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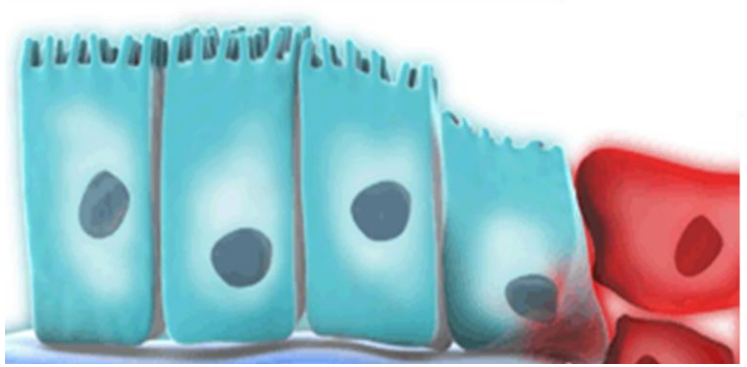


Oncobiology

Margarida Gama-Carvalho (DQB/FCUL) and Peter Jordan (INSA)

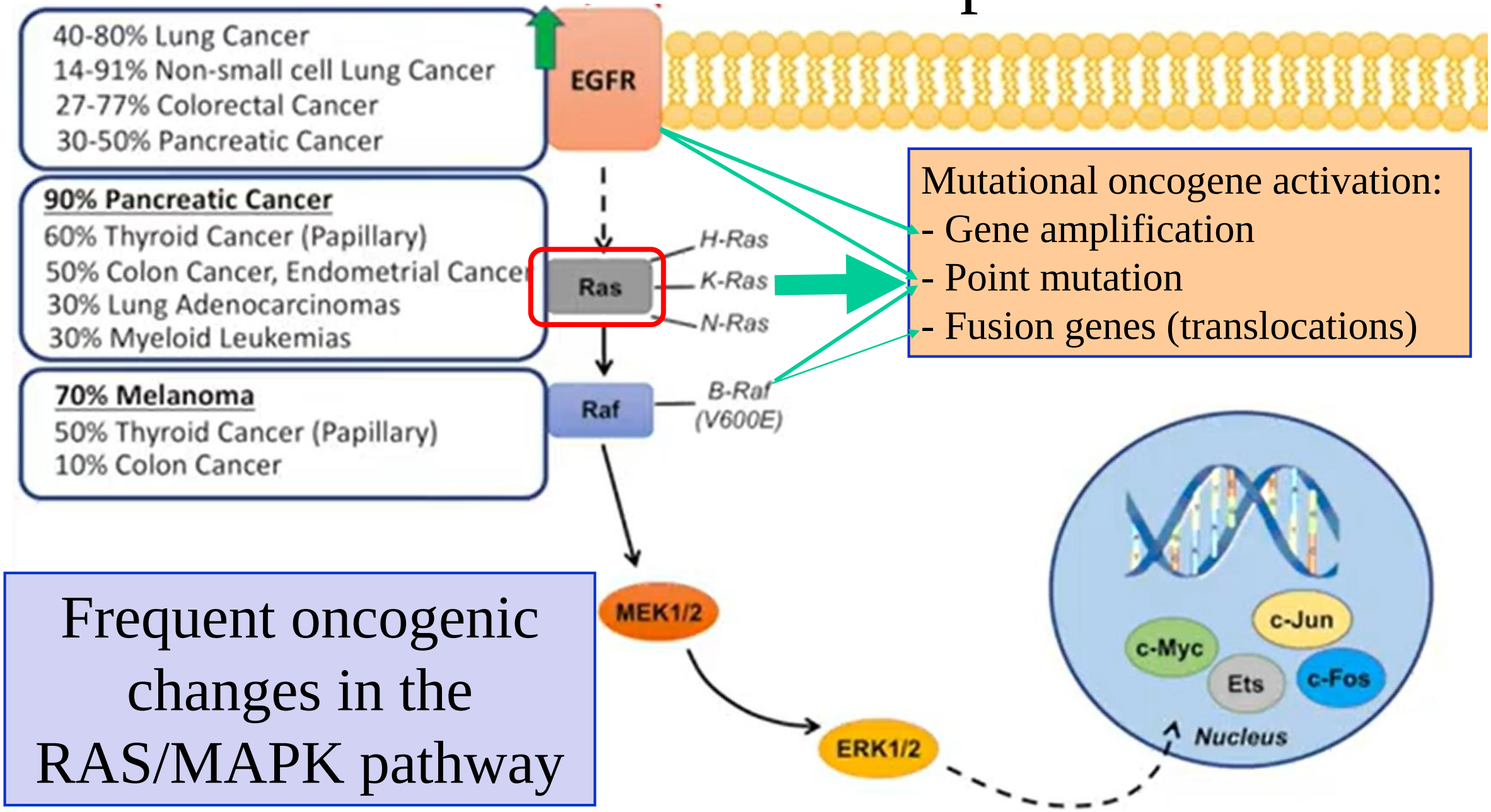
Tumour suppressor genes

Tumour suppressor vs Onco-genes

Oncogenes
promote
cell growth and division

Oncogenes encode proteins that participate in receiving or processing growth-stimulating signals

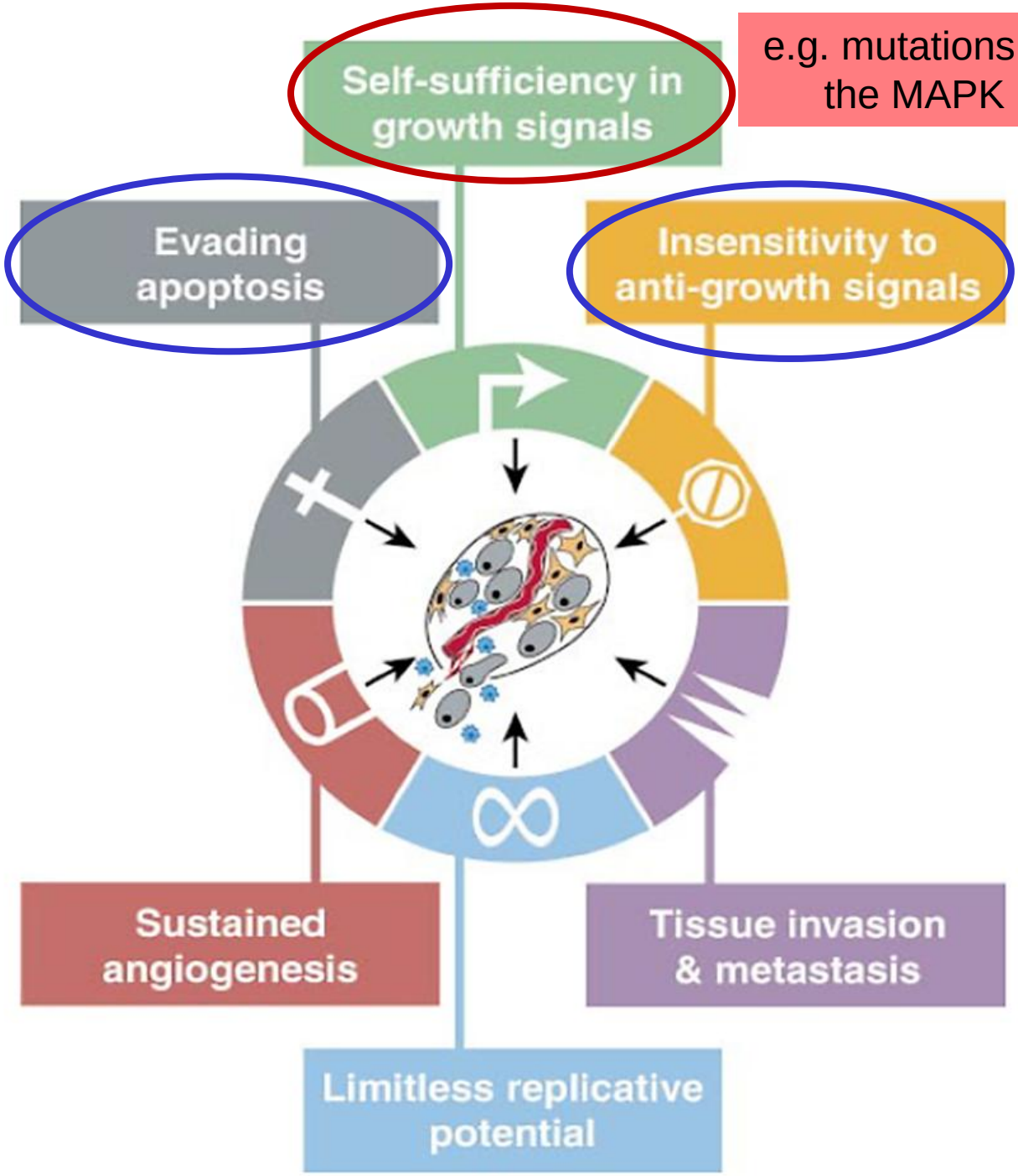
Example



Frequent oncogenic changes in the RAS/MAPK pathway

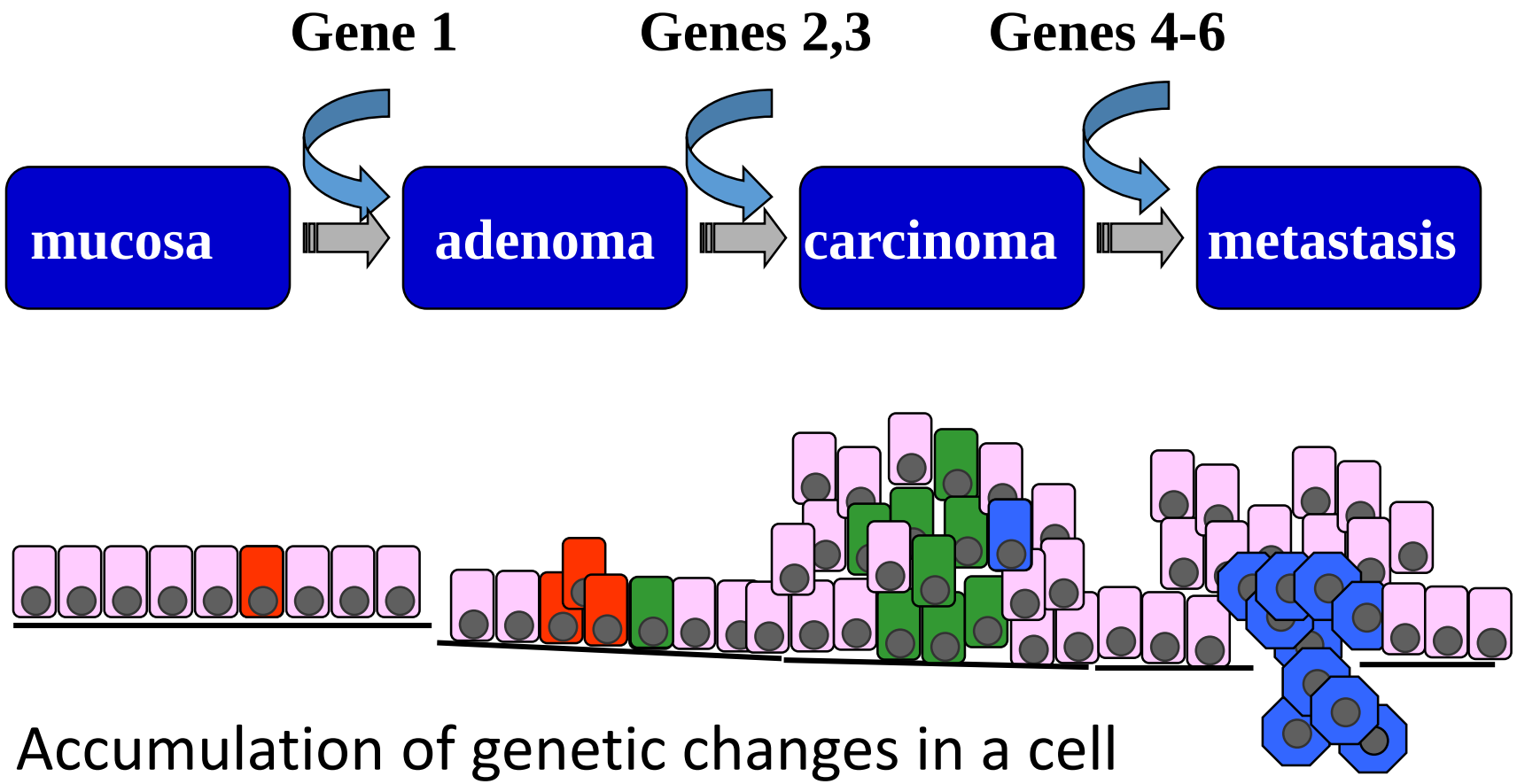
Oncogenes promote cell proliferation

Tumour supressor genes exert control over cell proliferation



The Hallmarks of Cancer
Cell 100, 57–70 (2000)
Hanahan & Weinberg

The classical model of tumorigenesis through *clonal selection*



Accumulation of genetic changes in a cell

in both: tumour suppressor and onco-genes

"a mutant gene (whether oncogene or TSG) may be necessary for tumor formation but, on its own, is not sufficient" - Weinberg, Robert, The biology of cancer -Second edition, Garland Science, 2014

tumour suppressor genes

control normal cell proliferation

(‘anti-growth genes’)

