Imperial College London

Oncogenes and Tumour Suppressors

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Learning Objectives

- *Define protooncogene, oncogene and tumour suppressor gene.*
- *Explain how a protooncogene can be activated to an oncogene.*
- *Explain how activating an oncogene can disrupt tightly controlled pathways in the cell.*
- *Describe how rare heritable cancers have led to an understanding of tumour suppressor genes.*
- *Summarise the role of the tumour suppressor gene p53 in cellular decision making.*
- *Describe the way in which successive gene mutations are thought to lead to clinical cancer.*

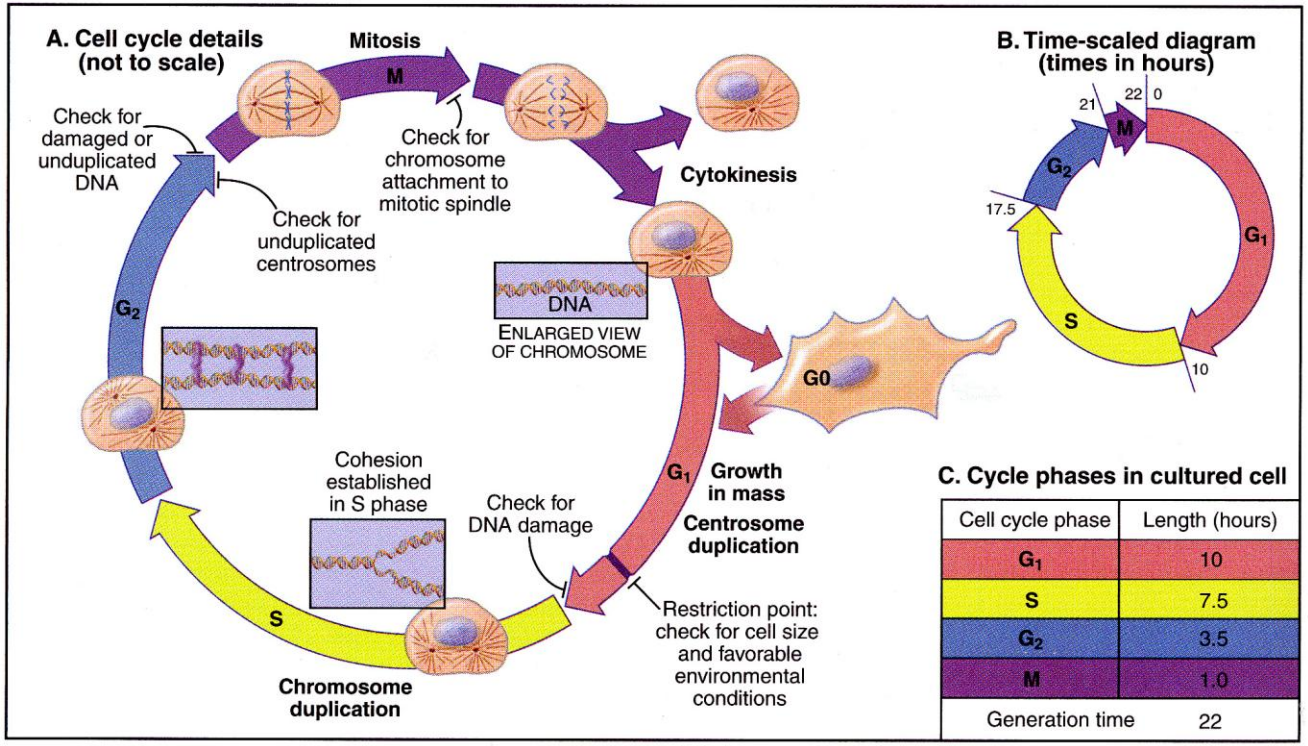
The Hallmarks of Cancer

The Cancer Cell Phenotype

- Disregard of signals to stop proliferating.
- Disregard of signals to differentiate.
- Capacity for sustained proliferation.
- Evasion of apoptosis.
- Ability to invade.
- Ability to promote angiogenesis.

Hanahan and Weinberg (2000)

Cell cycle – The key to life, death and cancer



- Cycle checkpoints (growth arrest ensures genetic fidelity).
- Specific proteins accumulate/ are destroyed during the cycle.
  - Cyclins, cycle dependent kinases, cycle dependent kinase inhibitors
- Permanent activation of a cyclin can drive a cell through a checkpoint.

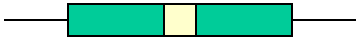
Critical gene targets
Proto-oncogenes

- Proto-oncogenes code for essential proteins involved in maintenance of cell growth, division and differentiation.
- Mutation converts a proto-oncogene to an oncogene, whose protein product no longer responds to control influences.
- Oncogenes can be aberrantly expressed, over-expressed or aberrantly active.
  - Eg *MYC, RAS, ERB, SIS*
- Proto-oncogenes can be converted to an oncogene by a single mutation.

