Molecular basis of tumours

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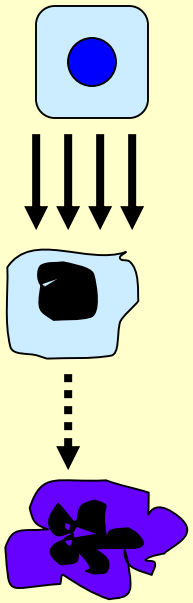
At the end of this lecture you should be able to..

- Outline the principles of carcinogenesis
- Define the terms :proto-oncogenes, oncogenes, tumour suppressor genes, DNA repair genes
- Give examples for each of the above genes.
- Outline the features of malignant phenotype
- Apply the knowledge of carcinogenesis to clinical practice ; i.e tumour diagnosis, treatment , follow up and screening

Molecular basis of tumours

- How do the tumours originate?
- The process of formation of tumour is known as **“oncogenesis”**



Normal cell

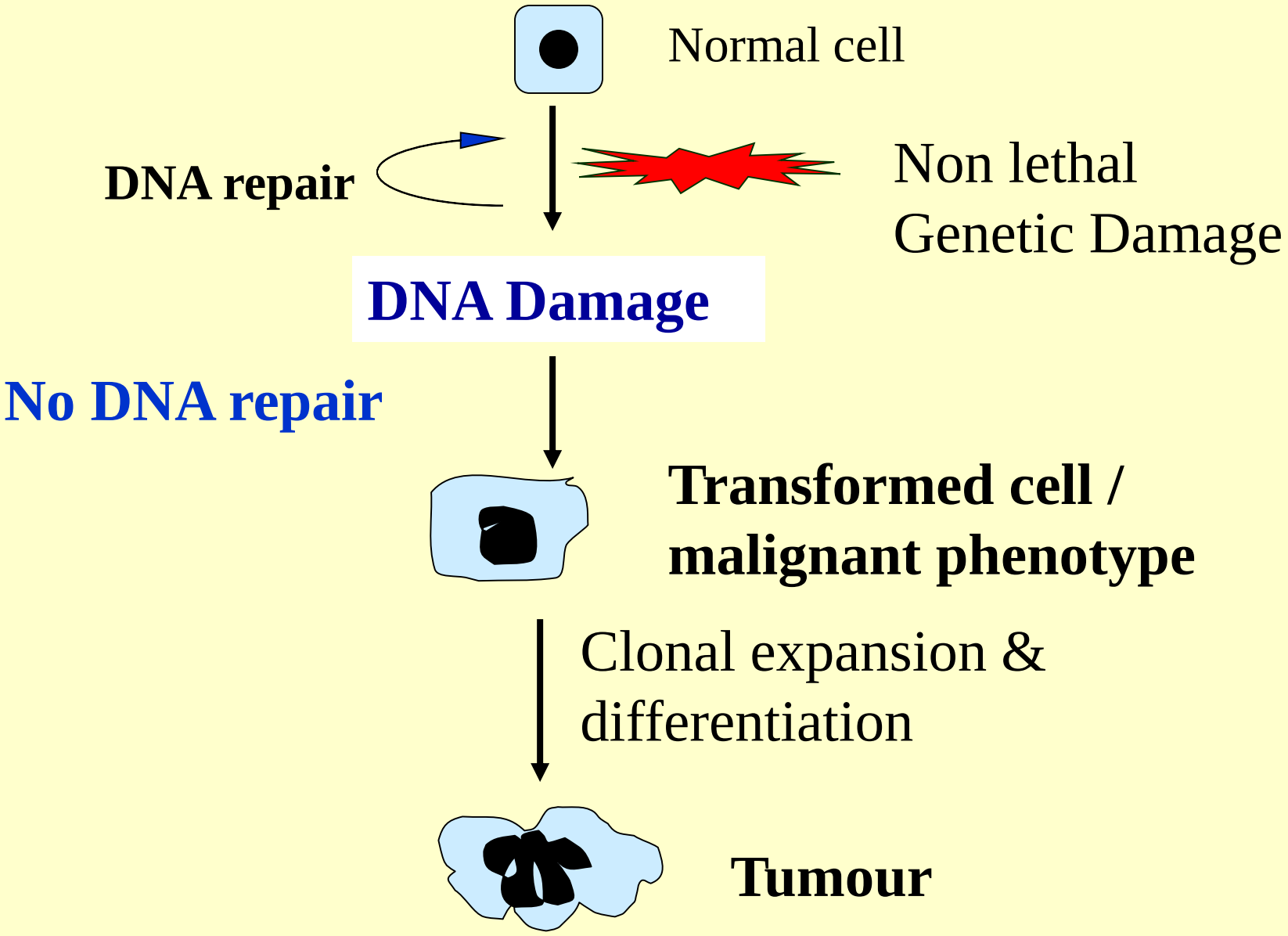
Tumour cell

Tumour/neoplasm

Tumours are monoclonal

‘Carcinogenesis’ applies to the process of formation of malignant tumours/ cancers

How do the tumours originate?



How does a transformed cell differ from a normal cell?

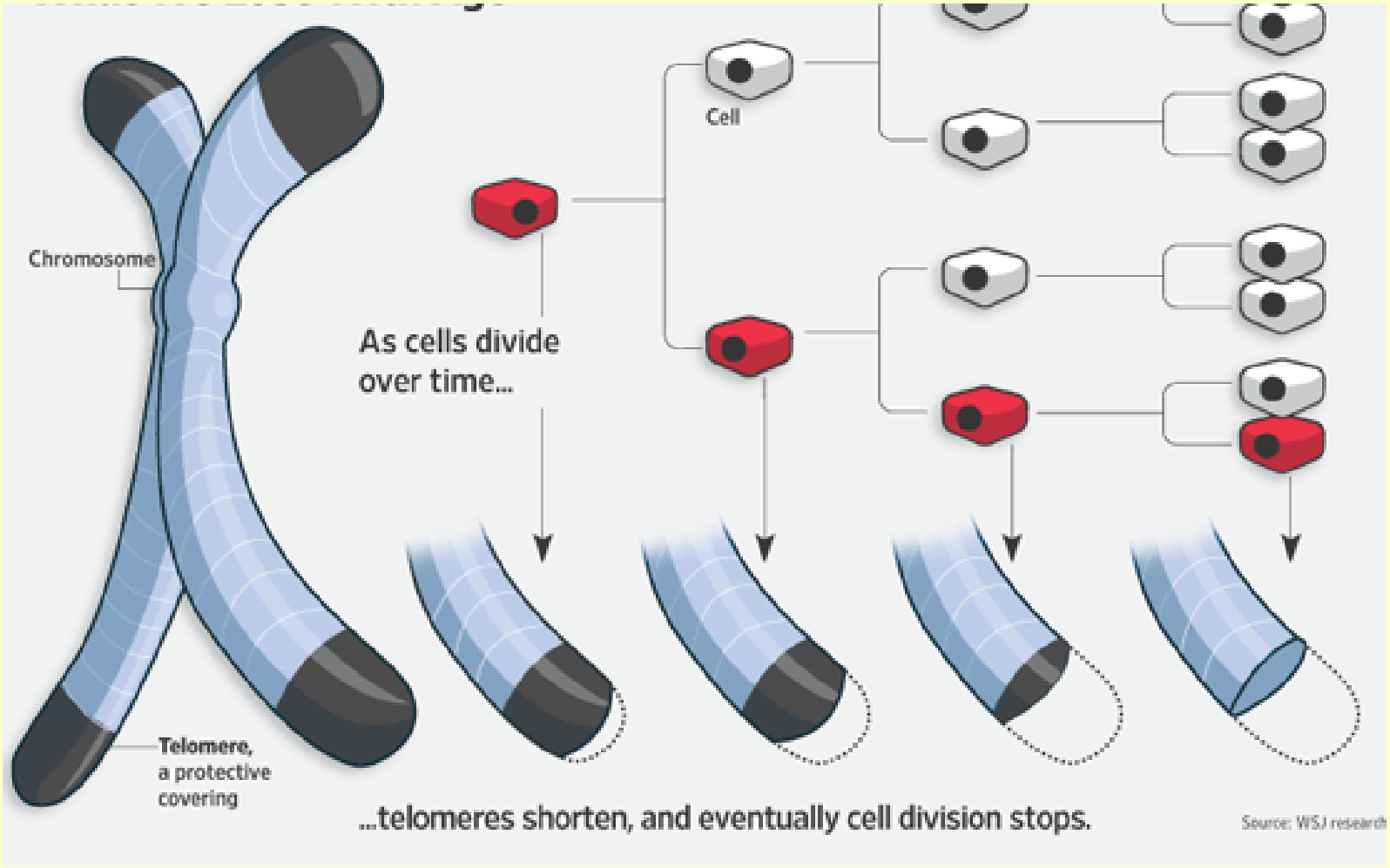
- Immortal- multiply indefinitely
- Unregulated and uncontrolled growth
- Escape from normal regulatory mechanisms
- Reduced requirement for their growth
- Tumourogenesity/Transplantability
- Reduced cohesiveness
- Anchorage independent

