MCB of Cancer

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Dr Katja Vogt

Cancer in UM2010

Core

- Molecular Cell Biology of Cancer
- Cancer Hallmarks
- Genetic factors in Cancer

GU

- Cervical Cancer and Cancer Staging
- Classification of Cancer

MSK

- White Blood Cell Disorders and Myelodysplastic syndrome
- Environmental influences of Cancer development and Progression

NEU

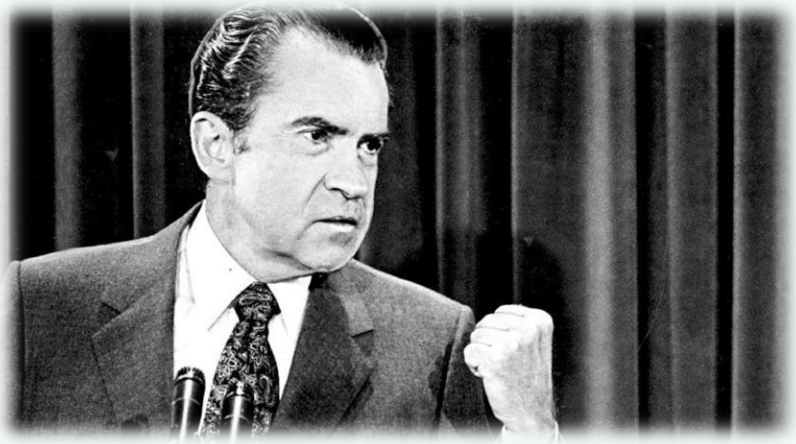
- Cancers of endocrine organs

Today, we are going to…

- … Identify and define important key concepts in cancer biology
- … identify DNA damage and repair mechanisms
- … investigate Genetic Predispositions to Cancer using selected examples
- … define the Multistage Model of Carinogenesis on the example of bowel cancer
- … explore the Chromosomal Aberrations in (Haematopoietic) Cancers

What is Cancer?

- Uncontrolled cell proliferation
- Cancer is more than one disease
- Cancer is caused by the accumulation of genetic mutation



Medical Literature Term Frequency Word Cloud

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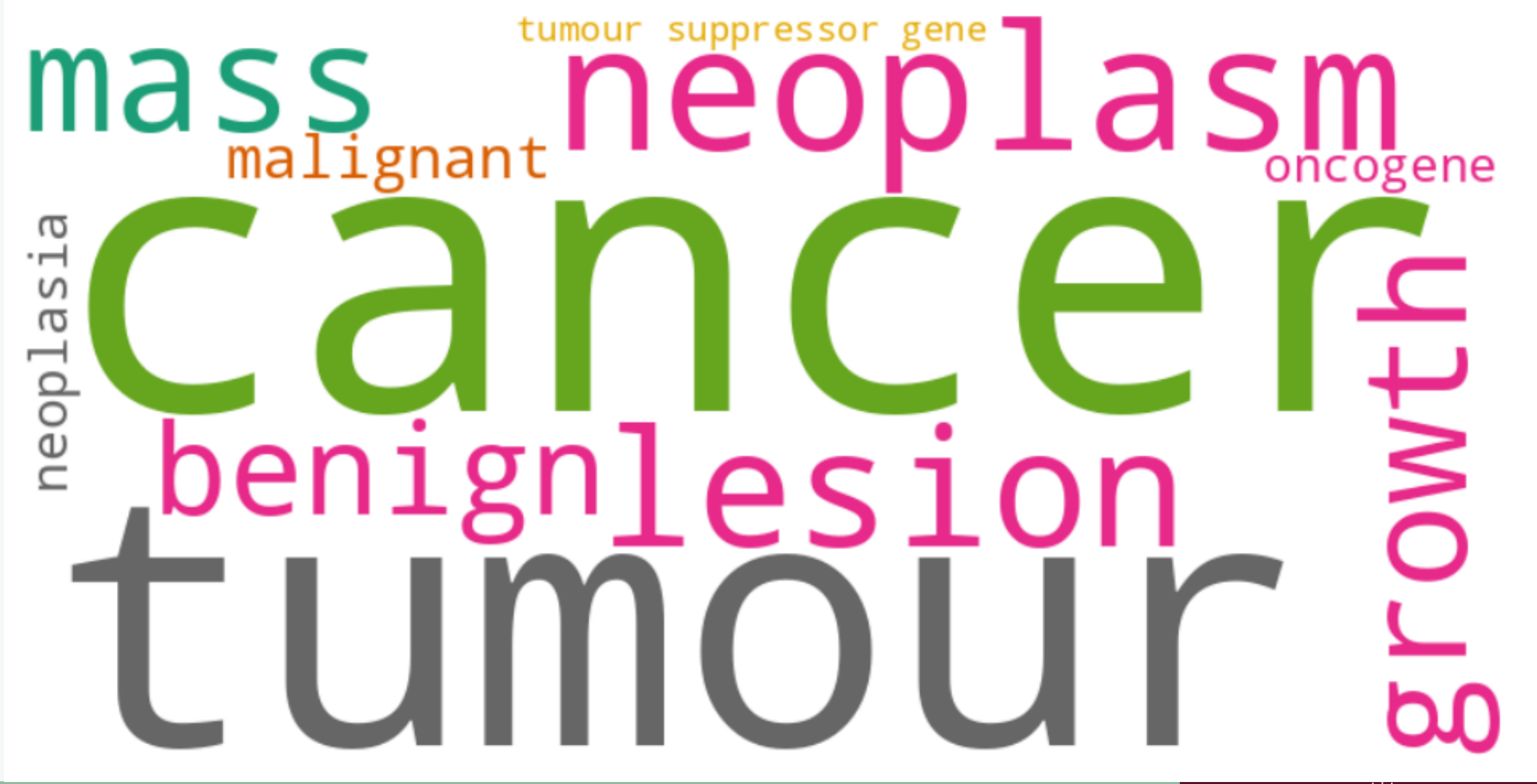


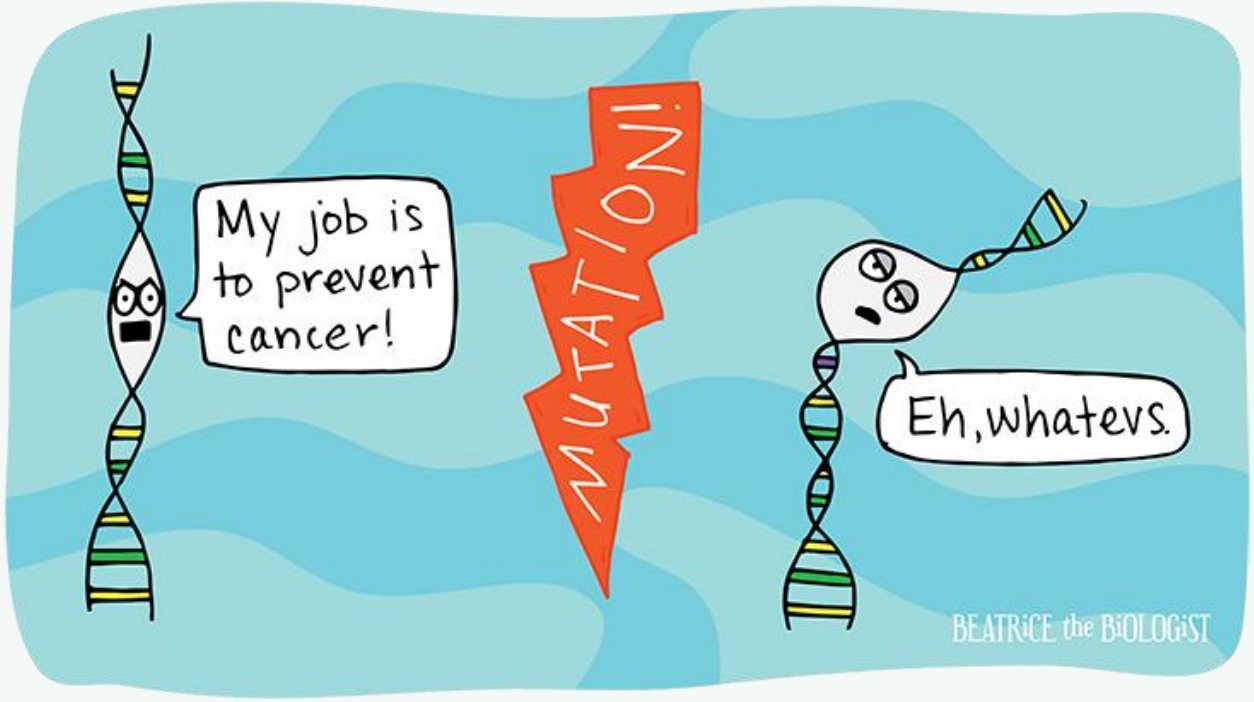
Tumour suppressor genes

- Present in all cells in our body
- Keep cell division in check

- When switched on, they prevent cells from growing and dividing
- When inactivated uncontrolled cell division might occur

- Most prominently genes that encode RB (retinoblastoma-associated) and TP53 proteins

⭐ Encodes a proteins that act to regulate cell division



Oncogenes

⭐ A mutated gene that has the potential to cause cancer.

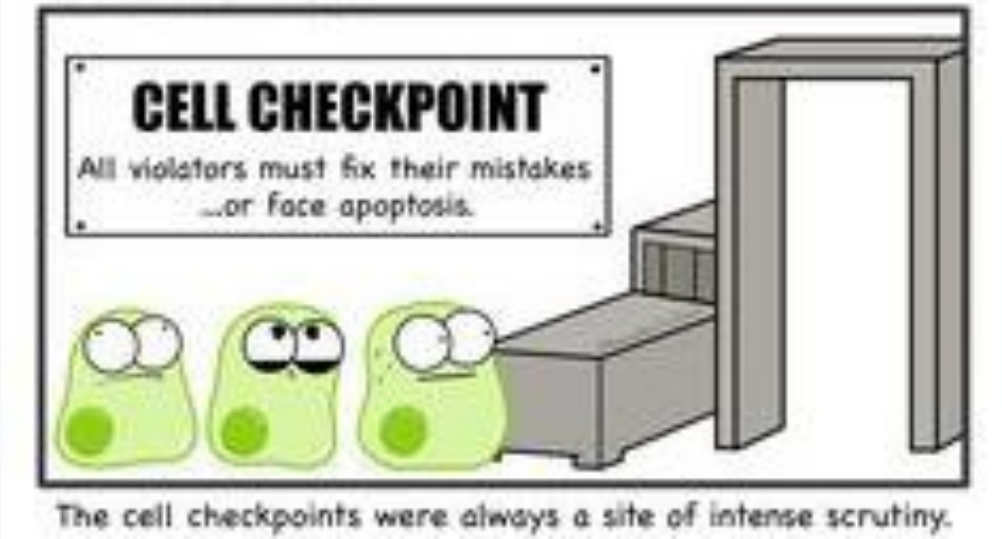
- Before an oncogene becomes mutated, it is called a proto-oncogene, and it plays a role in regulating normal cell division
- Initially identified in viruses
- Proto-oncogenes are key players in the regulation of normal cellular growth, division and apoptosis

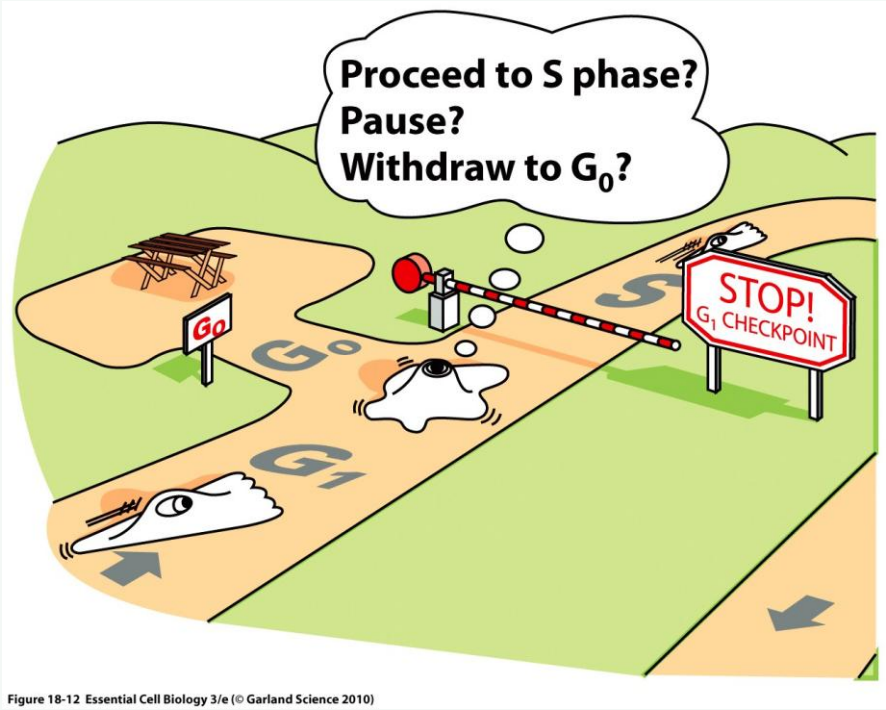
Dr Katja Vogt

DNA damage and repair mechanism

University of Lancashire

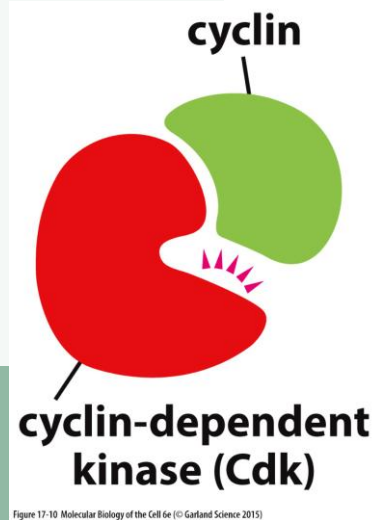
What happens when DNA gets damaged?
- Cell cycle checkpoints

