Molecular Basis of Carcinogenesis

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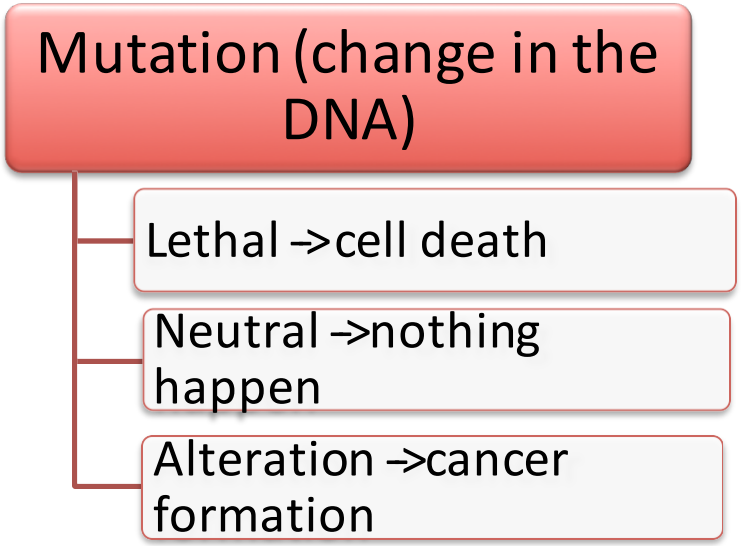
Outline

- Fundamental principle relating to cancer.
- Hallmark of cancer and target of genetic damage:
  - --Proto--oncogenes
  - –Tumor suppressor gene
  - –DNA repair gene
  - --Genesthat regulate apoptosis