Telomeres and telomerase

- Telomeres are tandem repeat sequences at the end of each chromosome.
- DNA polymerization starts at the telomeres at the time of mitosis
- This region is incompletely copied so that with each mitosis the length of the telomere is shortened.
- Eventually it become too short to allow the replication
- Therefore the cell can not replicate-

Cellular Senescence

Shortening of telomeres

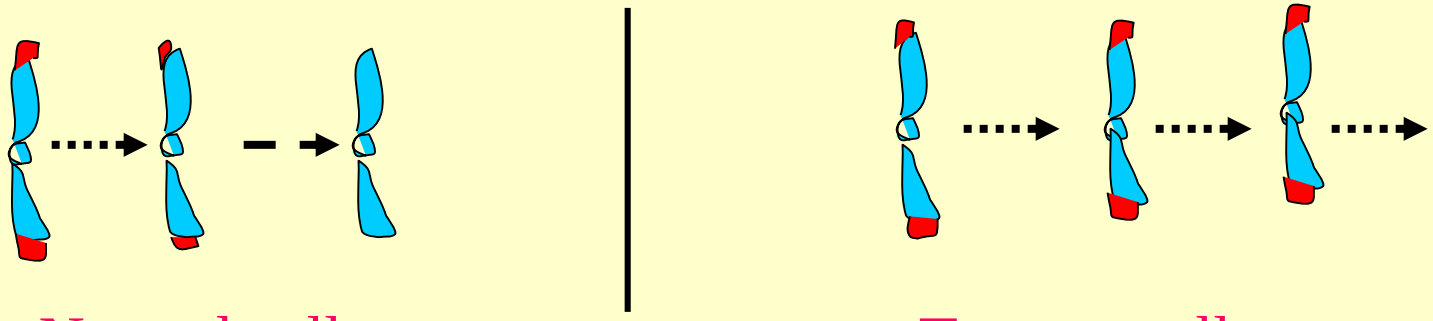


Each time a cell divides, an average person loses 30 to 200 base pairs from the ends of that cell's telomeres.

Telomerase and cancer

- Tumour cells express **Telomerase,** an enzyme which allows the cell to divide indefinitely /immortal

Telomerase causes replication of telomeres



Normal cell

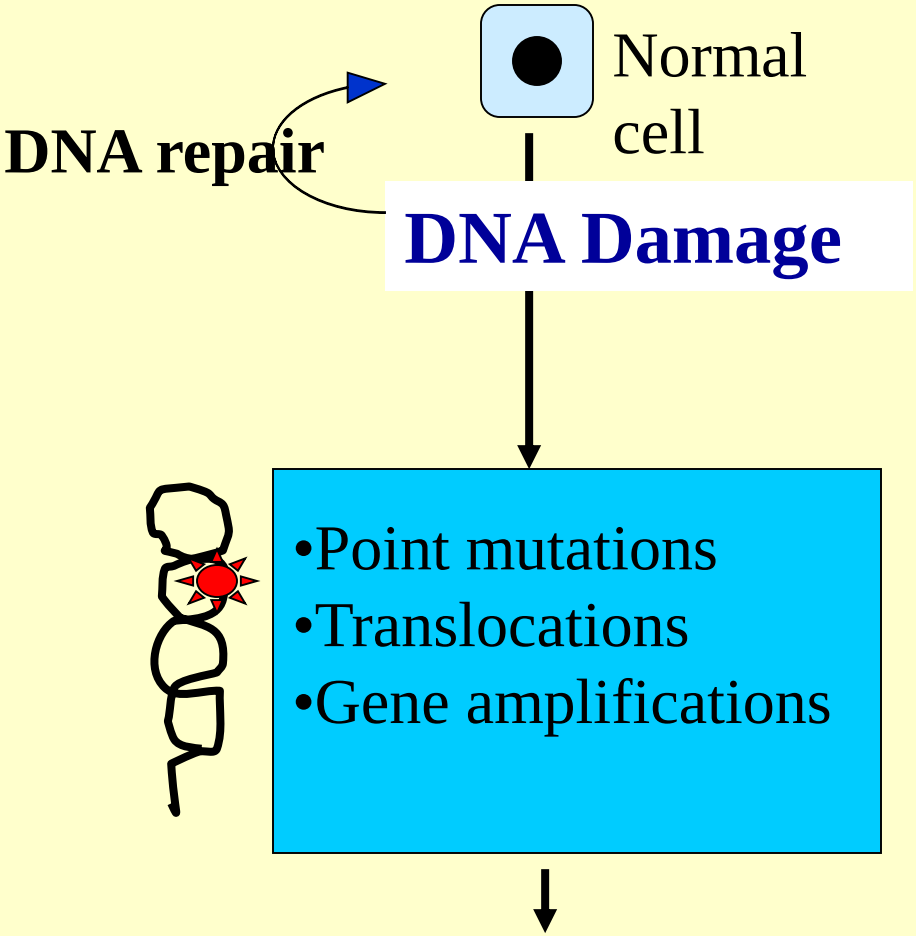
Tumour cell

Major genetic properties of cancer

- Excessive and autonomous growth
- Refractoriness to growth inhibition
- Escape cell death by apoptosis
- Avoid cellular aging
- Escape DNA damage repair
- Continued perfusion – angiogenesis
- Invasion and metastasis- dissemination
- Clonal expansion
- Escape the immune attack