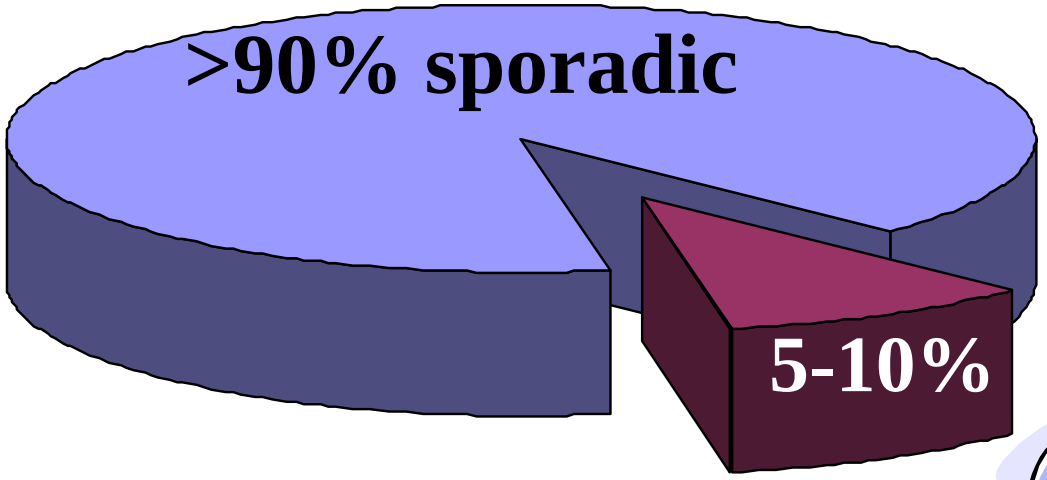
↓

their mutational inactivation

compromises

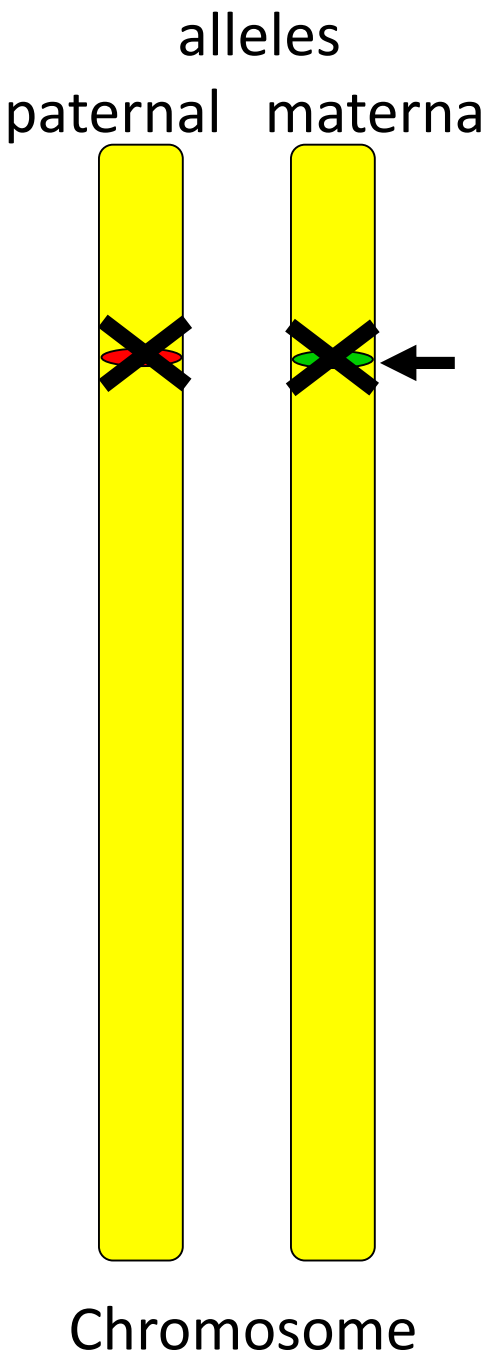
cell division control

Hereditary cancer cases helped to discover tumour suppressor genes



hereditary

Germline mutation in a *tumour suppressor gene*



tumour suppressor gene

1st copy
is lost in a cell
(can be hereditary or sporadic)

↓

2nd copy
becomes inactivated
(***2-hit hypothesis***)

↓

Tumour can develop
or progress

Loss of tumour suppressor genes: molecular mechanisms

genetic — Point Mutation

Truncated or non-functional gene product

genetic — Deletion*

Gene eliminated (deletion, or chromosome loss or translocation)

epigenetic — Promoter methylation

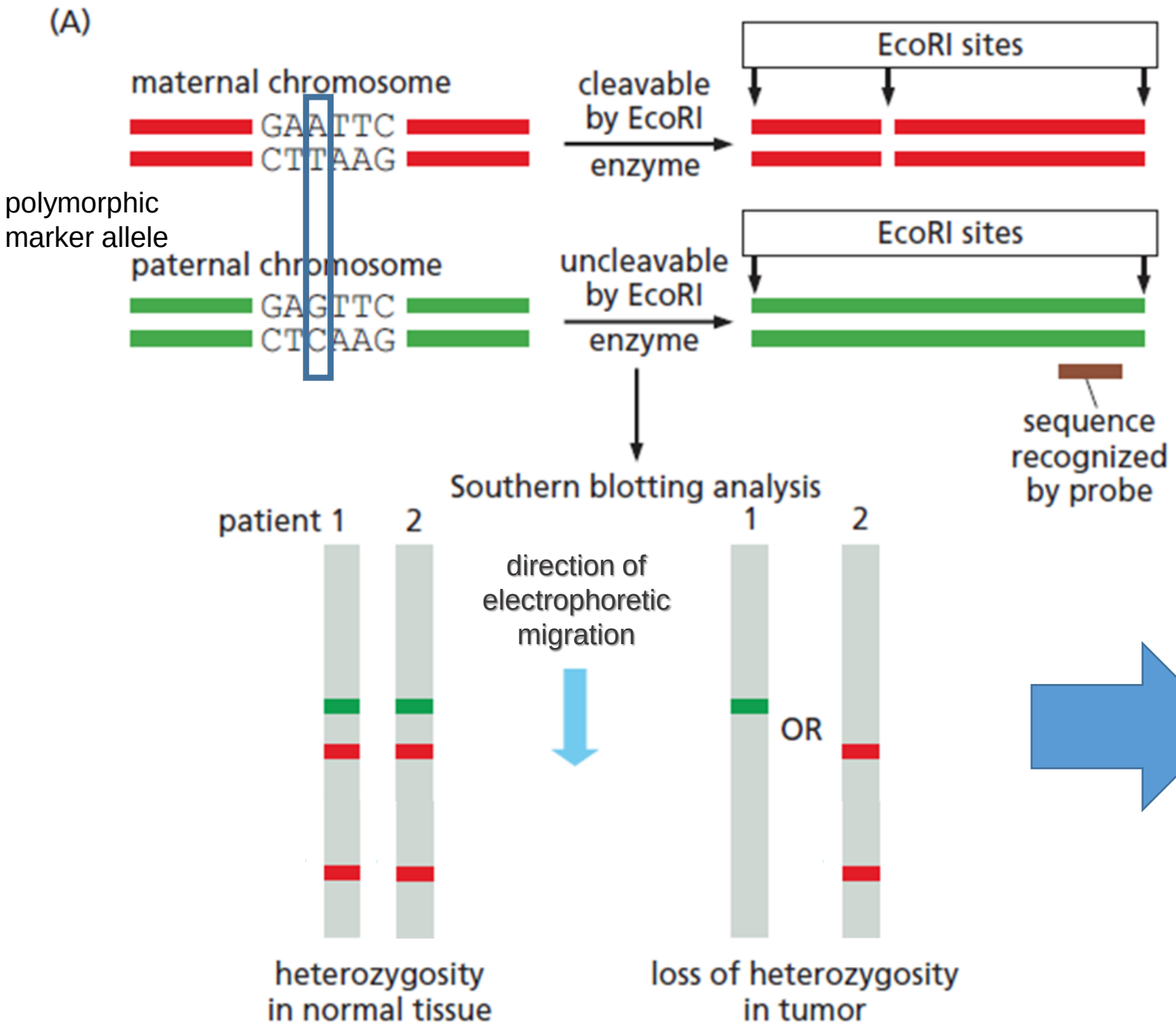
mostly in sporadic tumours

Gene without mutation but silenced

genetic — Mitotic recombination* (sister chromatids exchange)

* **Loss of Heterozygosity** (LOH)

Loss of heterozygosity in tumour suppressor genes



Restriction fragment length polymorphisms (RFLP)
for the detection of LOH

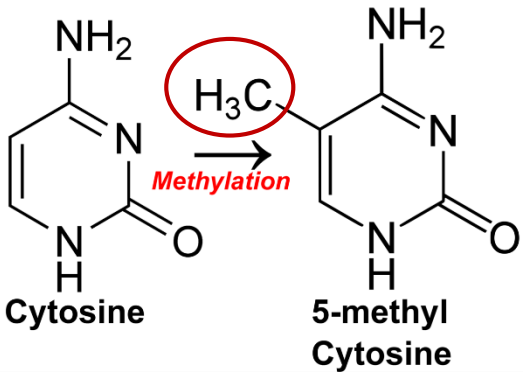
Figure 7.13 in: Weinberg, Robert, The biology of cancer - Second edition, Garland Science 2014

Today, largely substituted by methods like

- allele-specific PCR or MLPA
- SNP sequencing or array,
- NGS

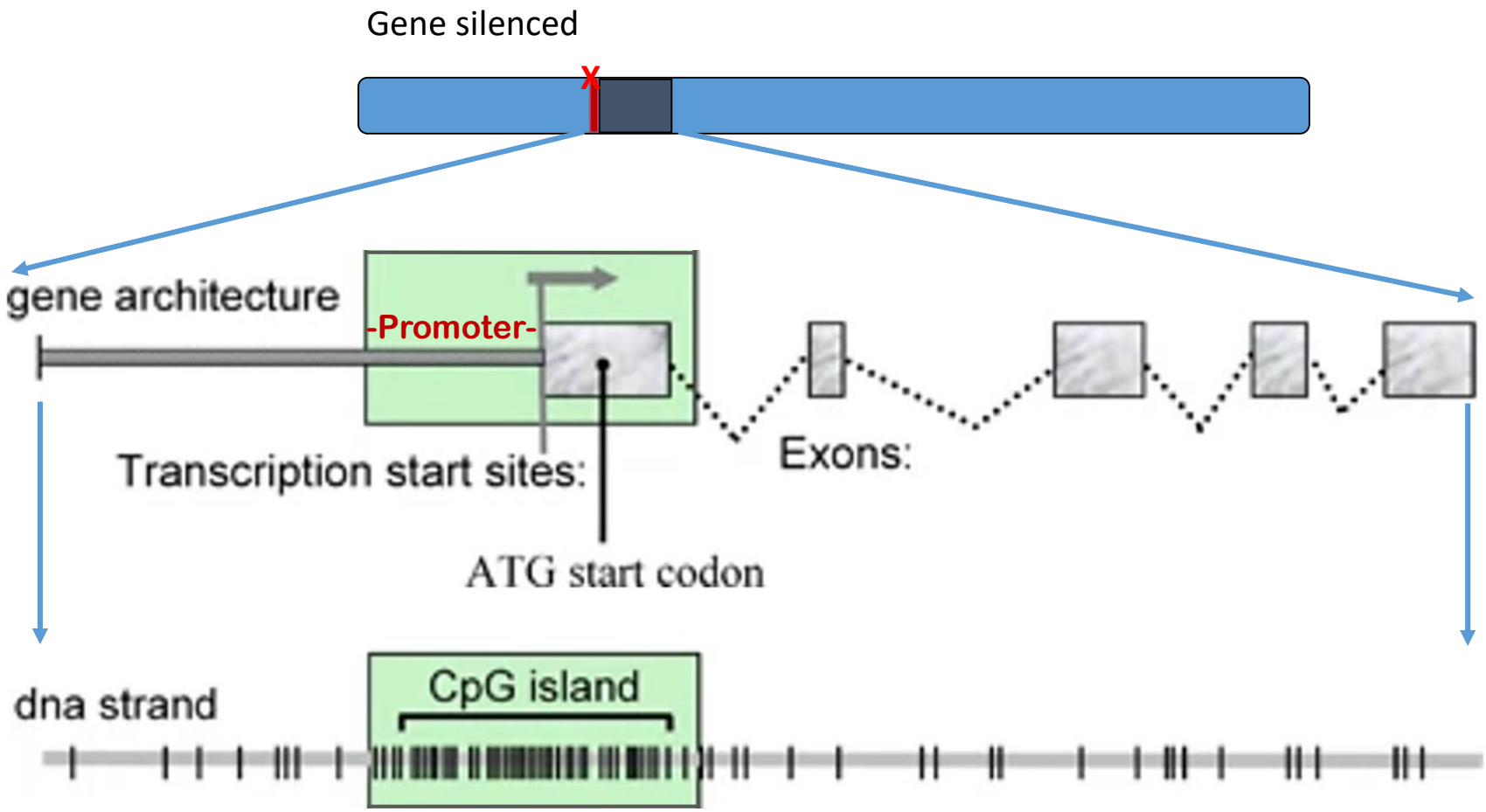
Promoter methylation in tumour suppressor genes

mostly in sporadic tumours



methylated CpG island:
recruits chromatin proteins involved in gene repression, or
inhibits binding of a transcription factor to the promoter