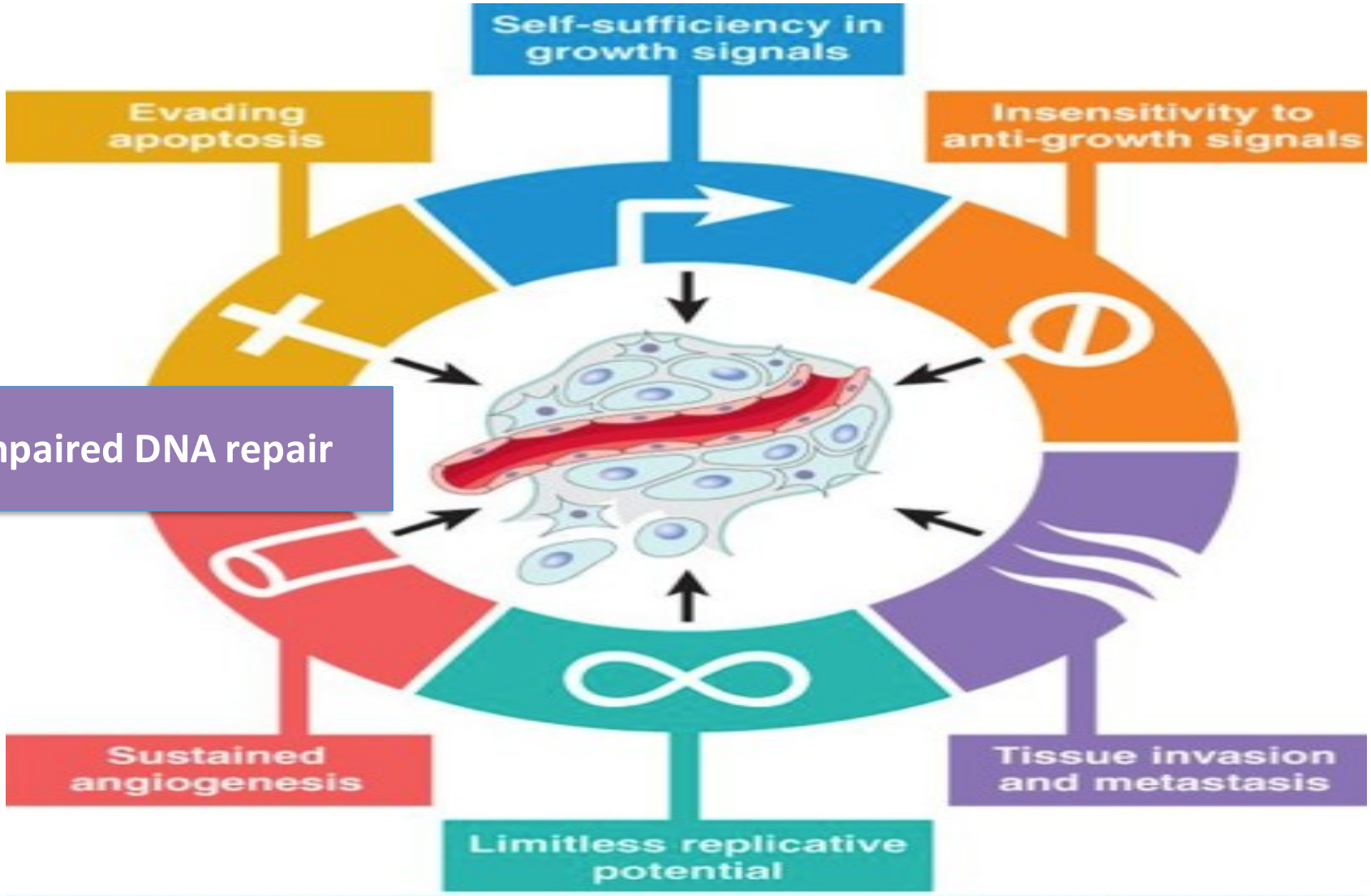
Fundamental principle

- Cancer: a malignant growth resulting from uncontrolled division of cells.



- Carcinogenesis: Non--lethal
- Monoclonality: arise from one cell

Hallmark of cancer



Impaired DNA repair

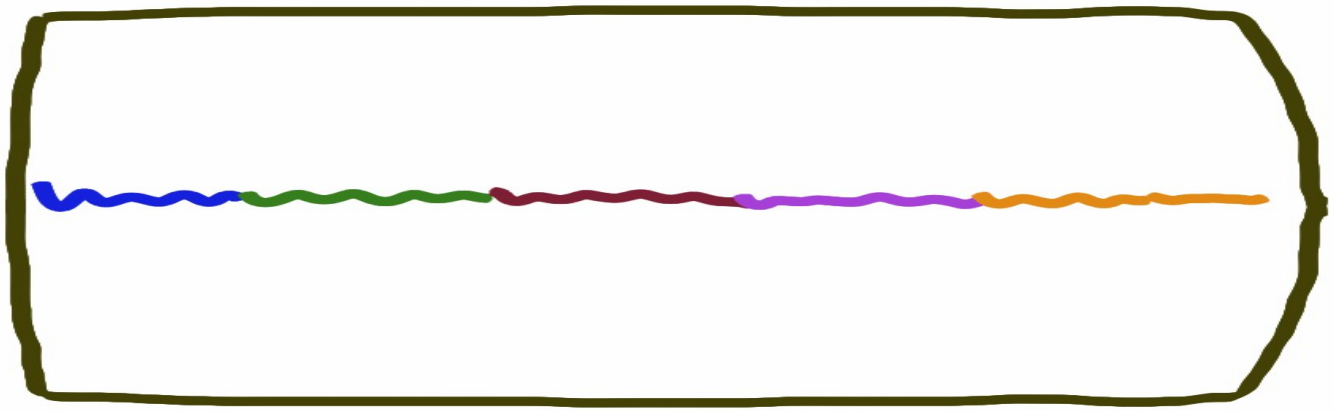
- Proto--oncogene: promote cell proliferation when there is a need.
  - **RADIATION**
  - **VIRUS**
  - **CHEMICALS**
  - **INHERETED**

MUTATION

- Oncogene: promote cell proliferation when there is **NO** need.