Oncogene activation

Normal proto-oncogene

Mutation in the coding sequence
(point mutation of deletion)



Aberrantly active protein

Gene amplification
(Multiple gene copies)

Overproduction of normal protein

Chromosomal translocation
(Chimaeric genes)

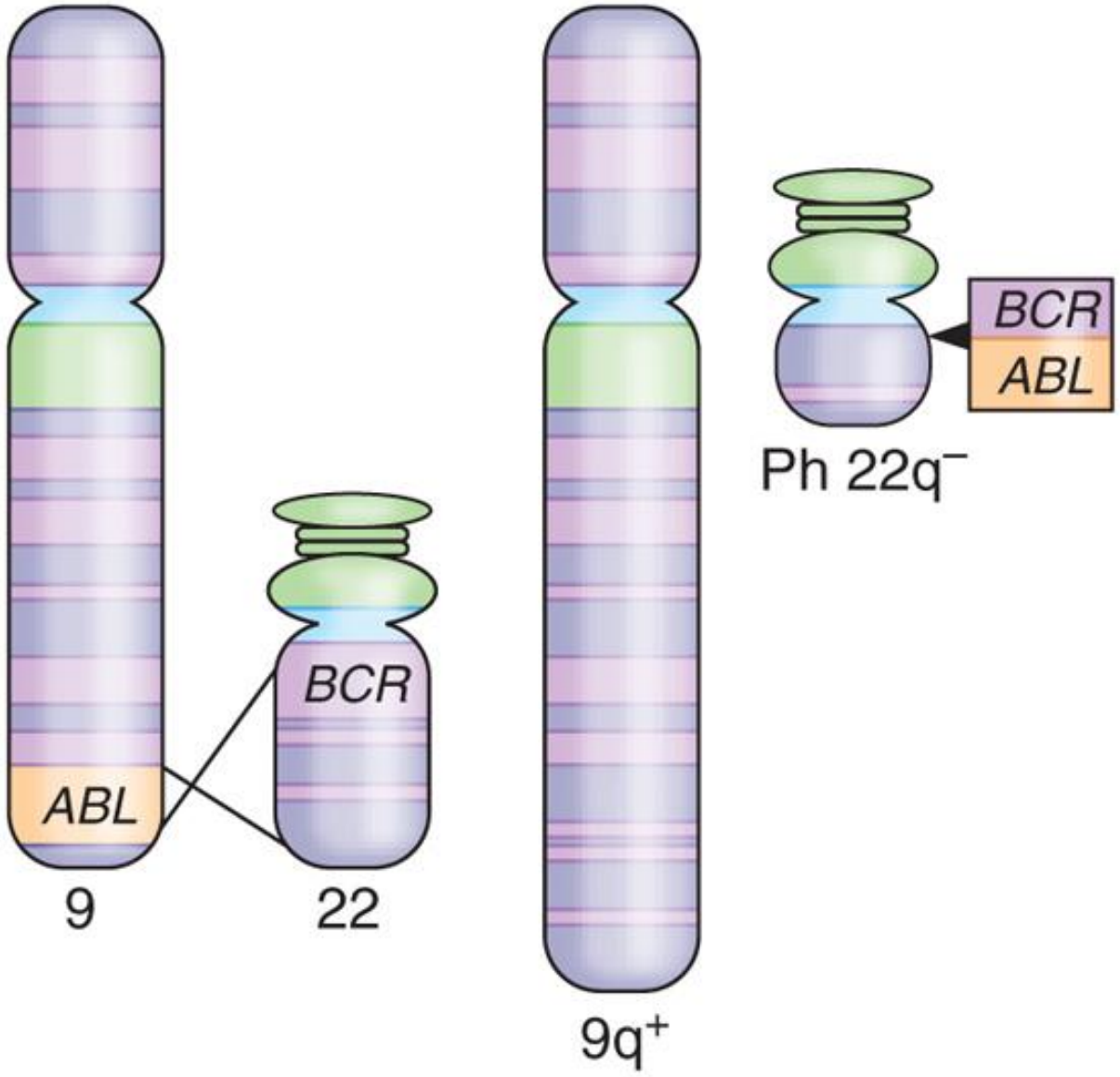
Strong enhancer increases normal protein levels
e.g. Burkitt's lymphoma