CG dinucleotide position



tumour suppressor genes

control normal cell proliferation

('anti-growth genes')

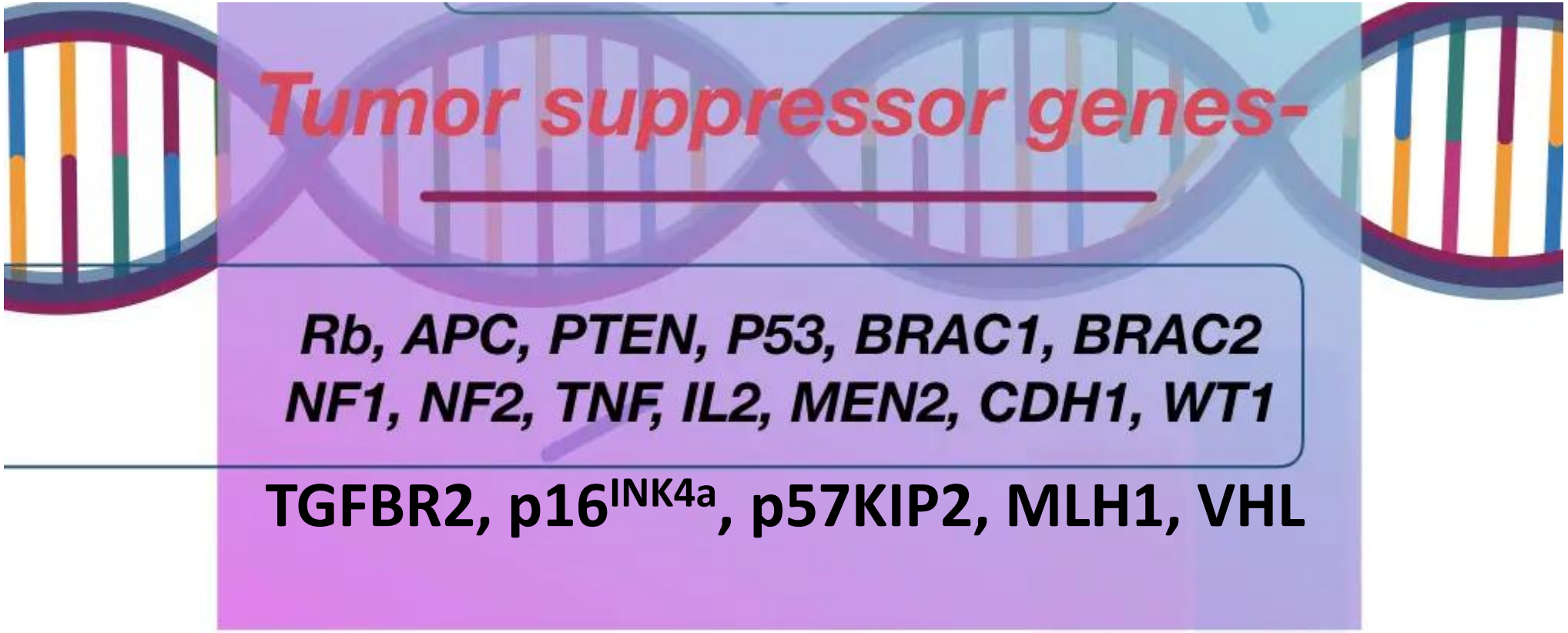
gatekeepers

- **Control or suppress cell division**
- **Promote apoptosis**

- **DNA damage repair**

caretakers

Some well-studied examples



tumour suppressor genes

control normal cell proliferation

('anti-growth genes')

- **Control or suppress cell division**
- **Promote apoptosis**
- **DNA damage repair**

Signaling Pathway of TGF-β

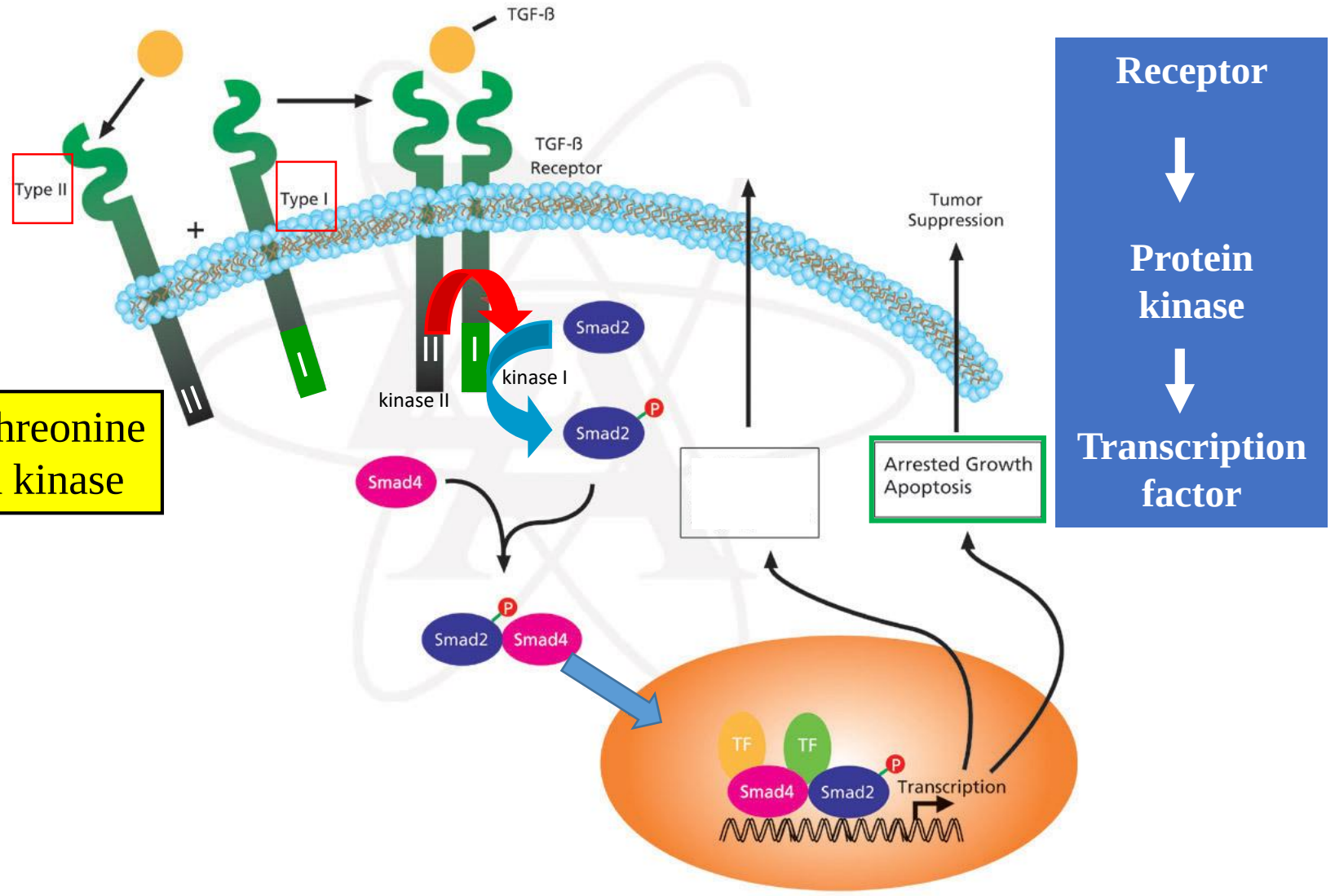
TGFBR2

Frameshift mutations

↓

in sporadic colon cancer with MSI

Growth-inhibitory signal for normal epithelial cells



Serine/threonine protein kinase

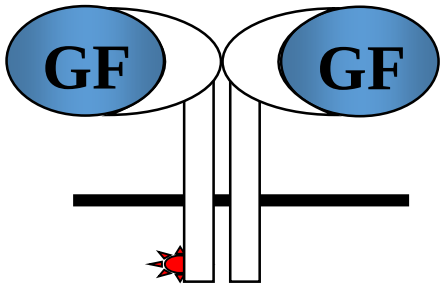
Receptor

↓

Protein kinase

↓

Transcription factor



intrinsic enzymatic activity

Adenomatous polyposis coli

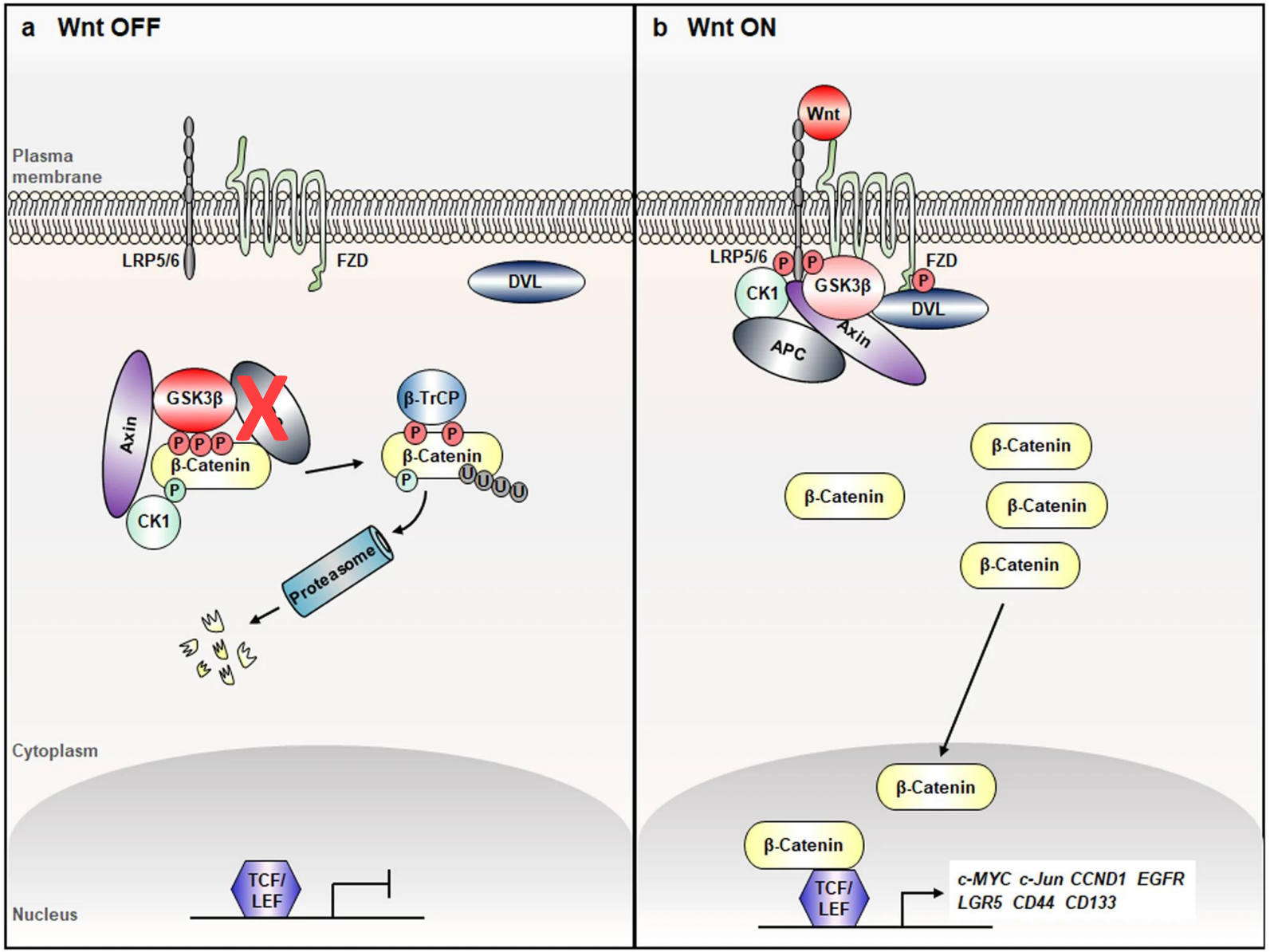
APC controls the transcriptional co-factor β-catenin