1) Self sufficiency in growth signals

Role of Proto--oncogene



Growth factor receptor

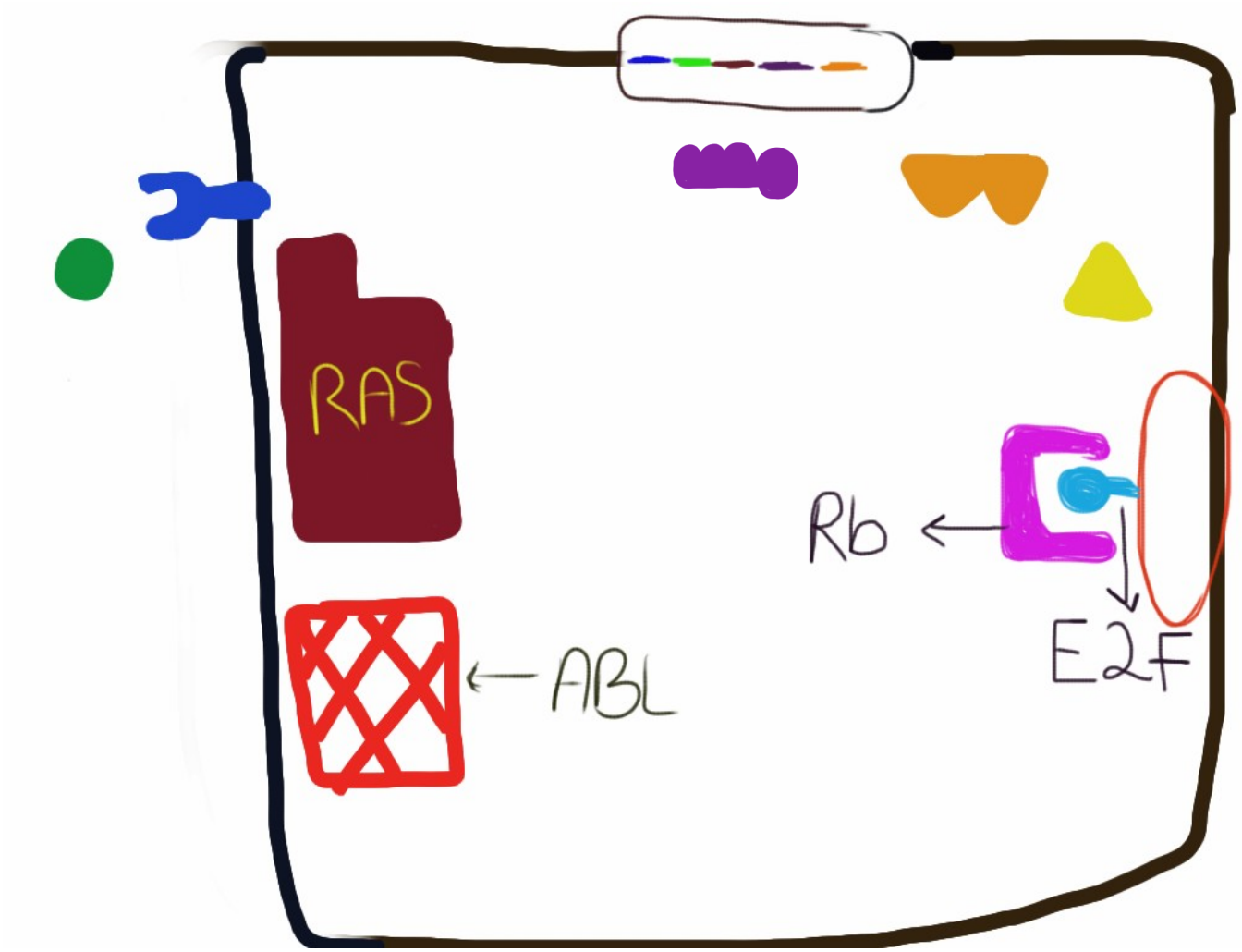
Growth factor

Transducer

Transcription factor

Cyclin

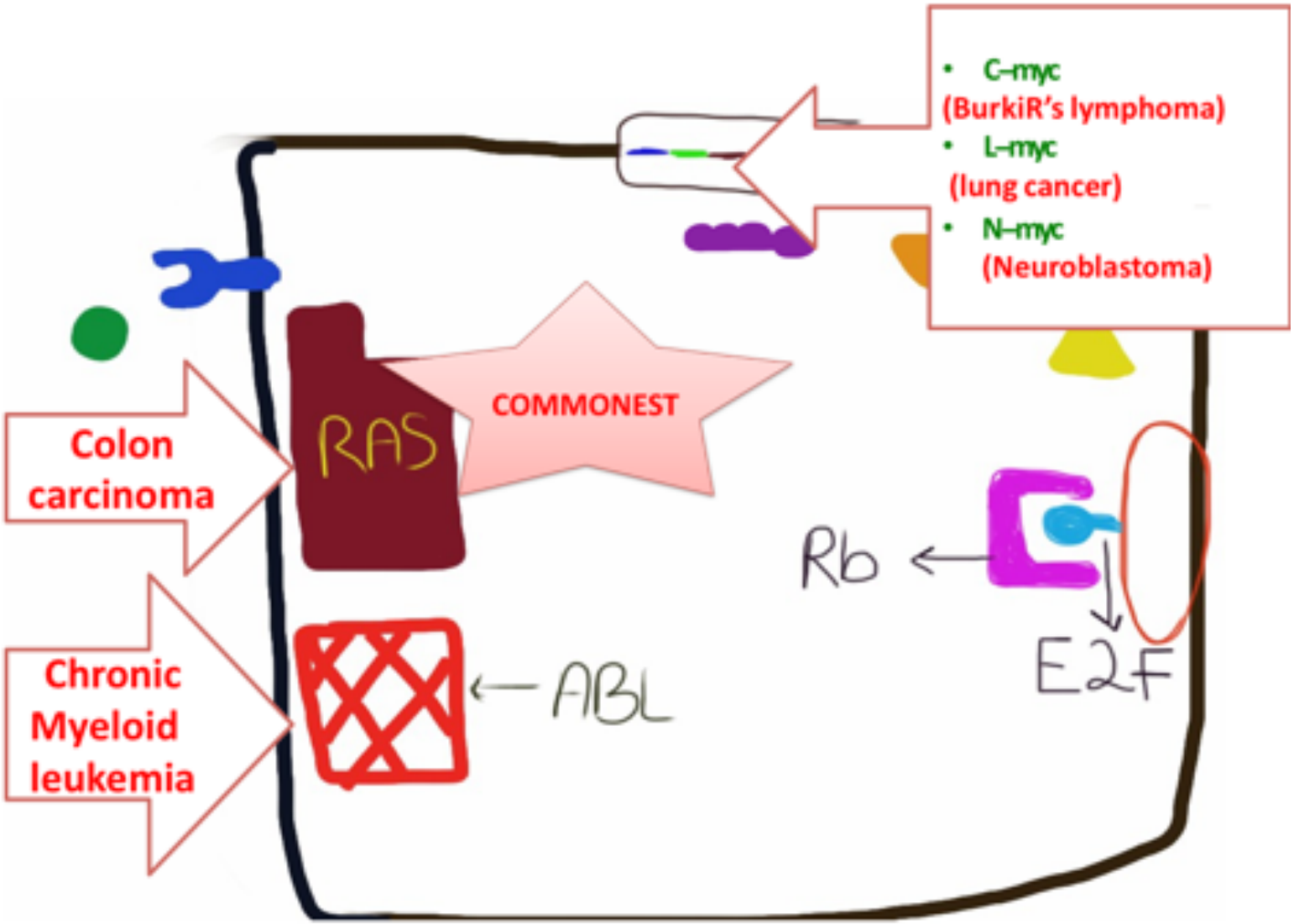
Cyclin dependent kinase (CDK)


RAS
Rb
E2F
ABL

Proto--oncogene/oncogene

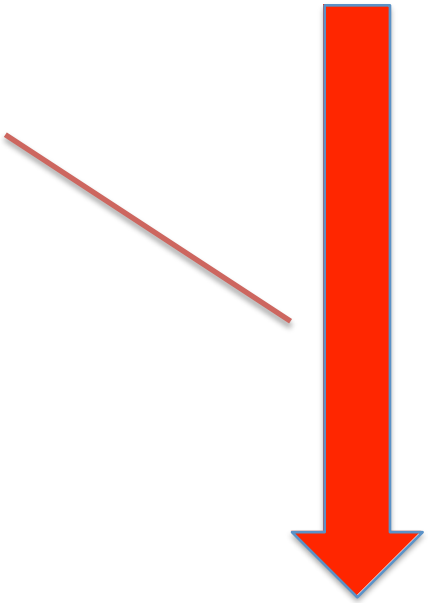
Type of Mutation	**Gain of function:** • **Point mutation** • **Gene amplification** • **Translocation**
Gene Expression of Damage	**Autosomal dominant (1 allele)**