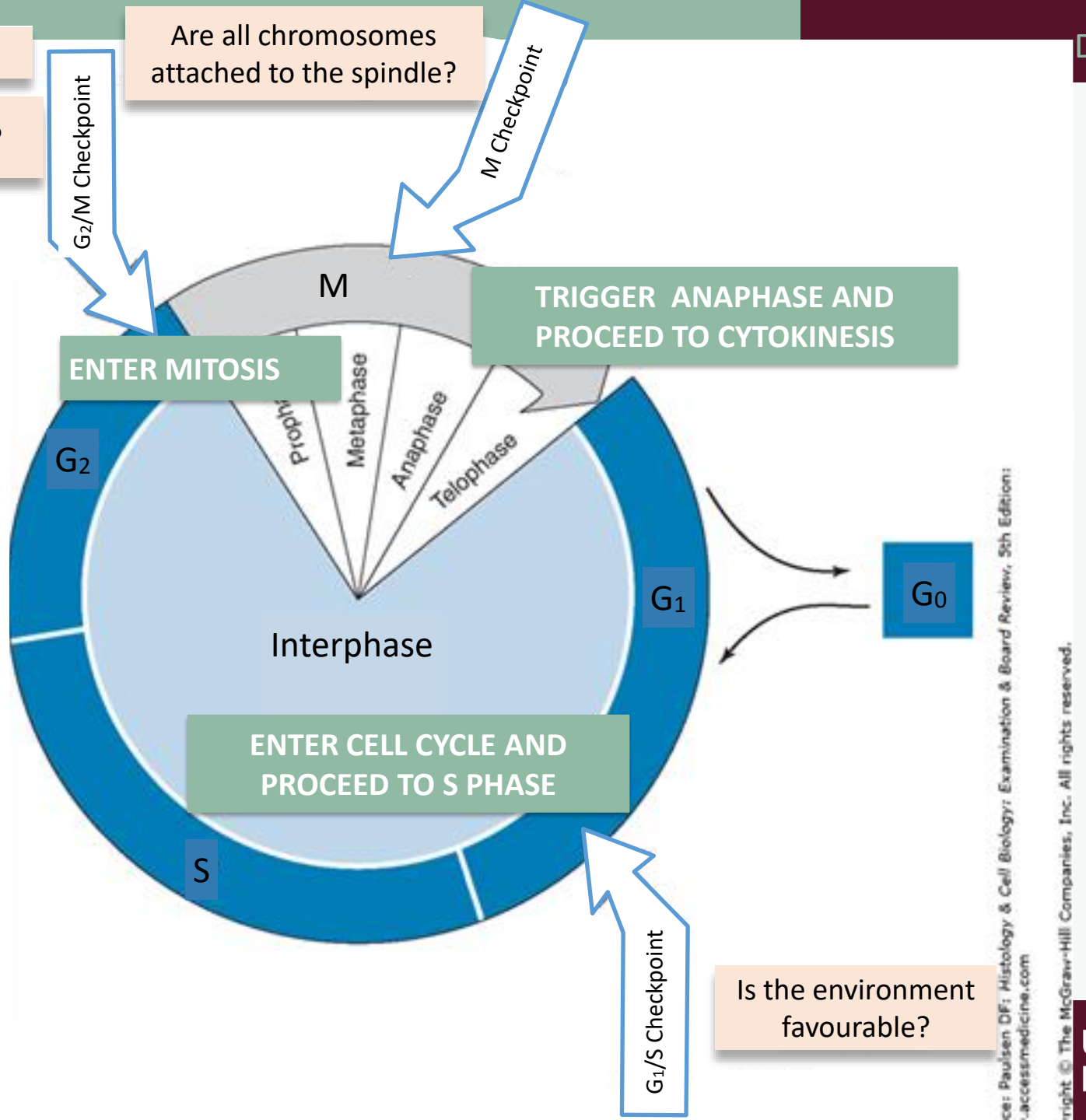




Checkpoints

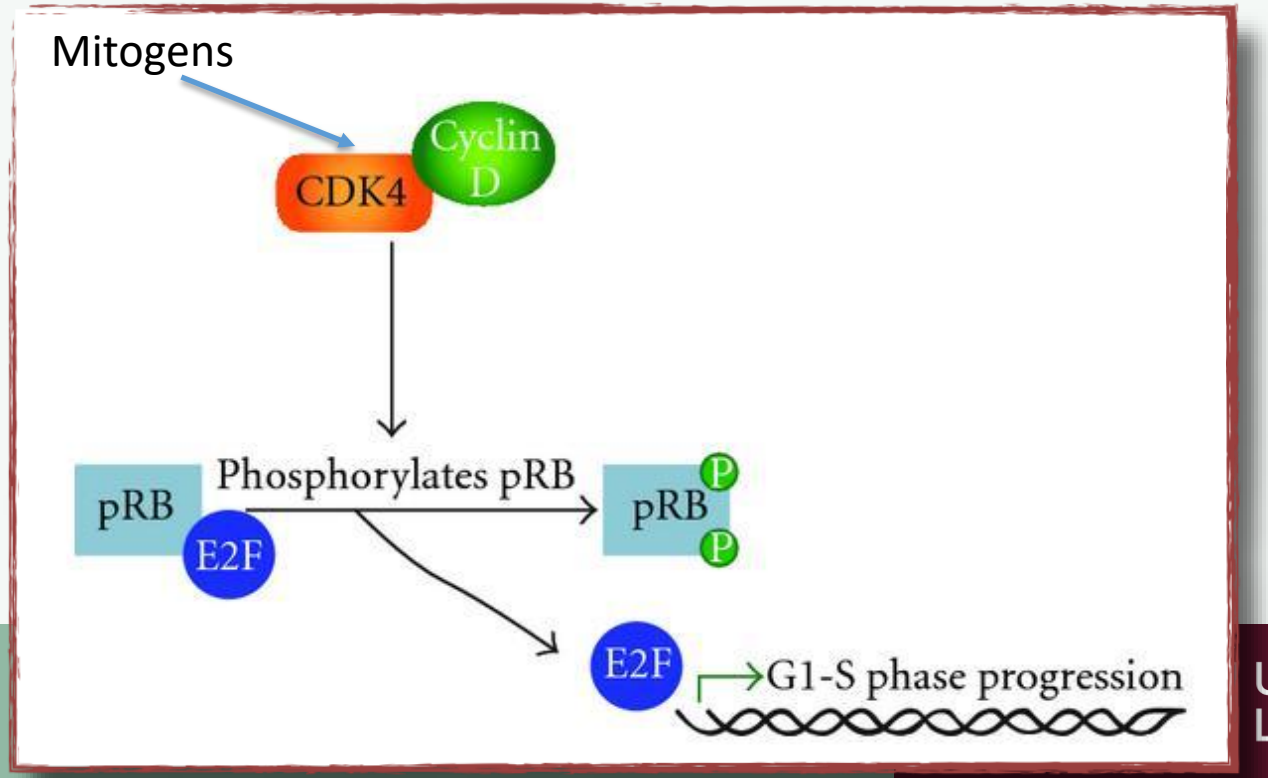
- Robust and reliable with backup mechanisms
- Highly adaptable
- Two key component system



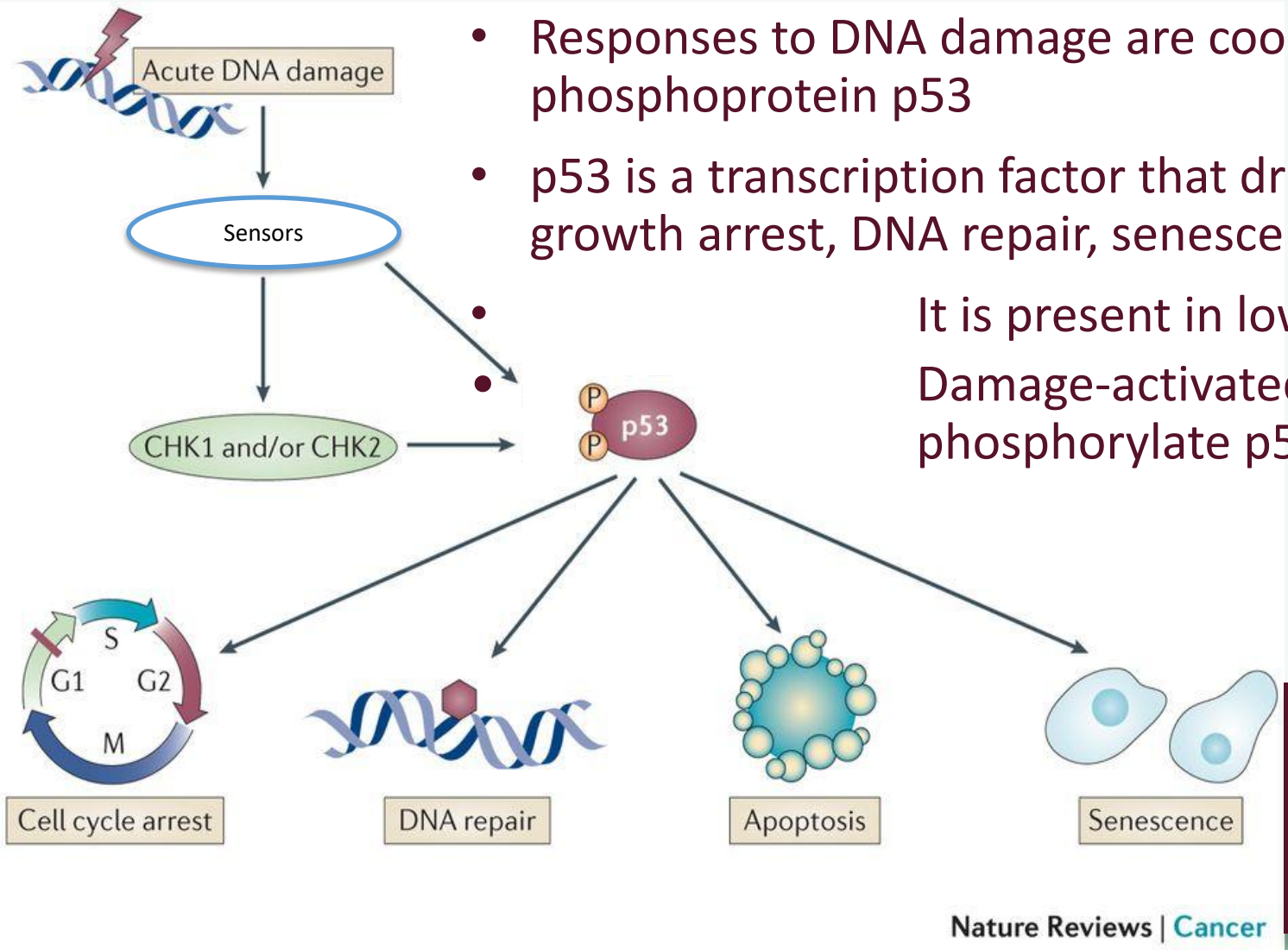


G1/S Checkpoint

- Mitogens push cells through the G_1/S checkpoint
- At the G_1 checkpoint, however, both pRb and E2F become phosphorylated by the kinase complexes of cyclins D and E
- Phosphorylated pRb falls off the transcription factor, and the genes can be transcribed.



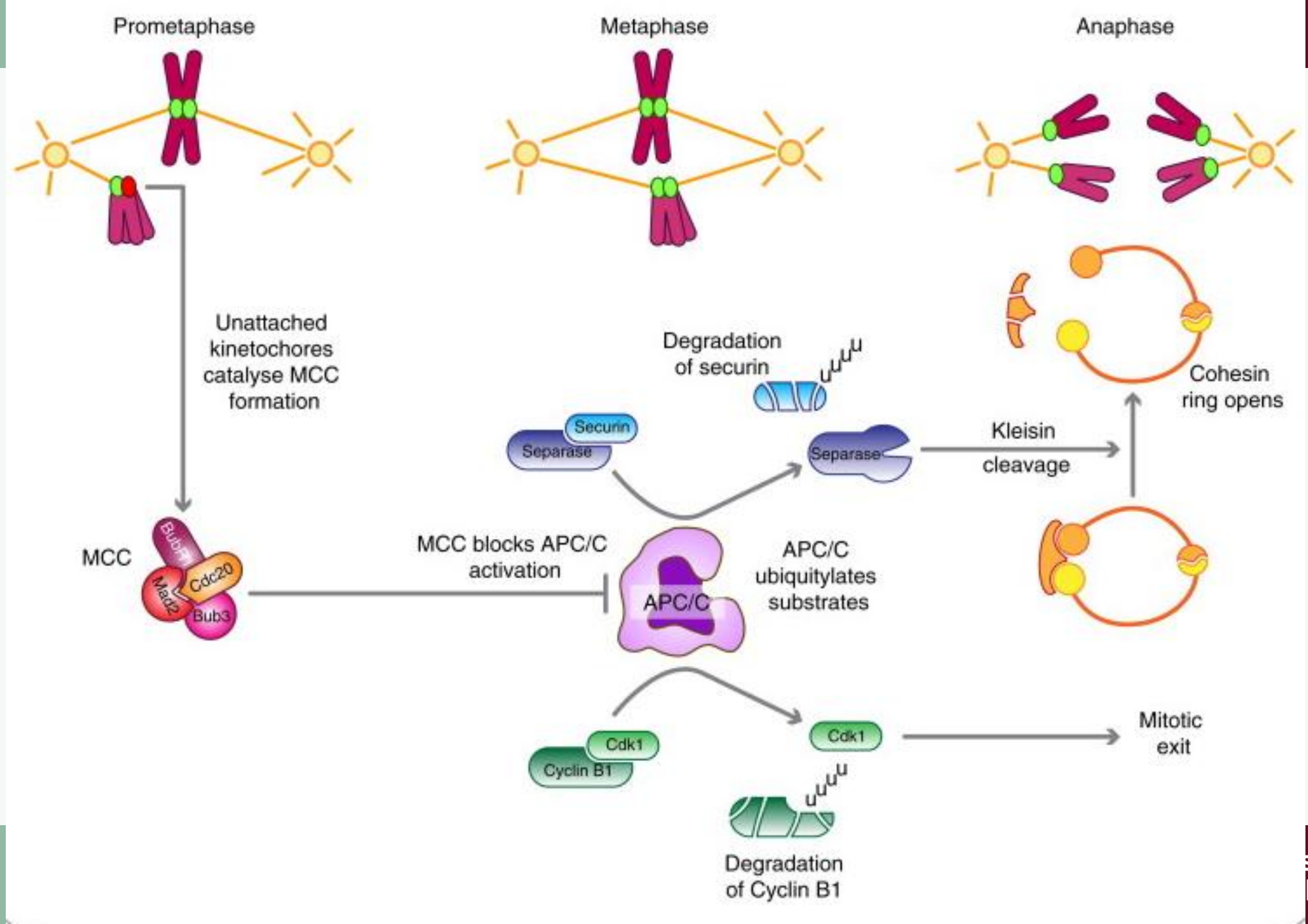
DNA Damage Checkpoints



- Responses to DNA damage are coordinated by the nuclear phosphoprotein p53
- p53 is a transcription factor that drives the expression of genes for growth arrest, DNA repair, senescence and apoptosis
- It is present in low concentrations at all times
- Damage-activated protein kinases that phosphorylate p53 and hence activate it