or

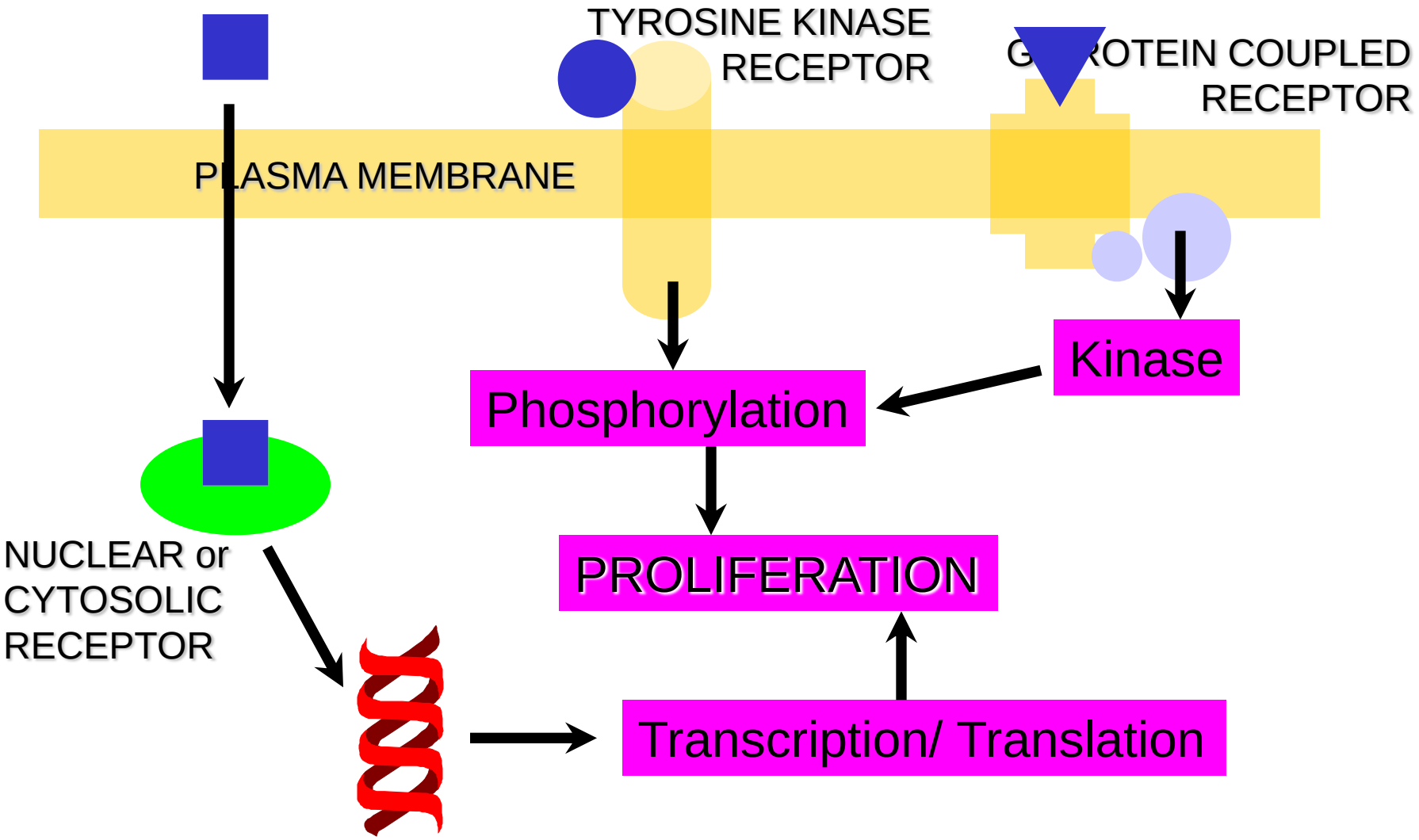
Insertional mutagenesis
(e.g. viral infection)

Fusion to actively transcribed gene overproduces protein or fusion protein is hyperactive.
e.g. Philadelphia chromosome

