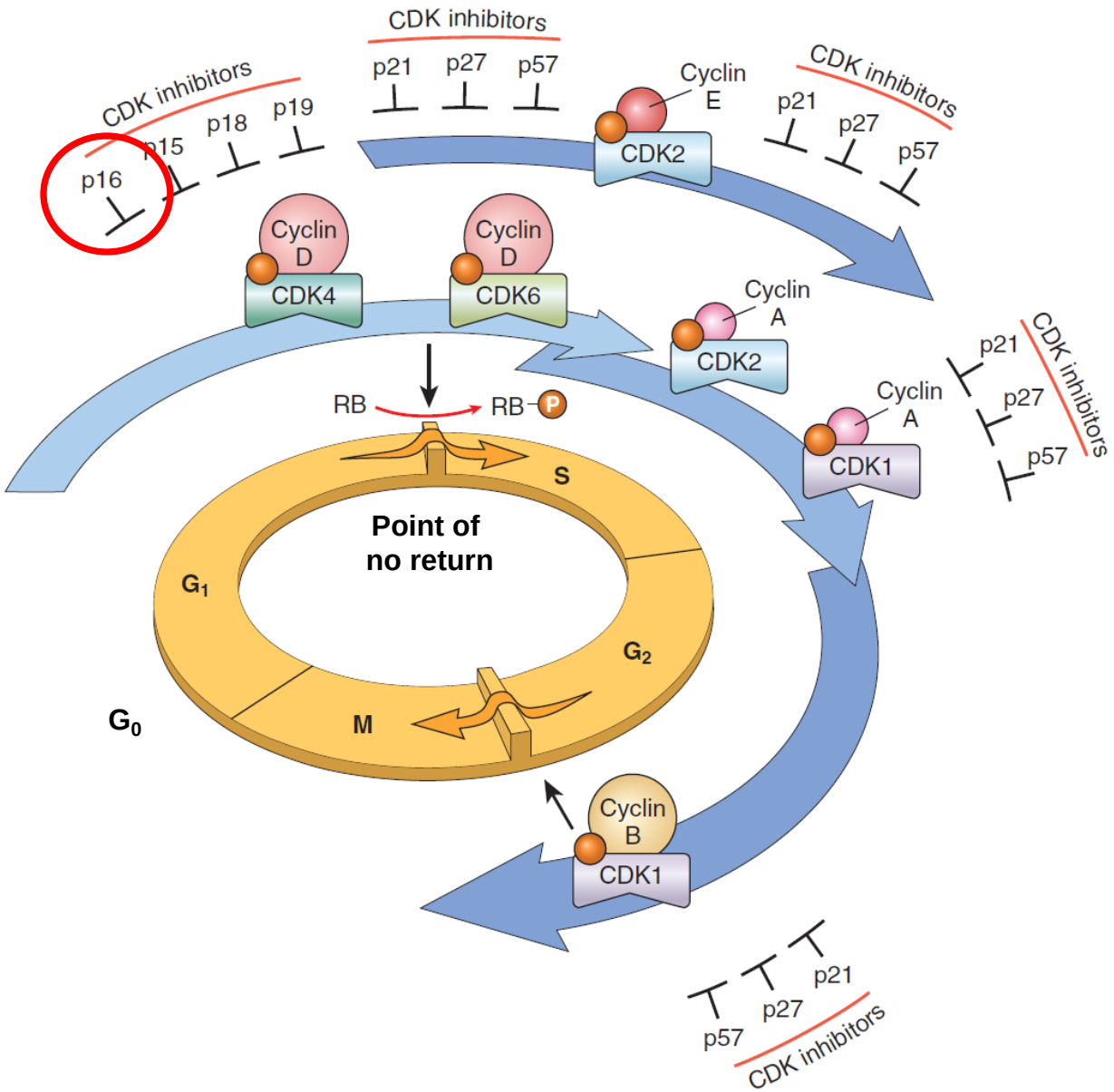
- G_1-S
- G_2-M
- Metaphase



Cyclins & CDKs

Cyclin D over-expression:
breast
esophagus
liver
lymphomas
plasma cell tumors

CDK4 amplification:
melanomas
sarcomas
glioblastomas

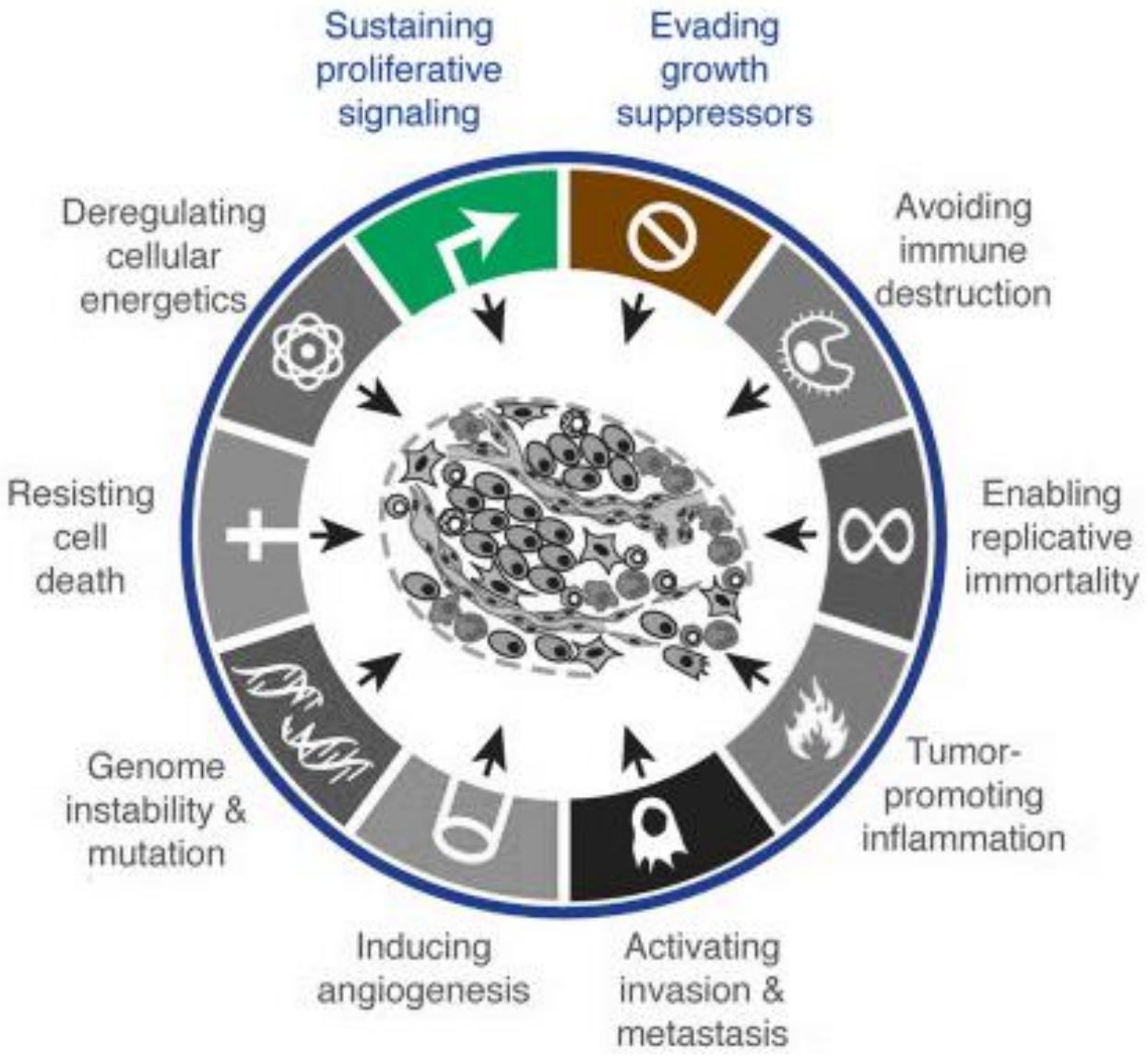


Cyclins & CDKs

CDKN2A germline mutations:
25% of melanoma-prone kindreds

CDKN2A somatic deletion/inactivation:
pancreatic carcinomas
glioblastomas
esophageal cancers
non–small cell lung carcinomas
soft tissue sarcomas
bladder cancers

Hallmarks of Cancer
Evading Growth Inhibition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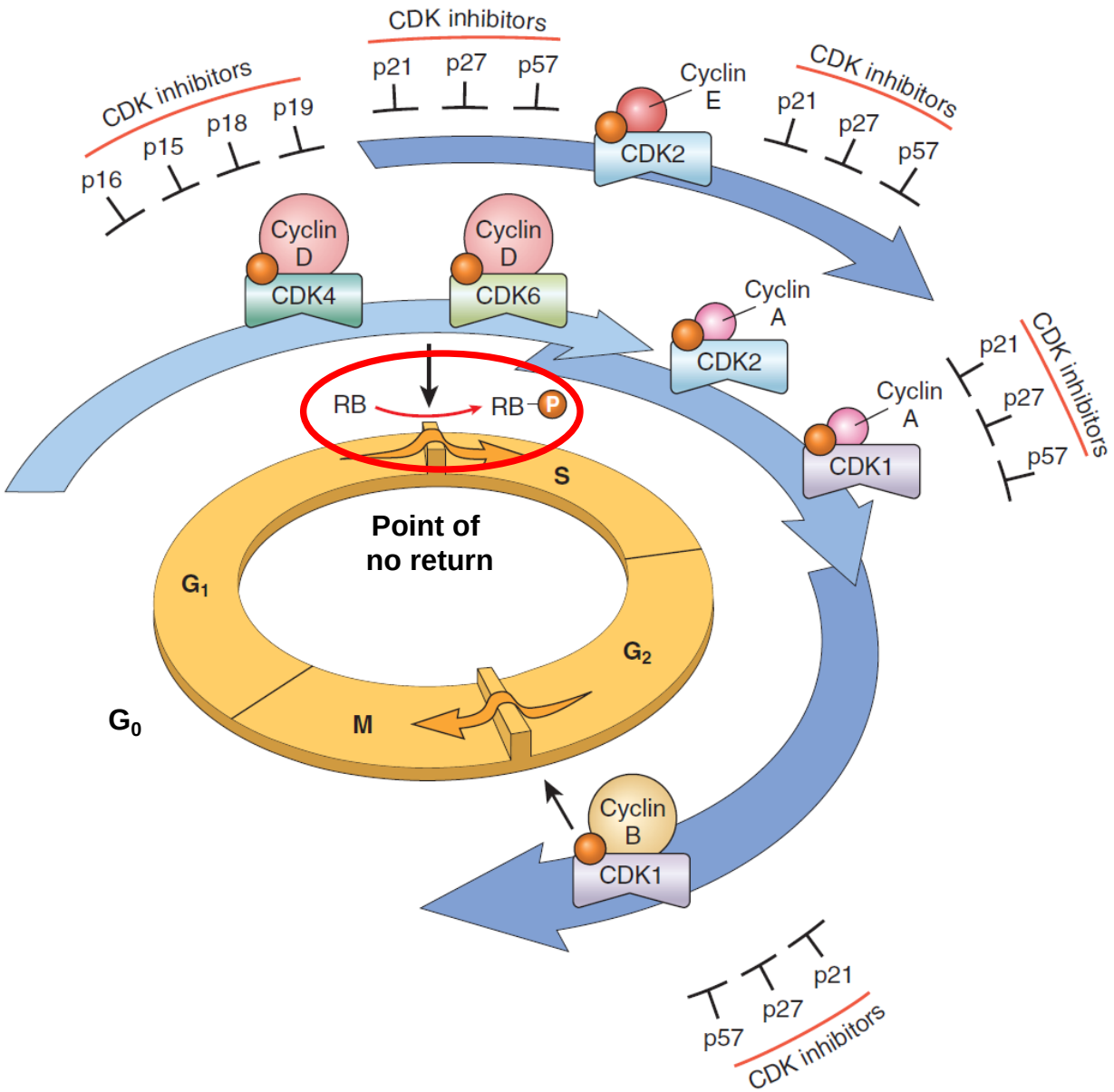