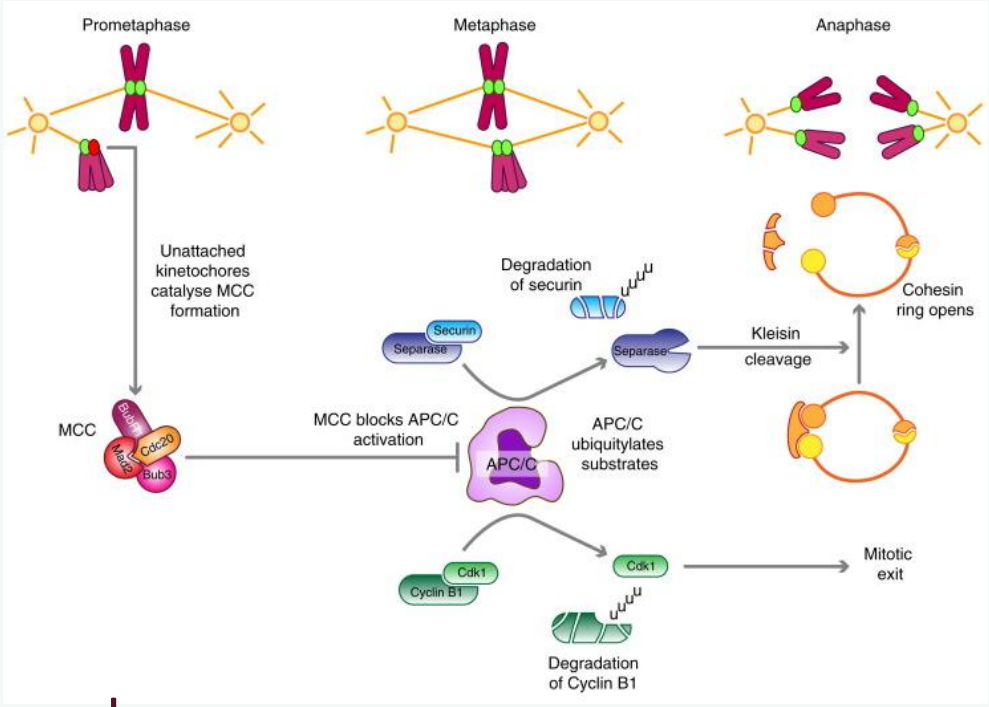
Other p53 activating stimuli include: oxidative stress, hypoxia, inhibition of transcription or translation, and osmotic stress

M checkpoint (spindle assembly checkpoint)

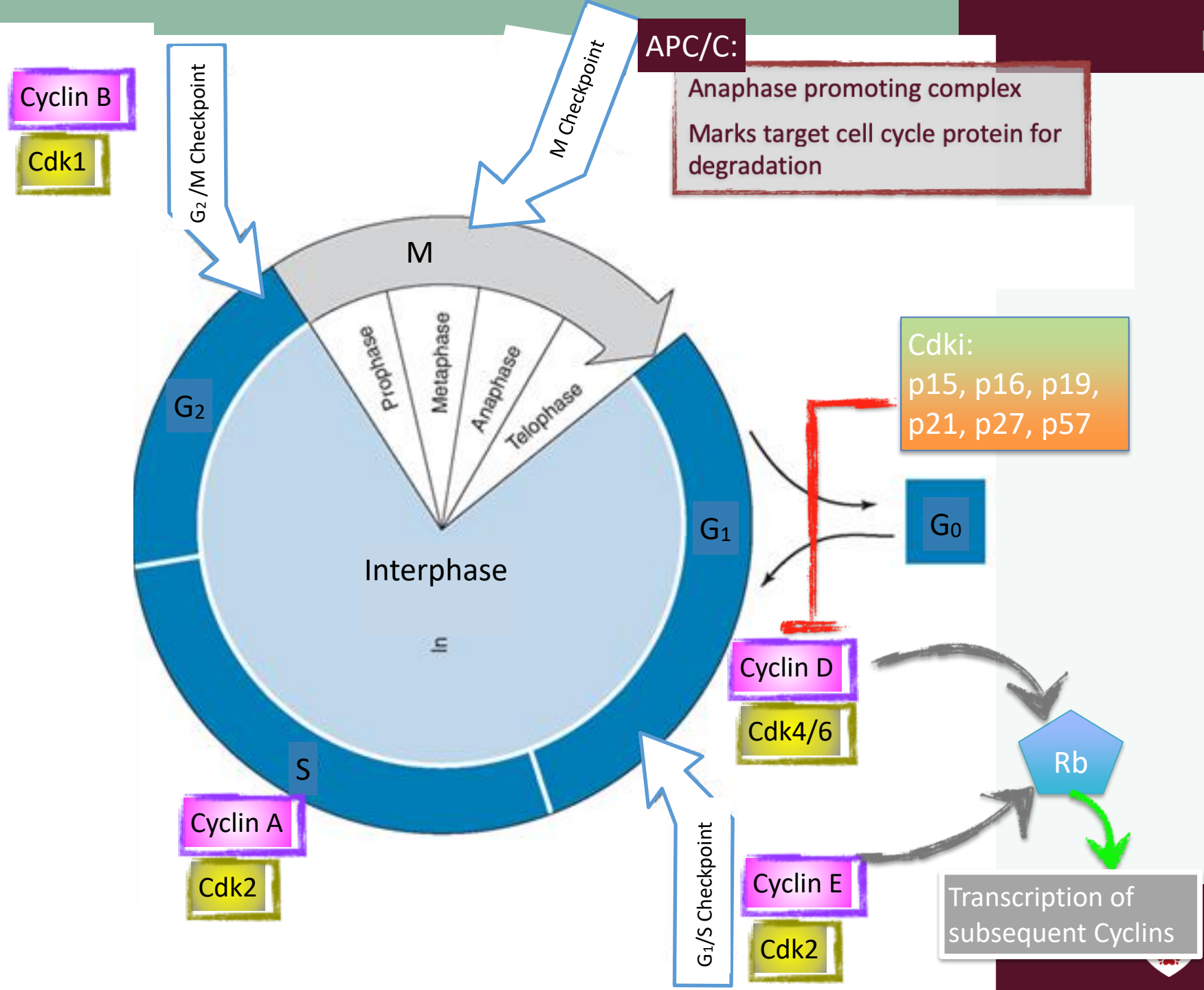


M checkpoint (spindle assembly checkpoint)

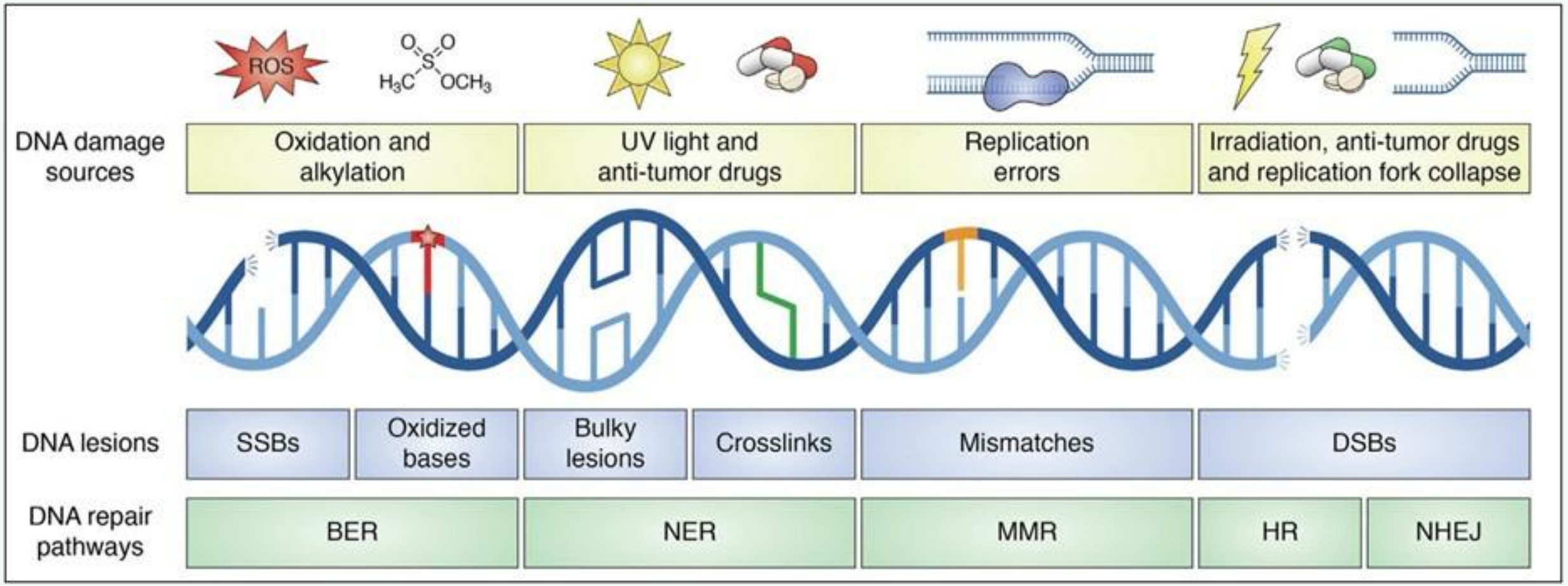
- Prior to entry of anaphase
- Senses the completion of microtubule binding to kinetochores at metaphase
- Its default setting is “on” as cells enter mitosis. It is silenced only when every chromosome is properly attached to the spindle
- Unattached kinetochore sends an inhibitory signal
- APC/C (anaphase-promoting complex/cyclosome) bound to substrate recognition factor Cdc20
- Key APC/C substrates are proteins that must be degraded for the cell to move from metaphase to anaphase
- Kinetochores without microtubules assemble the mitotic checkpoint complex (MCC), the inhibitor that inactivates APC/C



Summary


Cyclin B
Cdk1
G2 /M Checkpoint
M Checkpoint
APC/C:
Anaphase promoting complex
Marks target cell cycle protein for degradation
M
Prophase
Metaphase
Anaphase
Telophase
G2
G1
S
Interphase
In
Cdki:
p15, p16, p19,
p21, p27, p57
G0
Cyclin D
Cdk4/6
Rb
Cyclin A
Cdk2
G1/S Checkpoint
Cyclin E
Cdk2
Transcription of subsequent Cyclins

DNA repair mechanisms



Epigenetics

⭐ Phenotypic changes that do not result from changes in the nucleotide sequence of DNA

Hypermethylation of tumour suppressor genes – leading to their silencing.

Reactivation of ancient viral sequences – endogenous retroviruses that can disrupt normal gene regulation.

Distortion of histone modifications – altering chromatin structure and gene accessibility.

Remodelling of nuclear architecture – affecting how genes are spatially organized and regulated.

Epigenetic instability – enabling rapid adaptation and evolution of cancer cells.

Crosstalk between genetic and epigenetic alterations – where mutations and epigenetic changes reinforce each other..

Breaktime

- **"Nobody today can say for sure that cancer is preventable. But we can say that cancer is avoidable."**
  — Otto Warburg

Models of Cancer Development

Multistage model:

- Based on colon cancer and suggest that tumour development occurs through a series of genetic and epigenetic changes gradually transforming normal cells into malignant ones.

Clonal evolution model:

- Explains how cancer develops through successive mutations in cells, creating genetically distinct subclones, that compete, adapt and evolve within the tumour microenvironment

Cancer stem cell model:

- Proposes that a small subset of tumour cells drive tumour growth, resistance and recurrence through self-renewal and differentiation

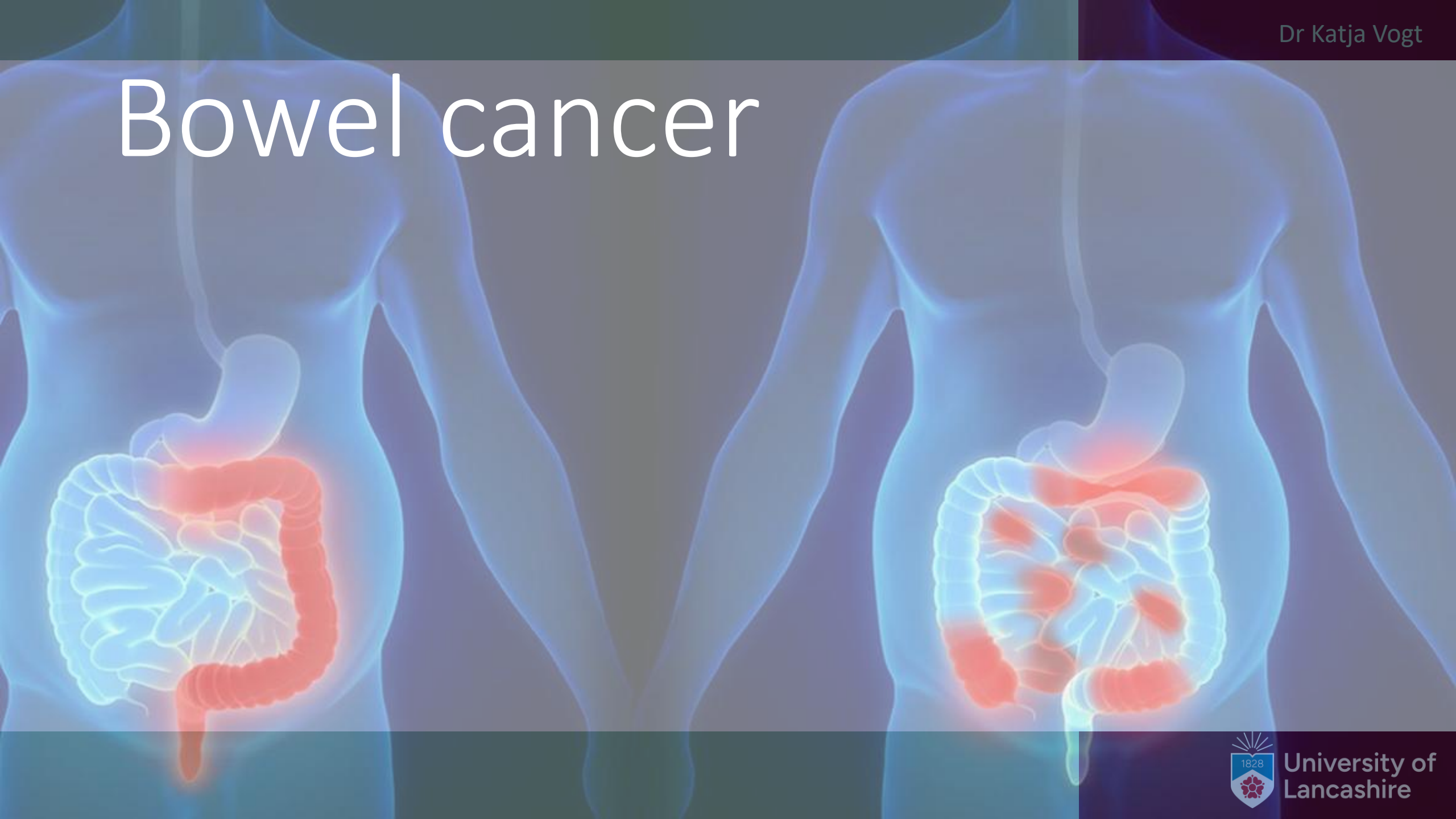
Multistage Model of Carcinogenesis

- Over time the cell accumulates mutations and these mutations have an additive effect, giving the cell:
  - Growth advantage
  - Survival advantage
  - Ability to initiate angiogenesis
  - Eventually the ability to invade surrounding tissue
- Based (originally) on bowel cancer
  - Easily accessible (close monitored possible)
  - Shows the distinct histological stages.