APC

point mutations creating premature stop codons

↓

Familial and sporadic colorectal cancer



Receptor

↓

Protein kinase inhibition

↓

Transcription factor stabilization

Cyclin-dependent kinases control the cell cycle

Rb

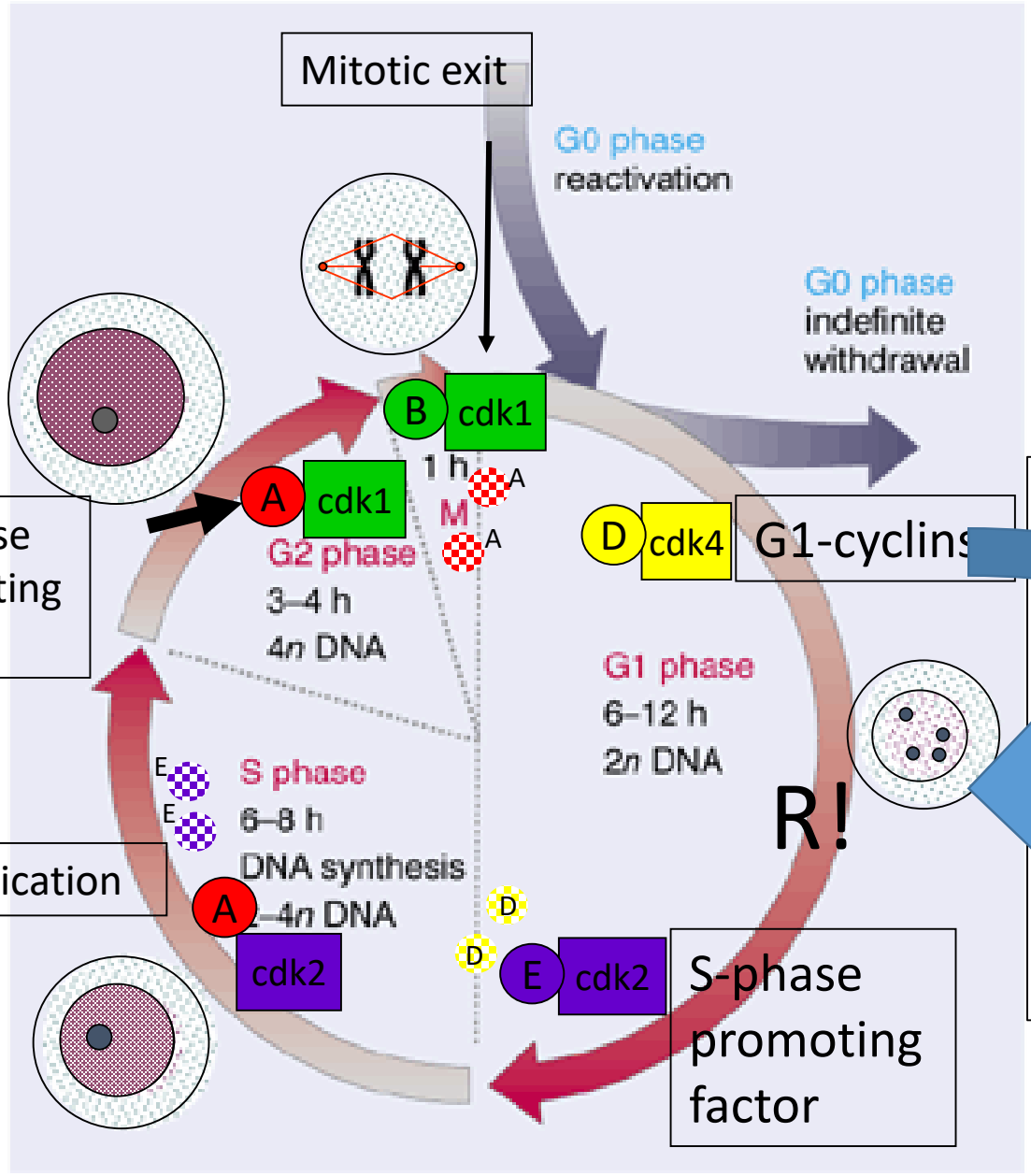
Retinoblastoma= Rare childhood eye tumour

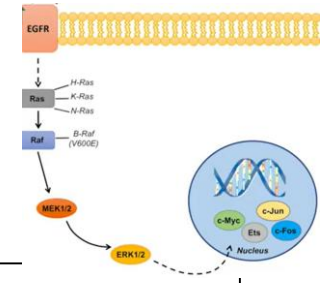
$p57^{KIP2}$
$p16^{INK4a/b}$

Gene deletion or gene silencing

↓

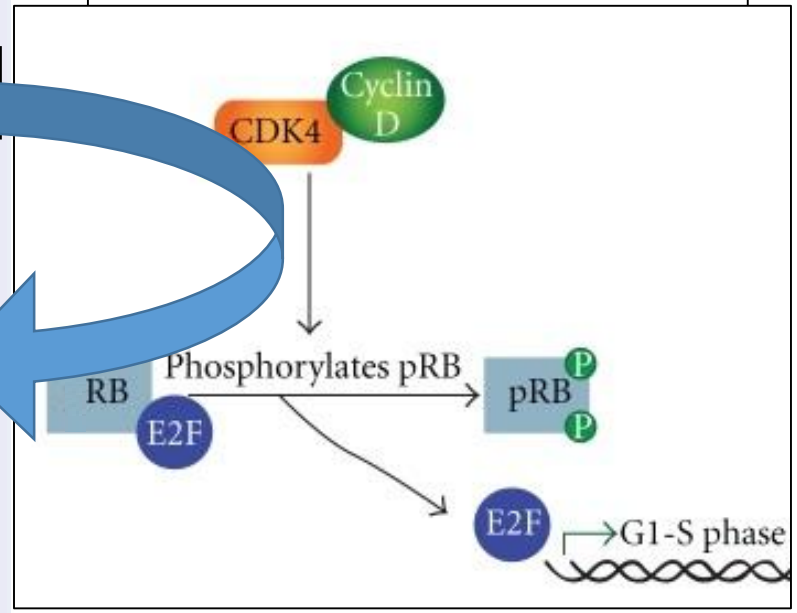
Familial melanoma; many sporadic tumors





Cyclin D1 levels rise after MAPK activation

Cyclins are subunits required for the activity of cyclin-dependent protein



E2F target genes:
- Cyclin E, cyclin A, CDK2
- initiation of replication

Cyclin-dependent kinase inhibitors (CDKI) can halt the cell cycle

1. **INK4 family (INhibit CDK4):**
   p16 (INK4a)/p15 (INK4b), p18 (INK4c), p19 (INK4d)
   - inhibit association of cdks with cyclin subunit
2. **CIP/KIP family**
   p21 (Cip1/Waf1), p27 (KIP1), p57 (KIP2)
   - inhibit kinase activity of already assembled cdk-cyclin complexes

Gene synbols

CDKN2a-d

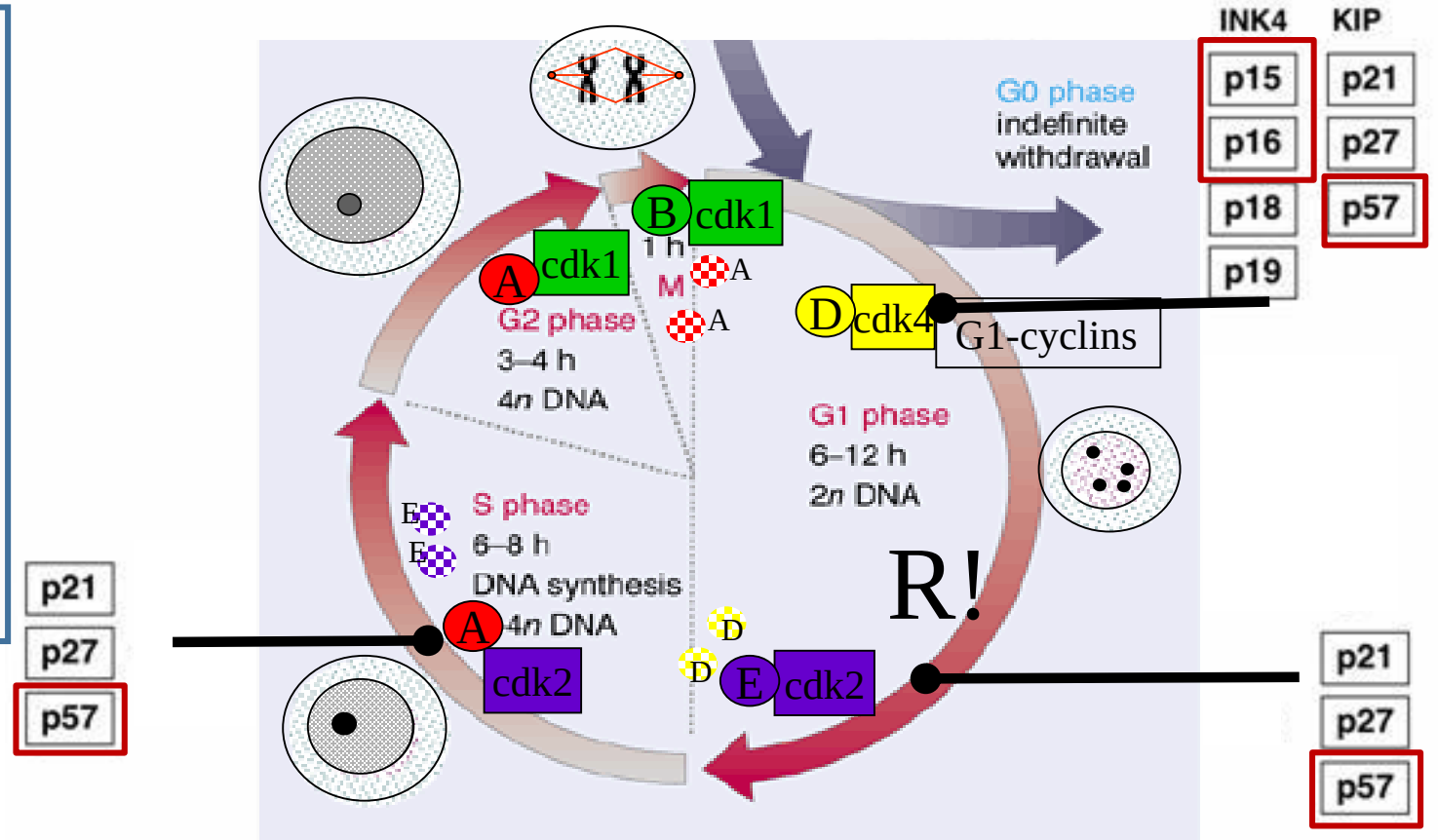
CDKN1a-c

$p57^{KIP2}$
$p16^{INK4a/b}$

Gene deletion or gene silencing

↓

Familial melanoma; many sporadic tumors



CDK inhibitor proteins can fine-tune cell cycle progression, or halt it for damage repair