Clinical correlates



- Tumor suppressor gene: inhibit cell proliferation act as a car break

  - **RADIATION**
  - **VIRUS**
  - **CHEMICALS**
  - **INHERETED**



MUTATION

Cell continue to proliferate

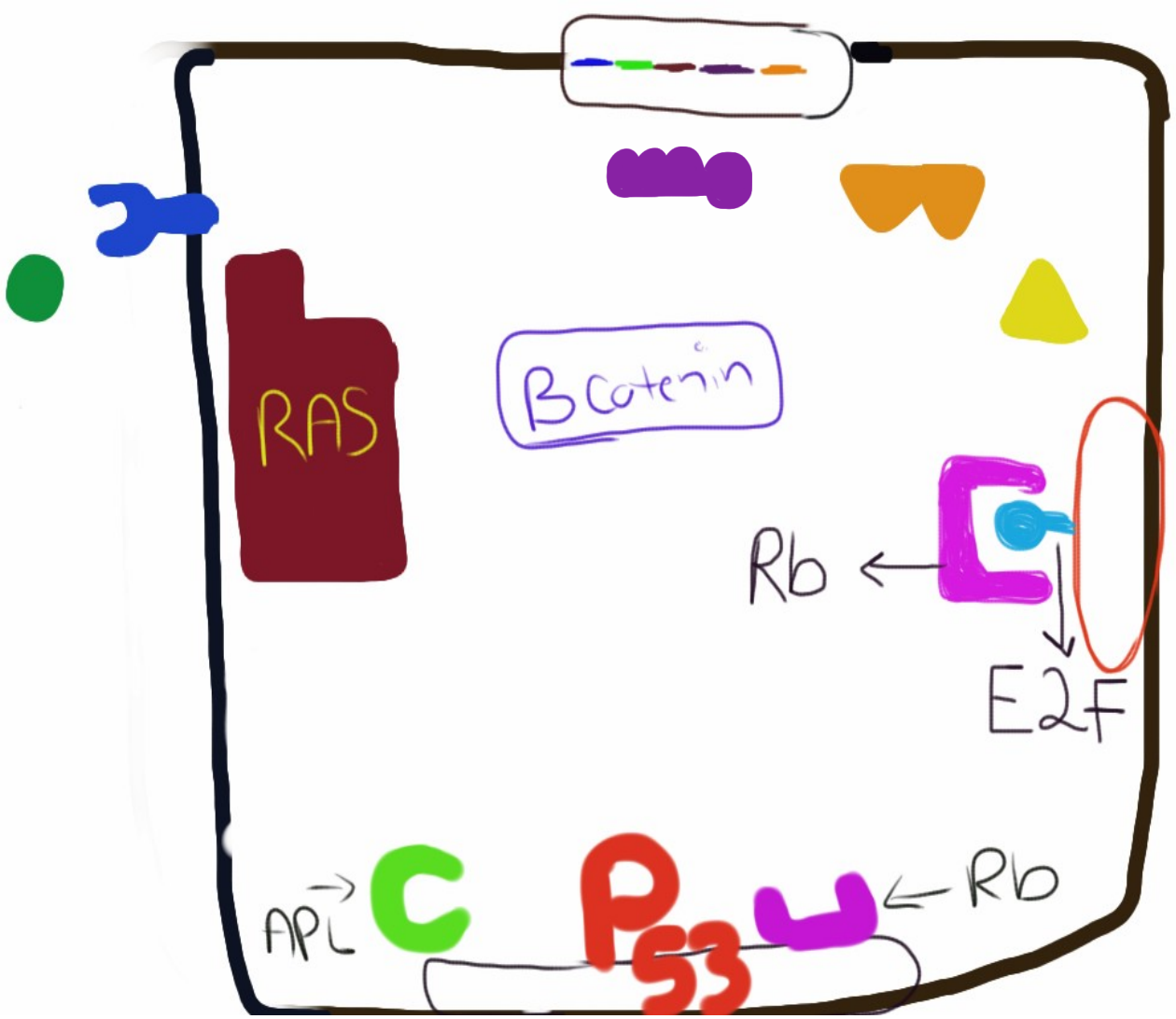
2) Insensitivity to growth inhibitory signals