Armitage Doll

Dr Katja Vogt

Bowel cancer



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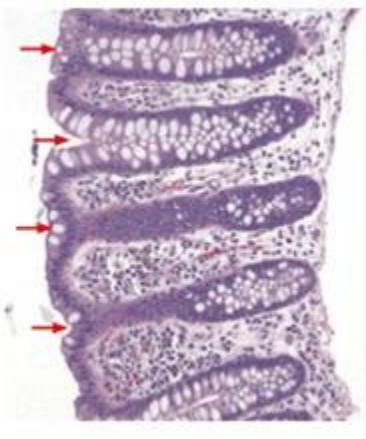
Multistage Model of Bowel Cancer I

BENIGN

normal mucosa

Normal growth

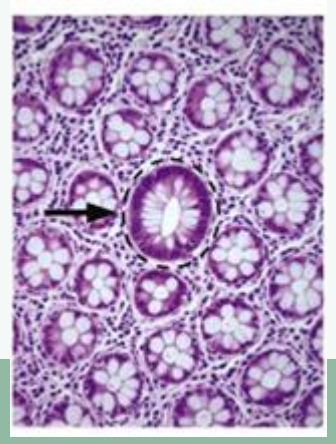


Multistage Model of Bowel Cancer II

BENIGN

normal mucosa → hyperplastic growth

almost normal histology
higher rate of cell division
leading to thicker epithelia

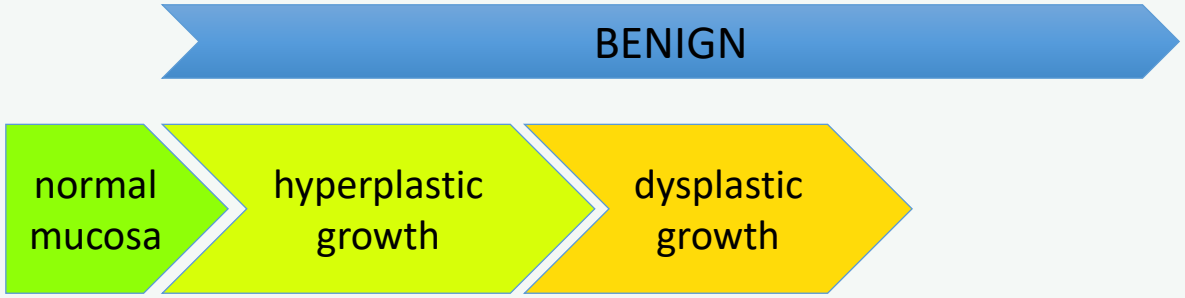


Terminology:

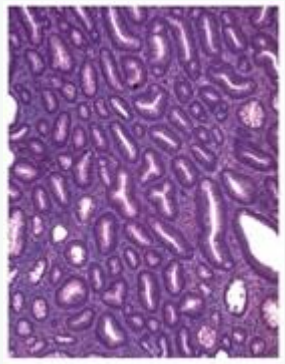
Hyperplasia

– Increase in rate of cell division within a tissue

Multistage Model of Bowel Cancer III



abnormal histology
no organisation
abnormal cell morphology



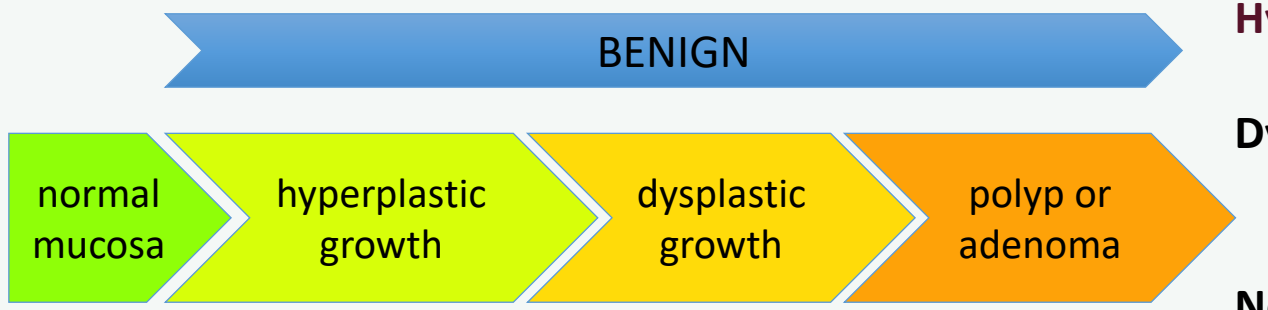
Terminology:

Hyperplasia
– Increase in rate of cell division within a tissue

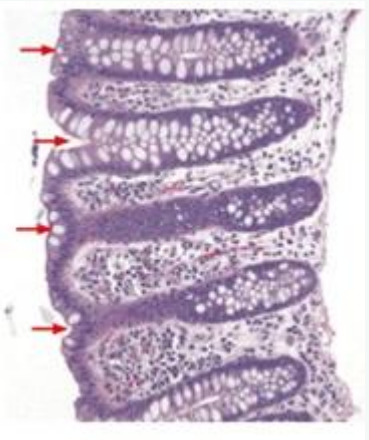
Dysplasia
– Cells have abnormal morphology but are not cancerous

You can have dysplasia without it becoming neoplastic (cancerous)

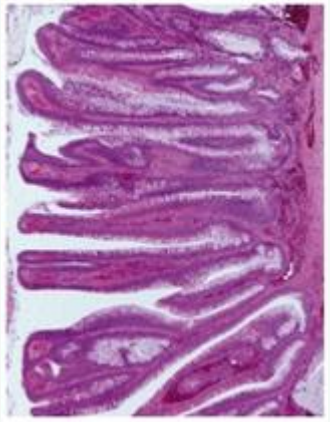
Multistage Model of Bowel Cancer IV



Normal growth



larger, deviant dysplastic growth



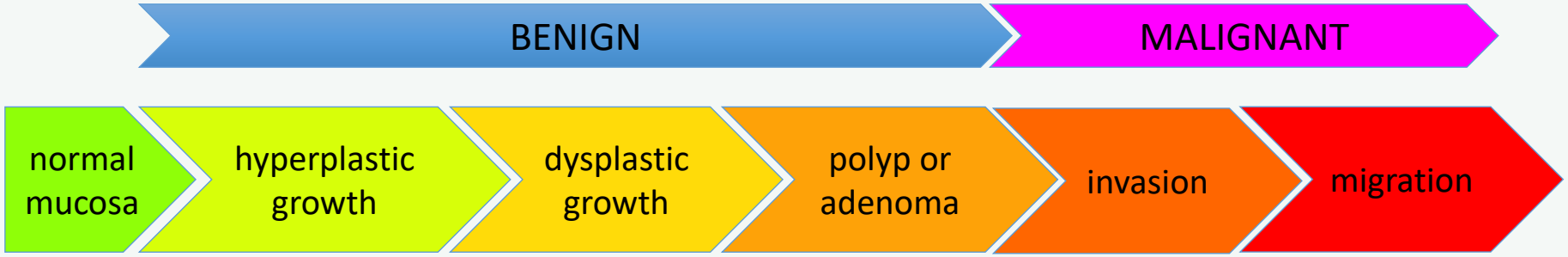
Terminology:

Hyperplasia
– Increase in rate of cell division within a tissue

Dysplasia
– Cells have abnormal morphology but are not cancerous

Neoplasia
– abnormal/uncontrolled tumour growth (can be benign or malignant)

Multistage Model of Bowel Cancer V



Normal growth

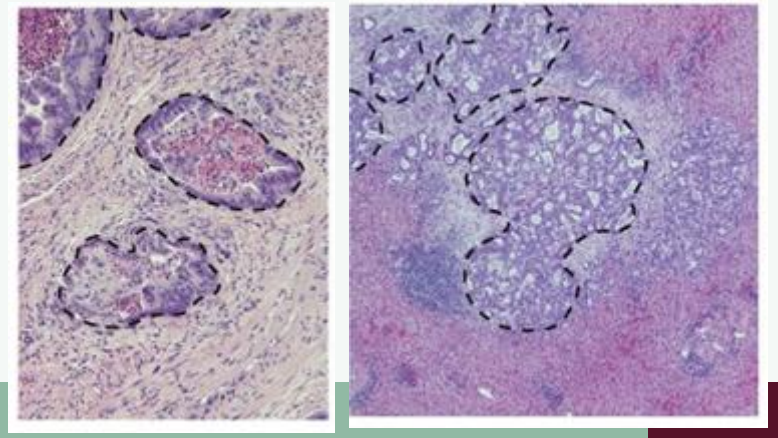
almost normal histology
higher rate of cell division leading to thicker epithelia

abnormal histology
no organisation
abnormal cell morphology

larger, deviant dysplastic growth

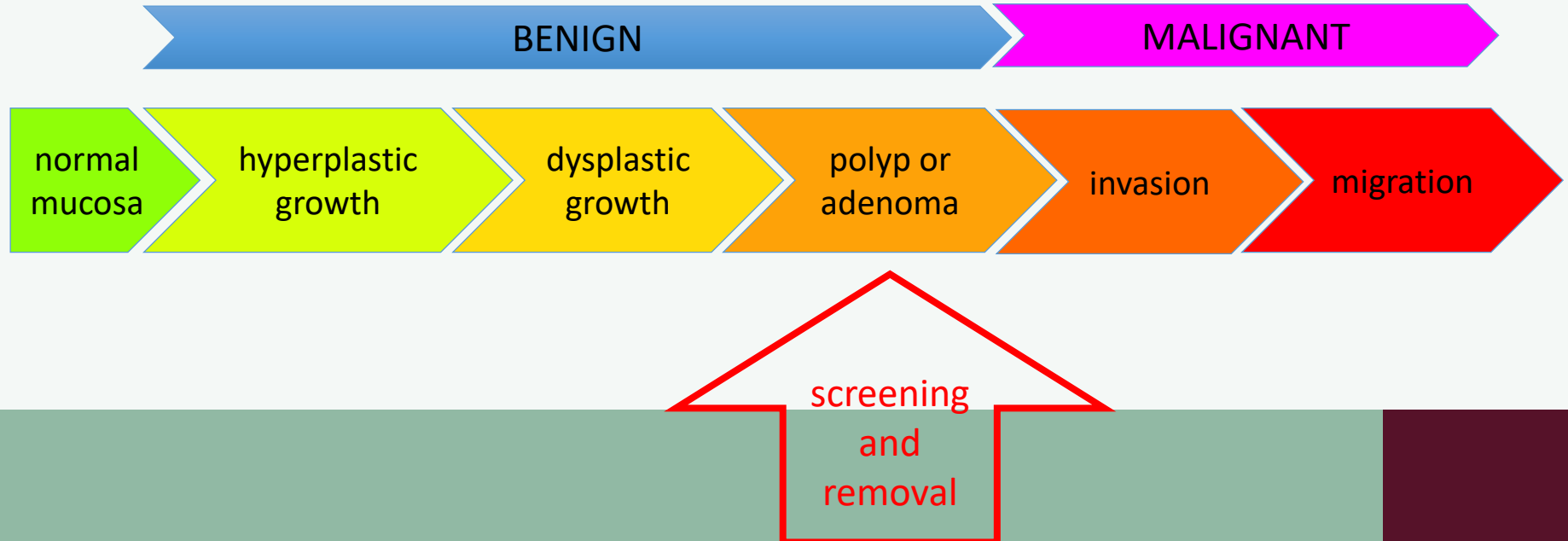
into surrounding stromal + smooth muscle layers

metastasis to distant sites



Bowel cancer screening

- Bowel cancer (epithelial in origin) makes up 11% of cancers in UK
- Common in people over 60
- National Screening Programme: In England, all men and women 54-74 are invited to carry out a faecal immunochemical test (FIT) test every 2 years
- Removal of polyps can prevent cancer
- Regular screening has been shown to reduce risk of dying of bowel cancer by 16%