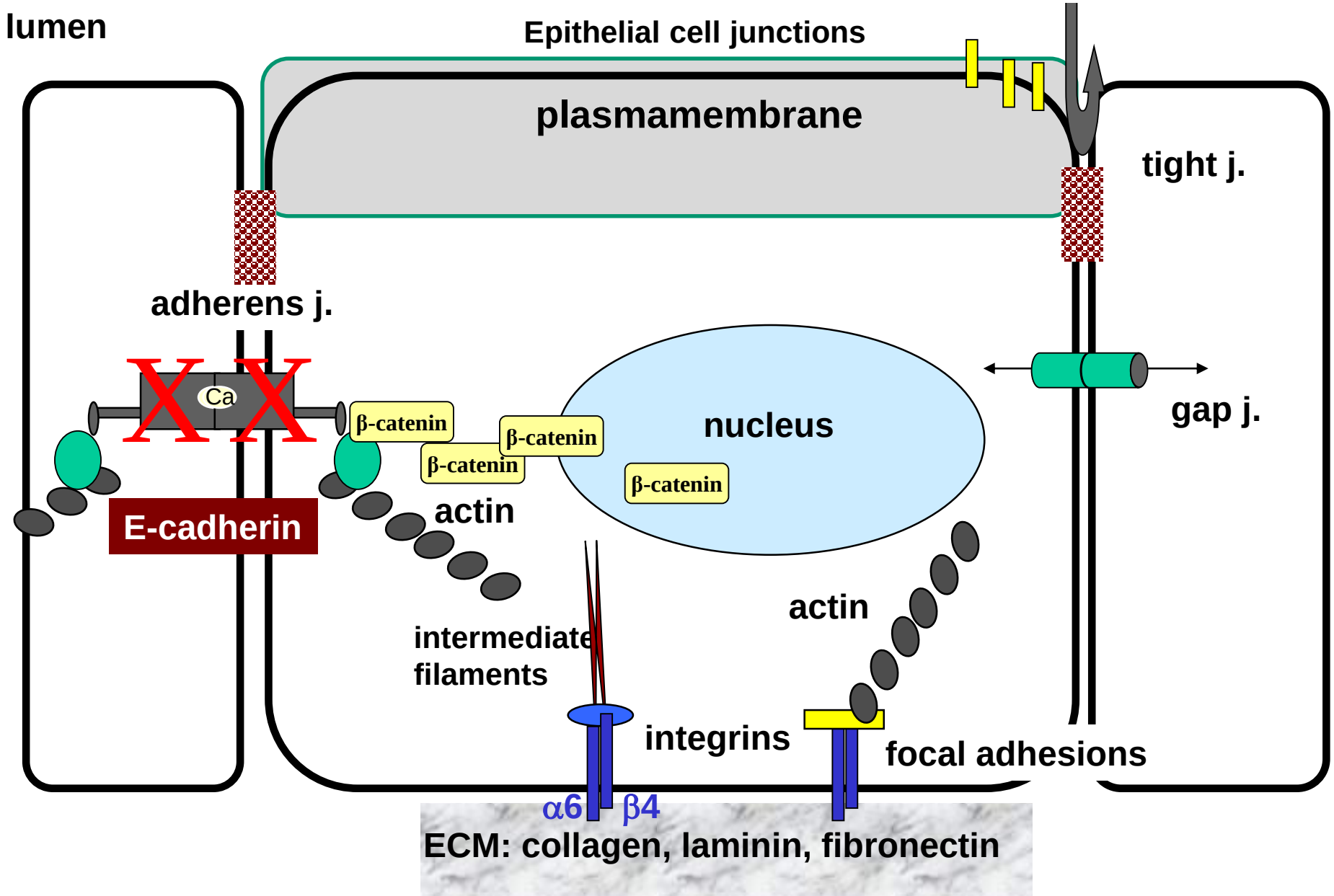
Well-differentiated epithelial cells have separate apical and basolateral membrane compartments

CDH1

Gene deletion or point mutation; gene silencing

↓

Familial gastric cancer; sporadic cancers



Well-differentiated epithelial cells lose their organized morphology upon E-cadherin loss and become more invasive

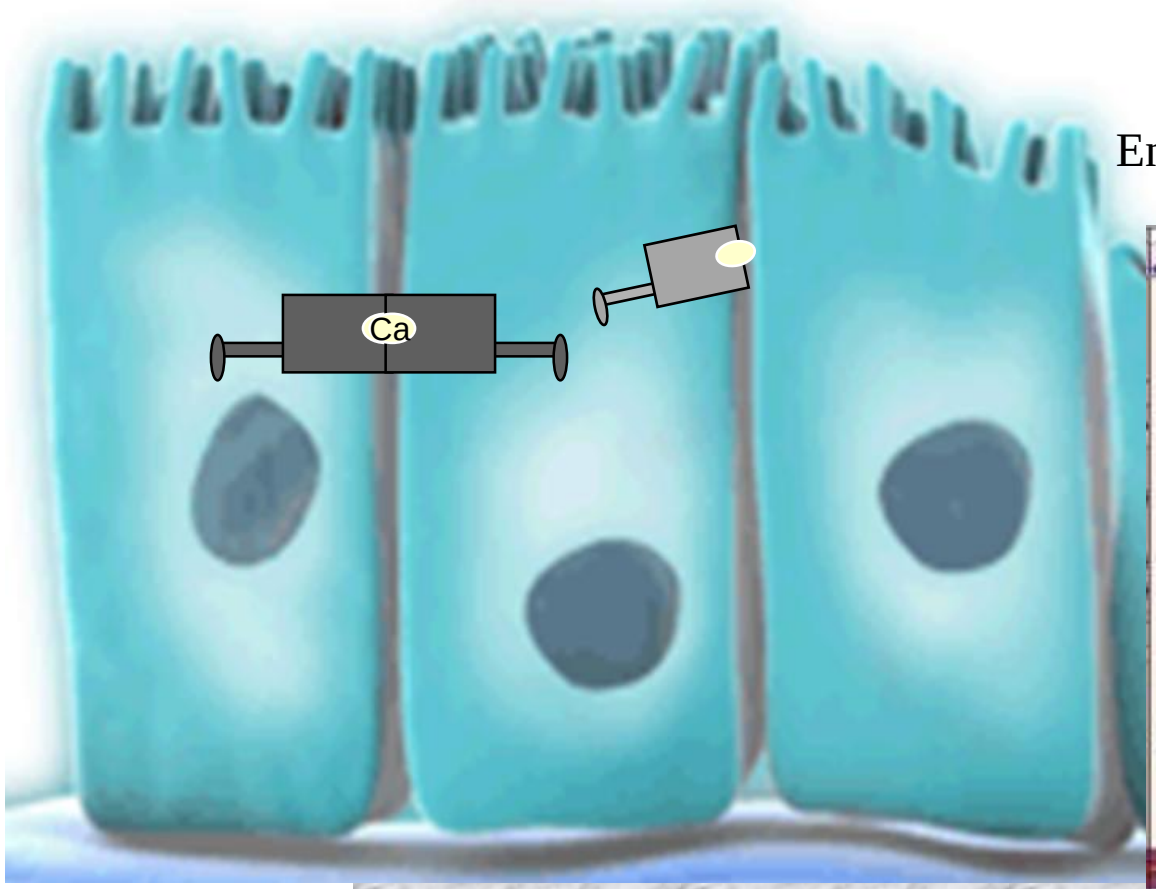
CDH1

Gene deletion or point mutation; gene silencing

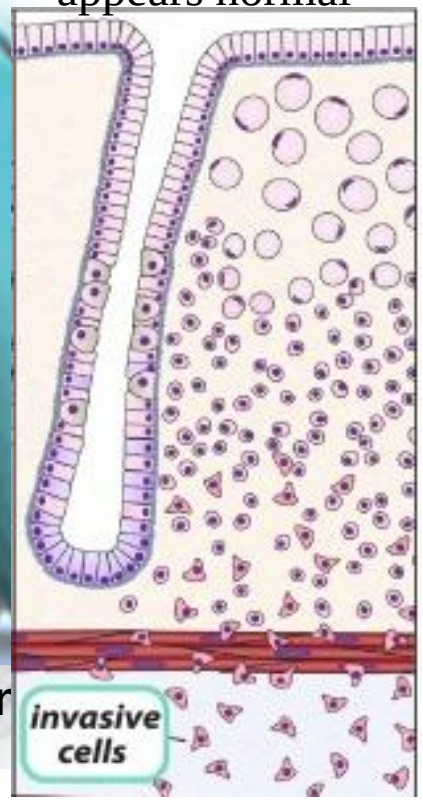
↓

Familial gastric cancer; sporadic cancers

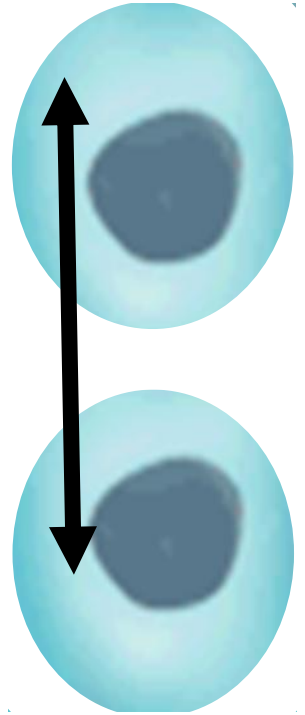
in sporadic tumours:



Endoscopic morpholgy appears normal



in HDGC: Loss of correct cell divison plane



https://doi.org/10.1016/j.bbcan.2022.188719

tumour suppressor genes

control normal cell proliferation

(‘anti-growth genes’)

- Control or suppress cell division
- **Promote apoptosis**

- DNA damage repair

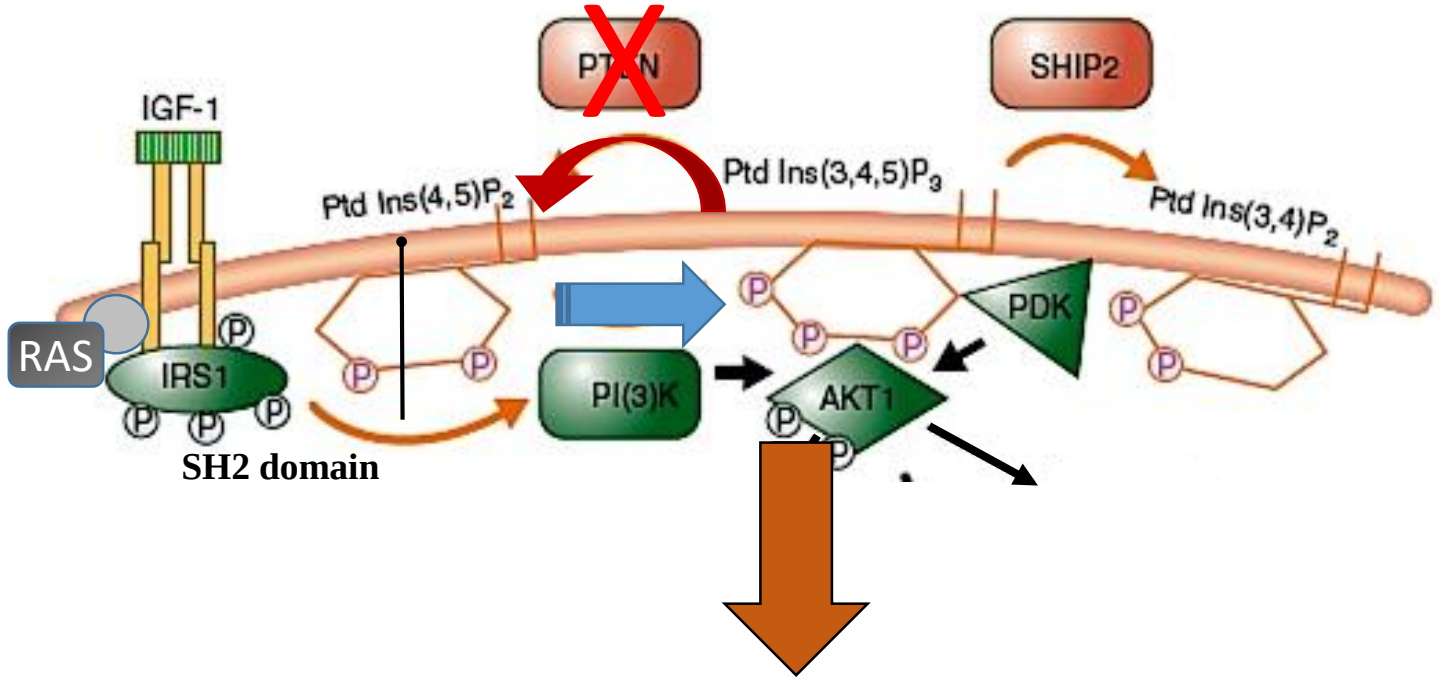
Phosphatidyl-inositol: the PI3 kinase pathway