RB : Governor of the Cell Cycle

First tumor suppressor gene to be discovered

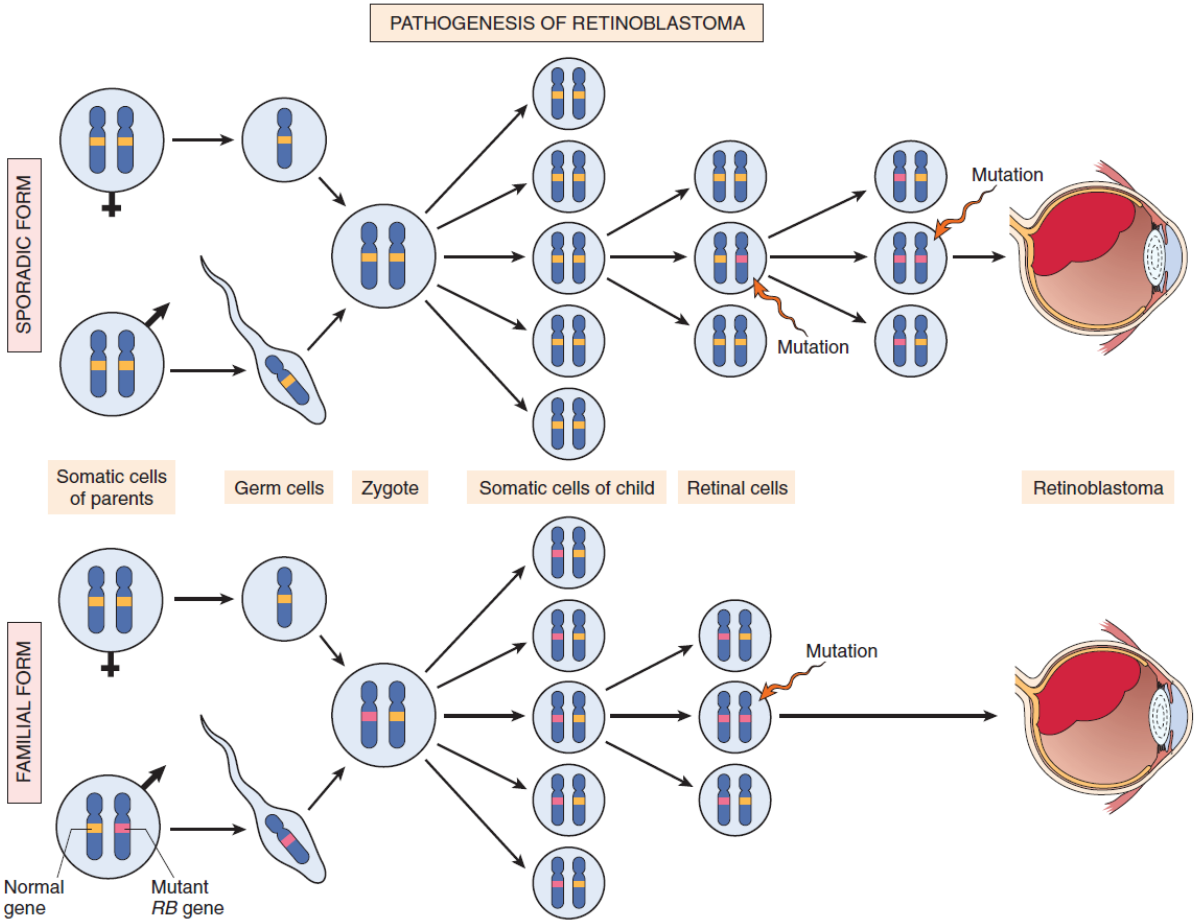
Identified in retinoblastoma patients

Chromosome 13q14

Rare disease but mechanisms learned apply to a wide range of tumors

60% sporadic
rest famillial AD

RB : Governor of the Cell Cycle

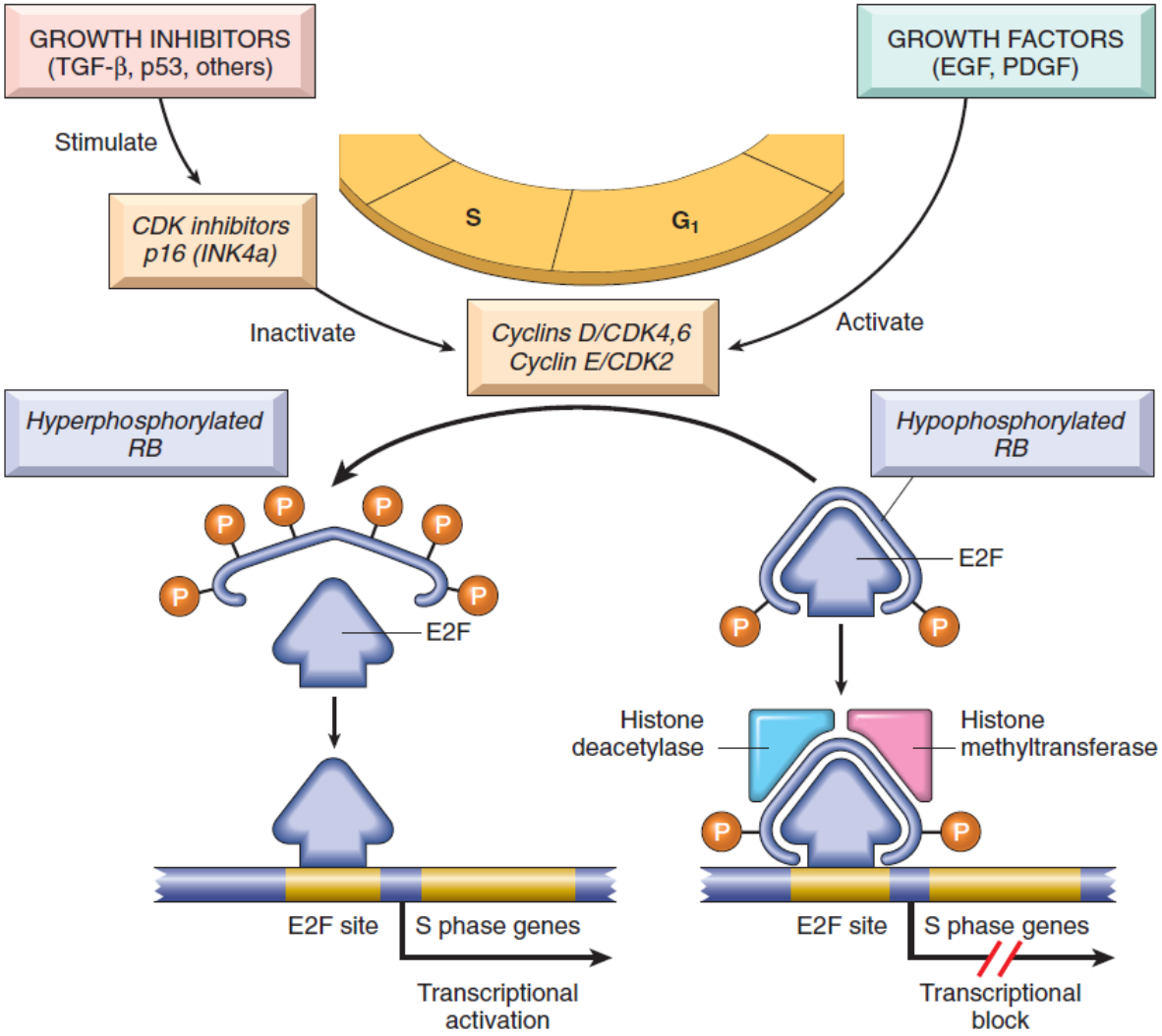


Knudson “two-hit” hypothesis

Two defective copies needed

Familial: -inherited
-somatic mutation

Sporadic: 2 somatic mutations



RB : Governor of the Cell Cycle

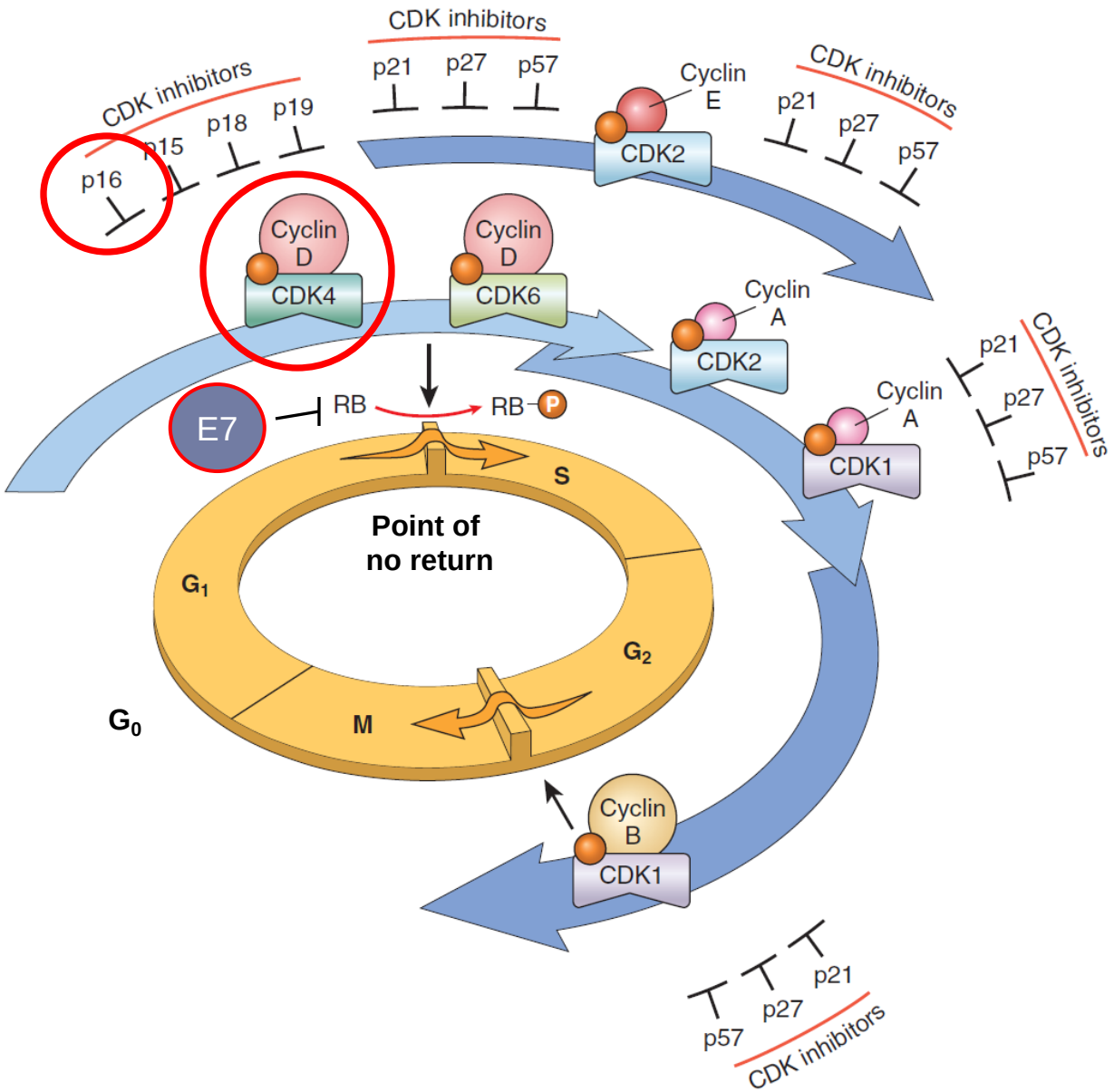
G1-S transition

Cyclin E expression control:

- E2F sequestration
- Chromatin remodelling

Rb phosphorylation control:

- Cyclin D/CDK4,6
- Phosphatases



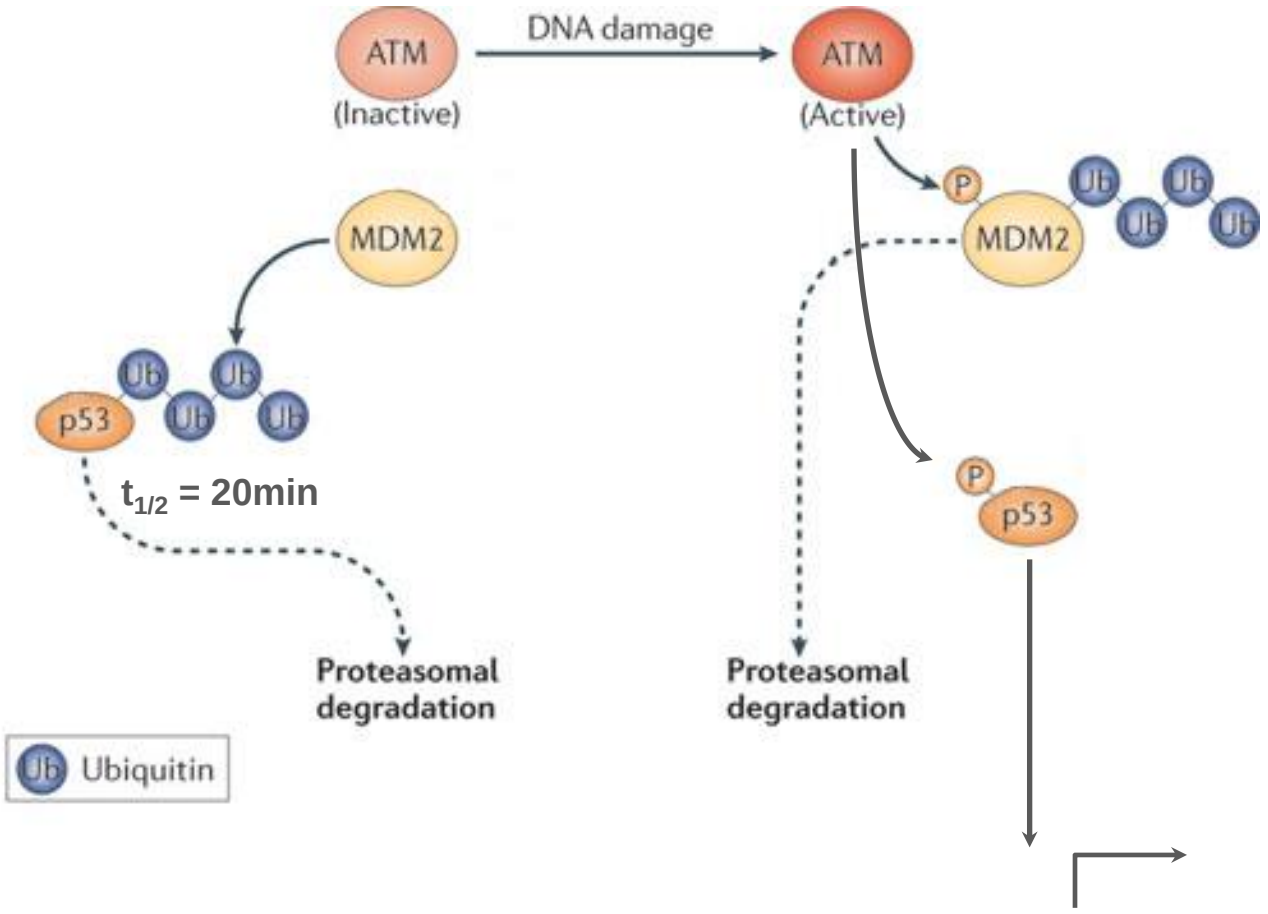
RB mutation mimicking

Activation of CDK4 *(mutation)*

Over-expression of cyclin D *(translocation/ amplification)*

Inactivation of CDKI (e.g. CDKN2A) *(mutation/ deletion/epigenetics)*

Oncogenic viruses (e.g. HPV E7 protein binds to Rb preventing E2F binding)



TP53 : Guardian of the genome

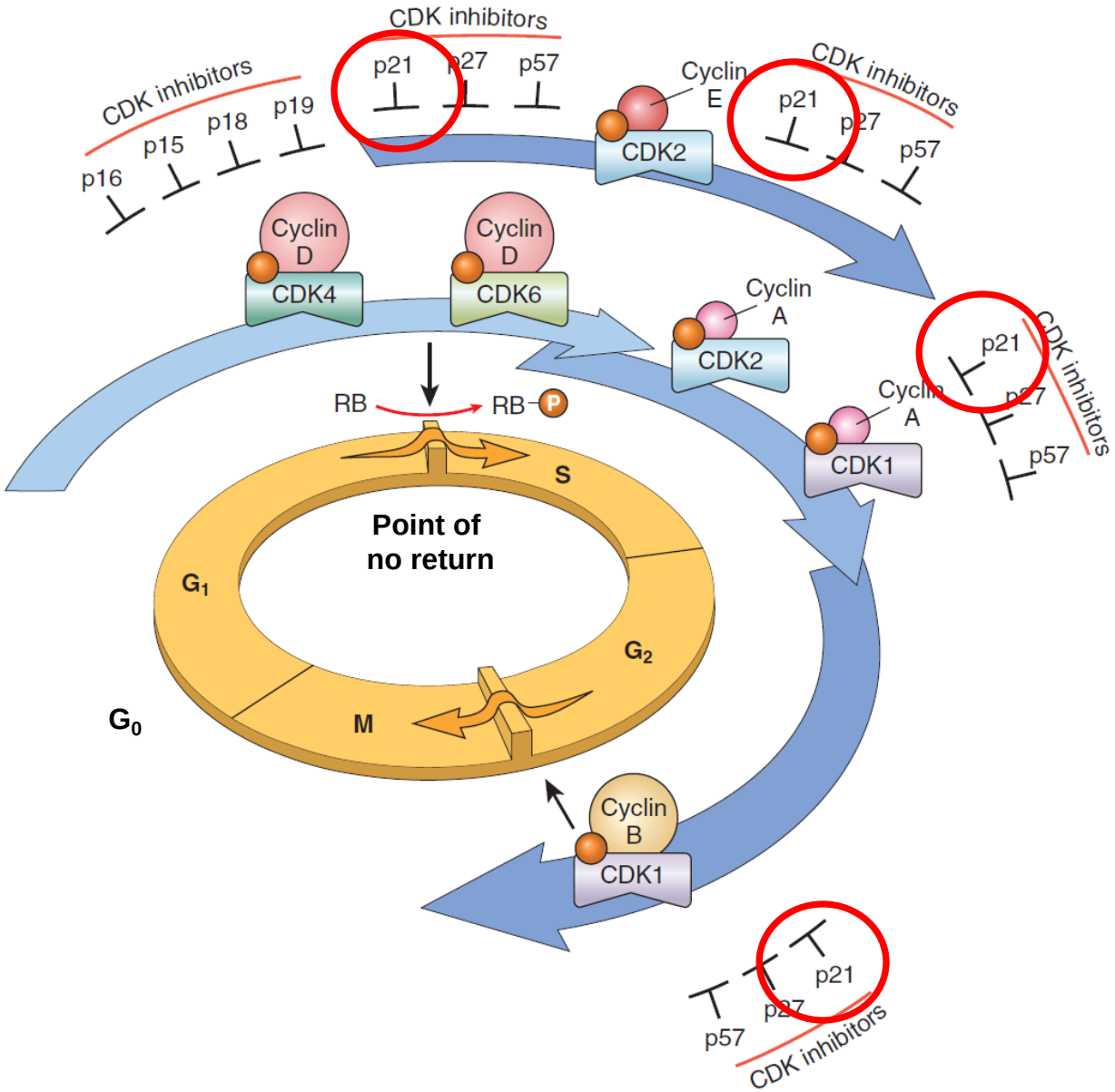
Li-Fraumeni syndrome

Tumor suppressor:

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

p53 senses:

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

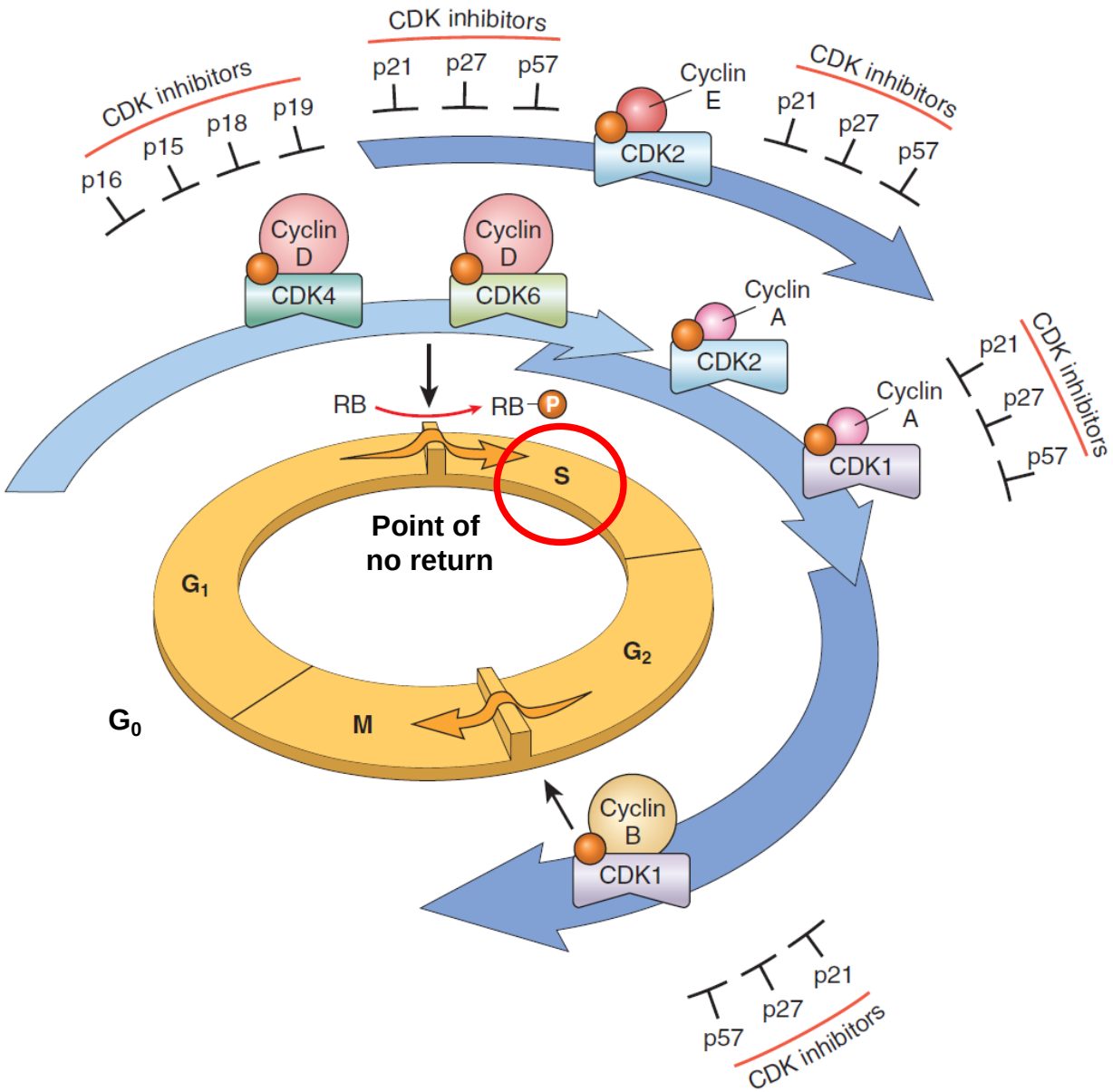


TP53 : Guardian of the genome

Transcriptional targets:

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

- *MDM2* (after repair)



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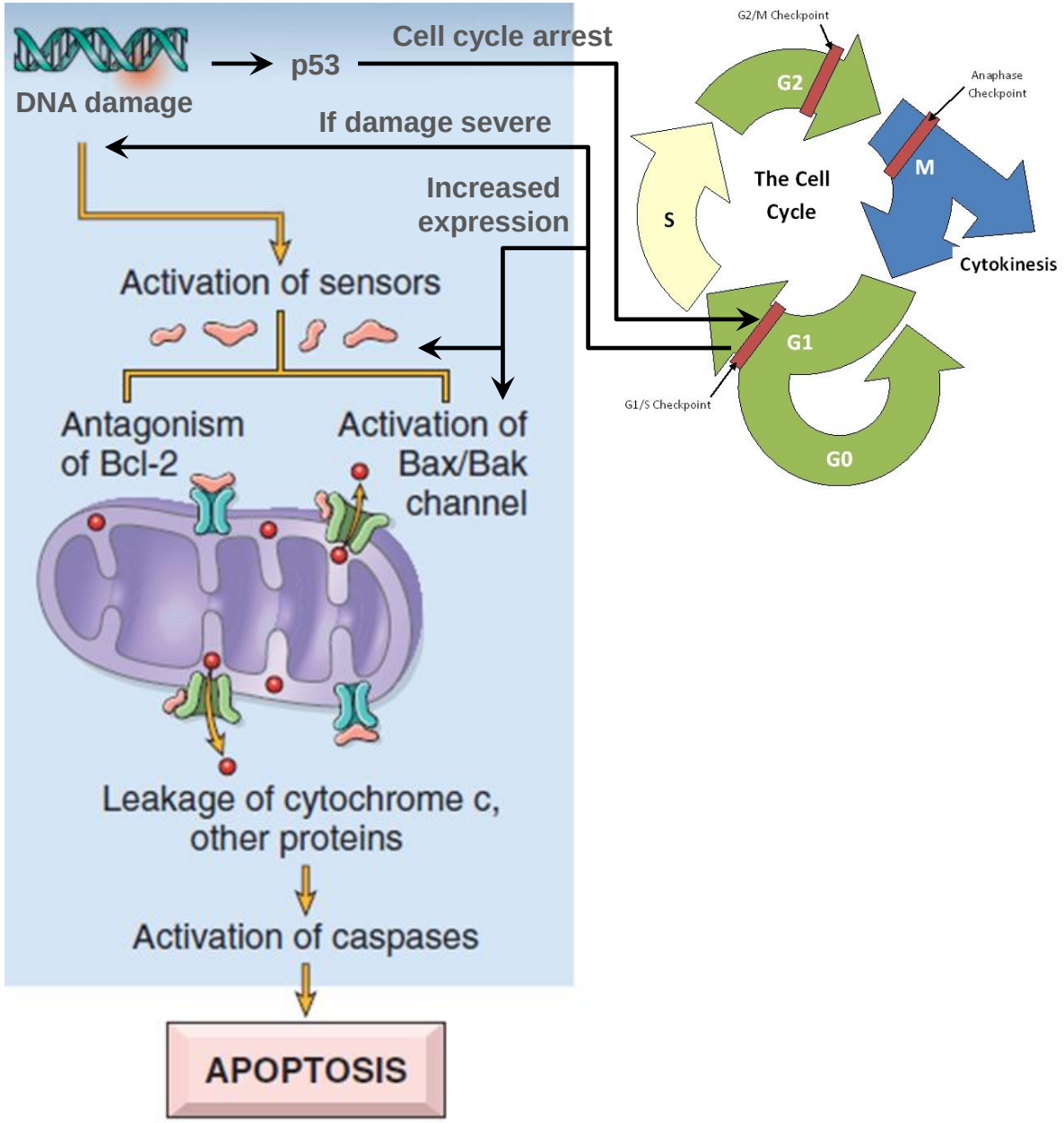

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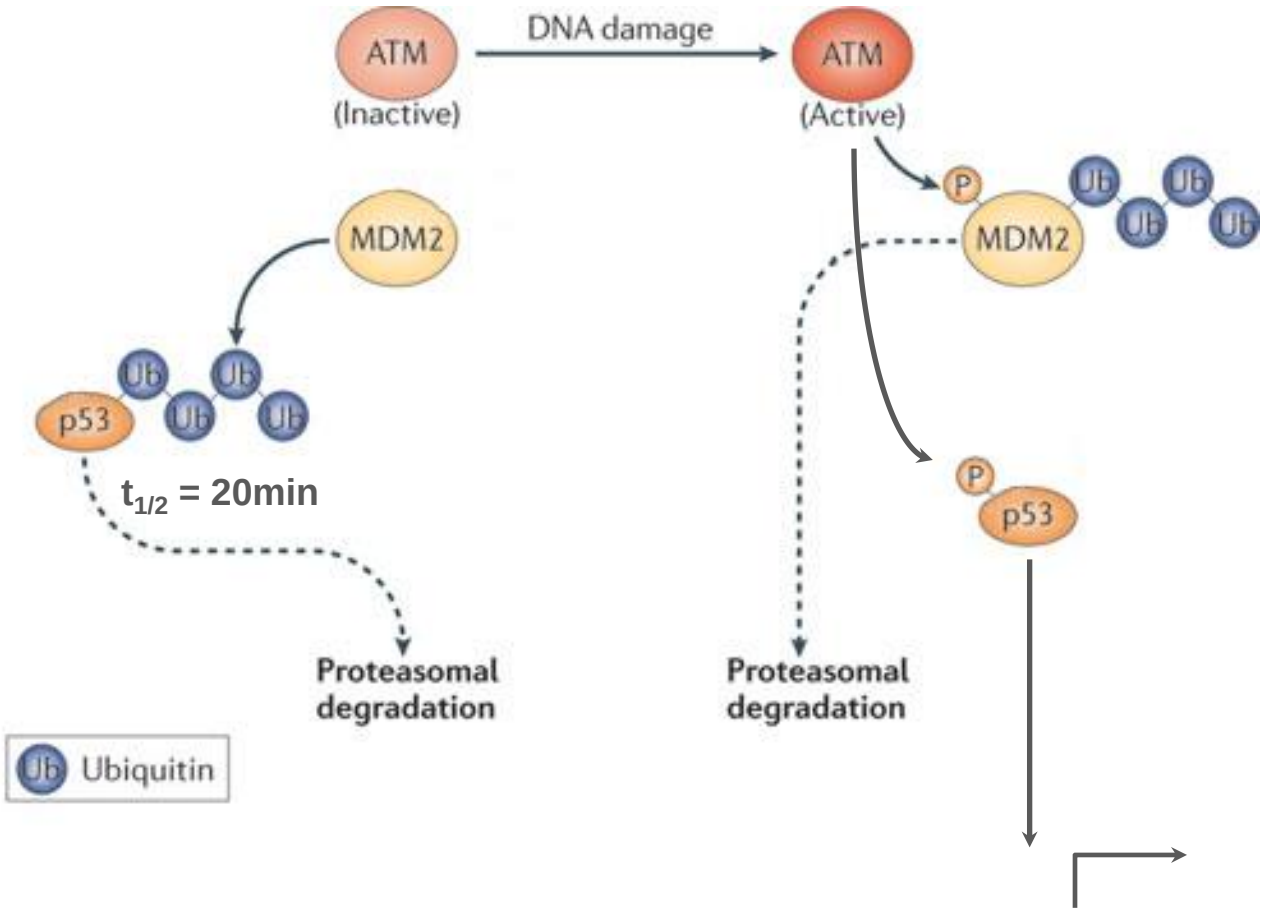