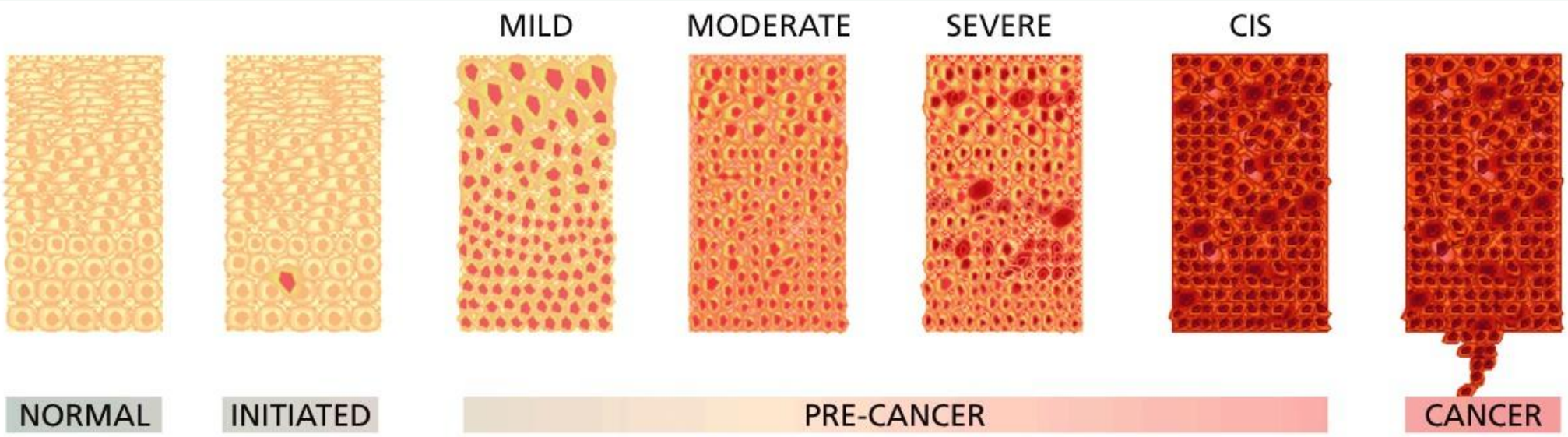
Terminology:

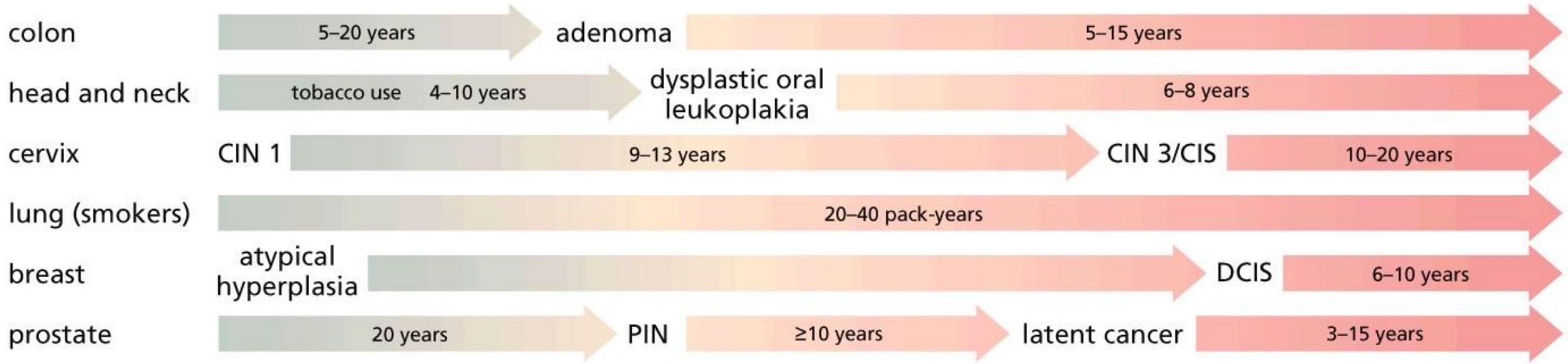
CIN – Cervical intraepithelial neoplasia

CIS – Carcinoma in situ

DCIS – ductal carcinoma in situ

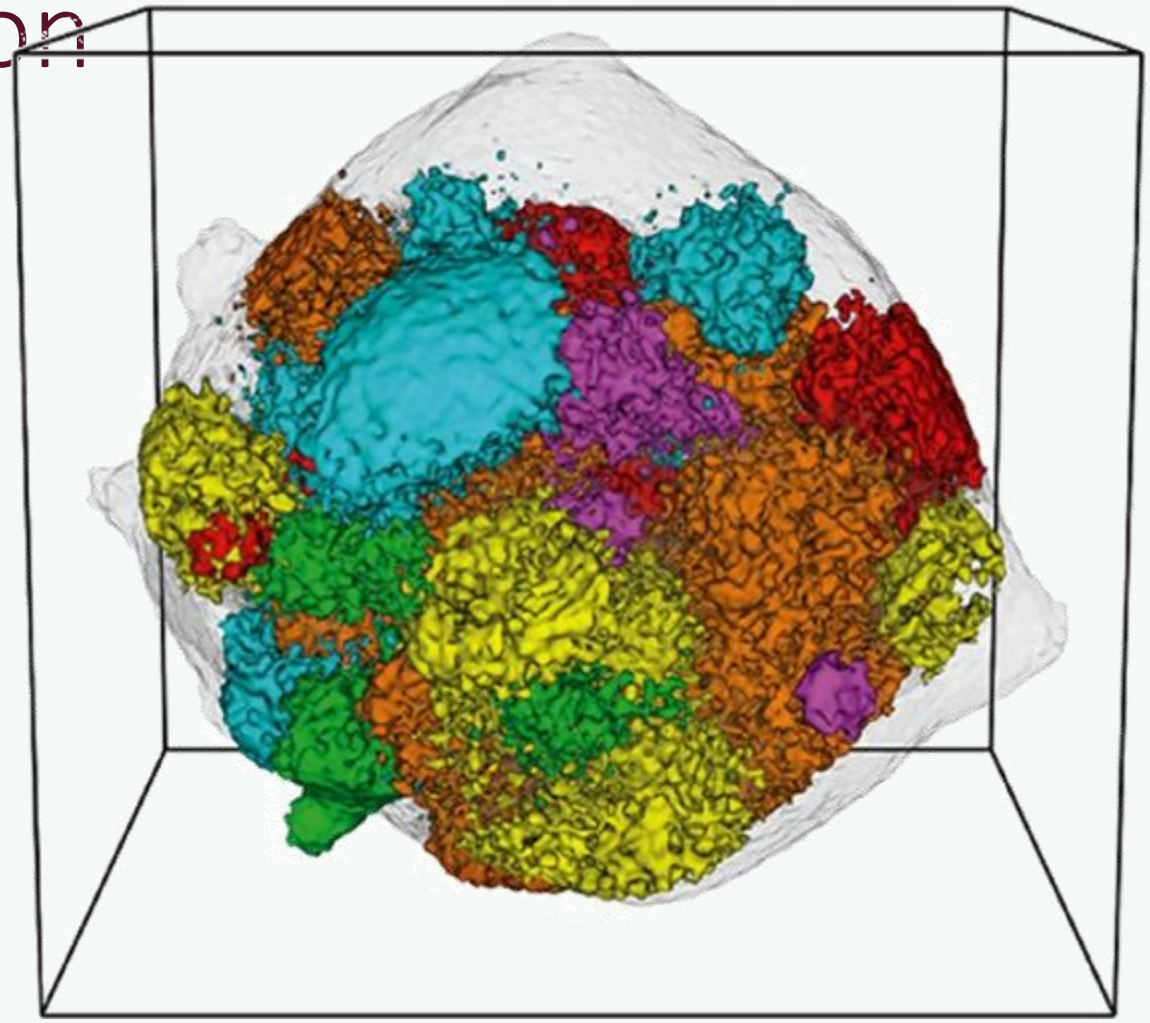
PIN – Prostate intraepithelial neoplasia



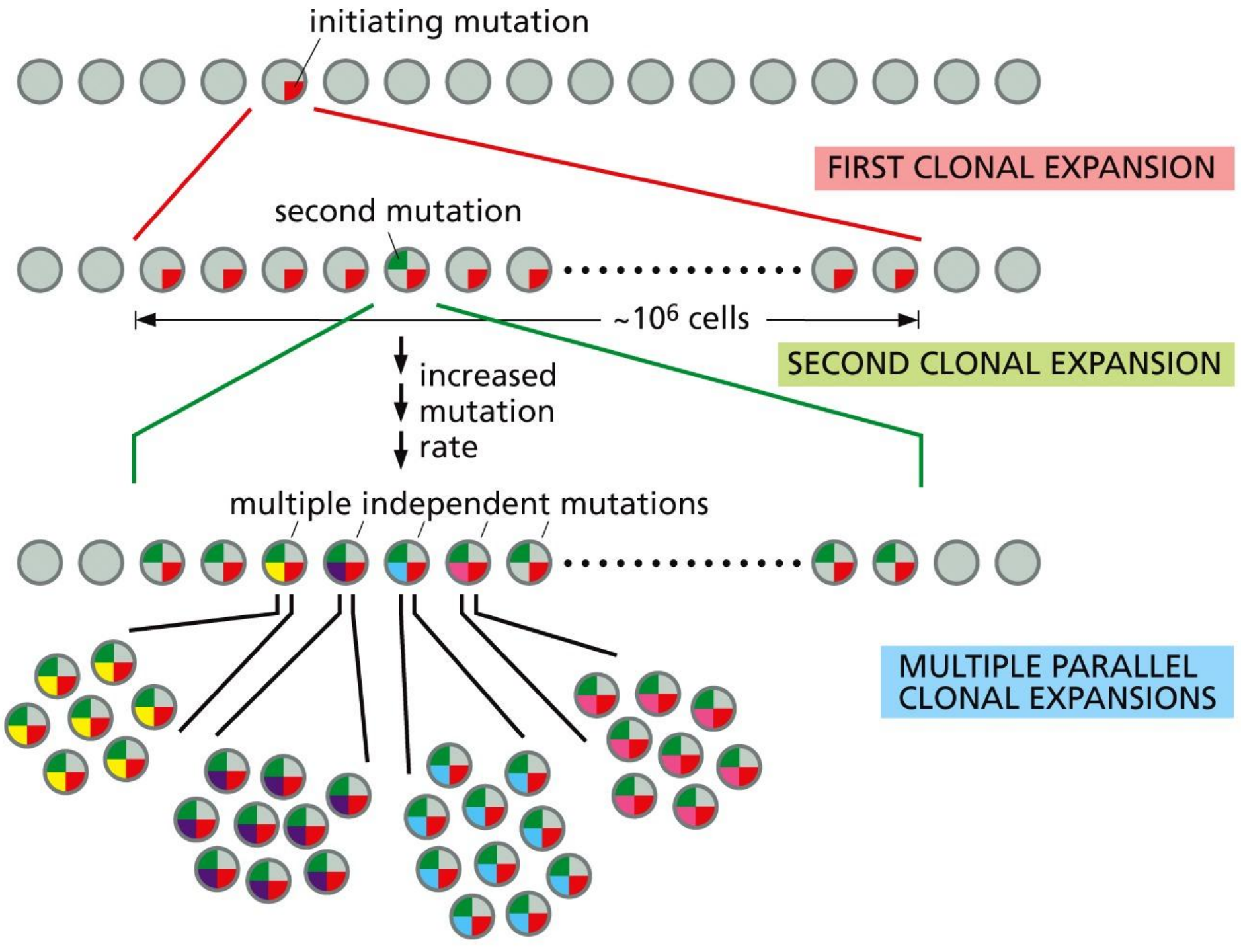


Theory of Clonal Expansion

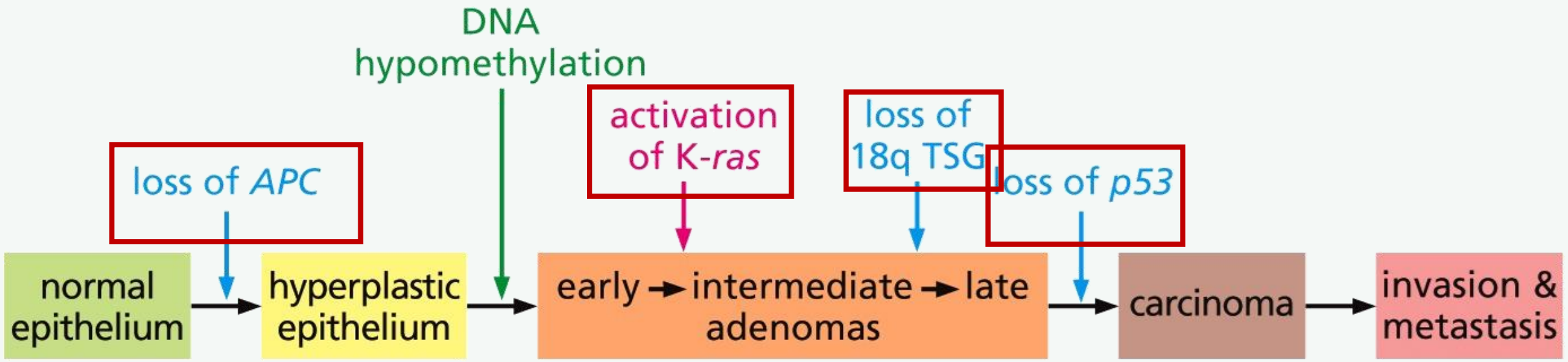
The theory of clonal expansion follows on from the multistage model in that it also assumes that the accumulation of mutations causes cancer but it does not assume that all the mutations happen in the same cell. A subset of mutations will confer a selective growth advantage/survival advantage and the cells carrying those mutations will out-grow their neighbouring cells.