Role of tumor suppressor gene

APC gene

P53 gene

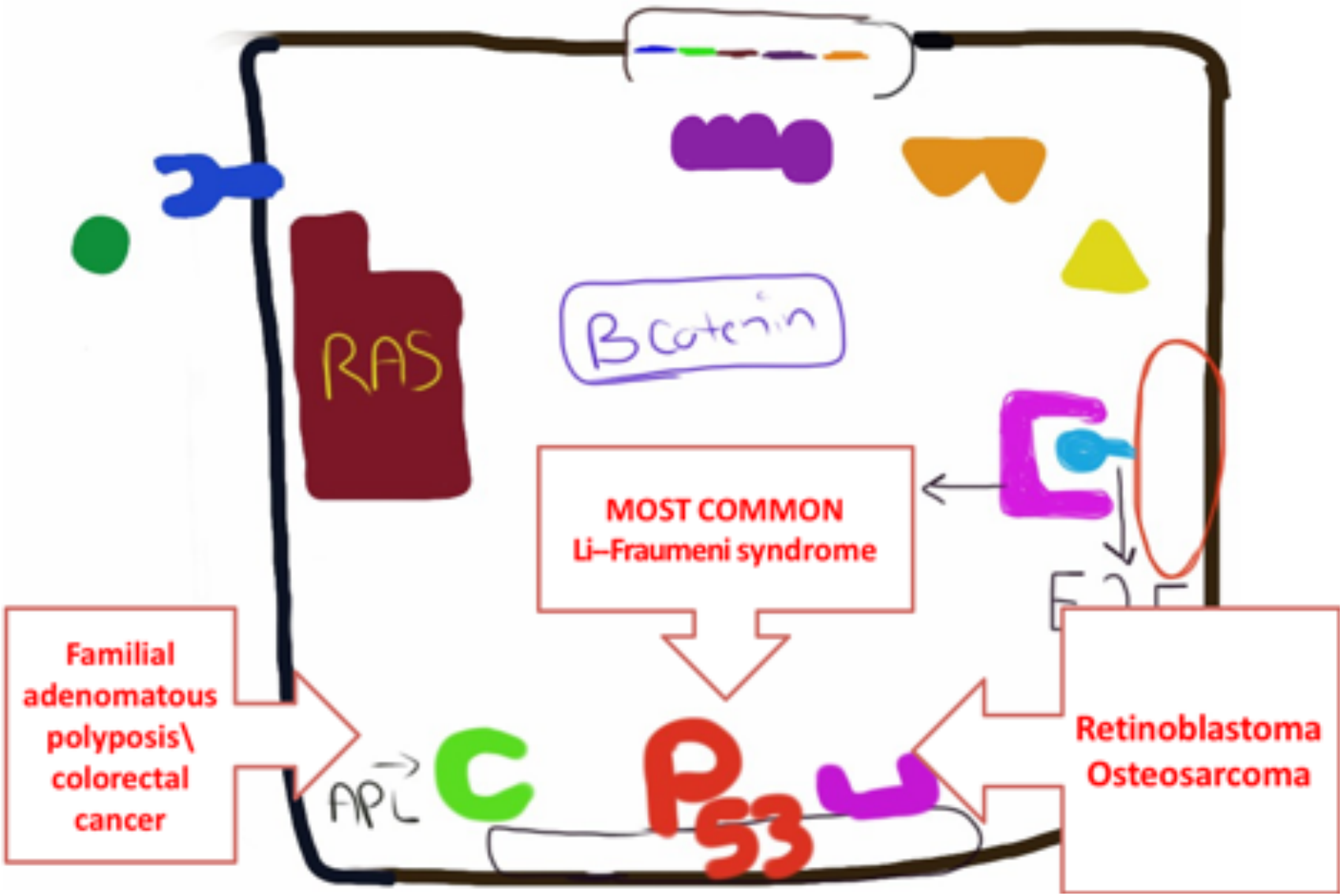
Retinoblastoma gene \ protein


RAS
BCatenin
Rb
E2F
APL
P53
Rb

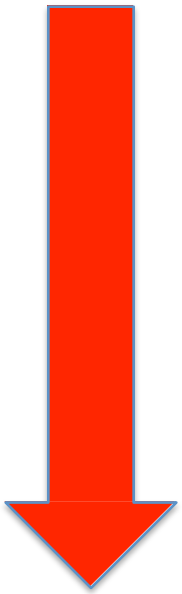
Tumor suppressor gene

Type of mutation	**Loss of function:** • Point mutation • Deletion (interstitial, chromosomal)
Gene Expression of Damage	**Autosomal Recessive (2 alleles)** • Inherited + somatic • Somatic + somatic