DNA Damage

carcinogens

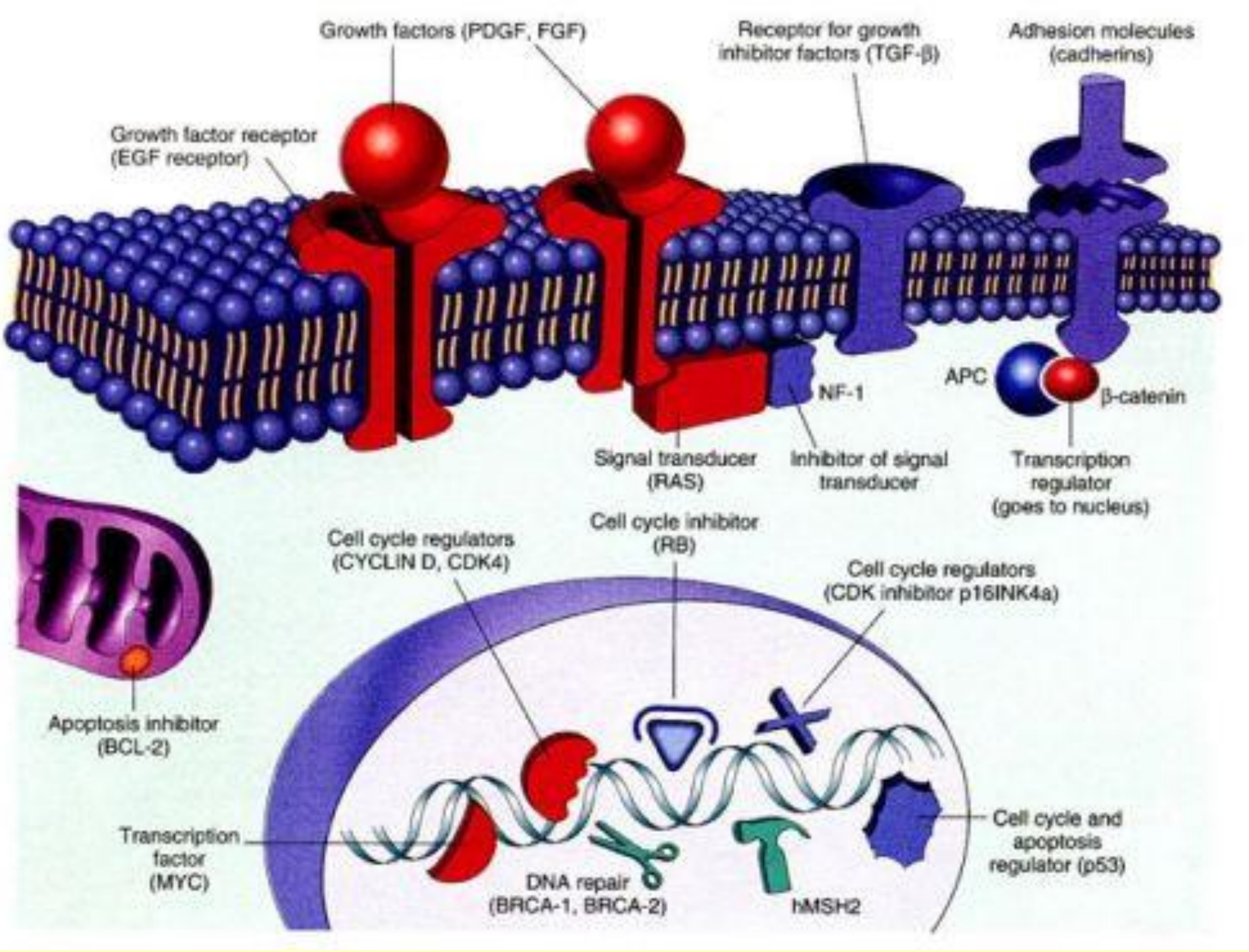


- **Acquired/environmental**
  - Chemical
  - Viral
  - Radiation
- **Inherited**

An Abnormal protein, which **allow the cell to become a tumour cell**

Target sites of genetic damage within the genome

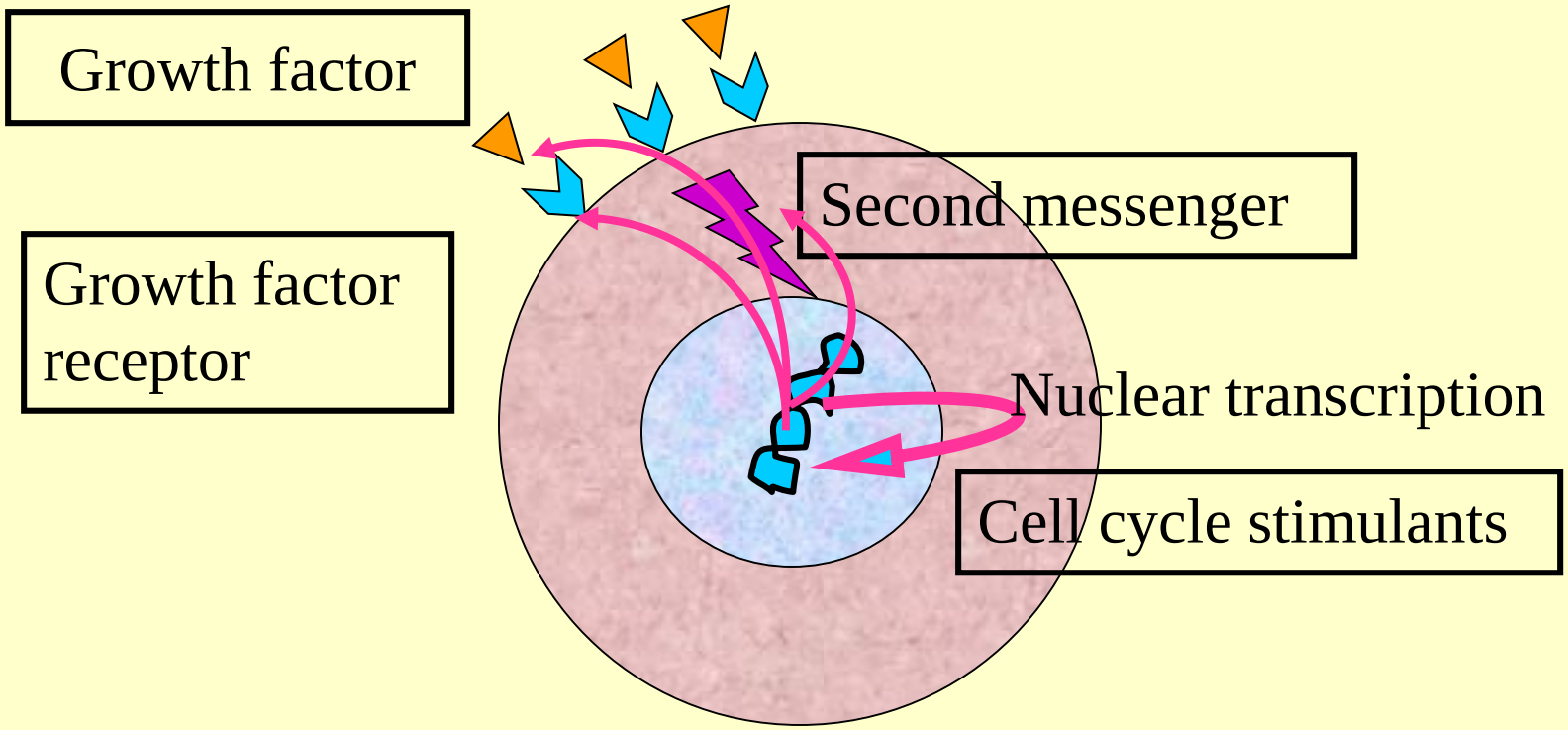
- Genes that promote normal growth & differentiation **Proto-oncogenes**
- Genes that inhibits growth –**Oncosuppressor /Tumour suppressor genes**
- **Genes that regulates apoptosis**
- **Genes that repair defective DNA**


Growth factors (PDGF, FGF)
Receptor for growth inhibitor factors (TGF-β)
Adhesion molecules (cadherins)
Growth factor receptor (EGF receptor)
NF-1
APC
β-catenin
Signal transducer (RAS)
Inhibitor of signal transducer
Transcription regulator (goes to nucleus)
Cell cycle inhibitor (RB)
Cell cycle regulators (CYCLIN D, CDK4)
Cell cycle regulators (CDK inhibitor p16INK4a)
Apoptosis inhibitor (BCL-2)
Transcription factor (MYC)
DNA repair (BRCA-1, BRCA-2)
hMSH2
Cell cycle and apoptosis regulator (p53)