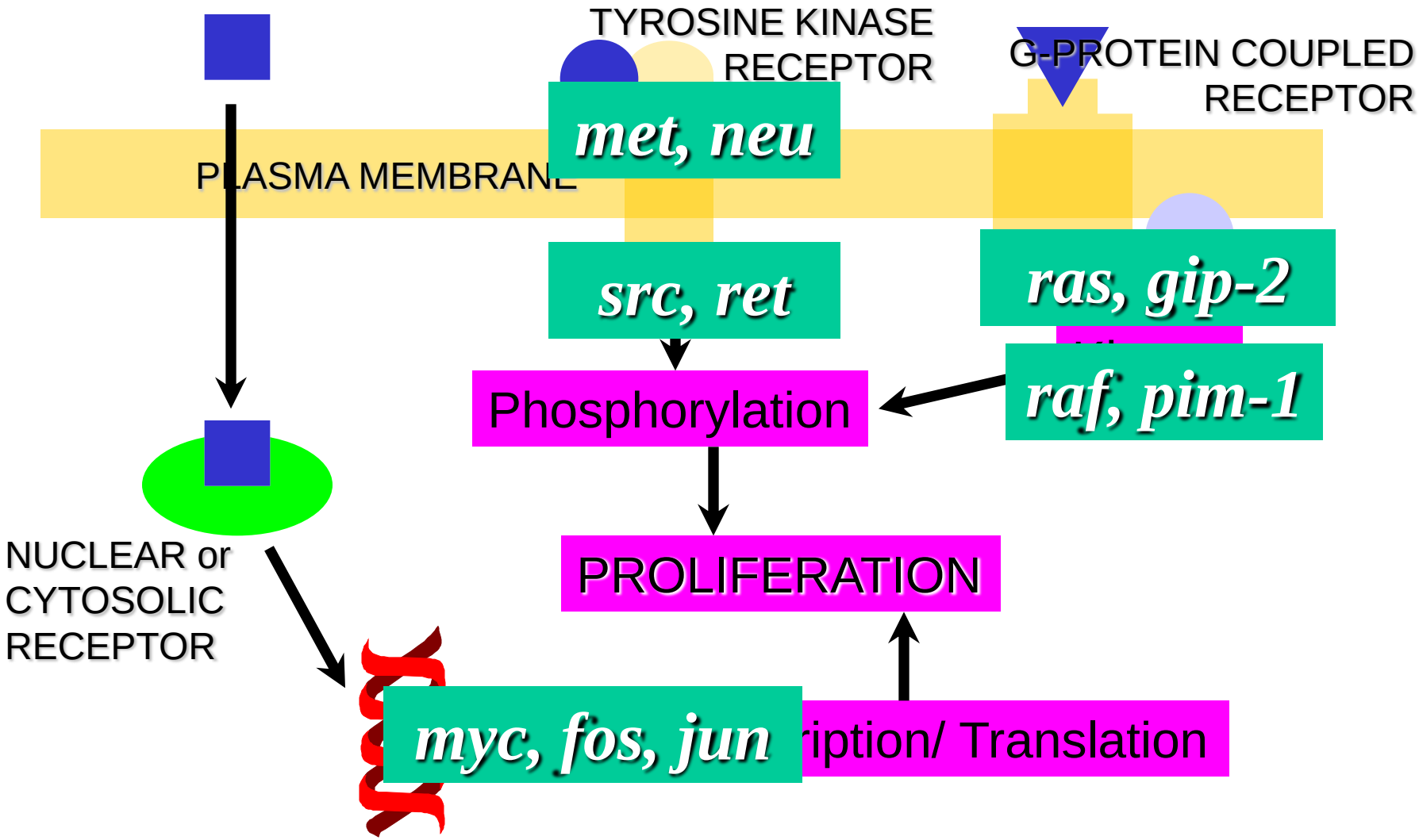
Philadelphia chromosome



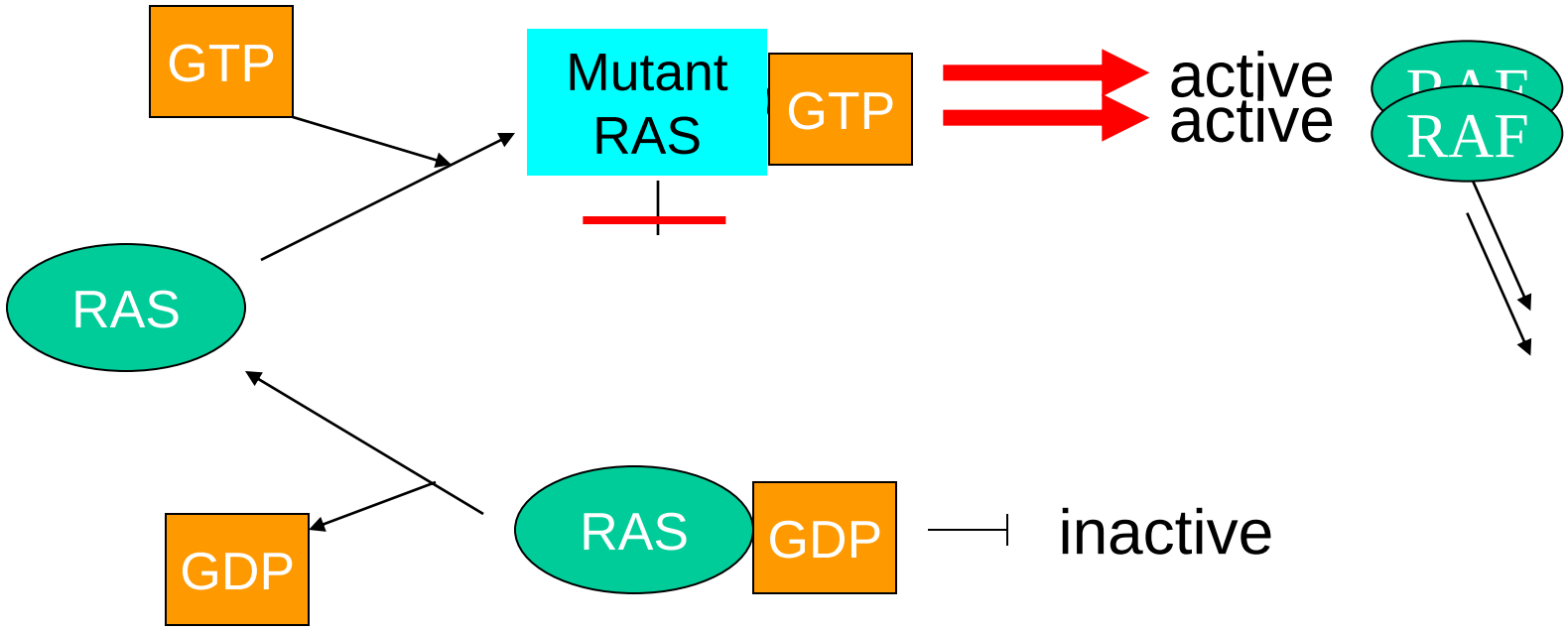
Proteins involved in signal transduction are potential critical gene targets (proto-oncogenes)