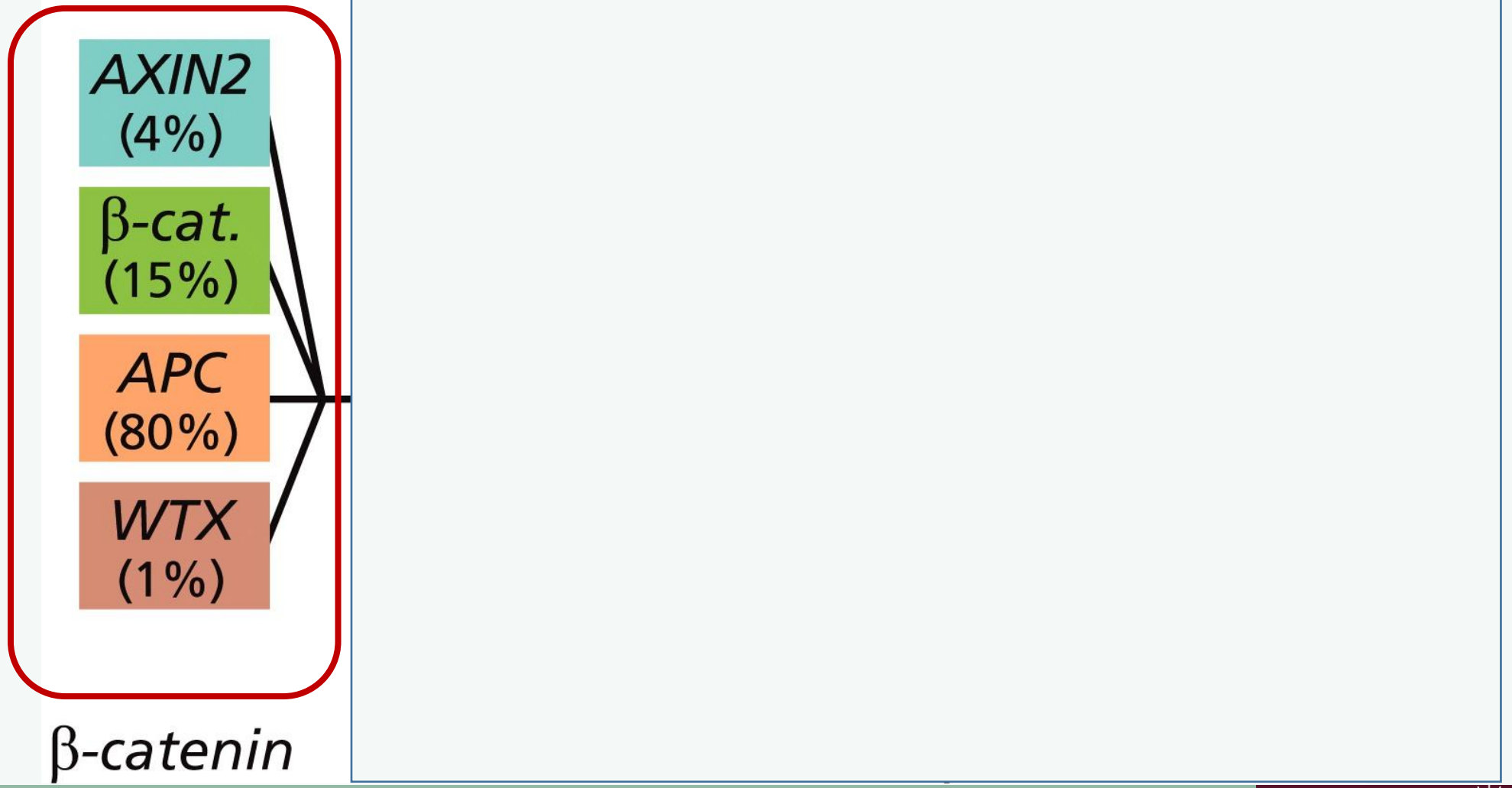
Clonal evolution Model



Multistage and Clonal Evolution Model in Bowel Cancer

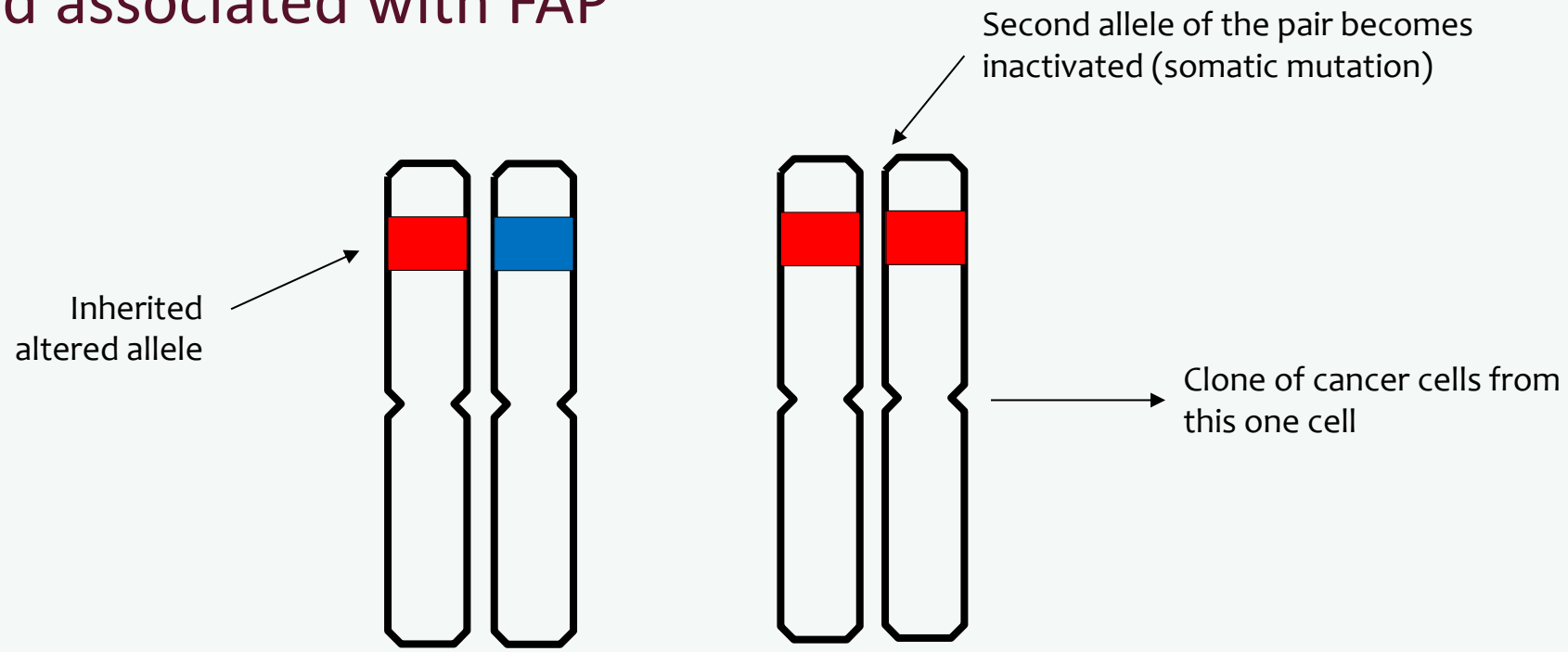


Loss of Adhesion

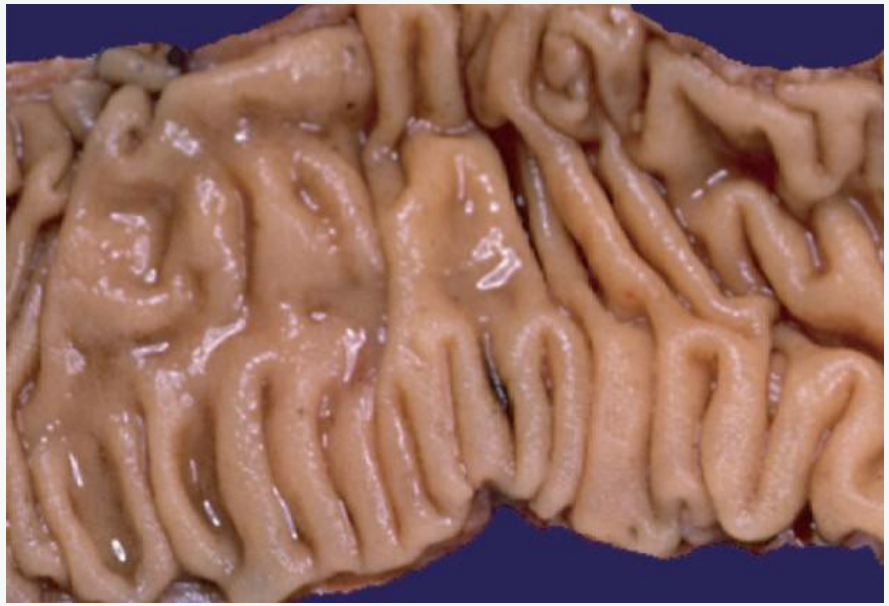


Familial Adenomatous Polyposis (FAP)

- APC first discovered associated with FAP



Familial Adenomatous Polyposis (FAP) II



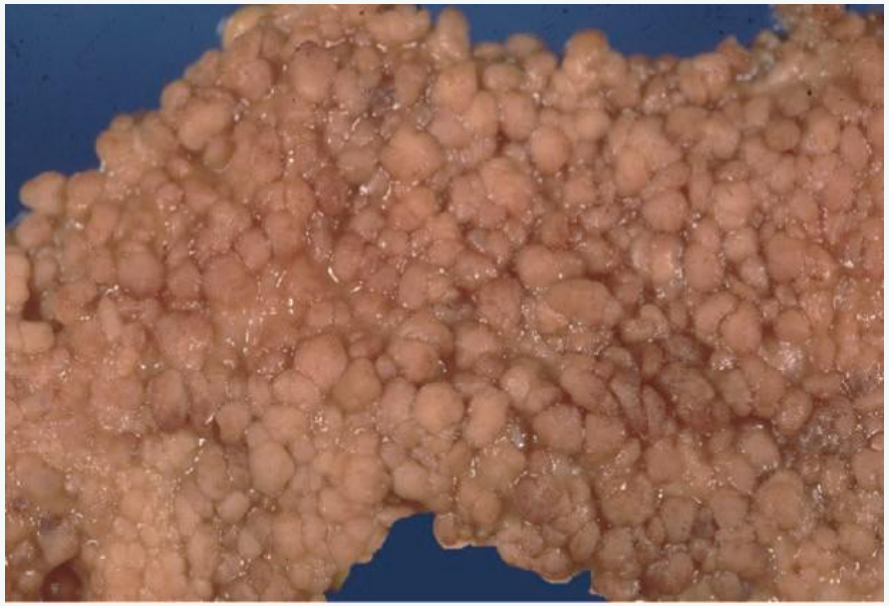
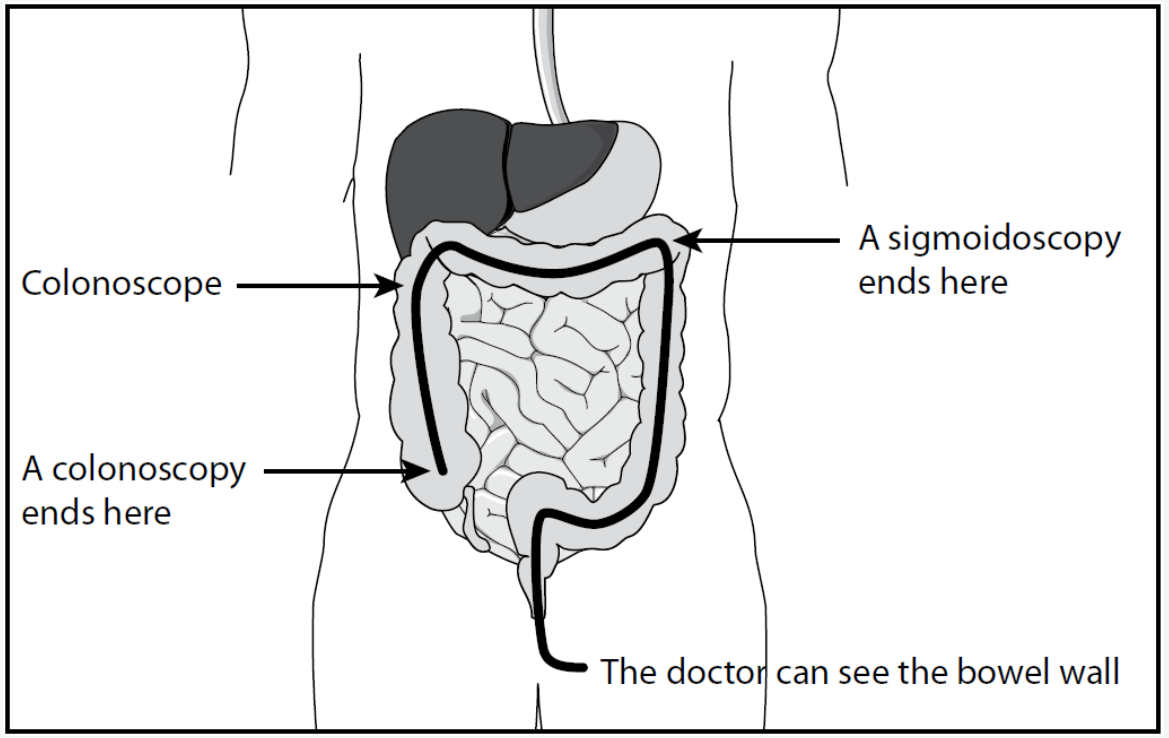


FIGURE 7.12 The inside surface of a normal colon versus a colon from a person with familial adenomatous polyposis (FAP). The image on the left shows the folds that are characteristic of the inner surface of a normal human colon. The image on the right shows a similar tissue that is covered with polyps as a result of inherited FAP. (Courtesy of Andrew Wyllie and Mark Arends.) from **Understanding cancer: an introduction to the biology, medicine and societal implications of this disease by McIntoch, J.R. (2019) CRC Press, NY, USA**

Regular monitoring of FAP patients

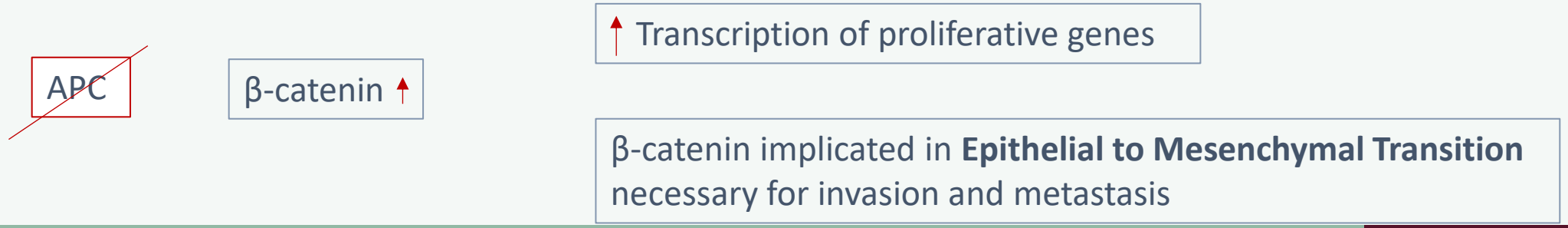
- Annual sigmoidoscopies from age 12 to 14.
- Colonoscopies once polyps have been detected (every 1-3 years) .
- Surveillance of remaining gut following colectomy.