PTEN

Gene deletion or gene silencing

↓

Brain and breast tumours



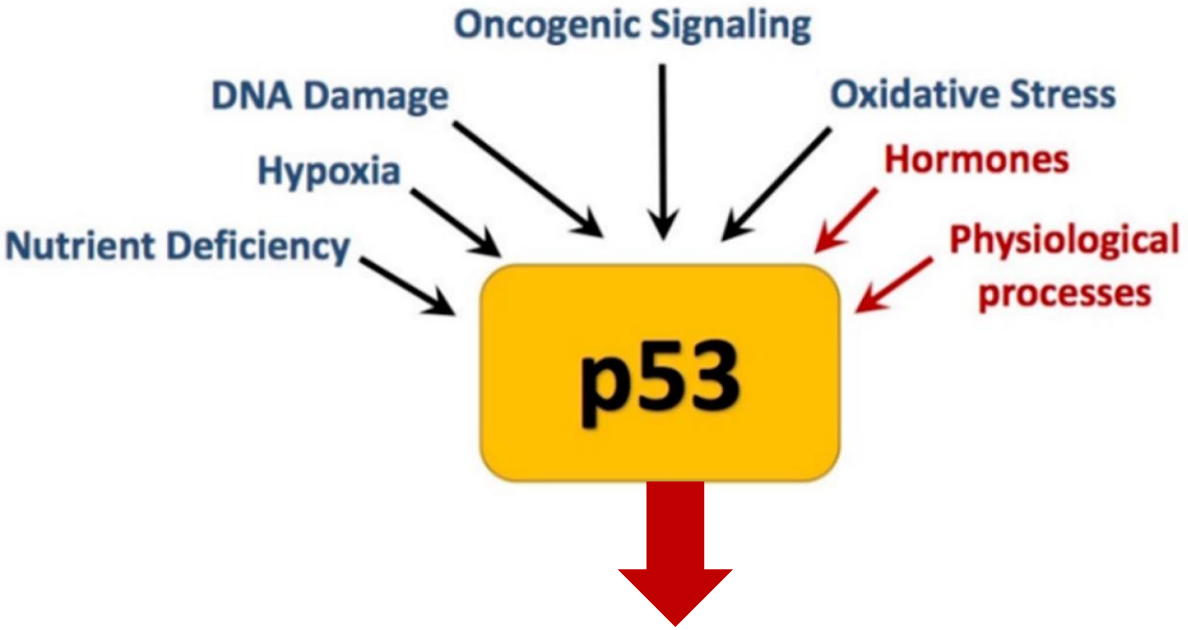
Inhibition of apoptosis-inducing proteins

TP53

Gene deletion or point mutations

↓

Li-Fraumeni syndrome; most sporadic cancer types



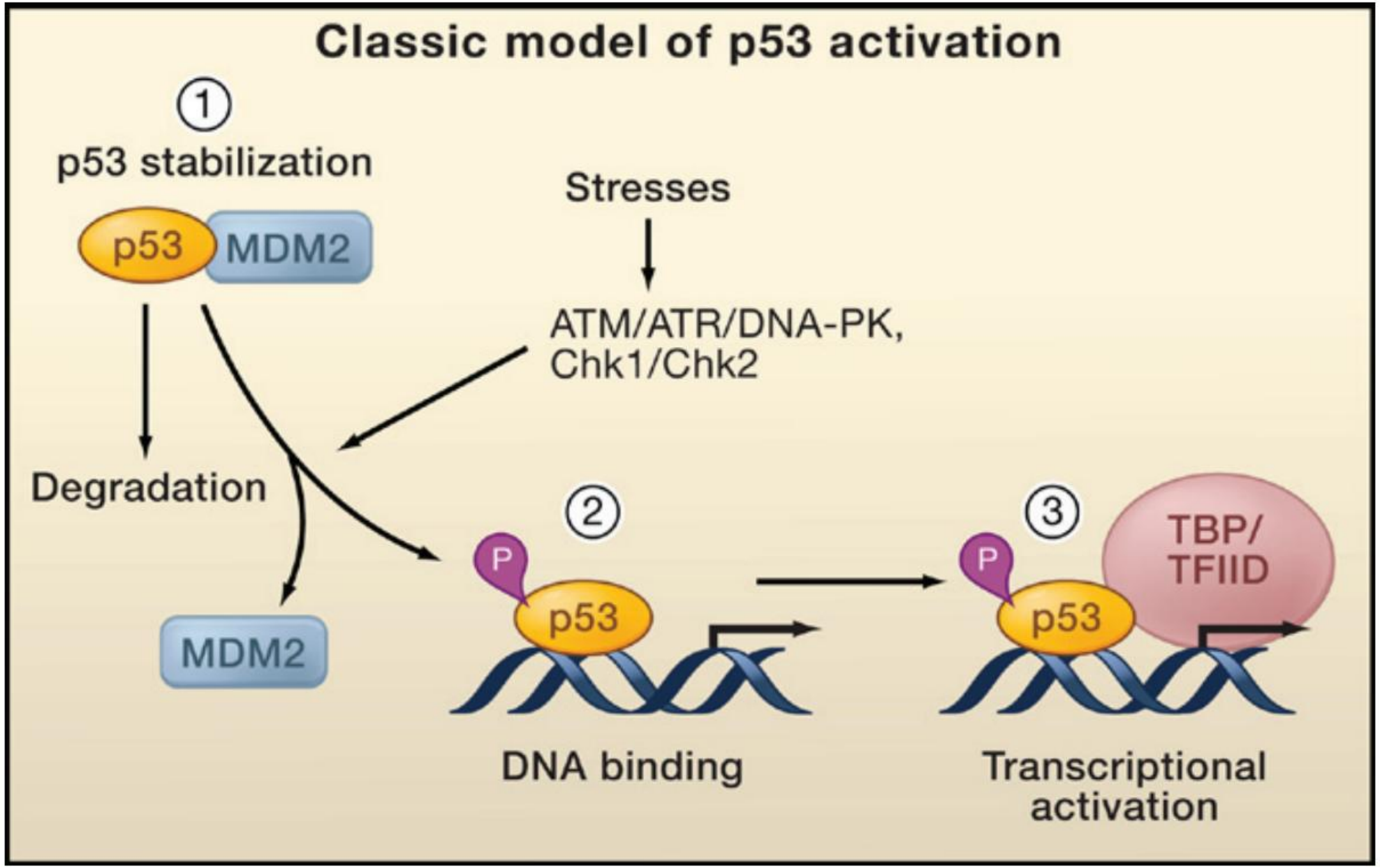
Gene transcription

↓

Programmed death

Apoptosis

p53-dependent apoptotic signalling pathwyas



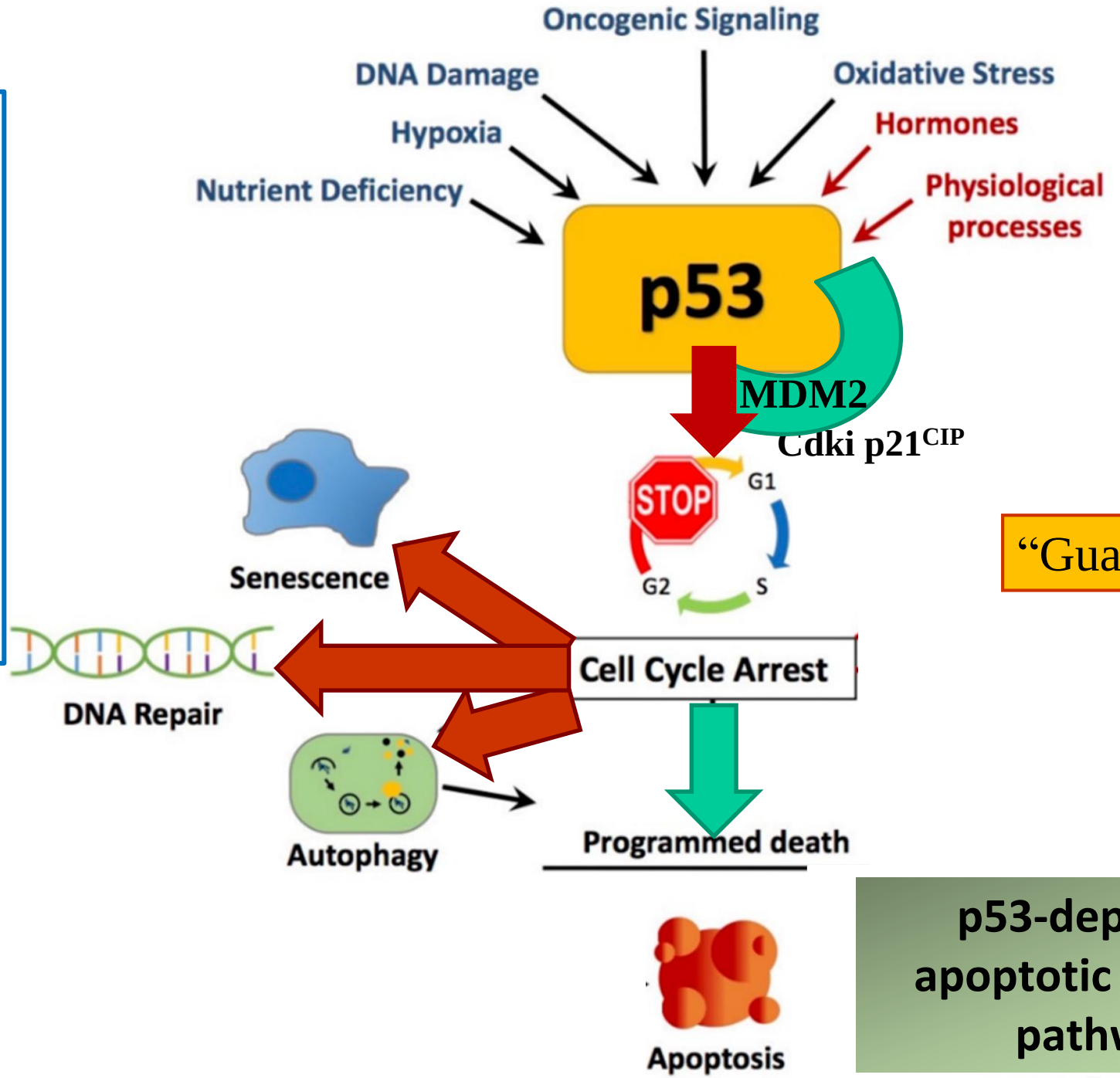
https://www.cell.com/cell/pdf/S0092-8674(09)00511-X.pdf

TP53

Gene deletion or point mutations

↓

Li-Fraumeni syndrome; most sporadic cancer types



"Guardian of the genome"

p53-dependent apoptotic signalling pathwyas

tumour suppressor genes

control normal cell proliferation

(‘anti-growth genes’)

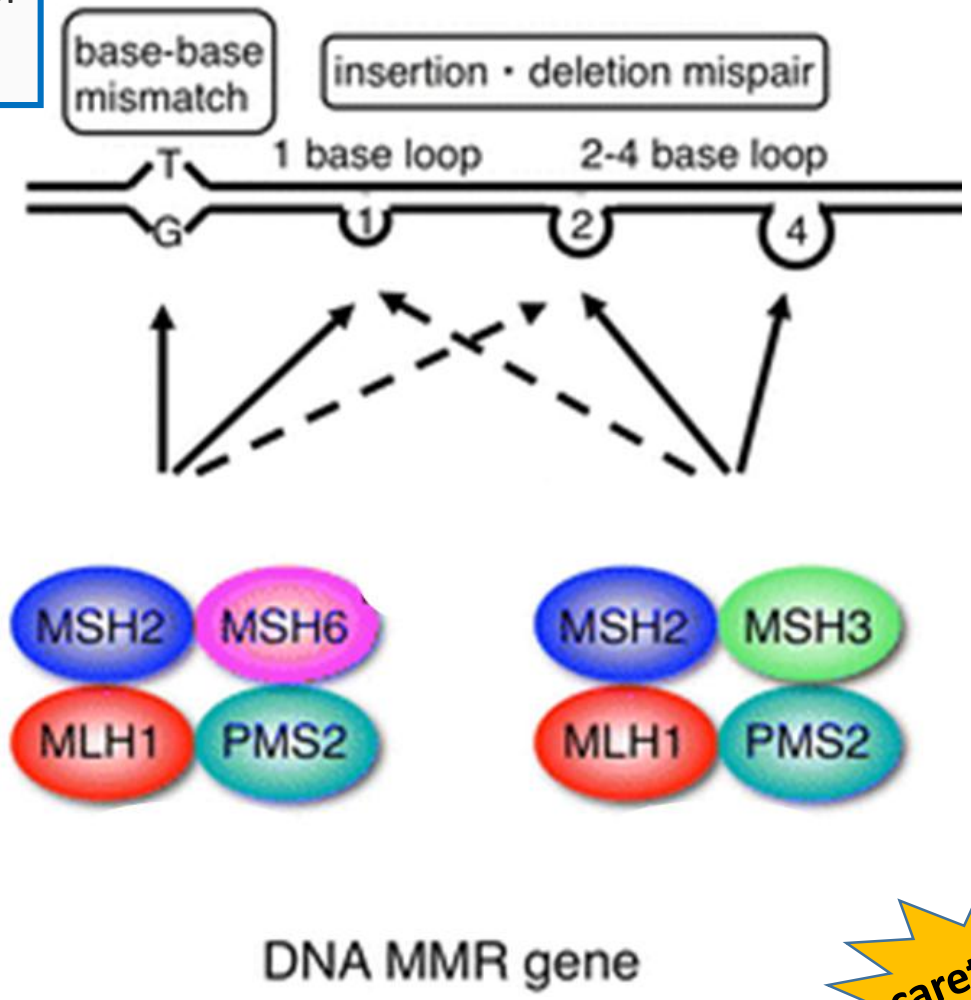
- Control or suppress cell division
- Promote apoptosis