Activation of proto-oncogenes to oncogenes disrupts normal activity



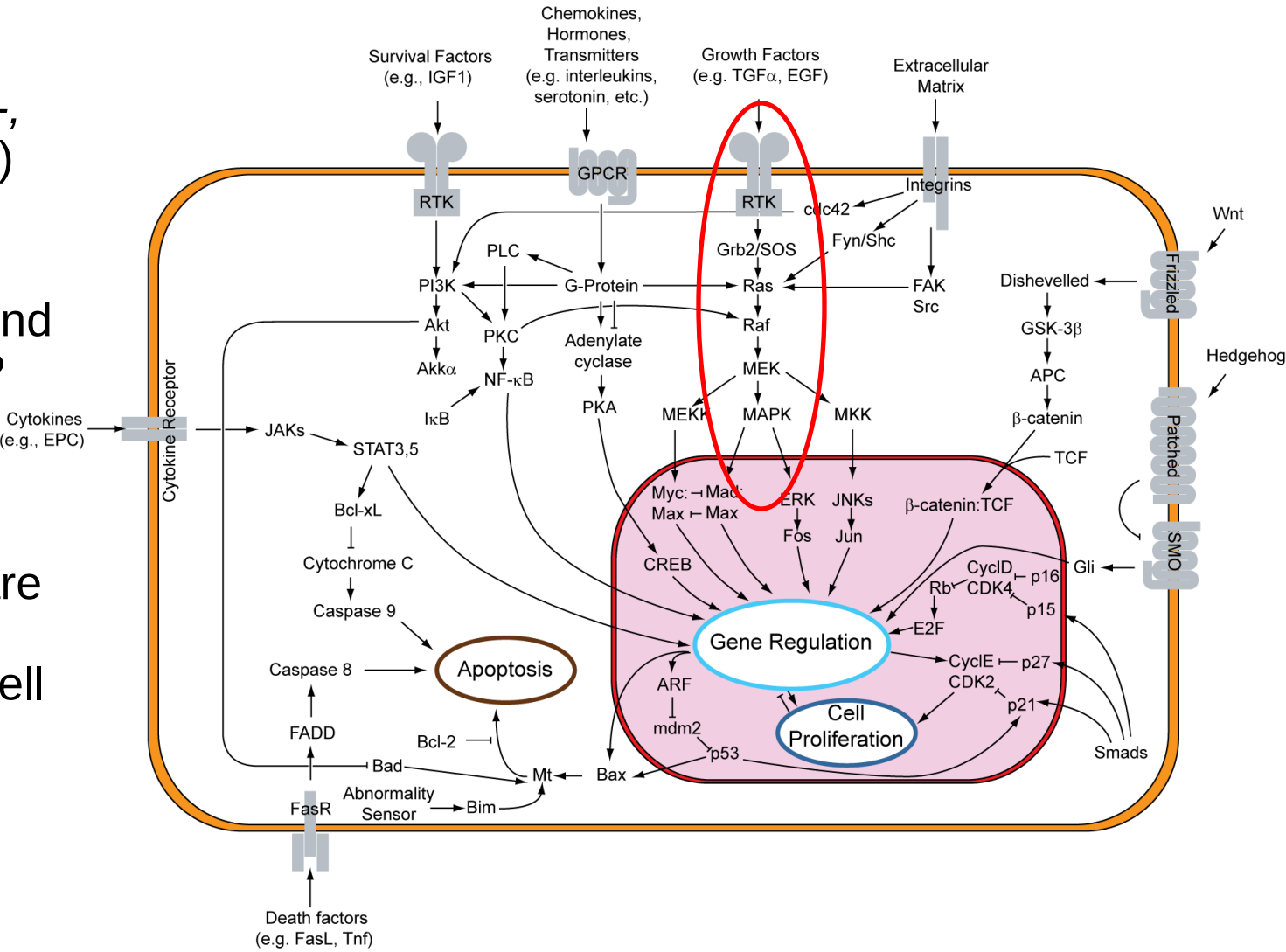
Mutant RAS has aberrant activity



- Upon binding GTP, RAS becomes active.
- Dephosphorylation of the GTP to GDP switches RAS off.
- Mutant RAS fails to dephosphorylate GTP and remains active.

The Mitogen-activated Protein Kinase (MAPK) Cascades

- *RAS* genes (*Ki-*, *H-*, and *N-RAS*) are highly conserved.
- Membrane bound GTPases (GTP bound - active, GDP bound – inactive).
- RAS proteins are central to the stimulation of cell proliferation.



Oncogenes and Human Tumours

Gene	Function	Mechanism of activation	Location	Associated human cancers
SRC	Tyrosine kinase	Overexpression/ C-terminal deletion	Cytoplasmic	Breast, colon, lung
MYC	Transcription factor	Translocation	Nuclear	Burkitt's lymphoma
JUN	Transcription factor	Overexpression/ deletion	Nuclear	Lung
Ha-RAS	G protein	Point mutation	Cytoplasmic	Bladder
Ki-RAS	G protein	Point mutation	Cytoplasmic	Colon, lung

Critical gene targets
Tumour suppressor genes

- Typically proteins whose function is to regulate cellular proliferation, maintain cell integrity.
  - *E.g. RB, .*
- Each cell has two copies of each tumour suppressor gene.
- Mutation or deletion of one gene copy is usually insufficient to promote cancer.
- Mutation or lost of both copies means loss of control.