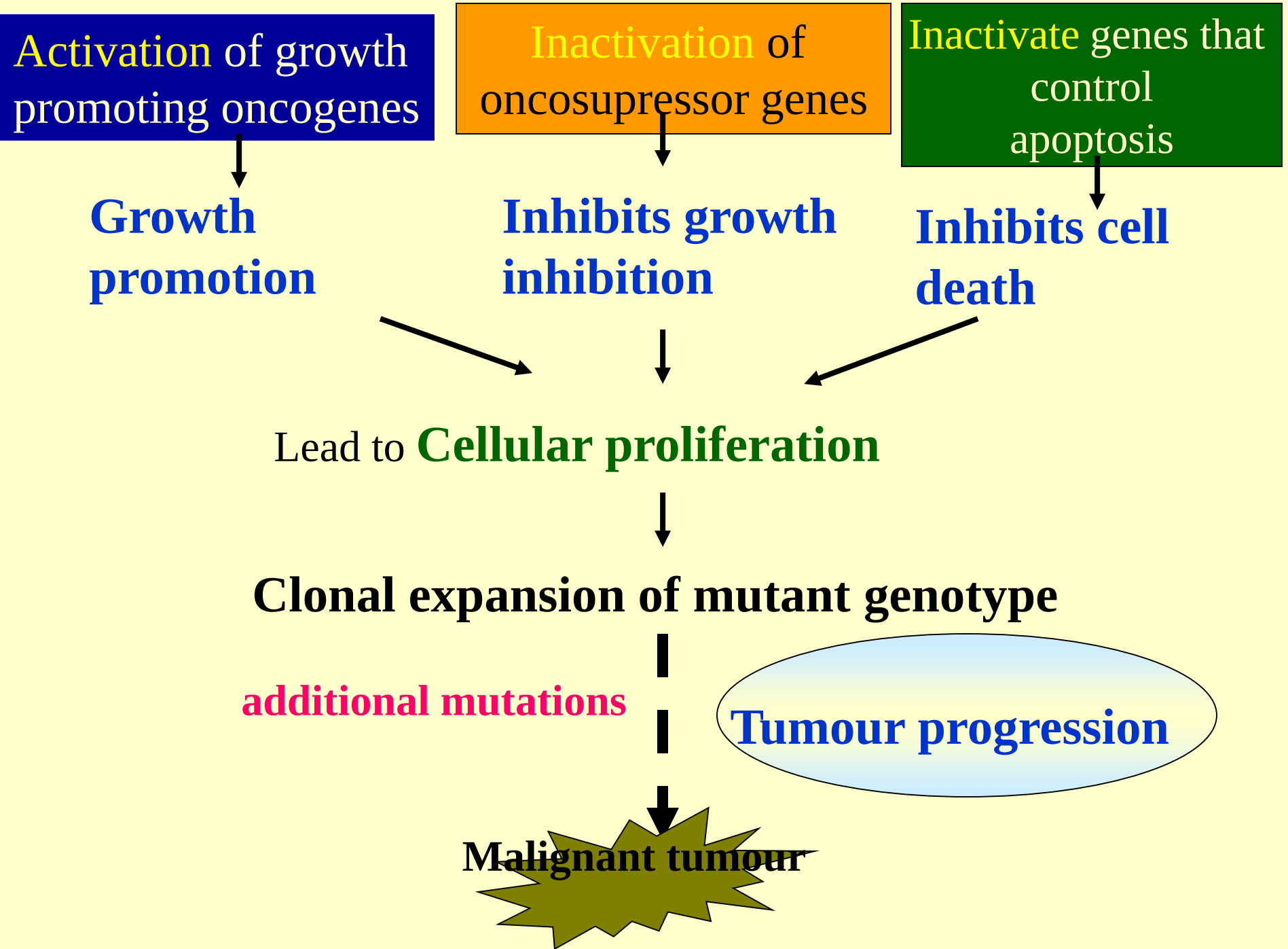
Proto-oncogenes

- Are the growth promoting genes
- Under physiological conditions the cell proliferation can be resolved into
  - Binding of growth factor (GF) to GF receptor
  - Transient and limited activation of GF receptor
  - Activation of signal transducing agents on the inner leaflet of plasma membrane
  - Transmission of the signals to the nucleus via second messengers
  - Induction & activation of nuclear transcription factors
  - Initiation of DNA transcription
  - Entry into cell cycle

Functions of protein products of proto-oncogenes



- Control normal cell proliferation and differentiation through the production of their proteins


Activation of growth promoting oncogenes
Inactivation of oncosupressor genes
Inactivate genes that control apoptosis
Growth promotion
Inhibits growth inhibition
Inhibits cell death
Lead to Cellular proliferation
Clonal expansion of mutant genotype
additional mutations
Tumour progression
Malignant tumour

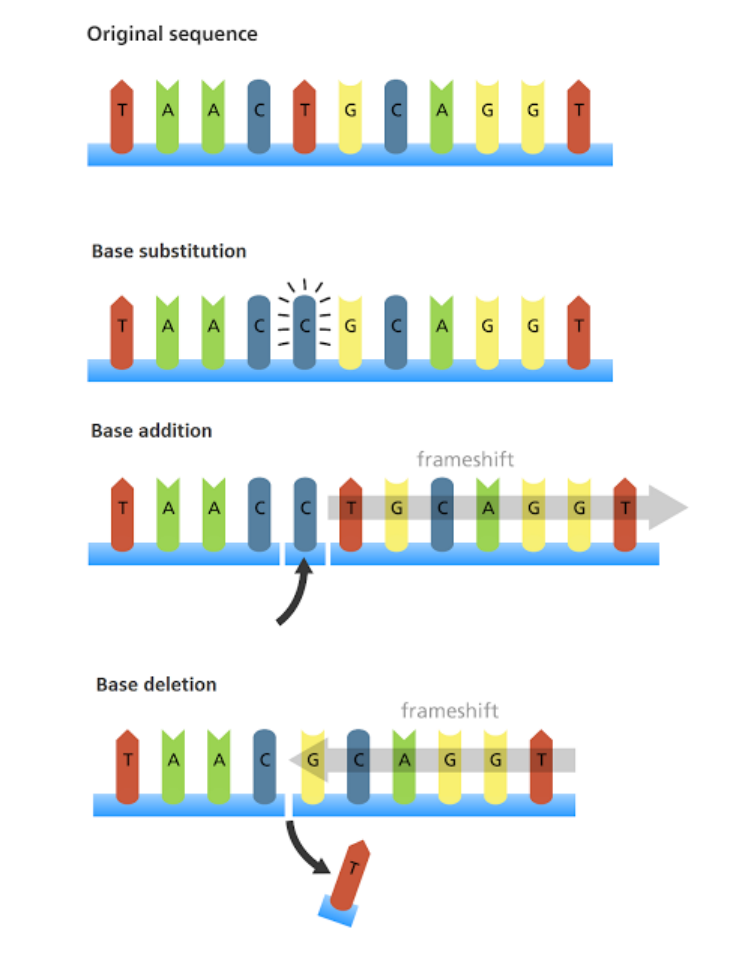
Oncogenes

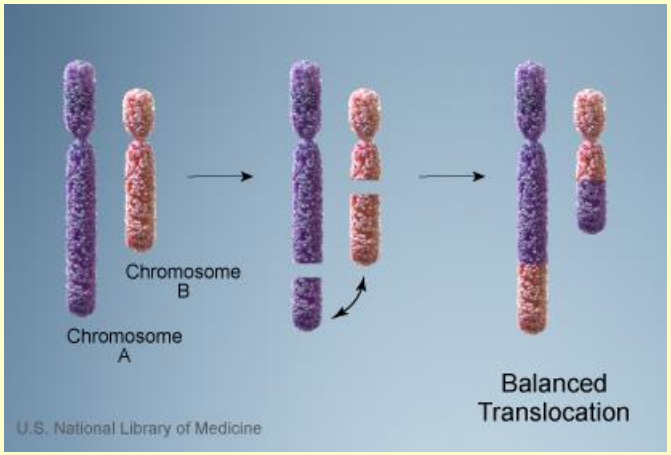
- Genes that promotes **autonomous** cell growth in cancer.
- They are the mutated counterparts of proto-oncogenes
- The protein product of oncogenes are called oncoproteins
- They resemble the normal products of proto-oncogenes **except** that they are
  - Devoid of important regulatory elements
  - Production does not depend on the growth factors or other external stimuli