- **DNA damage repair**

MLH1

Gene deletion or gene silencing

Mismatch error recognition

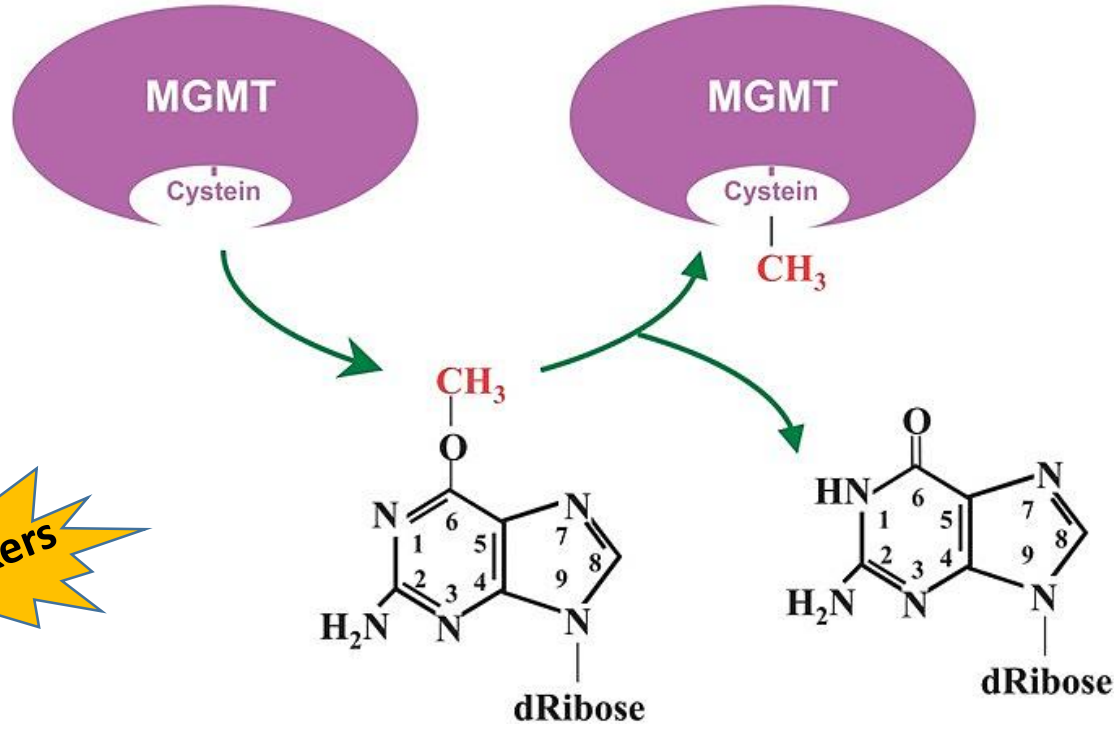


caretakers

MGMT

DNA repair protein

- defense against mutagenesis by alkylating agents,
- loss indicates sensitivity to chemotherapy with alkylating agents

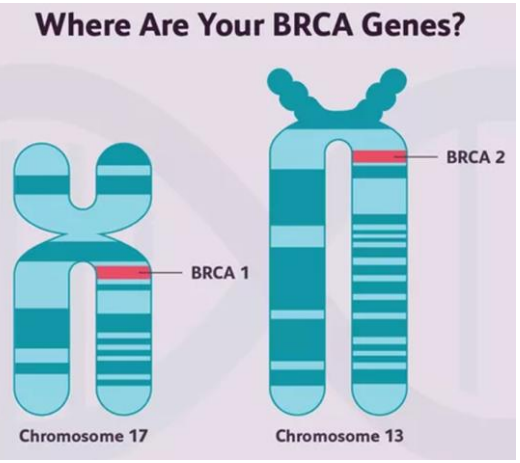


BRCA1
BRCA2

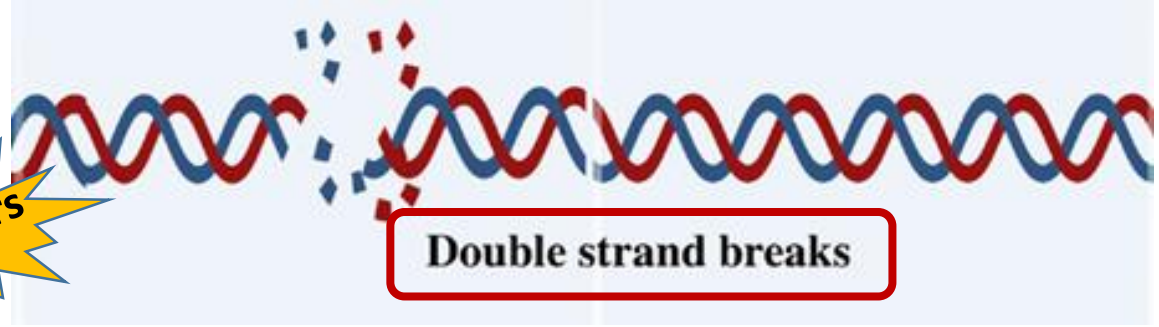
Gene deletion or nonsense mutation

↓

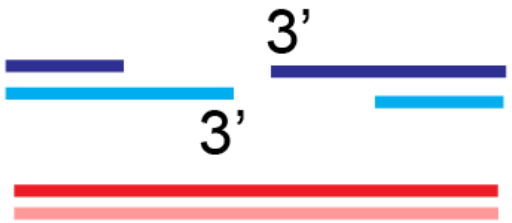
Familial and sporadic breast and ovarian cancer



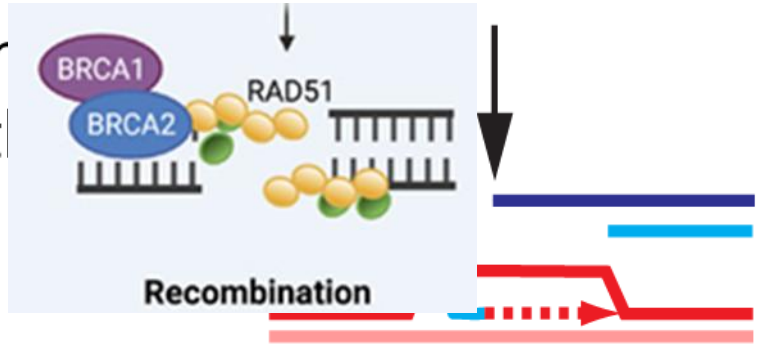
caretakers



End Resection



Strar
Synt

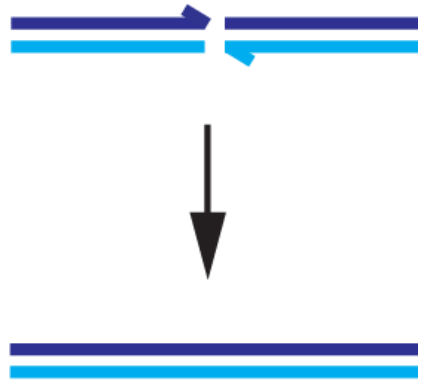


Synthesis-Dependent Strand Annealing

homologous recombination repair (HRR)

End Joining

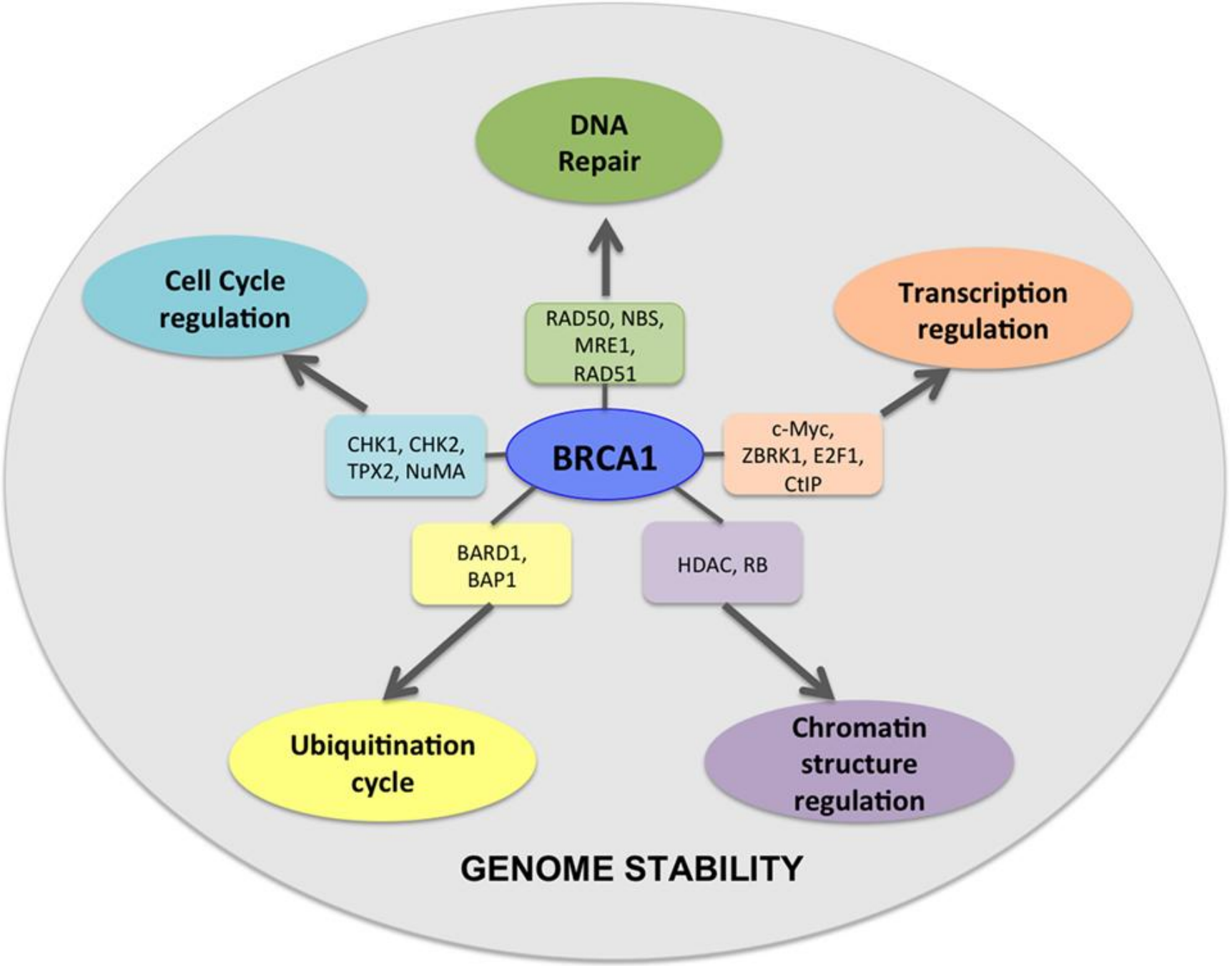
Ligation



BRCA1 and BRCA2 proteins act mostly as **scaffolds** to assemble a cohort of other DNA repair proteins into large physical complexes for HRR