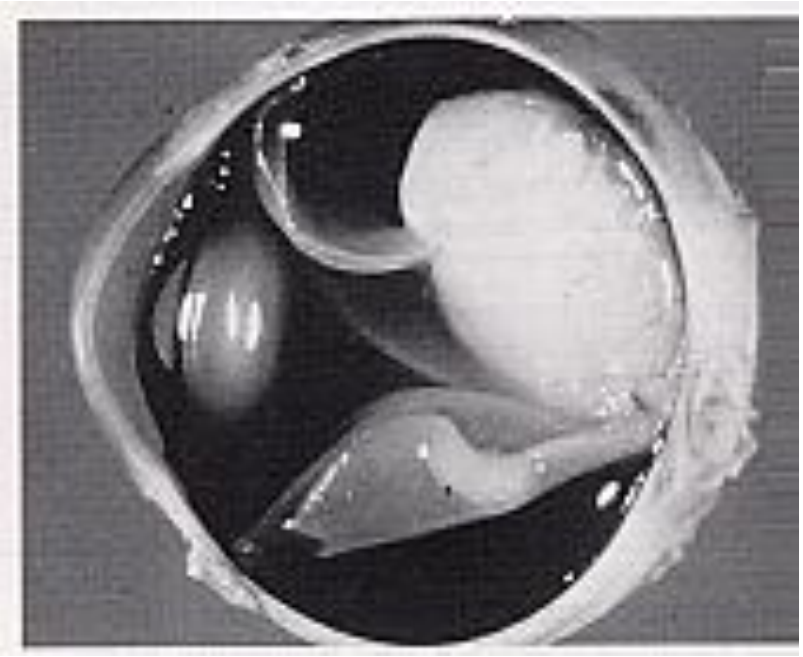
Inherited cancer susceptibility
(discovery of tumour suppressor genes)

Features

- Family history of related cancers.
- Unusually early age of onset.
- Bilateral tumours in paired organs.
- Synchronous or successive tumours.
- Tumours in different organ systems in same individual.
- Mutation inherited through the germline.

Retinoblastoma

- Malignant cancer of developing retinal cells.
- Sporadic disease usually involves one eye. Hereditary cases can be unilateral or bilateral and multifocal.
- Due to mutation of the RB1 ***tumour suppressor gene*** on chromosome 13q14.
- RB1 encodes a nuclear protein that is involved in the regulation of the cell cycle.



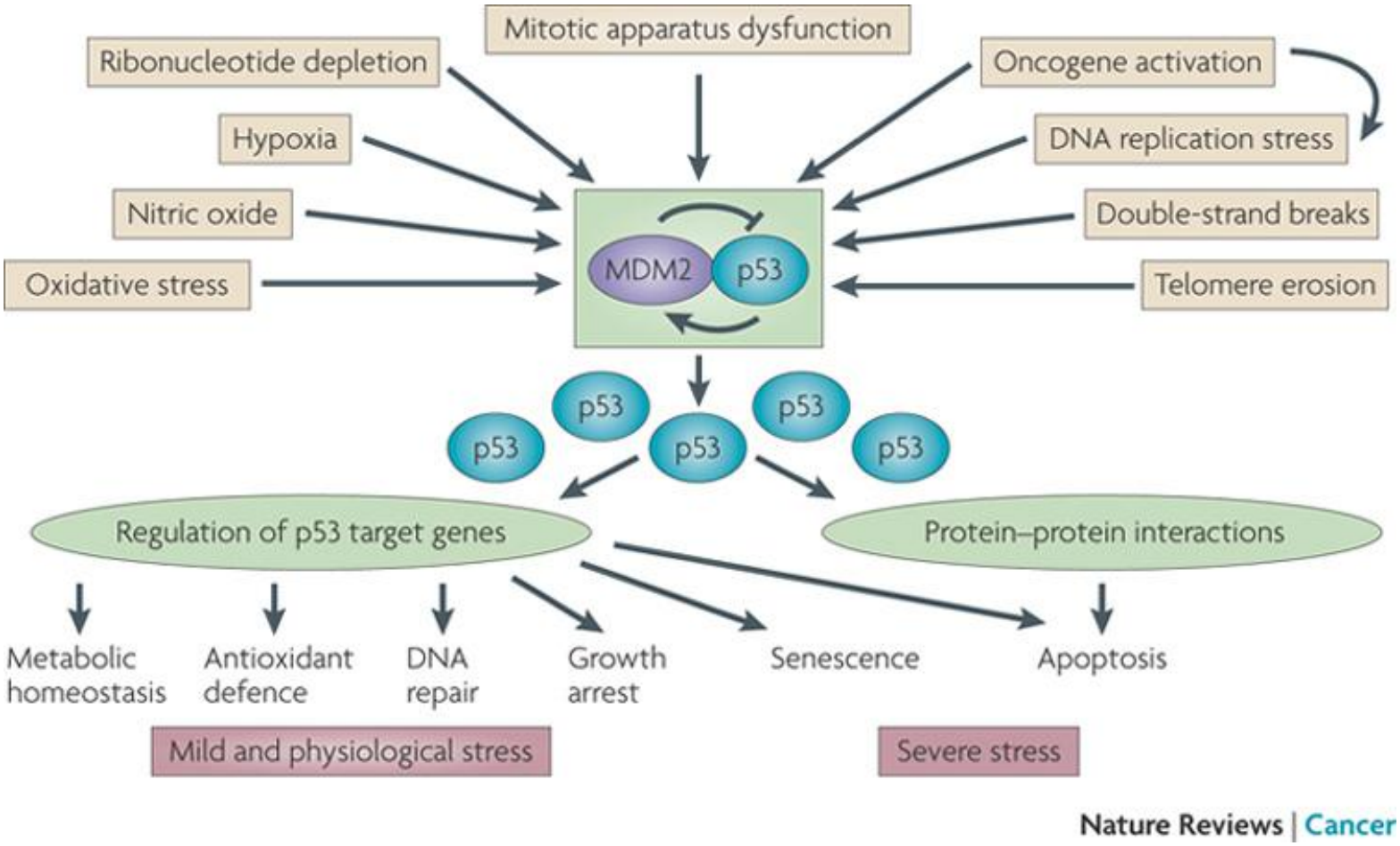
Functional classes of Tumour suppressor genes