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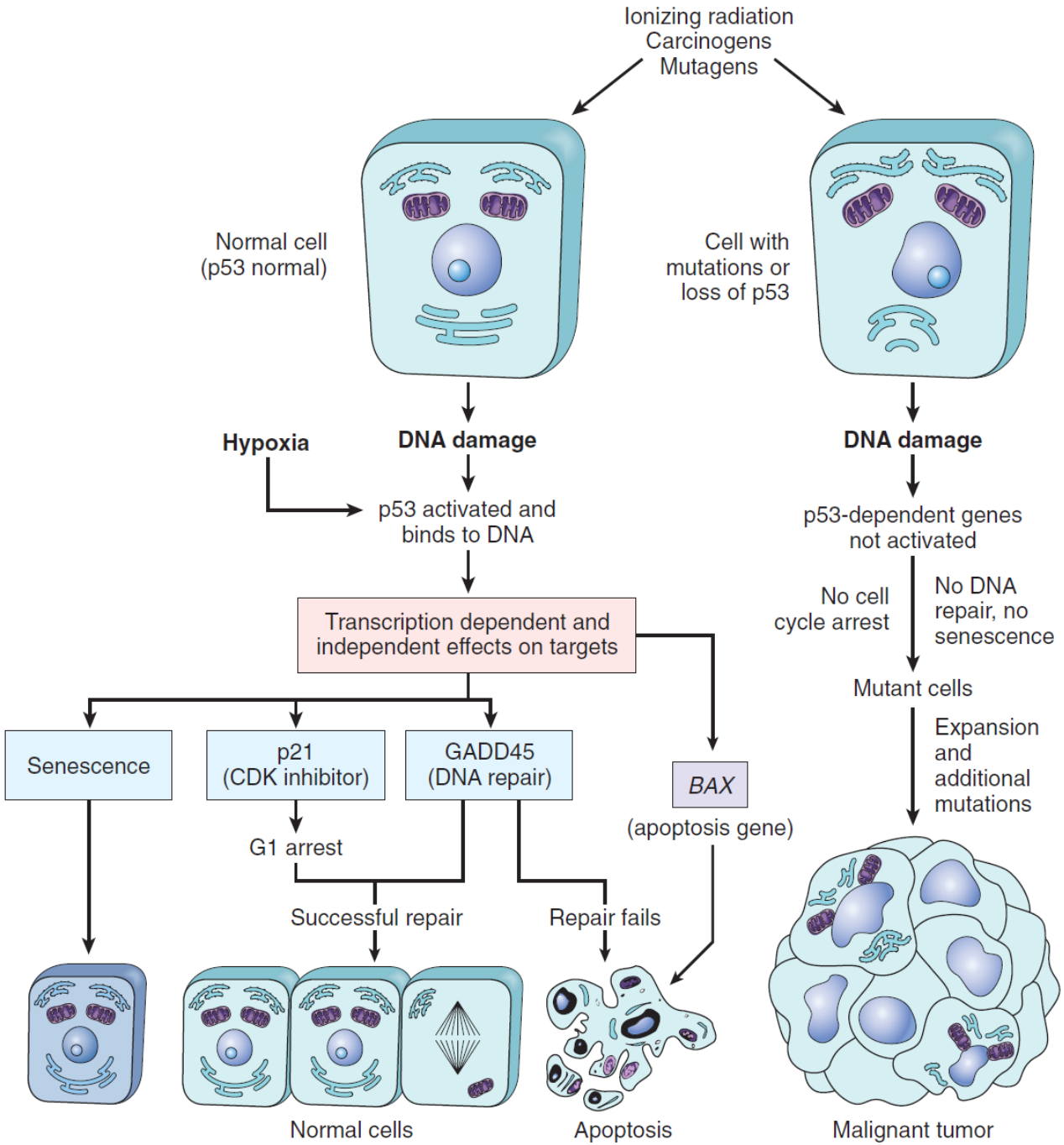
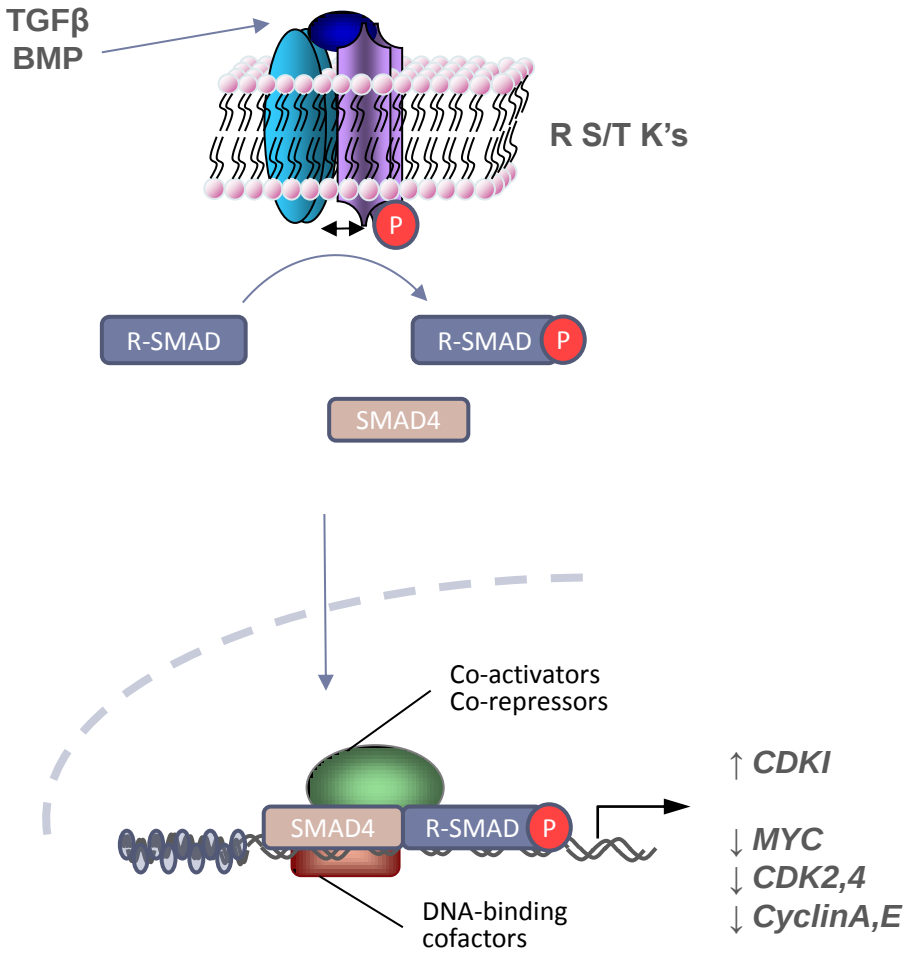


TP53 : Guardian of the genome

Summary

TGFβ pathway signalling



Potent inhibitor of proliferation

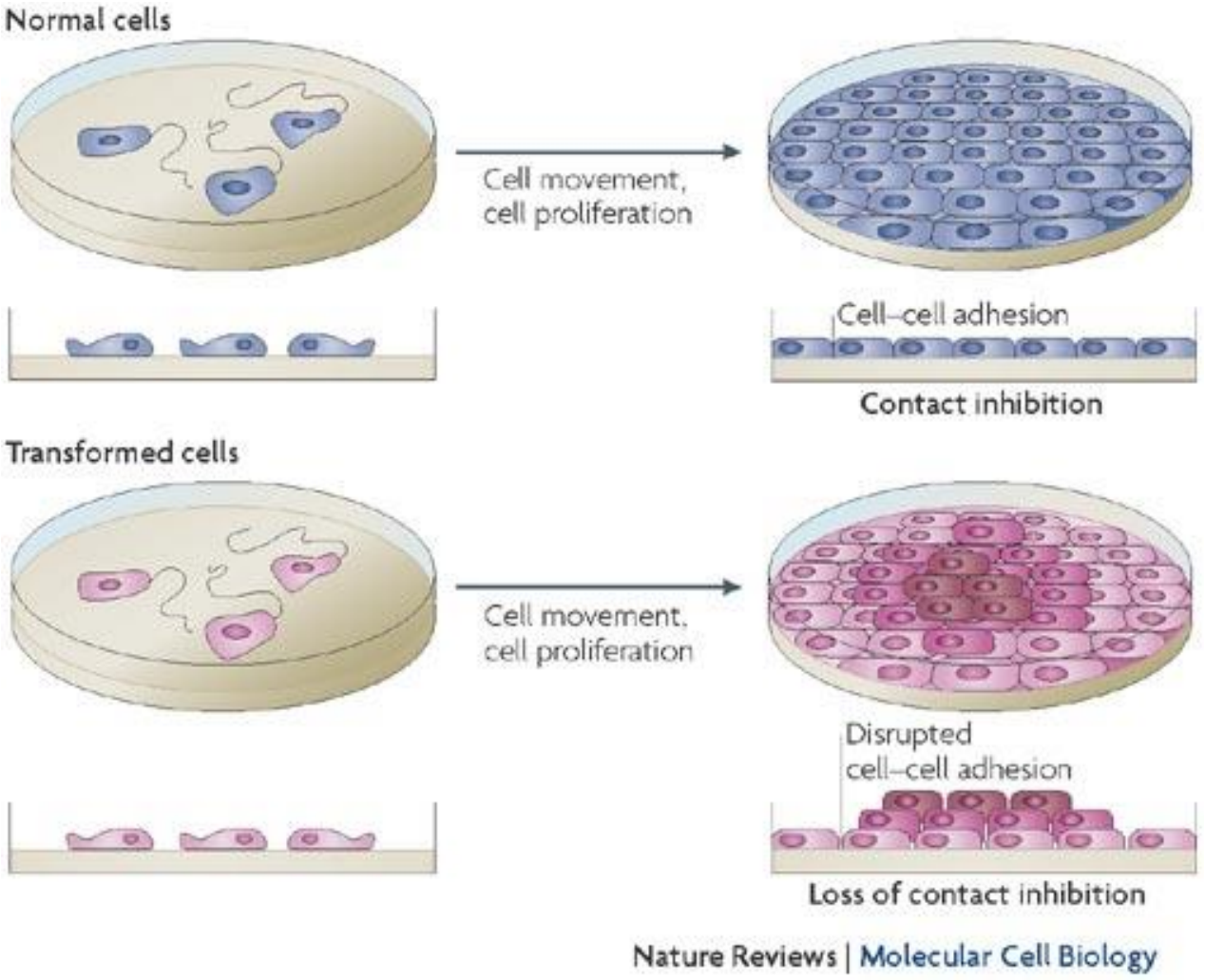
Type II receptor mutations:

- Colon
- Stomach
- Endometrium

SMAD4 mutations:

- Pancreas

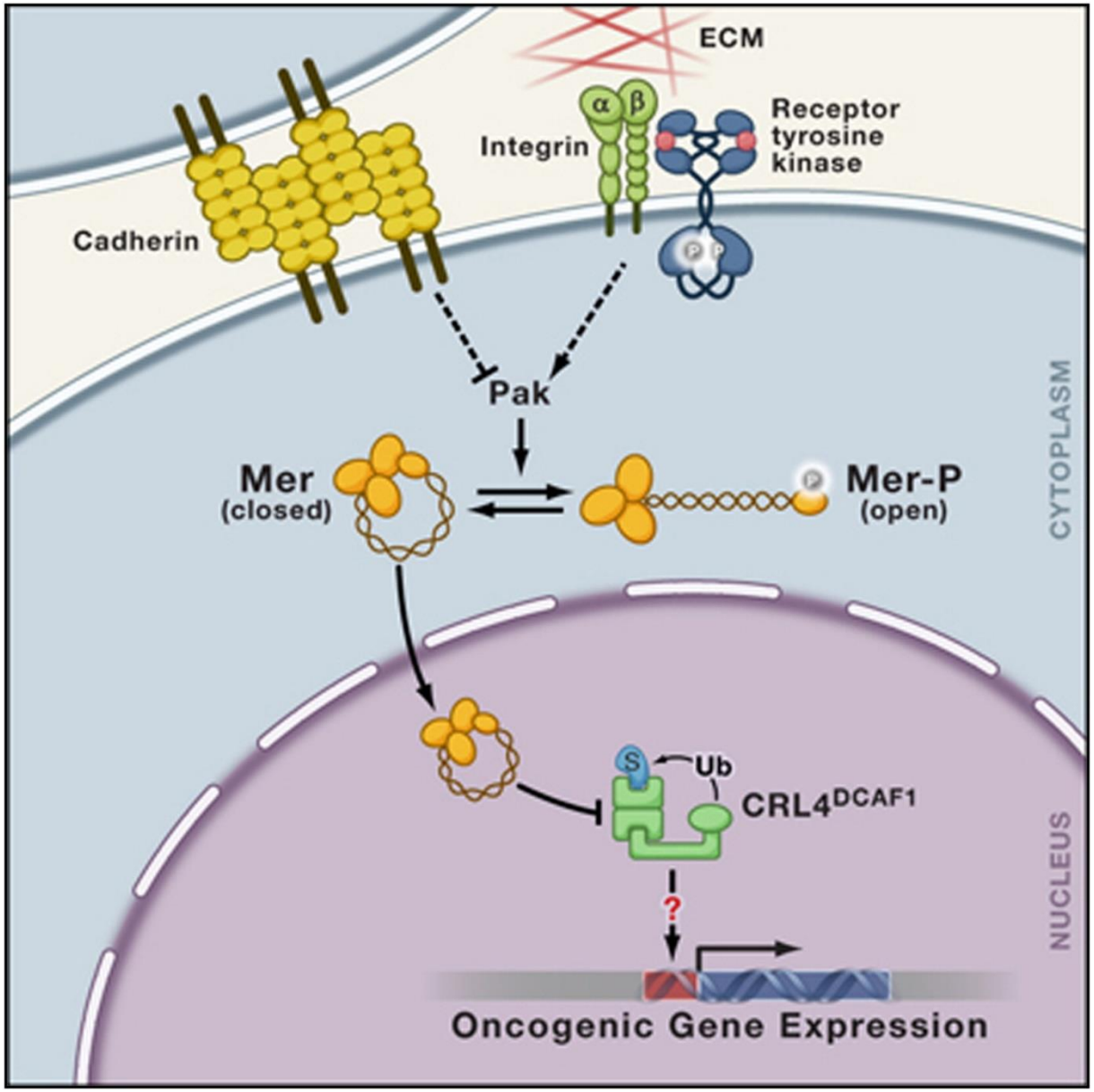
Immune evasion, Angiogenesis, EMT



Contact Inhibition, NF2, and APC

Not fully understood

E-Cadherin homodimeric interaction



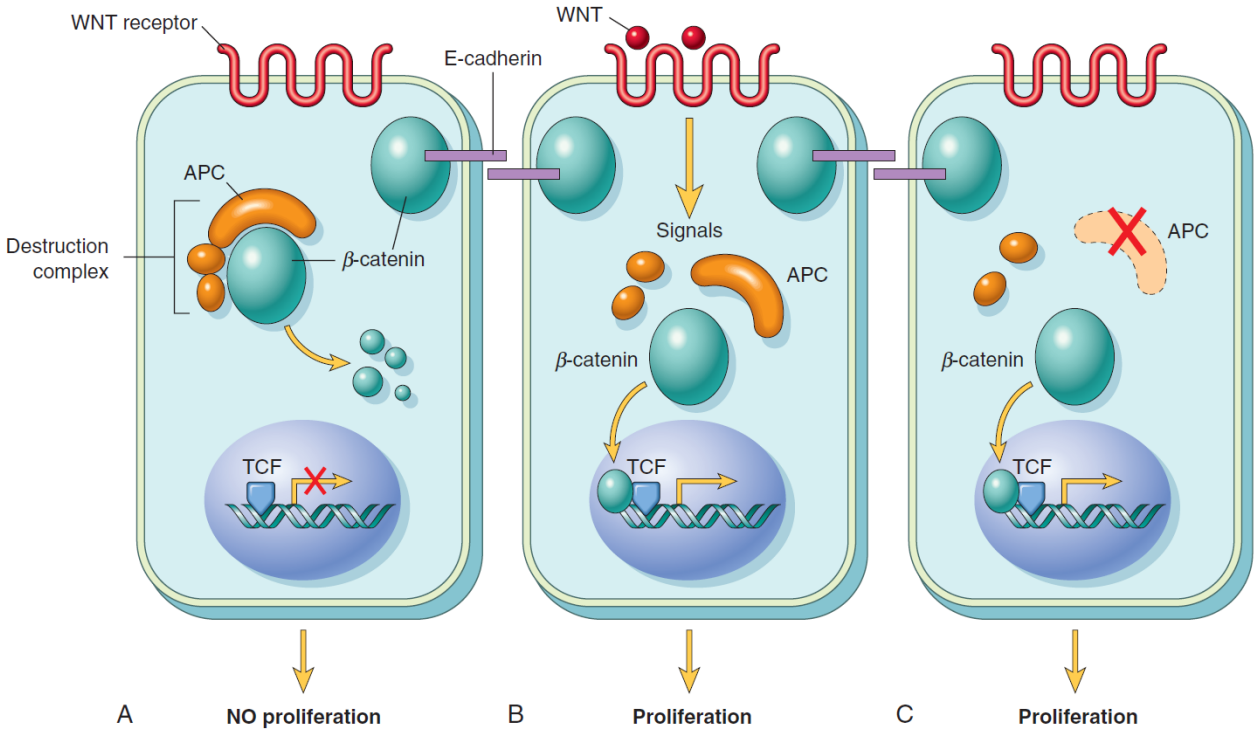
Contact Inhibition, NF2, and APC

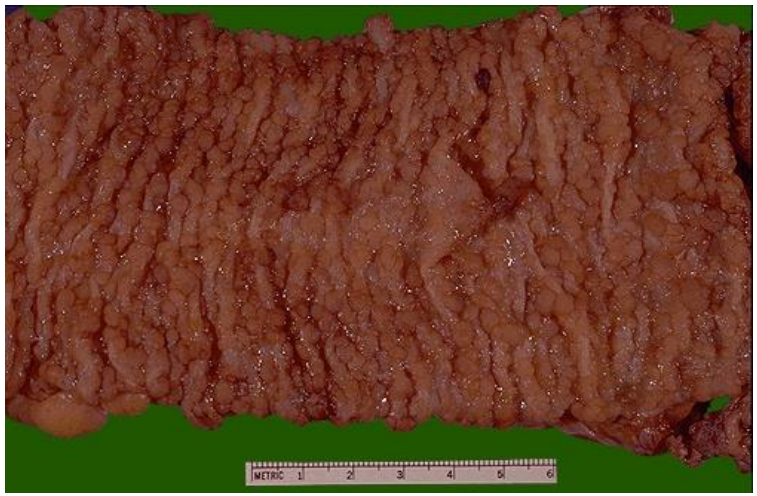
Neurofibromin-2 (merlin)

NF2 homozygous loss = neurofibromatosis type 2:

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

Model of Merlin's Function Li et al. Cell 140:447-90, 2010





Contact Inhibition, NF2, and APC

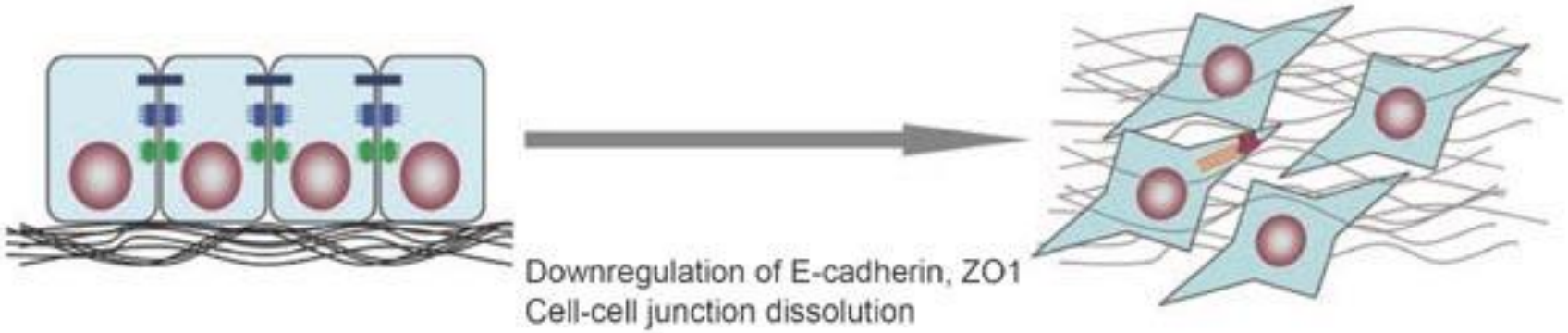
adenomatous polyposis coli

β-catenin targets:

- growth-promoting genes
  Cyclin D1
  MYC

- Transcriptional regulators
  TWIST
  SLUG/SNAIL
  ↓
↓ E-cadherin expression →
↓ Contact inhibition
Role in EMT

EMT



Downregulation of E-cadherin, ZO1
Cell-cell junction dissolution

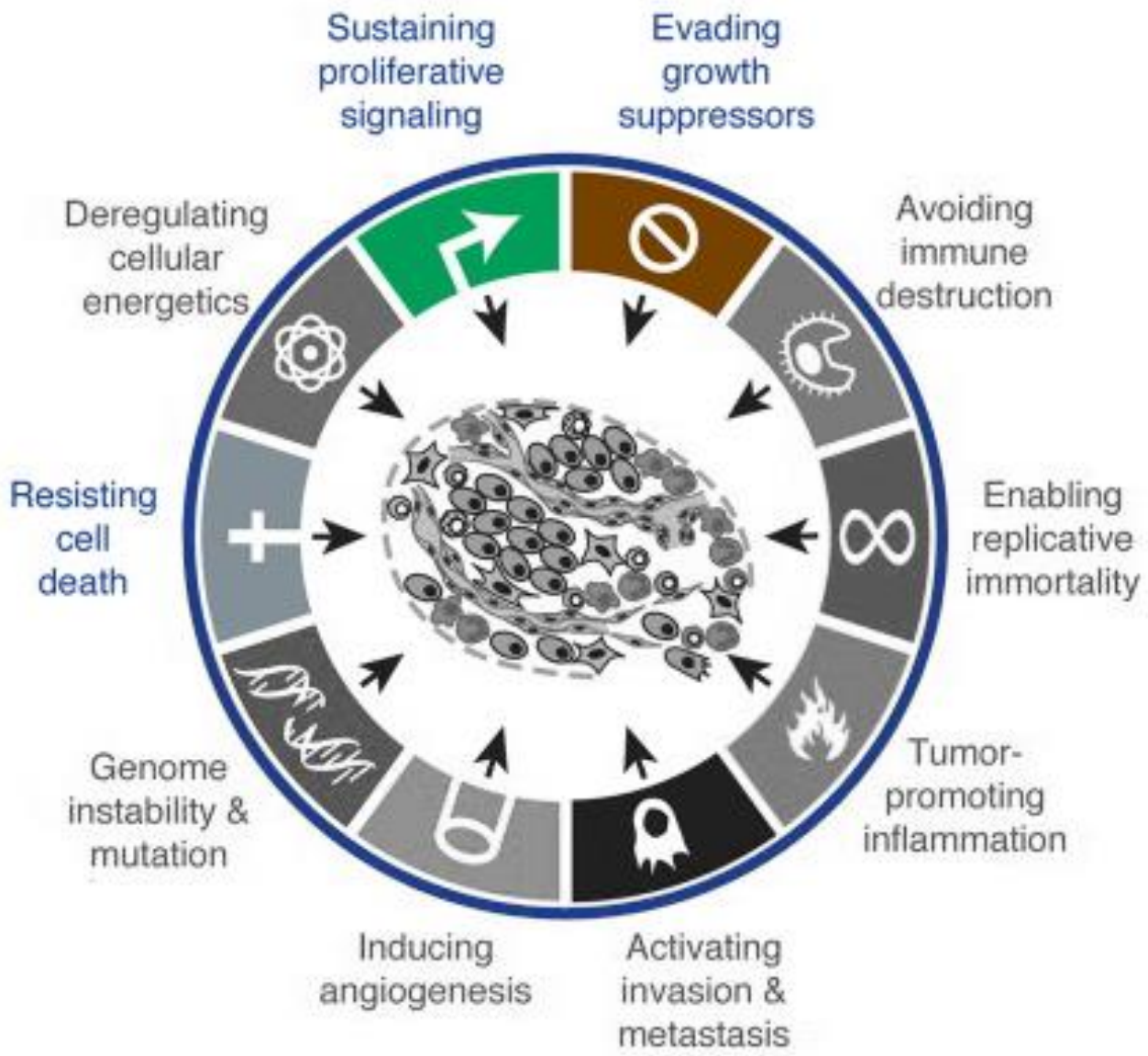
Loss of apical-basolateral cell polarity

Actin reorganization

Upregulation of metalloproteases
Increased deposition of extracellular matrix proteins