Clinical correlation



DNA repair gene: correction of damaged DNA



MUTATION

DNA damage and instability

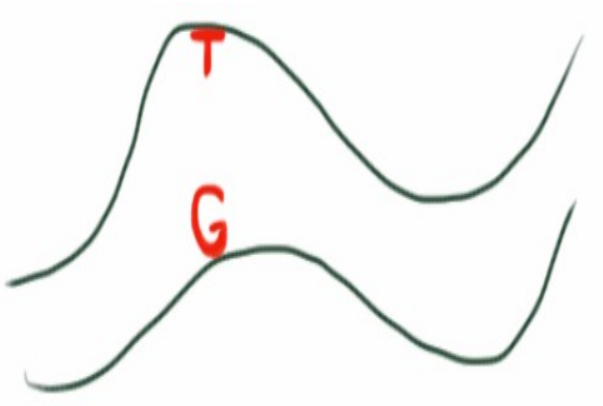
3) Impair DNA repair mechanism

DNA repair

Mismatch Repair System

Defect:

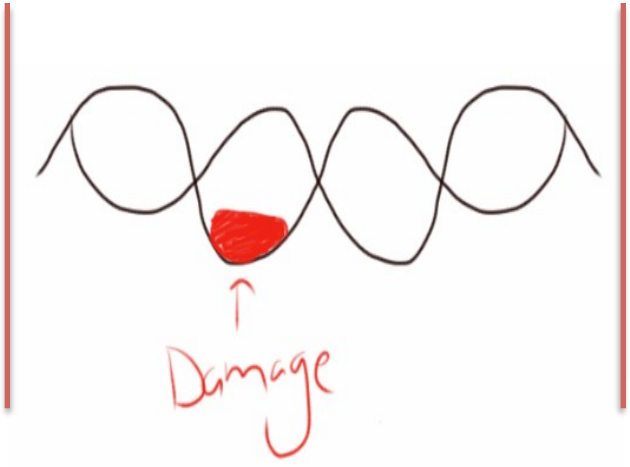
Hereditary Non Polyposis Colon Cancer (HNPCC)



Nucleotide Excision Repair system

Defect:

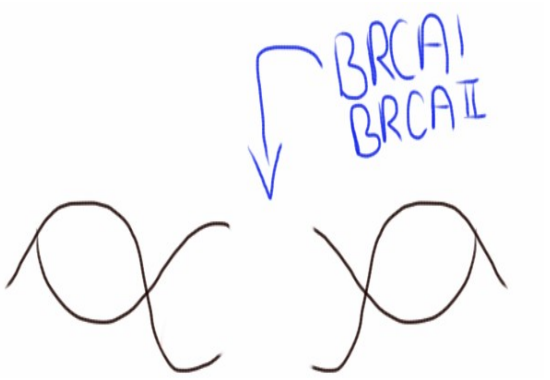
Xeroderma Pigmentosum



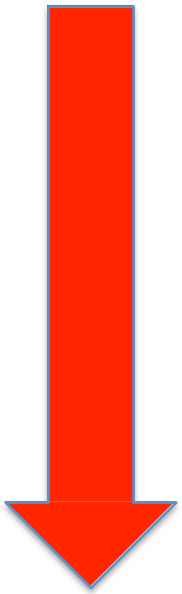
Homlogus Recombination System

Defect:

BRCA I&II (breast and ovarian cancer)