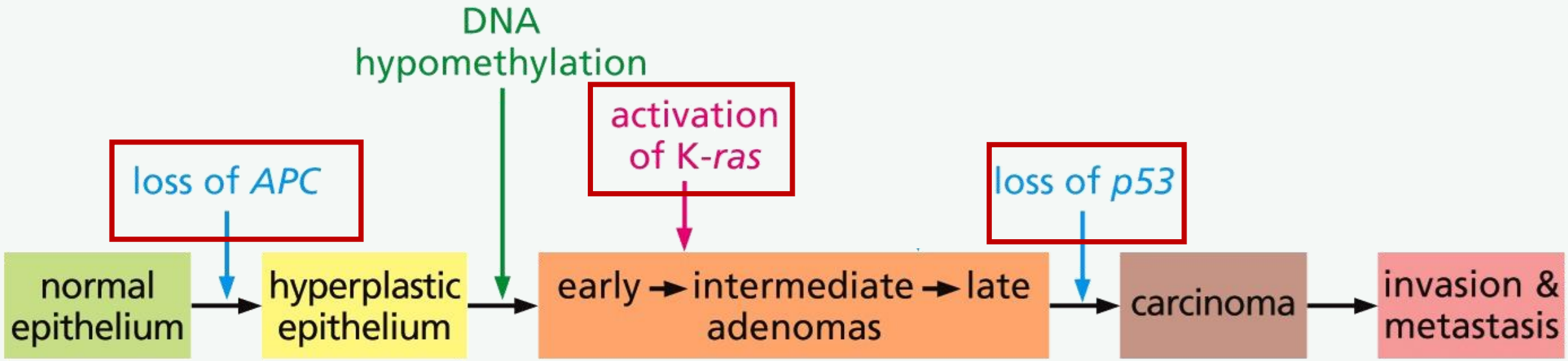
http://www.nice.org.uk/nicemedia/pdf/CSGCCfullguidance.pdf

Adenomatous Polyposis Coli APC gene

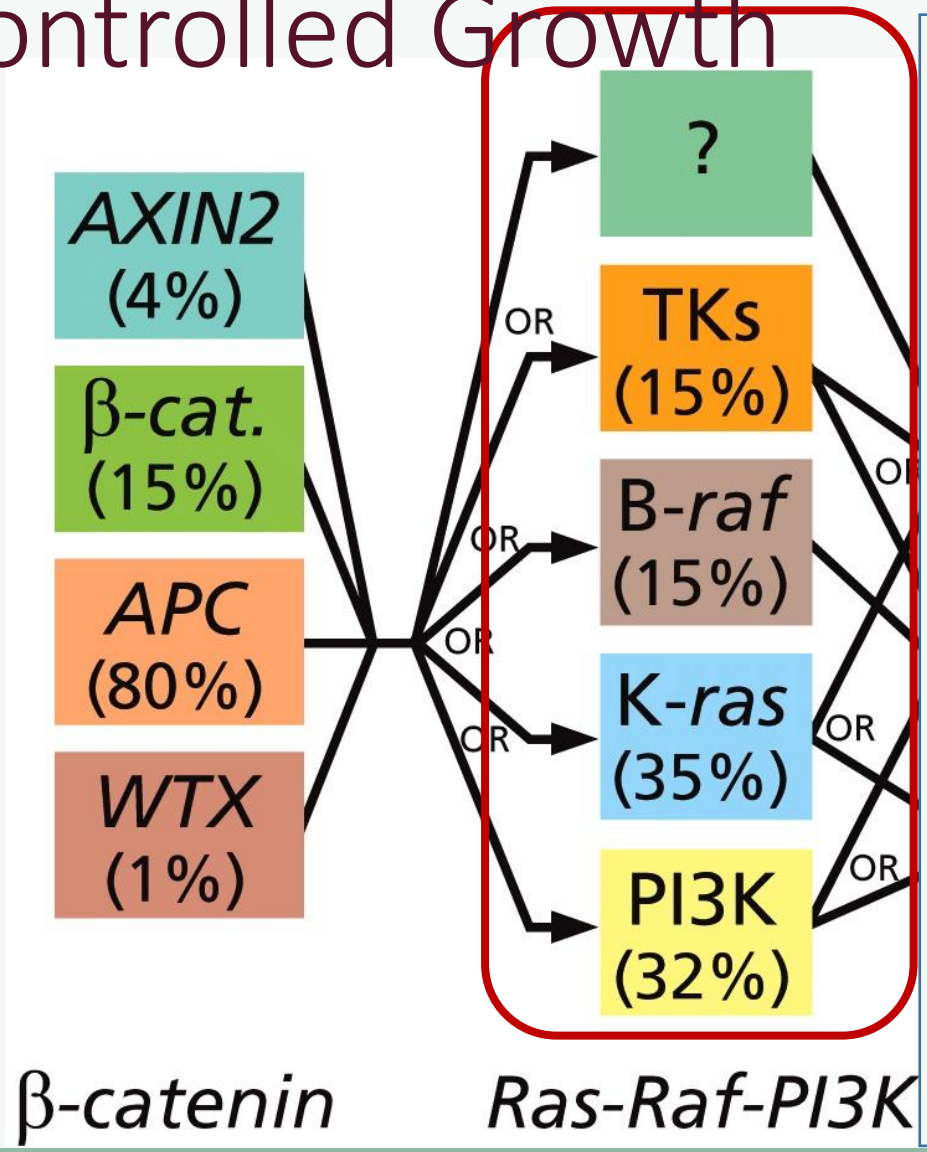
- APC protein is involved in cell growth and division.
- APC controls β-catenin concentration by targeting it for destruction
- β-catenin is involved in regulating cell-cell adhesion and is also a transcription factor for genes involved in proliferation.
- The β-catenin gene itself can also be mutated in FAP.
- APC also interacts with E-cadherin (cell-cell adhesion).



Back to the Multistage Model of Bowel Cancer

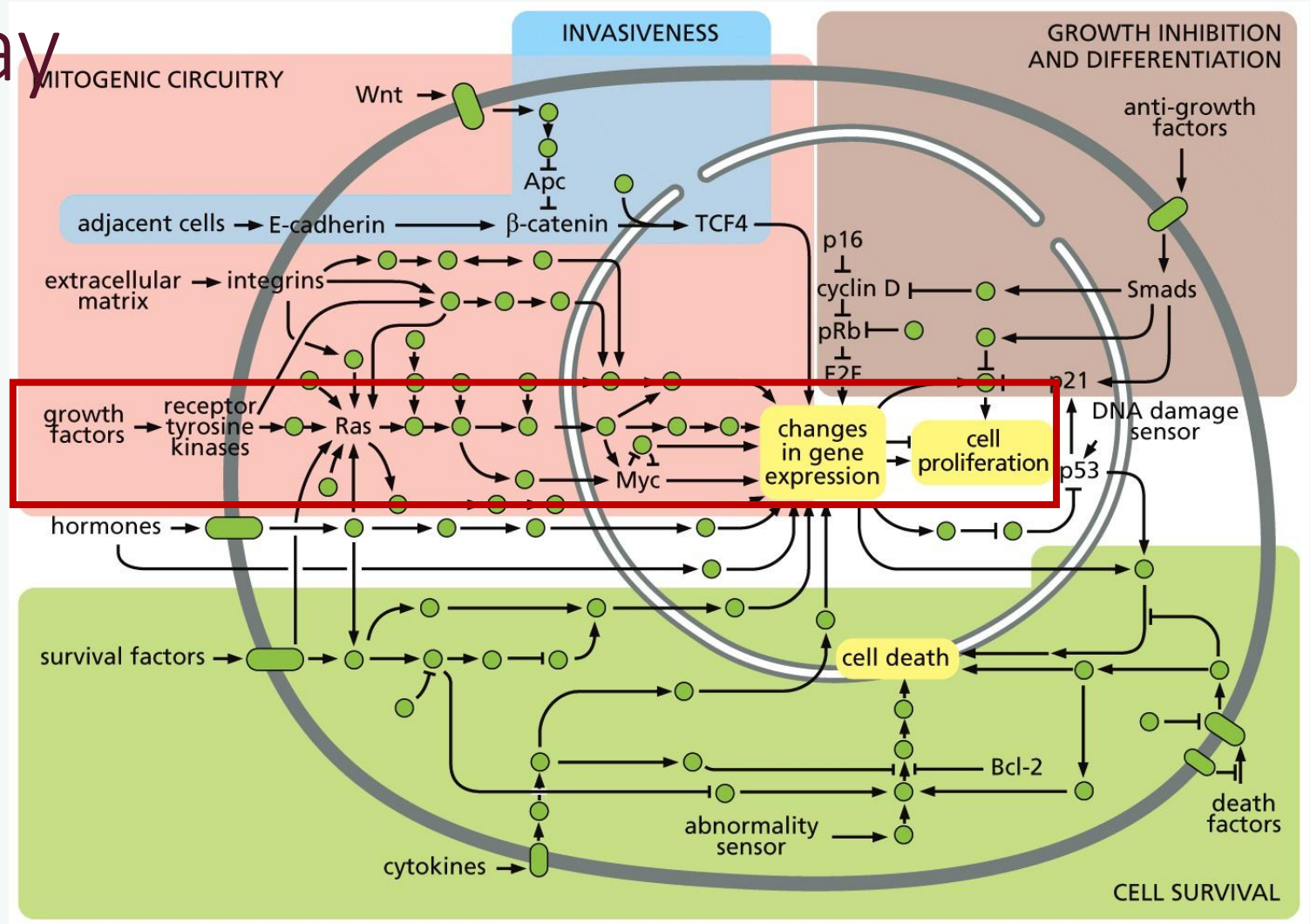


Uncontrolled Growth



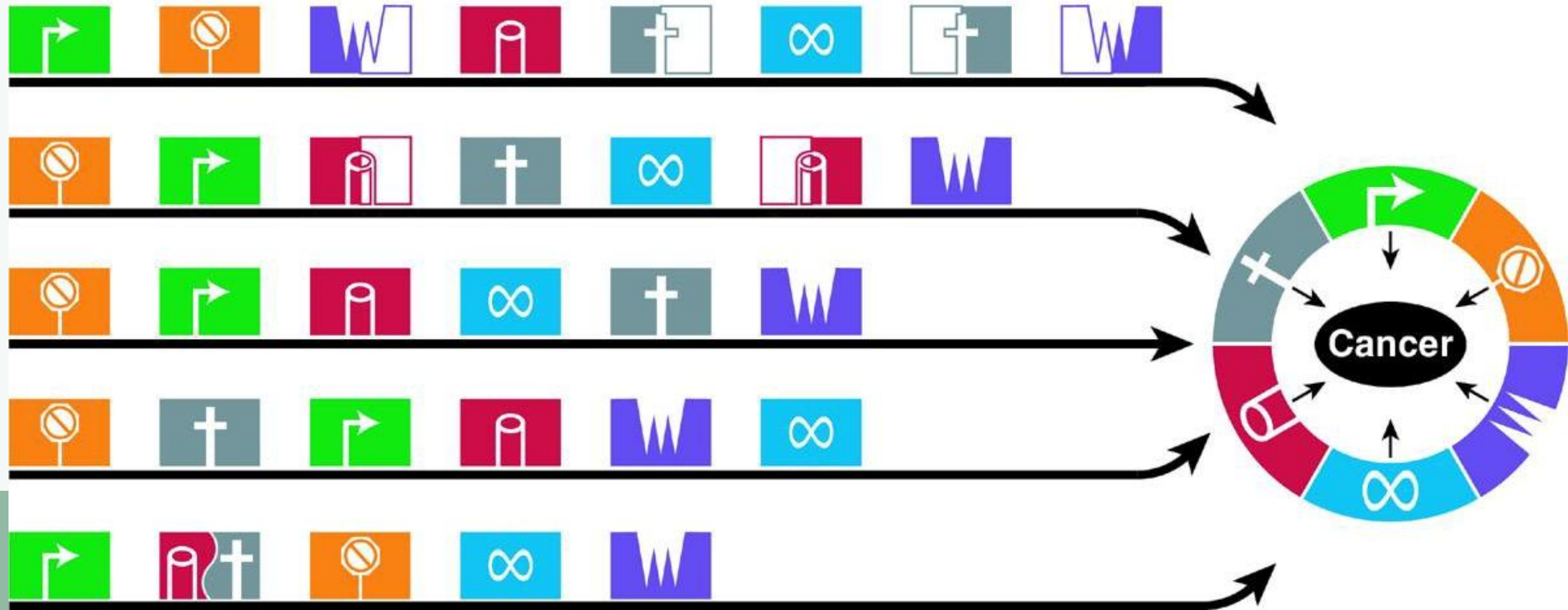
Ras-Raf-PI3K pathway

- Over expression/ activation of growth factor receptors mostly, Tyrosine Kinase (receptors) like ras/raf/PI3K results in cell proliferation