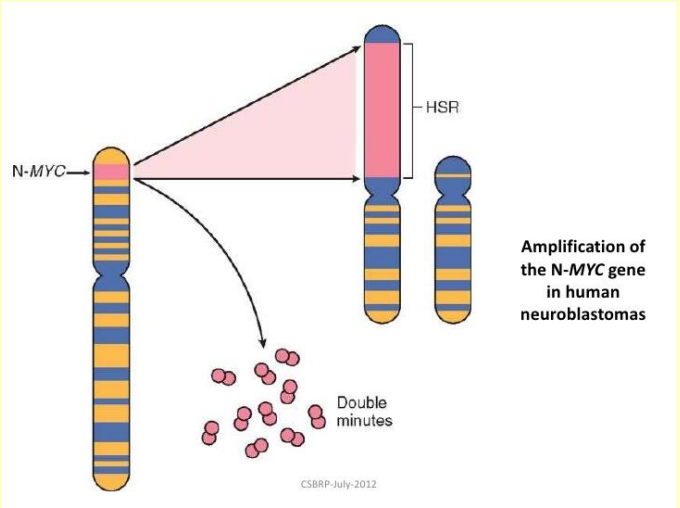
Mechanisms of formation of oncogenes

- **Point mutation-** alteration of a single base in DNA
  - RAS oncogene
- **Translocation**-transfer of apportion of one chromosome carrying a proto-onchogene to another chromosome
  - Philadelphia chromosome in CML-9: 22 translocation
- **Gene amplification-** increasing the number of copies of DNA sequence in proto-oncogenes
  - ERB –B1 in breast cancer

Mechanisms of genetic changes



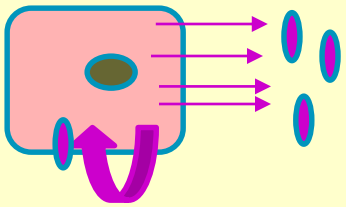




Amplification of the N-*MYC* gene in human neuroblastomas

How oncogenes encode for cell signaling system

- **GF**- cancer cells may synthesize GF that can stimulate the cell itself - Autocrine loop



PDGF β
TGFα
FGF

- **Receptor for GF**-mutated form of GF receptors stimulate cell proliferation even without the binding of GF
  - EGFR and ERB B_2
  - c-KIT

How oncogenes encode for cell signaling system

- **Signal -transducing agents**
  - Located in the inner leaflet of plasma membrane
  - Mutated firms continuously transmit the signal from cell membrane to the nucleus

RAS family of genes are a group of signal transducing oncoproteins.

Point mutation of *RAS f*amily gene is the single most common abnormality in proto-oncogenes in human cancers

How oncogenes encode for cell signaling system

- Nuclear Transcription factors-This induces the cell to enter the cell cycle
  - Normal MYC protein binds to DNA and regulate the cell cycle. Its activity immediately ceases when the cell enters the cell cycle
  - MYC oncoprotein causes persistent expression or over expression causing autonomous proliferation and is found in many tumours
    - Translocation of MYC gene-Burkitt lymphoma
    - MYC amplification in breast , colonic cancers

How oncogenes encode for cell signaling system

- **Cell cycle regulatory proteins**
  - Cyclins & cyclin dependent kinase-CDKs

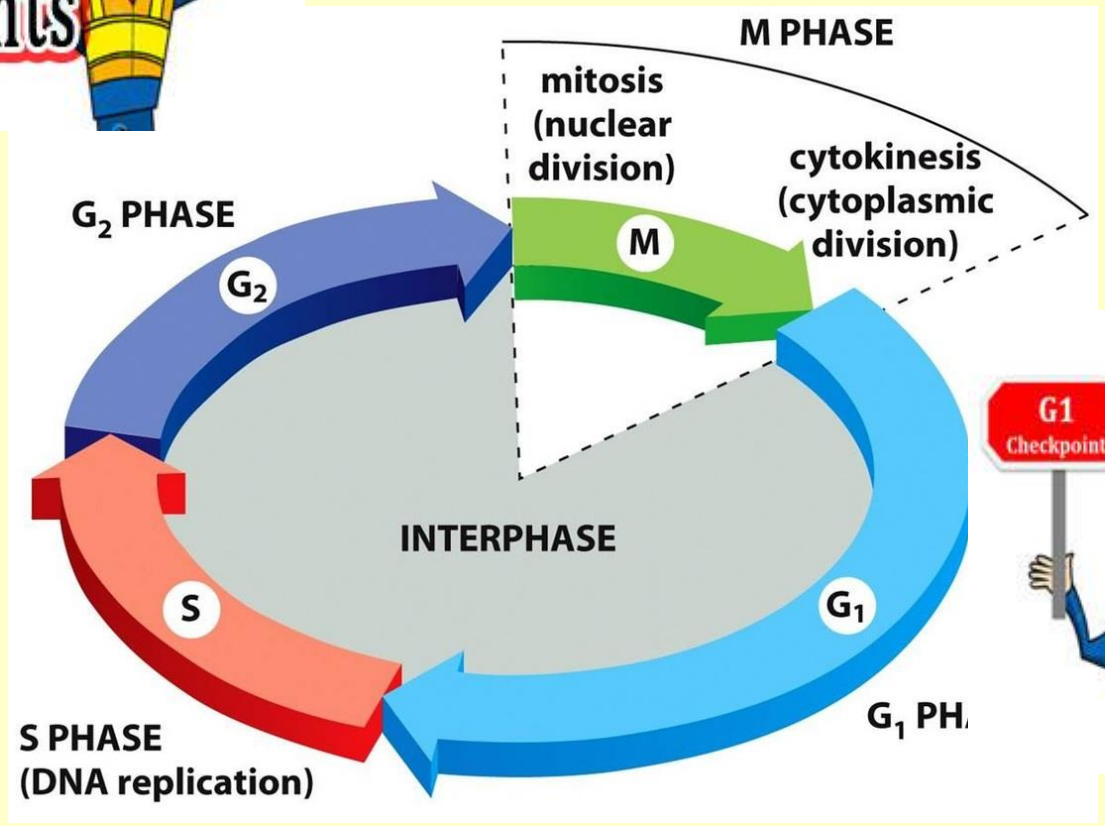
regulate the orderly progression of cells through the various phases of cell cycle.