Apoptosis: Programmed cell death if DNA damage beyond the repair

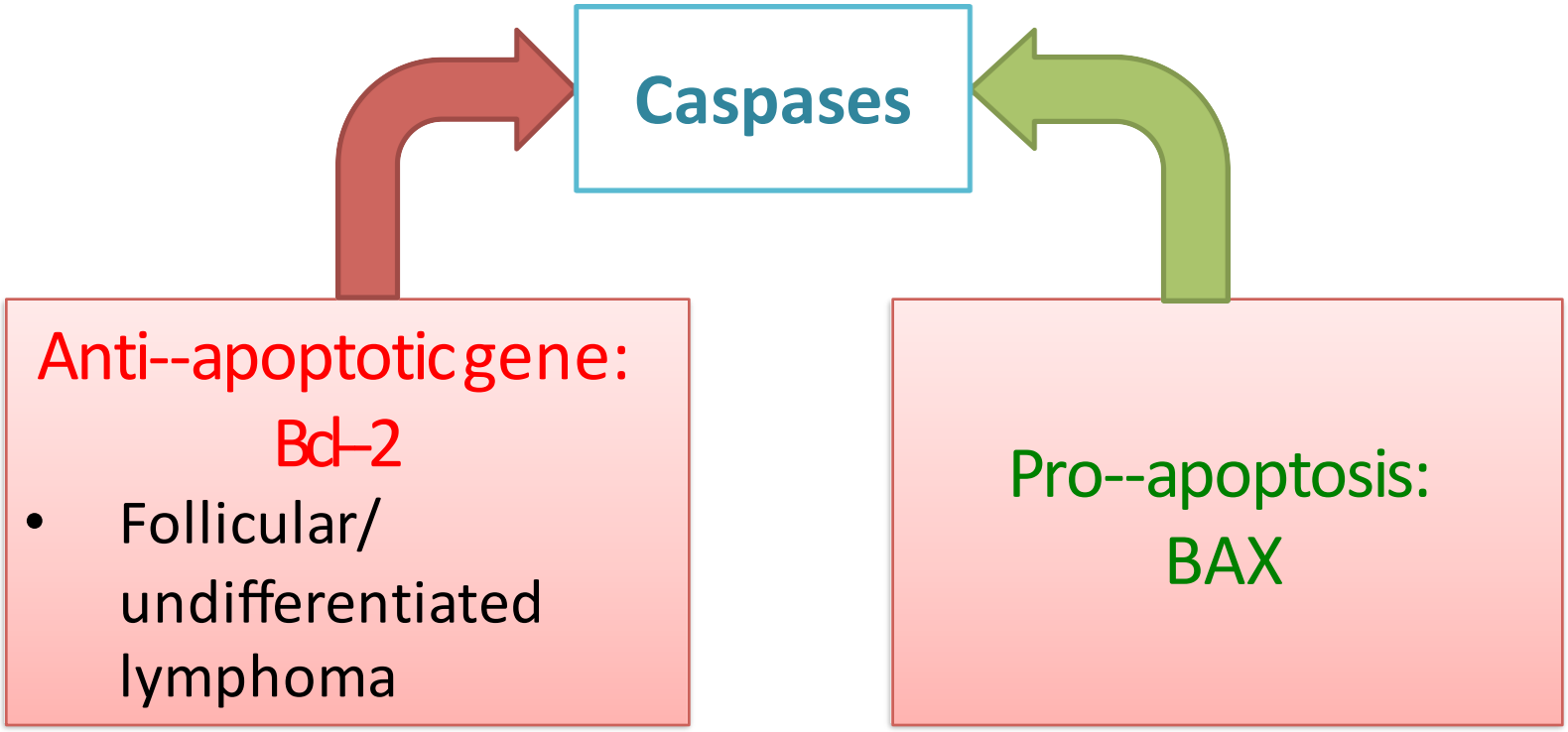


MUTATION

No apoptosis = cell lives for long time

4) Evading Apoptosis

Apoptosis



- BCL2 + BAX = Cell live
- BCL2 + BAX = Apoptosis

- 5) Unlimited replication capacity Telomerase
- 6) Angiogenesis VEGF, PDGF
- 7) Invasion and metastasis

Now Malignant Cell has developed

Reference:

- Robbins Basic pathology.
- Dr Najeeb Neoplasia(cancer and gene) lecture.
- Kaplan pathology lecture note.
- First aid USMLE step 1.
- Davidson's Principles and Practice of Medicine.
- Pathology made ridiculously simple.
- https://www.youtube.com/watch?v=74c9--kOrmgA – http://www.merckmanuals.com/professional/hematology--and--oncology/overview--of--cancer/cellular--and--molecular--basis--of--cancer
- http://www.ncbi.nlm.nih.gov/pubmed/15077154
- http://www.ncbi.nlm.nih.gov/pubmed/11852992

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