Migration and invasion

Hallmarks of Cancer
Evasion of Cell Death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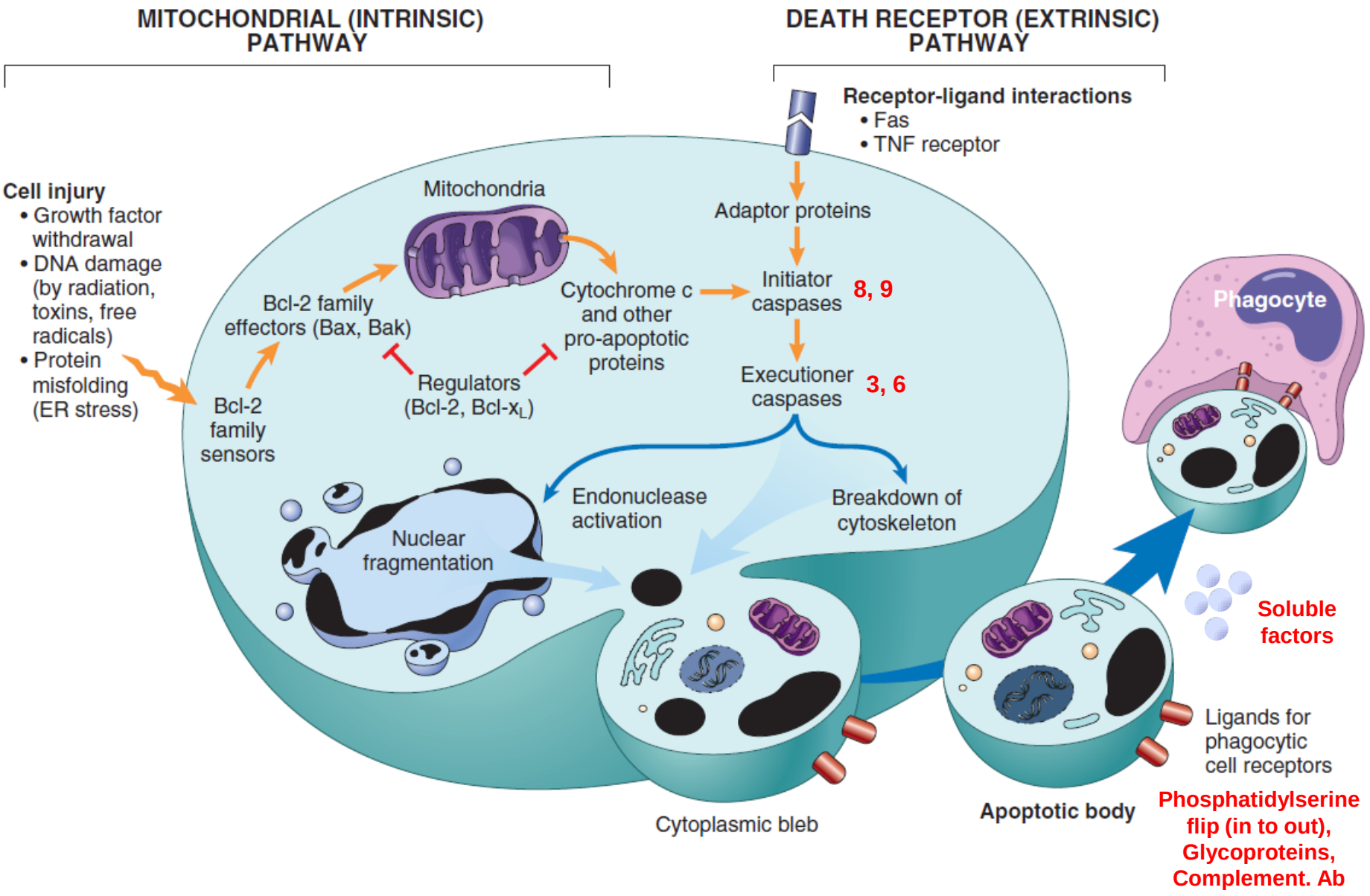
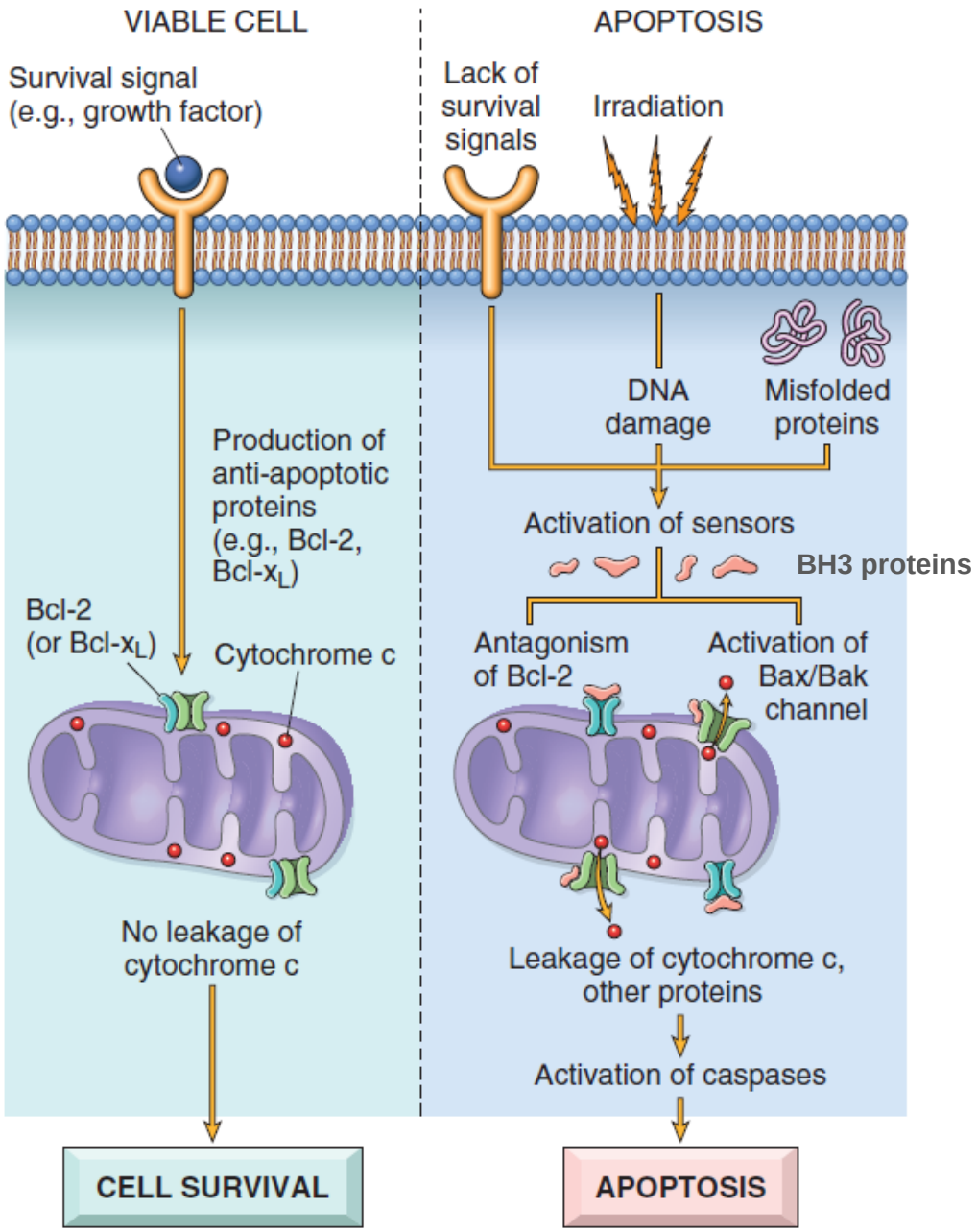

MITOCHONDRIAL (INTRINSIC) PATHWAY
DEATH RECEPTOR (EXTRINSIC) PATHWAY
Receptor-ligand interactions
• Fas
• TNF receptor
Cell injury
• Growth factor withdrawal
• DNA damage (by radiation, toxins, free radicals)
• Protein misfolding (ER stress)
Mitochondria
Adaptor proteins
Bcl-2 family effectors (Bax, Bak)
Cytochrome c and other pro-apoptotic proteins
Initiator caspases
8, 9
Regulators (Bcl-2, Bcl-xL)
Executioner caspases
3, 6
Bcl-2 family sensors
Endonuclease activation
Breakdown of cytoskeleton
Nuclear fragmentation
Phagocyte
Soluble factors
Ligands for phagocytic cell receptors
Cytoplasmic bleb
Apoptotic body
Phosphatidylserine flip (in to out), Glycoproteins, Complement. Ab



Mitochondrial (intrinsic)