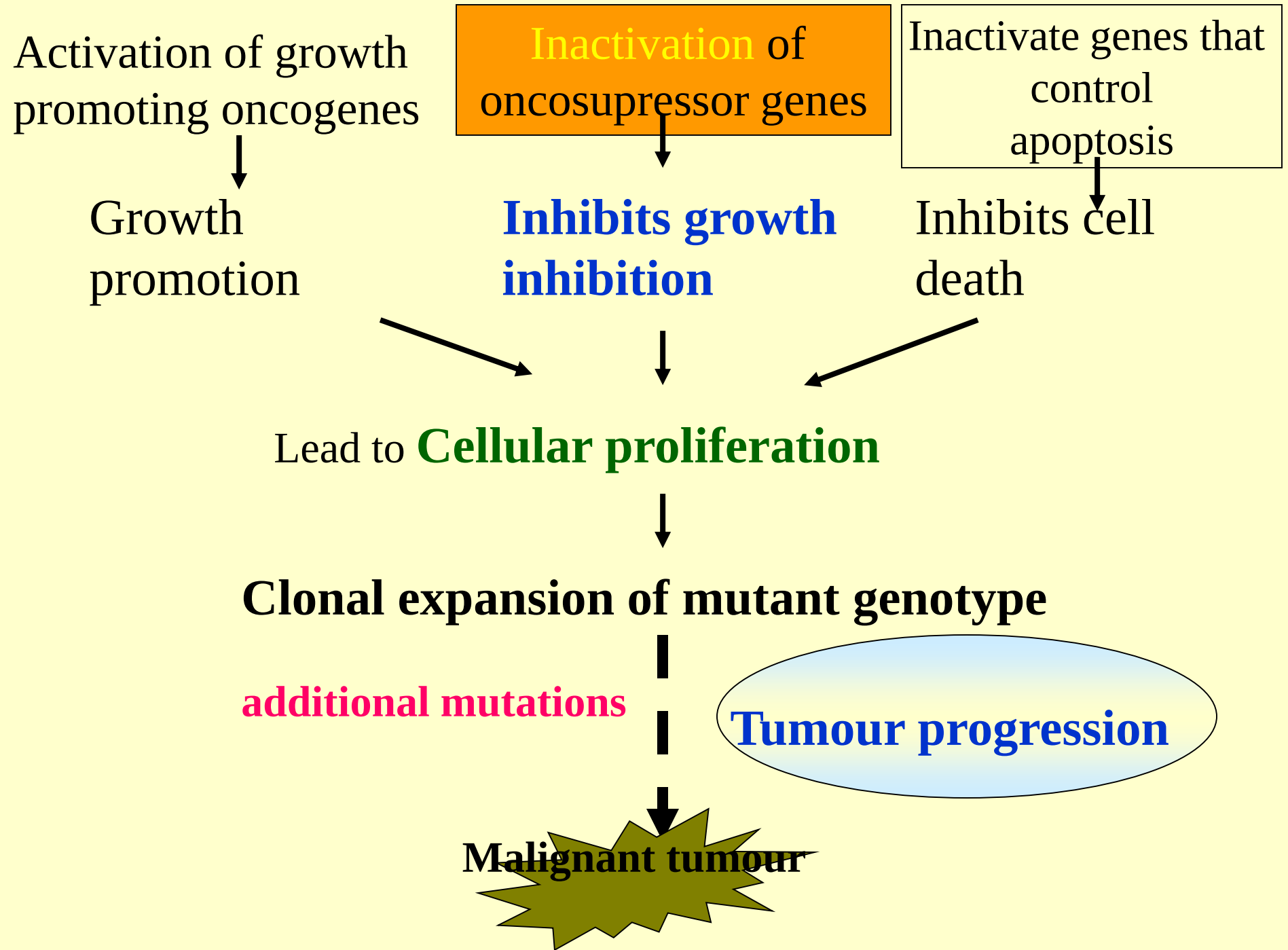
Mutations of these results in uncontrolled cell proliferation

Eg: mutation in cyclin D in breast & liver cancers and in some lymphomas.

What are cell cycle checkpoints?

Recall the cell cycle and cell cycle control

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Onco-suppressor genes /tumour suppressor genes

- Physiological function of onco-suppressor genes is to **regulate** cell growth
- There are 2 groups of onco-suppressor genes
  - Caretaker genes- repair damaged DNA

  - Gatekeeper genes-inhibit the proliferation or promote death of cells with DNA damage

p53 gene & TP 53 protein

- A growth regulatory gene / tumour suppressor gene located in chromosome 17
- Single most common target for genetic alteration in human cancers
- The protein product of p ^{53} (TP 53) act as a critical gatekeeper against formation of cancers

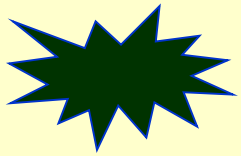
"molecular policeman"

- It prevents propagation of genetically damaged cells by
  - Temporary allowing them to undergo repair
  - if repair is failed, causes cell death by apoptosis

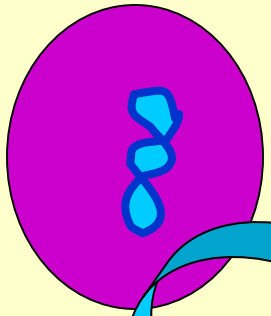
p53 gene & TP 53 protein

- TP53 prevents propagation of genetically damaged cells by
  - Temporary arrest of cell cycle
    - Allowing DNA repair
  - Permanent arrest of cell cycle
    - Cellular senescence
  - Cell death by apoptosis

Cells with mutant p^{53}



Mutagenic agent



Cell with mutant/ loss of p53

DNA damage

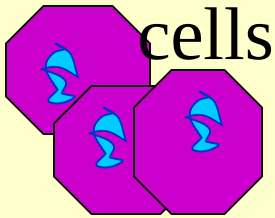
>75% of human cancers have homzygous loss of p53

P53 dependent genes are not activated

No cell cycle arrest

No DNA repair

Proliferation of mutant cells



Tumour

Inherited mutation of p53

- Inherited germline mutation of p53 gene occurs in Li-Fraumani syndrome
- Affected individuals have an inherited predisposition to a wide range of cancers.

  Eg; breast , bone brain and sarcomas

Write a short note on TP53

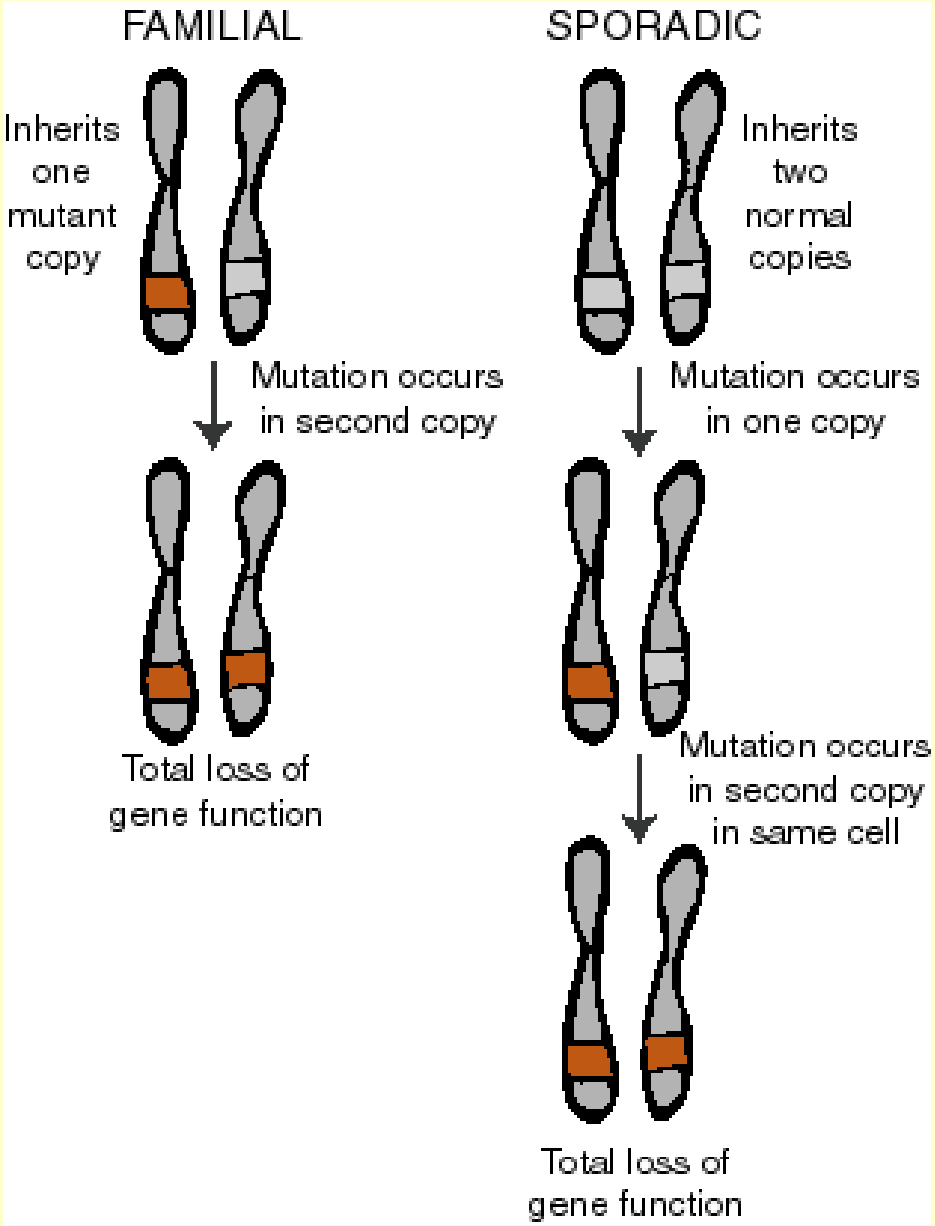
Major onco-suppressor genes implicated in human cancers