- Regulate cell proliferation
- Maintain cellular integrity
- Regulate cell growth
- Regulate the cell cycle
- Nuclear transcription factors
- DNA repair proteins
- Cell adhesion molecules
- Cell death regulators
  - Suppress the neoplastic phenotype

Tumour Suppressor Genes and Human Tumours

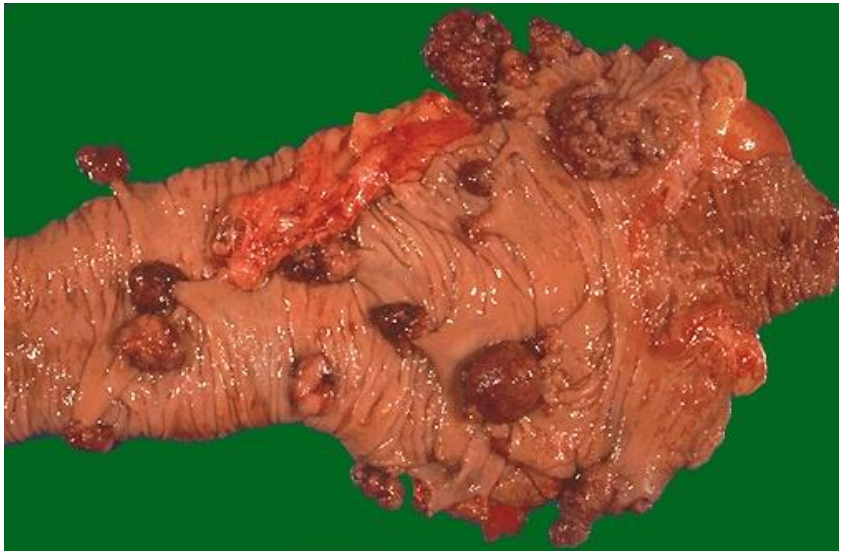
Gene	Function	location	Associated human cancer
p53	Cell cycle regulator	Nuclear	Many (colon, breast, bladder, lung etc)
BRCA1	Cell cycle regulator	Nuclear	Breast, ovarian, prostate
PTEN	Tyrosine and lipid phosphatase	Cytoplasmic	Prostate, glioblastoma
APC	Cell signaling	Cytoplasmic	Colon
p16^{-INK4A}	Cell cycle regulator	Nuclear	Colon and others
MLH1	Mismatch repair	Nuclear	Colon, gastric

P53 – the guardian of the genome



Although p53 is a tumour supressor gene, mutants of p53 act in a dominant manner and **mutation of a single copy** is sufficient to get dysregulation of activity.

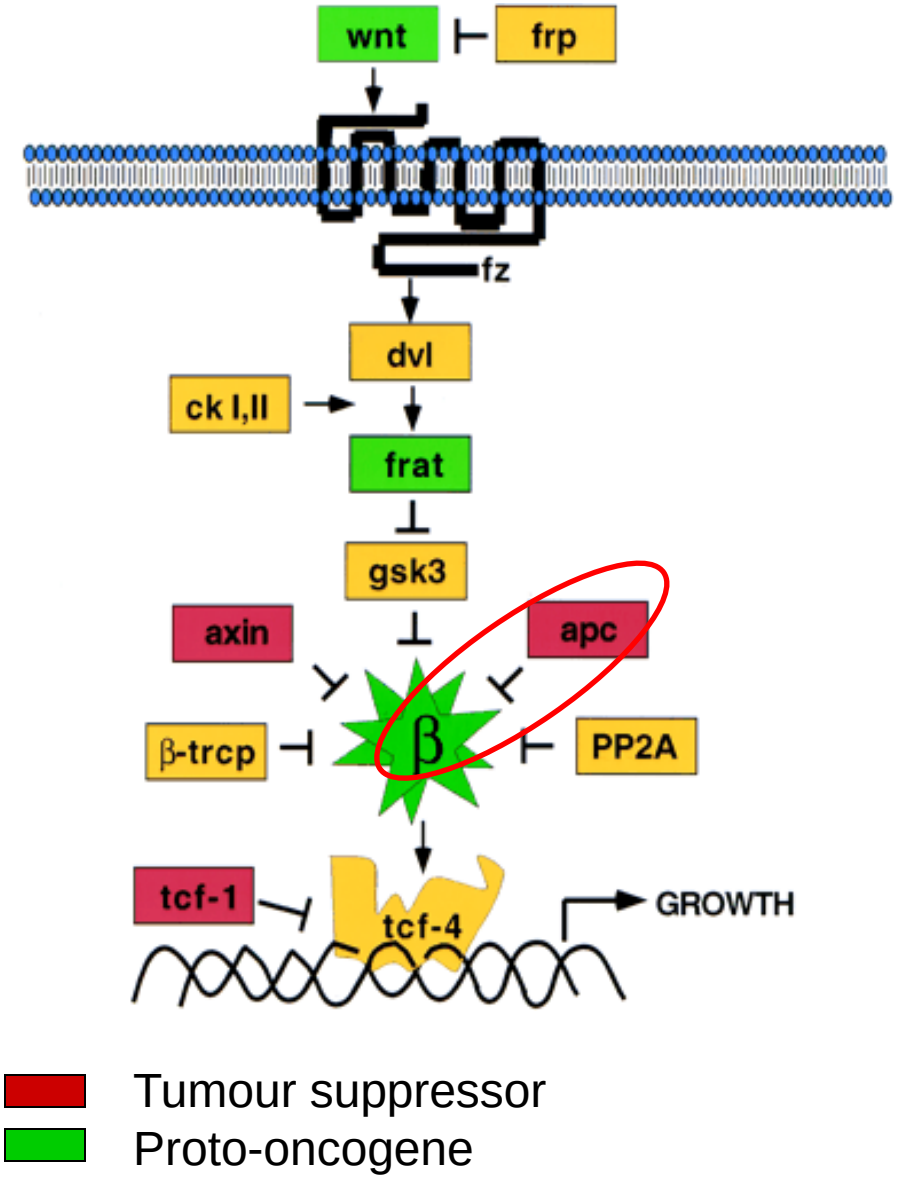
APC tumour suppressor gene
(Familial adenomatous polyposis coli)