Mitochondrial permeability is key

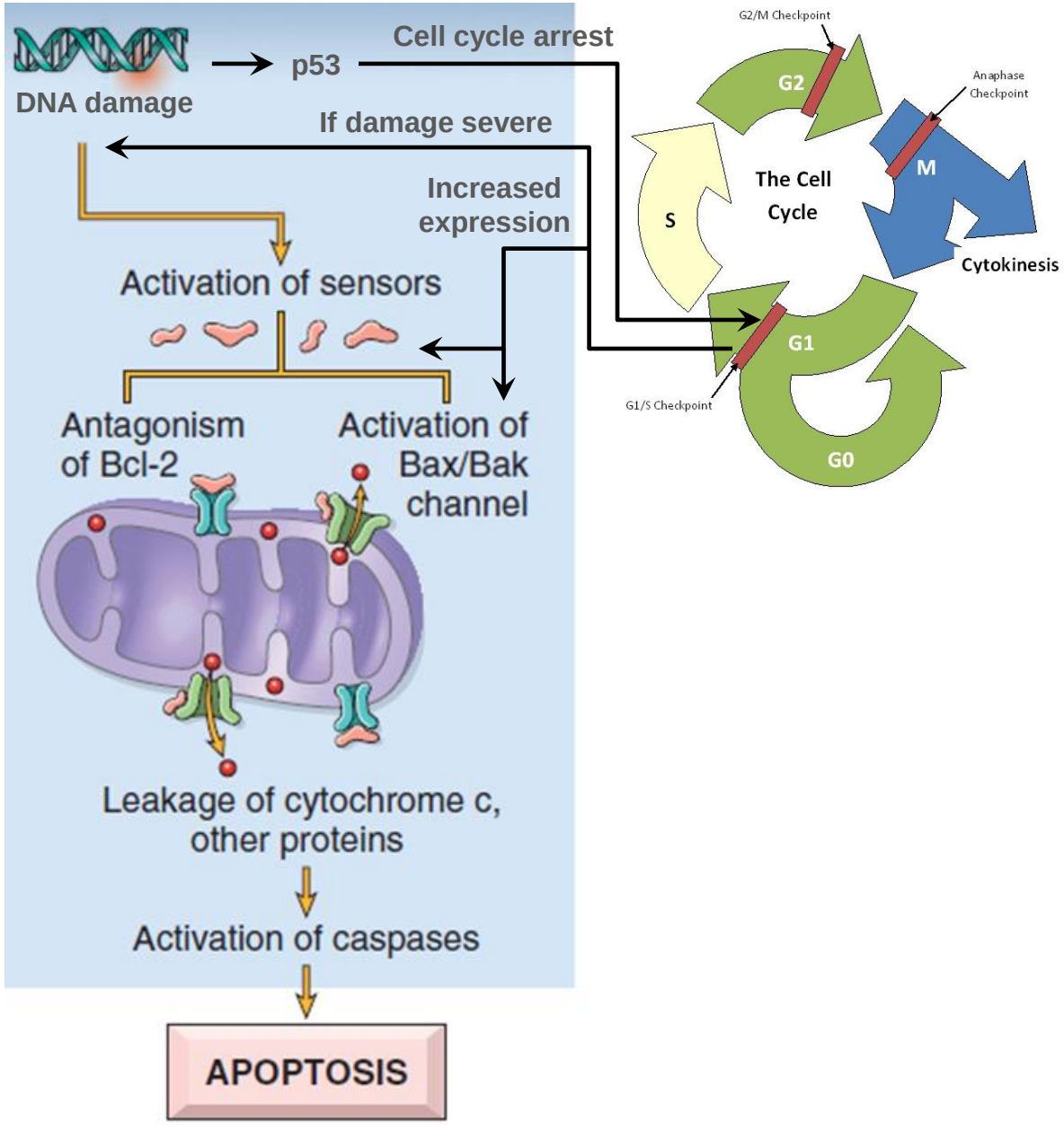
controlled > 20 proteins

Cytochrome c + cofactors, activates caspase-9

Anti-apototic proteins are inhibited

Bcl-2 & Bcl-x_L levels are reduced

Responsible for apoptosis in most situations

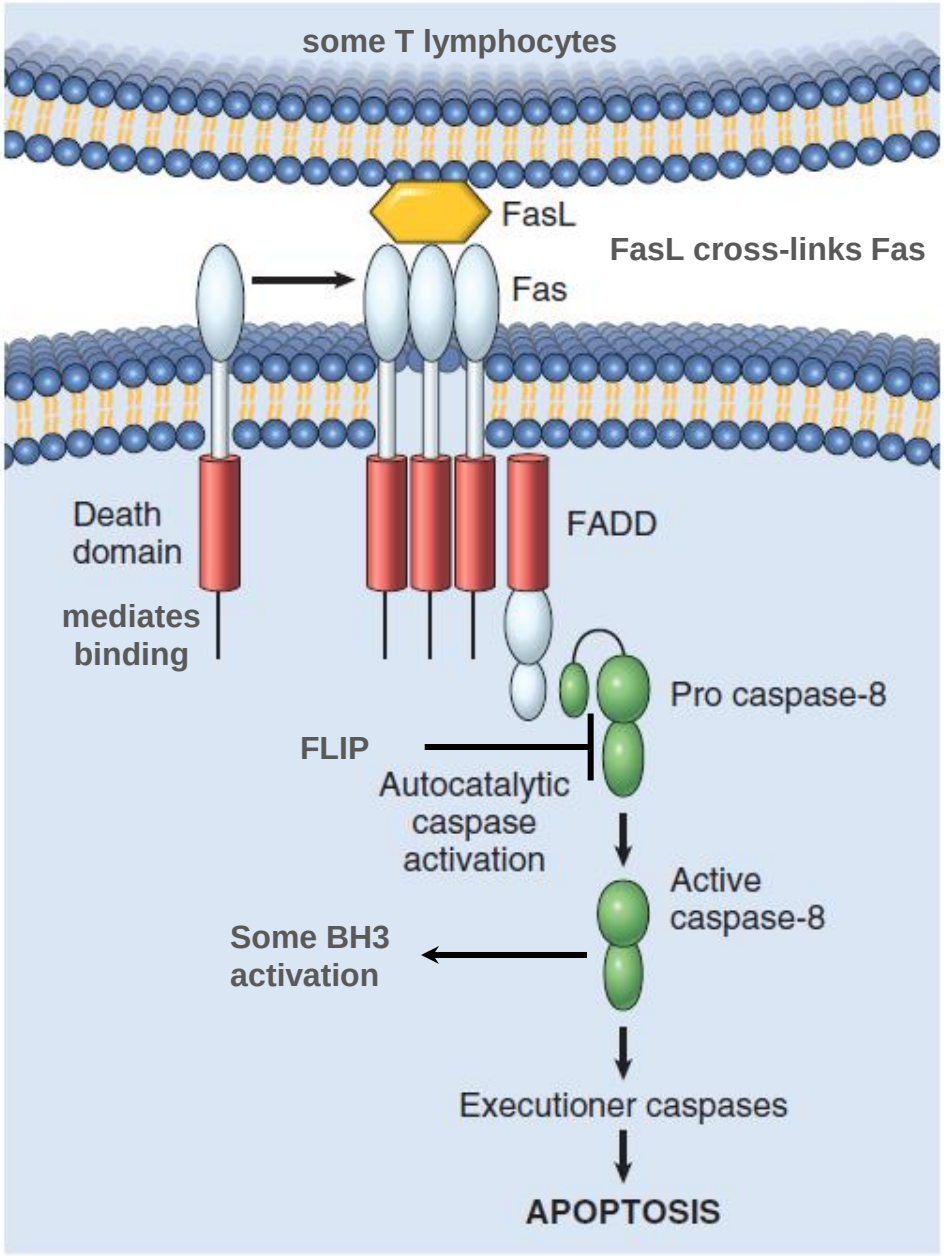


DNA damage

p53 accumulation

G1 arrest

p53 absence/mutation in certain cancers



Death receptor (extrinsic)

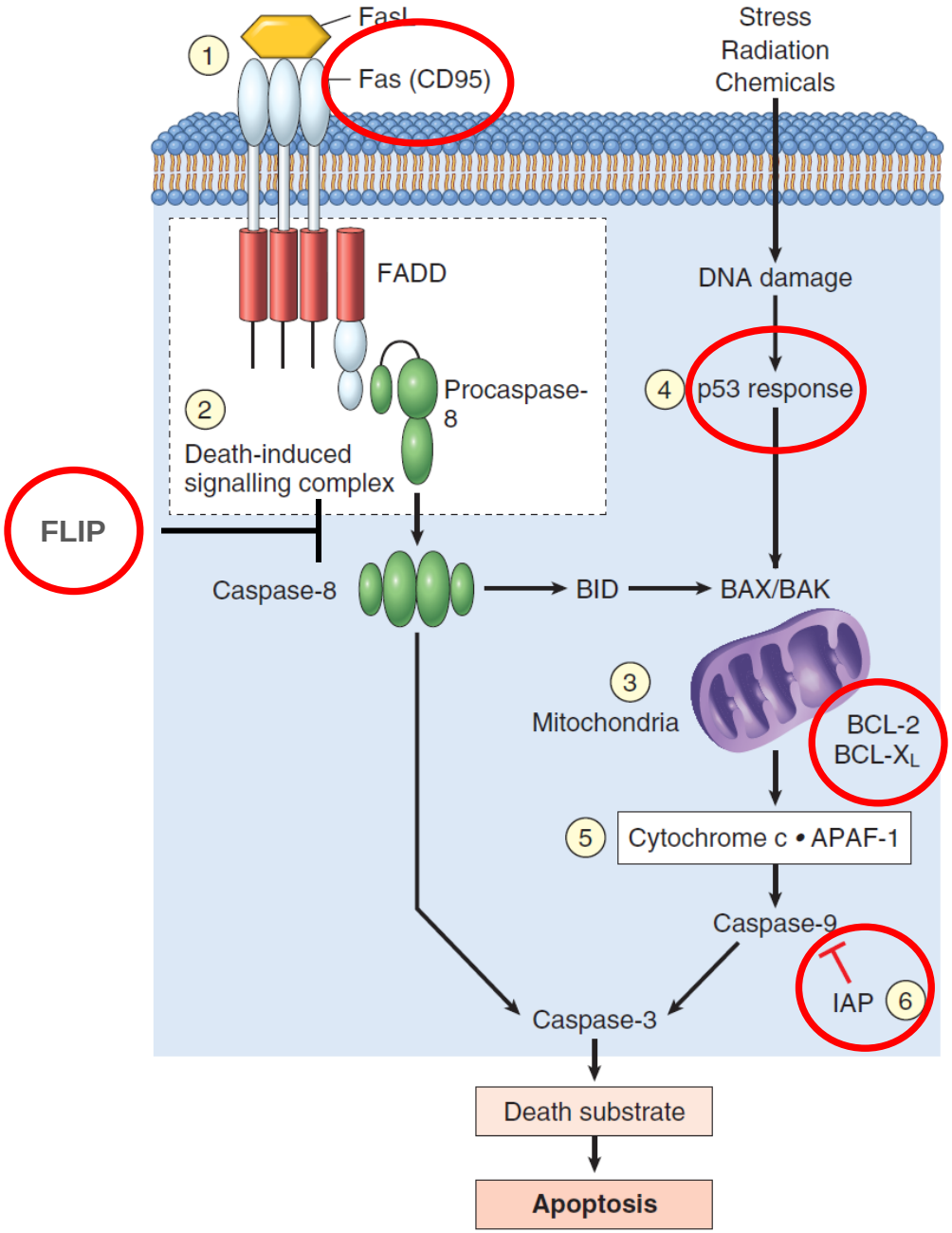
TNF receptor family

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:

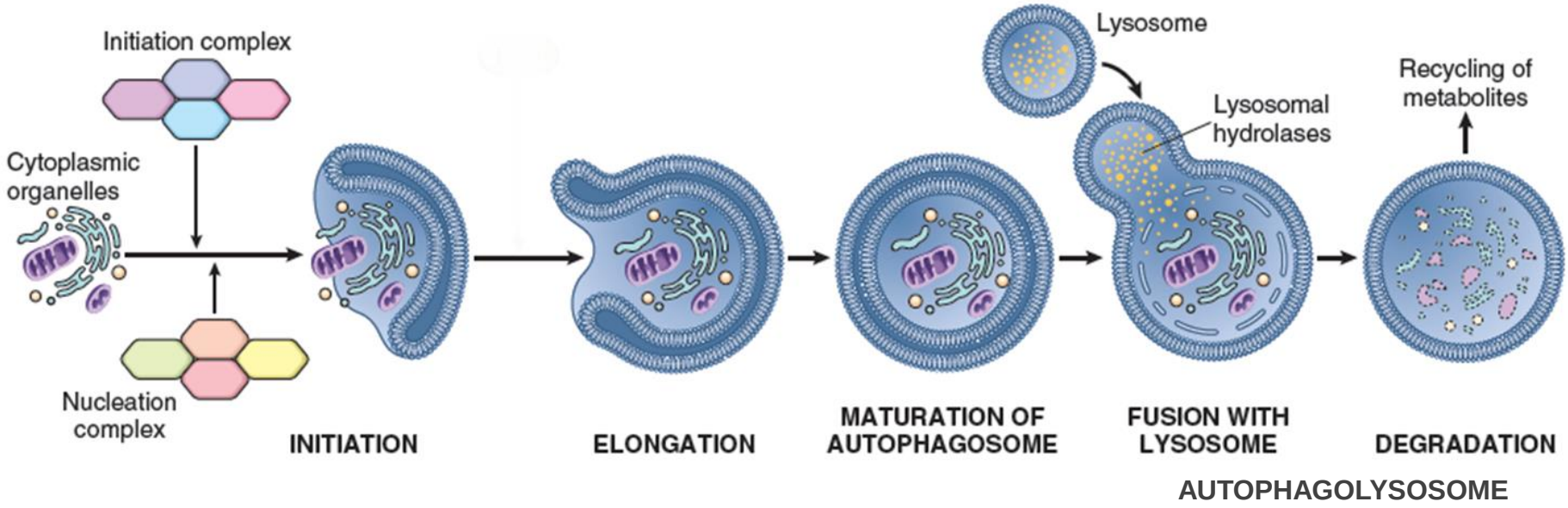
- Follicular B cell lymphoma (85%)
- t(14;18)
- Indolent growth

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