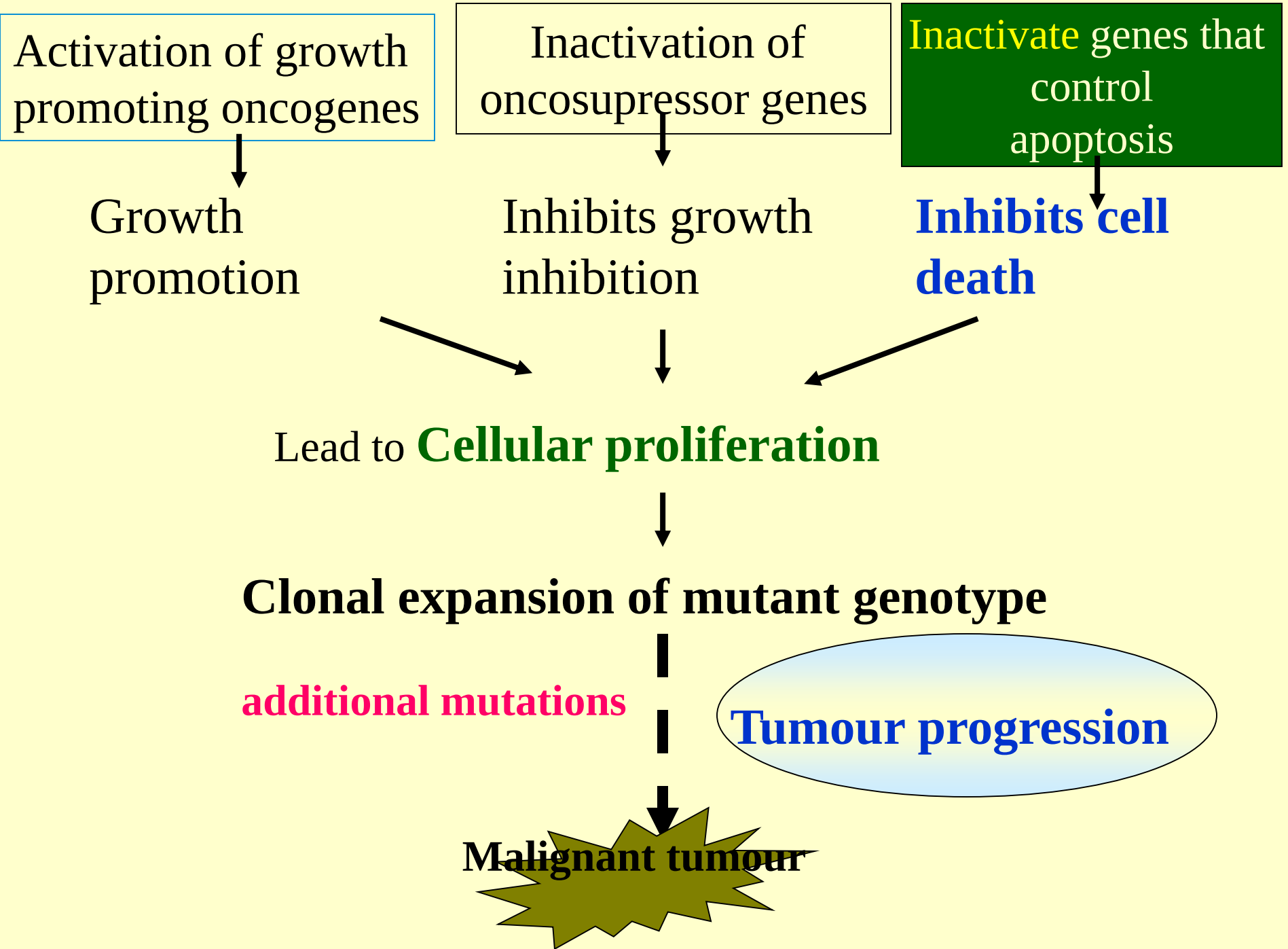
- P53- most human cancers
- Rb gene- most human cancers
- APC gene- colon, stomach, pancreas, melanomas
- BRCA 1 and BRCA 2 gene- breast , ovary, endometrium
- WT -1 and WT-2 gene-Wilm tumour

Read more on onco-supressor genes

Familial Retinoblastoma

- Retinoblastoma is a cancer of retina occurring in children.
- Transmitted as an autosomal dominant trait
- Both alleles of RB locus must be inactivated for the development of retinoblastoma.
- Children with familial retinoblastomas have an inherited absence in the retinoblastoma (Rb) gene on chromosome 13.
- Therefore another mutational loss will result in complete absence of this tumour suppressor gene.
- This results in the formation of bilateral malignant retinal tumour.


FAMILIAL
SPORADIC
Inherits one mutant copy
Inherits two normal copies
Mutation occurs in second copy
Mutation occurs in one copy
Mutation occurs in second copy in same cell
Total loss of gene function
Total loss of gene function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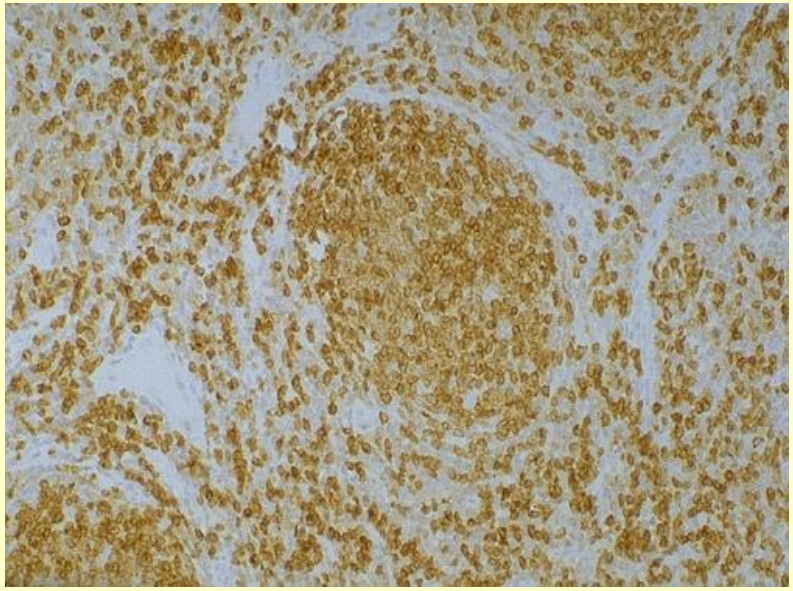
Genes that regulate apoptosis