- Due to a deletion in 5q21 resulting in loss of APC gene (***tumour suppressor gene***)***.***
- Involved in cell adhesion and signaling.
- Sufferers develop multiple benign adenomatous polyps of the colon.
- There is a 90% risk of developing colorectal carcinoma.

APC tumour suppressor gene

- The tumour suppressor gene *APC* participates in the WNT signalling pathway.
- APC protein helps control the activity of β-catenin and thereby preventing uncontrolled growth.
- Mutation of *APC* is a frequent event in colon cancer.

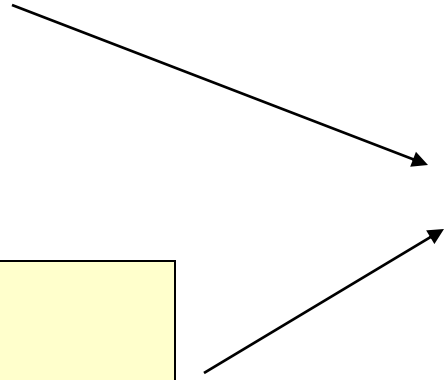


The route to cancer

Proto-oncogene
Tumour suppressor gene

Oncogene
Tumour suppressor gene

Proto-oncogene
Defective tumour suppressor gene



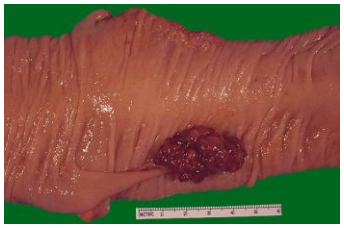
Cell growth and proliferation

Cancer

The development of colo-rectal Cancer

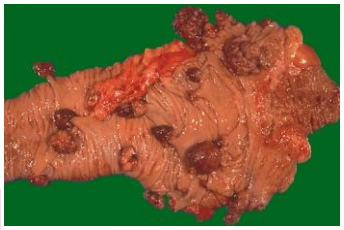
Normal epithelium

Apc



Hyperproliferative epithelium

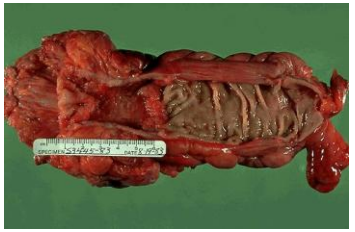
K-ras



DNA hypomethylation

Adenoma

p53



Carcinoma

Metastasis

Oncogenes and tumour suppressor genes

Oncogene	Tumour suppressor gene
Gene active in tumour	Gene inactive in tumour
Specific translocations/point mutations	Deletions or mutations
Mutations rarely hereditory	Mutations can be inherited
Dominant at cell level	Recessive at cell level
Broad tissue specificity	Considerable tumour specificity
Leukaemia and lymphoma	Solid tumours

Summary

- Human cancer involves damage to DNA, or inheritance of aberrant sequences, **at critical gene targets**.
- These targets, proto-oncogenes and tumour suppressor genes, regulate cell cycle decisions (mitosis, arrest, differentiation, apoptosis).
- The ‘guardian of the genome’, p53 is a key player in decision making during the cell cycle.
- Studies of rare heritable cancers have led to an understanding of tumour suppressor genes.
- Colon cancer is a model for many of these factors.

Reading material

- The Cancer handbook 2nd Ed (*MR Alison, 2007, Wiley pub*).
- Cells *(B. Lewin et al. 2007, Pub Jones and Bartlett)*
- Review articles in journals *Cell* and *Cancer Research.*