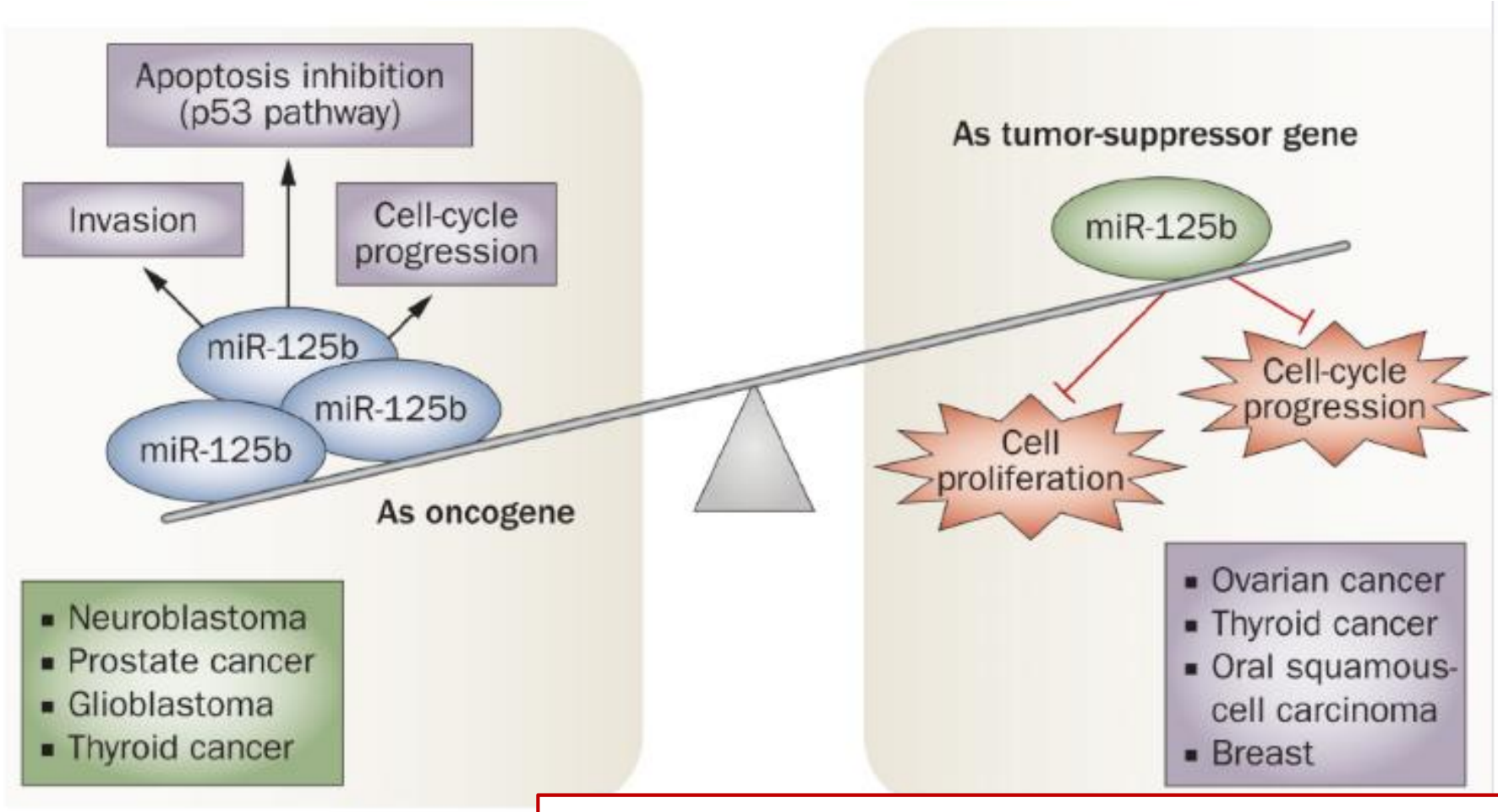
BRCA1:
Multiple functions by interacting with proteins that function in checkpoint activation, DNA repair and transcriptional control

BRCA2:
Function in the core mechanism of homologous recombination



Up to 20% of BRCA1 missense mutations may cause defects in other pathways (Non-HRR mutations)

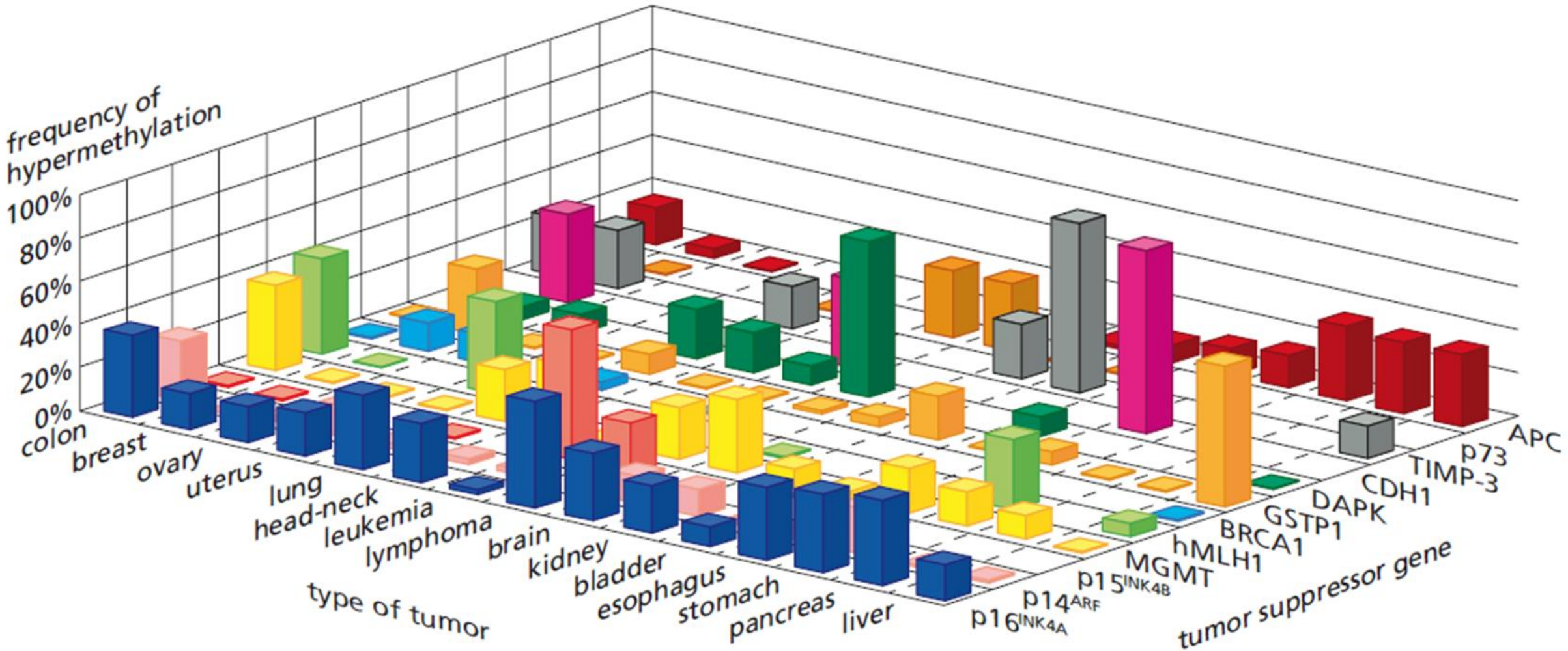
Can miRNA genes be tumour suppressor genes??



Doi: 10.1038/nrclinonc.2011.76

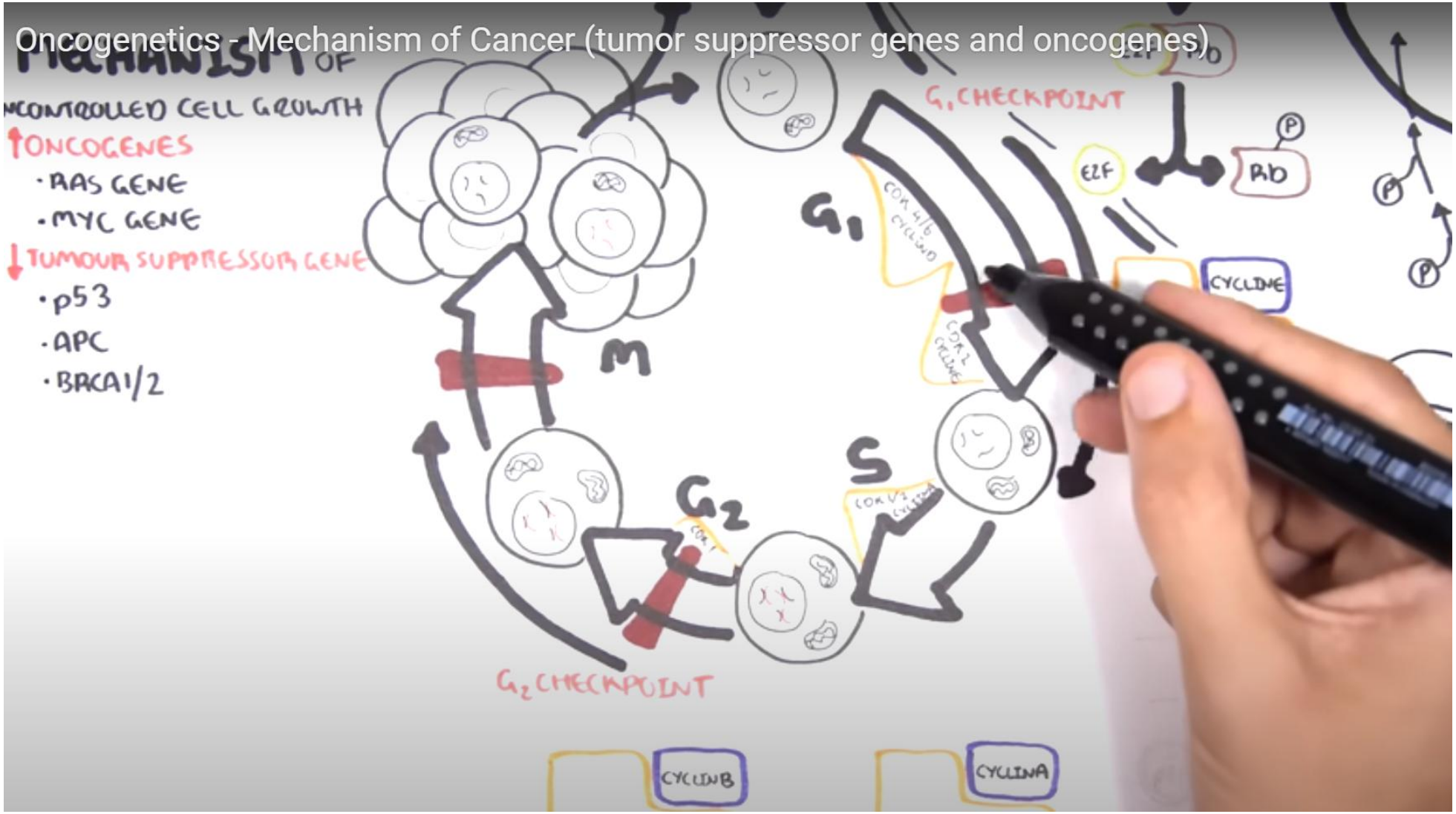
‘Tumour suppressor gene’ is an operational definition

Different tumour types differ in their TSG promoter methylation frequency



Weinberg, Robert, The biology of cancer -Second edition, Garland Science 2014

Recommended 11 min-video animation: Cell cycle and Tumour suppressor genes



https://www.bing.com/videos/riverview/relatedvideo?q=list+od+tumor+suppresor+genes&mid=695A5080A85A3175AD41695A5080A85A3175AD41&FORM=VIRE

Lecture 4- Some take-home concepts

- **Tumour suppressor genes control cell division and can act as ‘gatekeepers’ or ‘caretakers’**
- **The inactivation of tumour suppressor genes generally occurs in both alleles (two-hit hypothesis)**
- **Gene promotor methylation is frequently observed as the inactivation mechanism in sporadic tumours**

- **Important TSG examples are APC, BRCA1 and -2, CDH1, CDKN members, PTEN and TP53**
- **Control of the cell cycle is lost by inactivation of CDKNs, or upstream signalling regulators like APC or CDH1**
- **Control of apoptosis is lost by mutations in PTEN or TP53**
- **Caretakers encode proteins involved in several DNA repair pathways such as MLH1, MGMT, BRCAs**