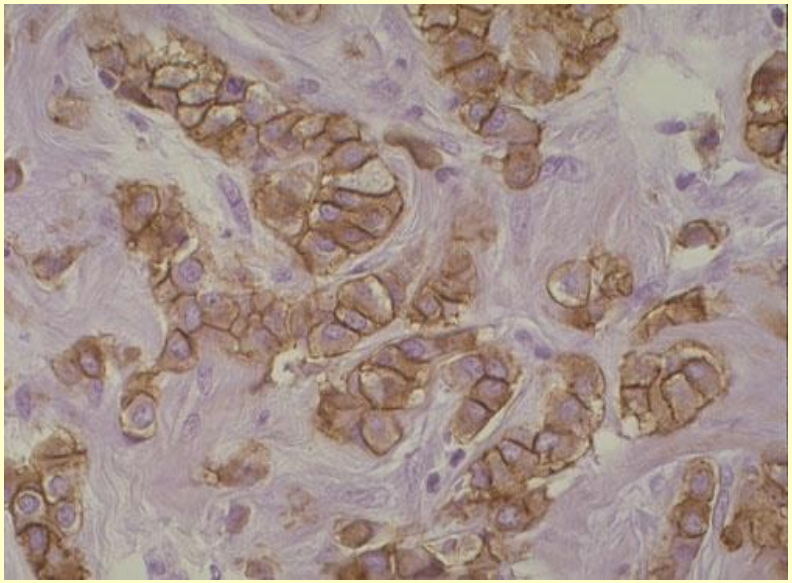
- Genes that regulates programmed cell death
- Inactivation of these genes causes tumours

- Example
  - *bcl* -2 gene inhibits apoptosis
  - over expression of *bcl* –2 gene prevents B lymphocytes from apoptosis and allow them to survive for long periods
  - leads to B lymphomas

Application of knowledge in carcinogenesis in tumour diagnosis



Bcl_2 oncogene expression by neoplastic lymphoid cells in a follicular lymphoma



ERB B2 oncogene expression by tumour cells in breast carcinoma

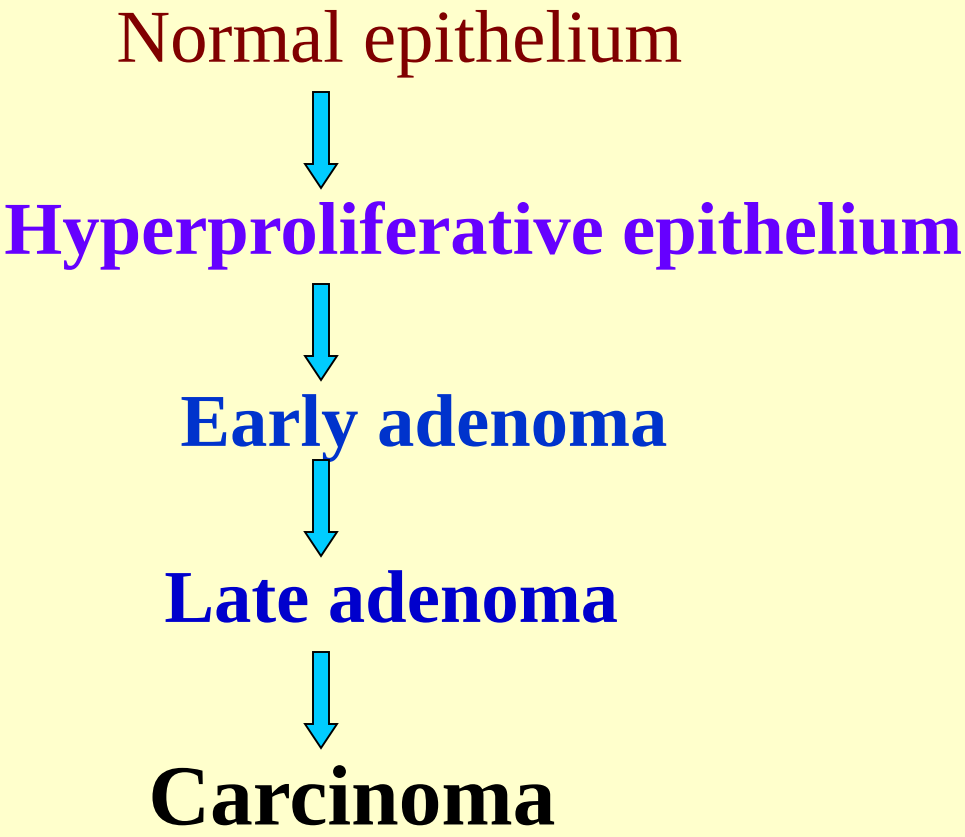
Carcinogenesis is a Multistep Process

- No single oncogene can produce a tumour

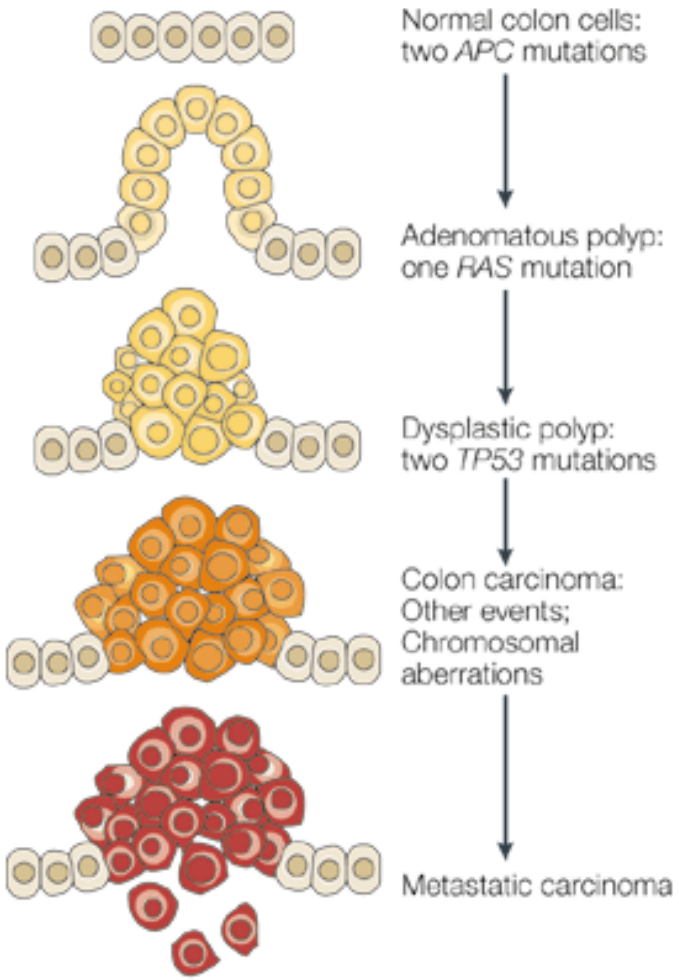
- Every human cancer shows multiple genetic alterations involving activation of several oncogenes and loss of more than 2 tumour suppressor genes

Carcinogenesis is a Multistep Process

- The best example is evolution of colorectal carcinoma through adenoma-carcinoma sequence



Evolution of colorectal carcinoma through adenoma-carcinoma sequence



summary

- Proto-oncogenes
- Oncogenes
- Tumour suppressor/onco-suppressor genes
- Genes that regulate apoptosis
- Defective DNA repair genes
- P53 gene
- Features of a transformed cell
- Application of this knowledge to clinical practice

Summary

- A non-lethal genetic damage
- Targeted on the proliferating sites of the genome
  - Growth promotion
  - Inactivation of growth inhibition
  - Inhibition of cell death
- Forms a transformed cell
- Clonal expansion
- Agents of cancer???????????

Reference

- Robbins
- Muir’s
  - Page 100 on14 th ed