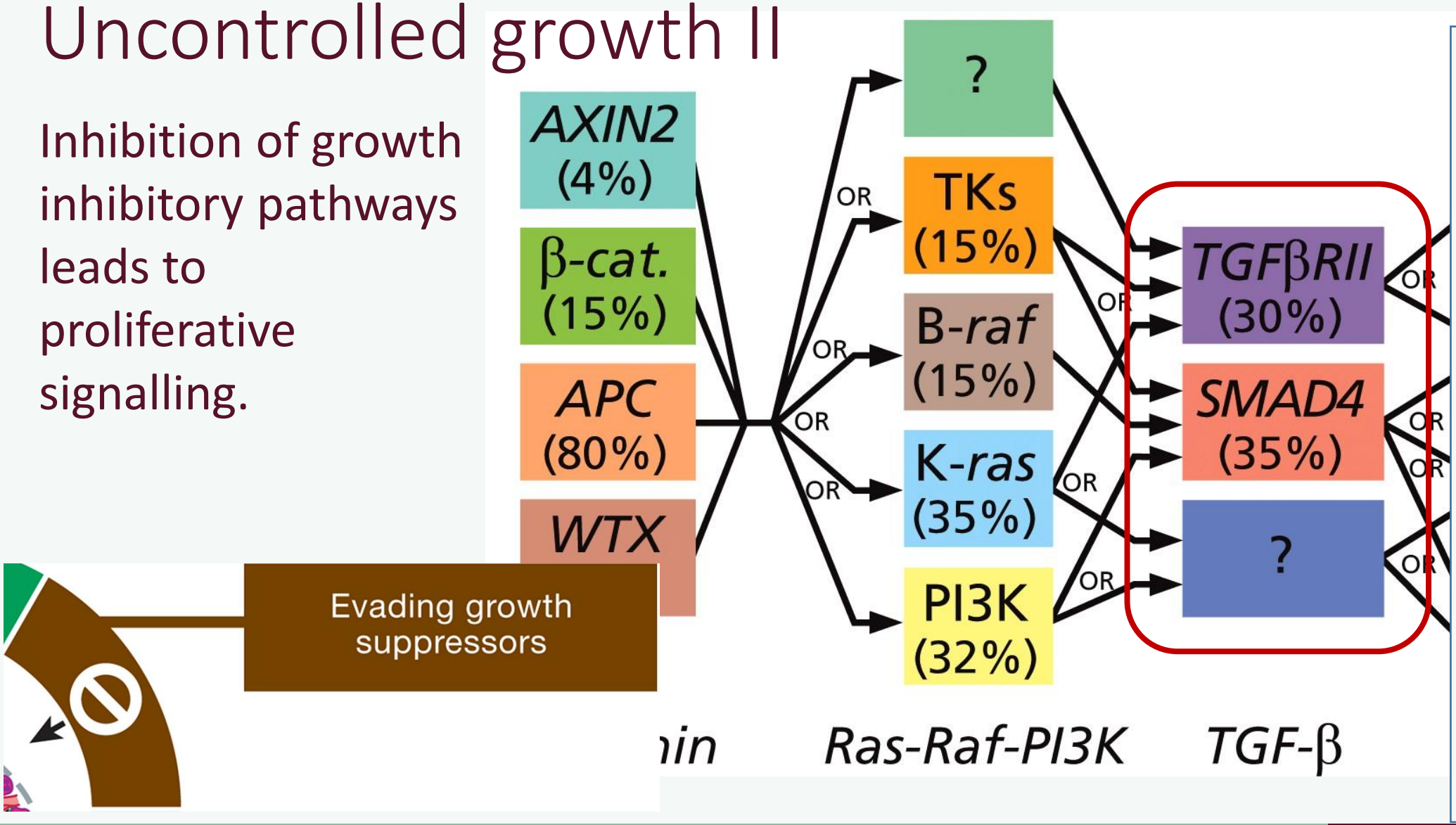
A

Component	Acquired Capability	Example of Mechanism
	Self-sufficiency in growth signals	Activate H-Ras oncogene
	Insensitivity to anti-growth signals	Lose retinoblastoma suppressor
	Evading apoptosis	Produce IGF survival factors
	Limitless replicative potential	Turn on telomerase
	Sustained angiogenesis	Produce VEGF inducer
	Tissue invasion & metastasis	Inactivate E-cadherin



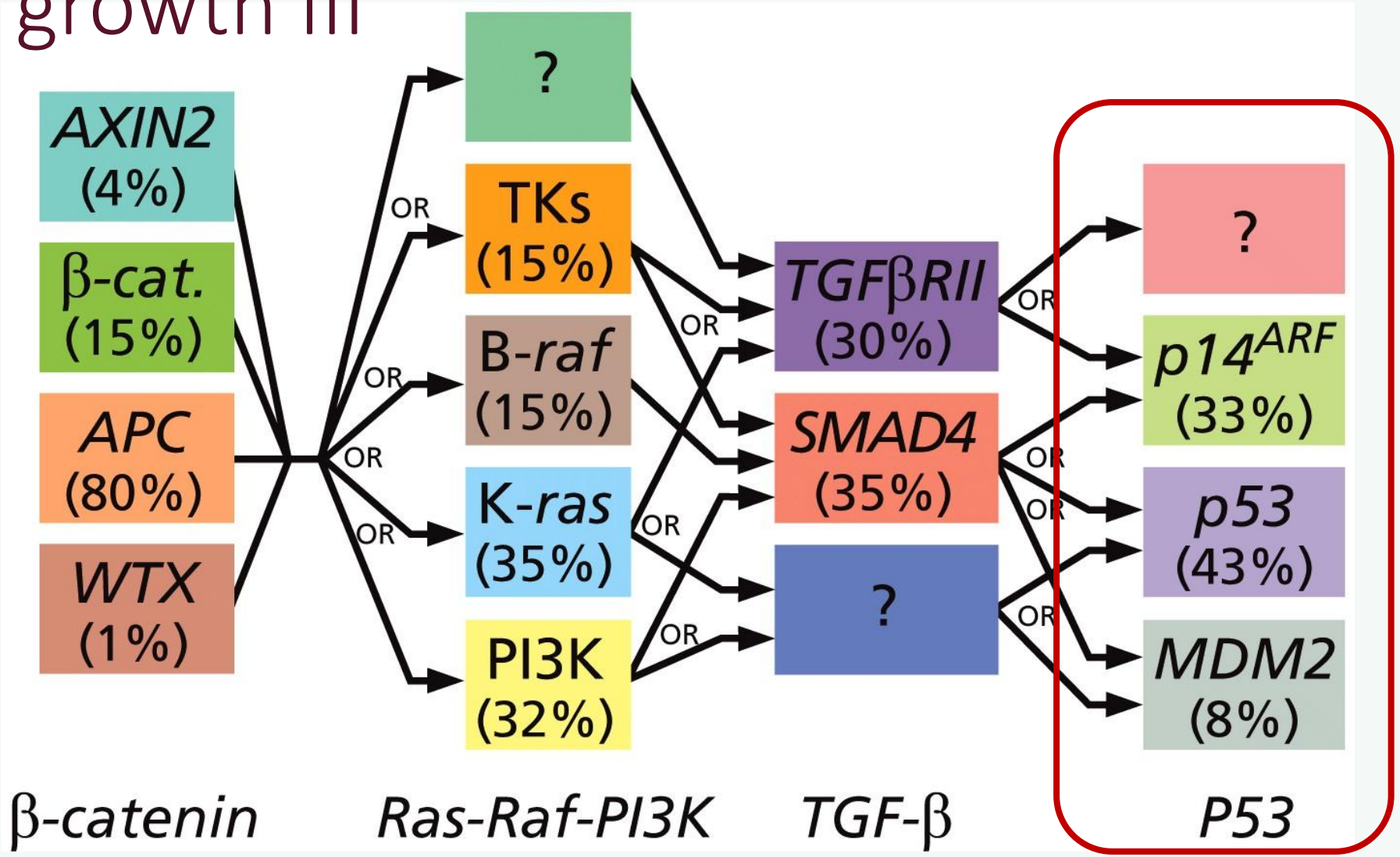
Uncontrolled growth II

Inhibition of growth inhibitory pathways leads to proliferative signalling.



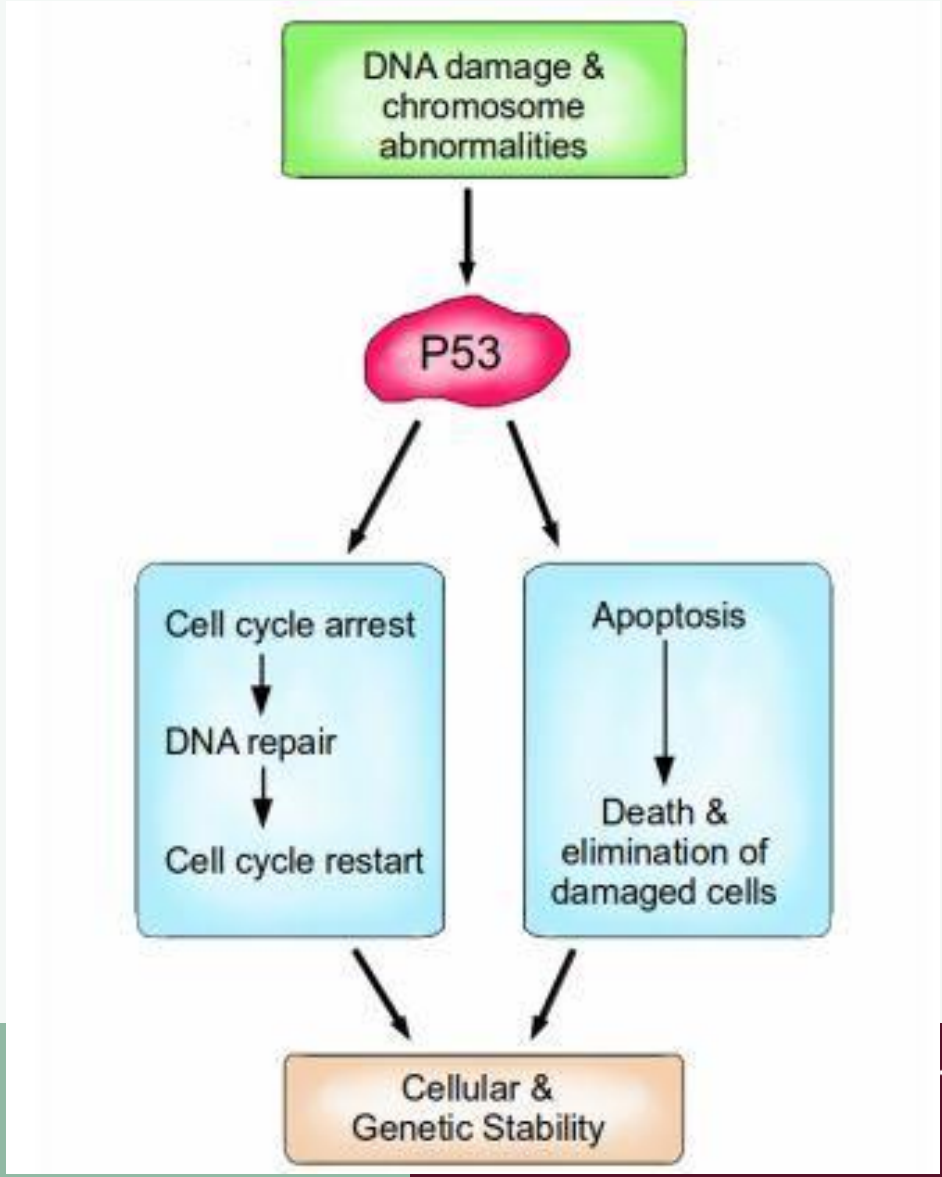
Uncontrolled growth III

Loss of function of p53 signalling promotes cell cycle progression without checkpoint control and prevents the p53-initiated apoptosis.



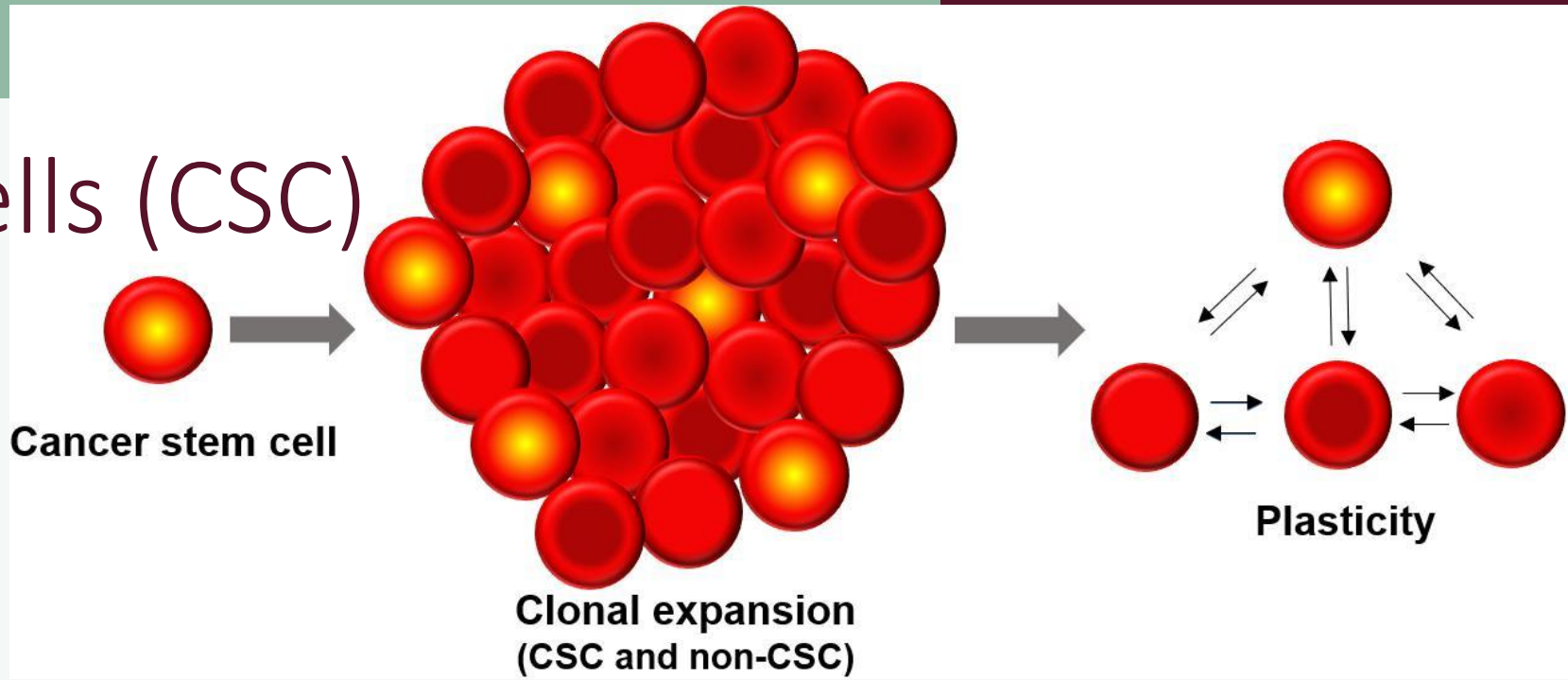
p53 is master, guardian and executioner

- p53 responds to intracellular signals:
  - DNA damage
  - Suboptimal levels of:
    - Oxygen
    - Glucose
    - Growth promoting signals
    - Nucleotide pool levels
- Is able to halt cell cycle if conditions are unfavorable



Cancer stem cell model

Cancer stem cells (CSC)



- Pivotal roles in:
  - Tumour initiation
  - Progression
  - Metastasis
  - Recurrence
  - Therapeutic resistance
- Exhibit self-renewal and differentiation properties
- Intrinsic plasticity
  - → transition between quiescent and proliferative states
  - → adopt epithelial or mesenchymal phenotypes
  - → reprogram their metabolic and epigenetic landscapes
- Lack of universal biomarkers
- Specific therapies in pre-clinical stages

After today, you should be able to …

- … Identify and define important key concepts in cancer biology
- … identify DNA damage and repair mechanisms
- … define the different Models of Carcinogenesis
- … explain the Multistage Model of Carcinogenesis on the example of bowel cancer

MBBS learning outcomes

- Outline the stepwise progression of carcinogenesis using bowel cancer as an example
- Recognise the histological changes relevant to the progression to malignancy
- Outline the molecular genetics of common diseases