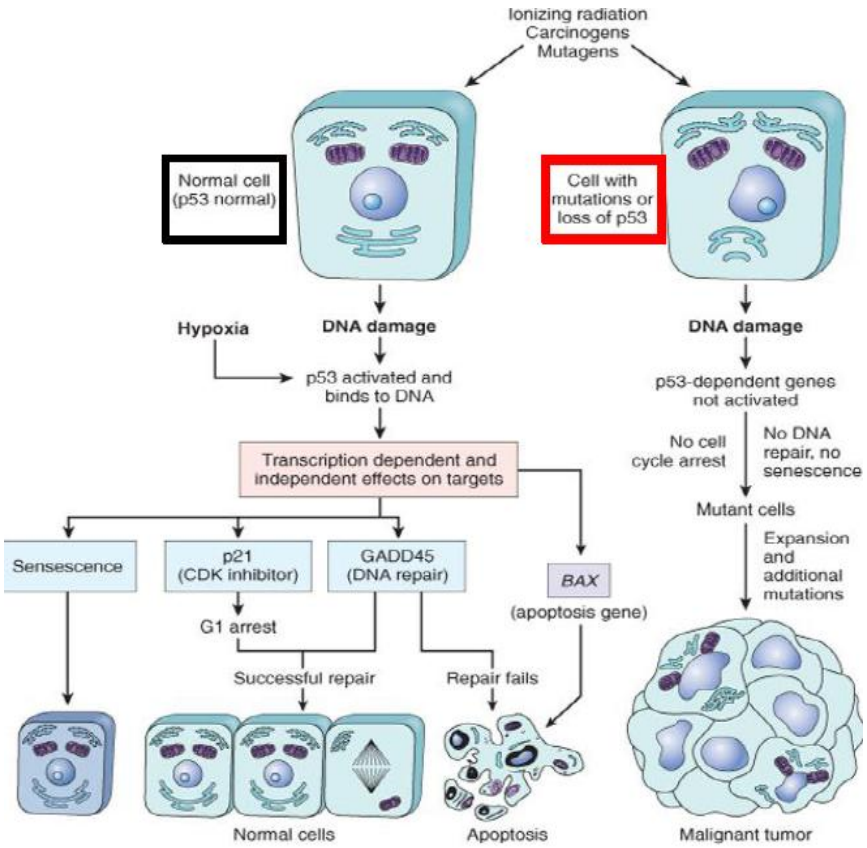
Unit I – Problem 9 – Pathology: Molecular Basis of Cancer

- **Unregulated cell growth:**
  - Accumulated somatic mutations → affect genes, cell growth and cell differentiation.
- **Malignant cells are monoclonal which means that they are all derived from a single precursor cell.**
- **Cell proliferation:**
  - A growth factor will bind to a receptor on the cell → activating a second messenger system → which will further activates transcription factors in the nucleus.
  - In malignancy, one of the steps mentioned above will be affected or will go wrong resulting in uncontrolled proliferation of cells.
  - Malignant cells have what is known as self-sufficiency (for example, they have their own blood supply which allows them to grow).
- **Apoptosis:**
  - It is also known as programmed cell death which aims at maintain the number of cells in the body.
  - Apoptosis is inactivated in malignancy!
  - Apoptosis is mediated by the gene: (BAX).
- **Targets:**
  - **Proto-oncogens**: they stimulate proliferation of cells. Examples include: MYC and RAS. Notice that oncogens are altered proto-oncogens.
  - **Tumor suppressor genes**: they inhibit cell proliferation. Examples include retinoblastoma gene (Rb) and p53.
  - **DNA-repair genes**: they prevent occurrence of mutations.
- **Changes in physiology of cells during malignancy:**
  - **Autocrine growth**: no external signals are needed by the cell to progress through the cell cycle and proliferate.
  - **Cells have no response to growth-inhibitors.**
  - **Cells have defects in DNA-repair.**
  - **There is no apoptosis (cells do not die!).**
  - **Malignant cells are characterized by invasiveness and metastasis.**
- **Malignant cell proliferation:**
  - **Growth signals:**
    - ✓ Paracrine: signals coming from other cells.
    - ✓ Endocrine: represented by hormones.
  - **Autocrine growth**: such as in glioblastoma.
  - **Overexpression of growth factor receptors:**
    - ✓ ERB1 (in lungs).
    - ✓ ERB2 (in breasts).
  - **Protein kinases:**
    - ✓ RAS: it is a G-protein (combines with GTP and GDP).
    - ✓ ABL: it has tyrosine kinase activity.
- **Cell cycle checkpoints:**

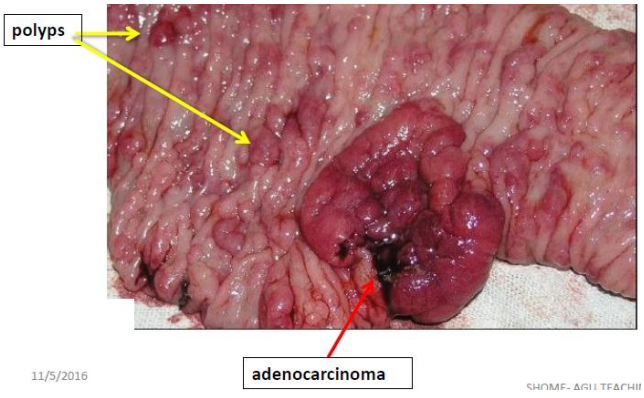
	G1 to S phase	S phase	G2 to M phase
Cyclins	D	A	B
CDKs	4 and 6	1 and 2	1
CDK-inhibitors	15, 16, 18 and 19	21, 27 and 57	21, 27 and 57

- **One of the most important checkpoints is (Rb) → between G1 and S phases.**

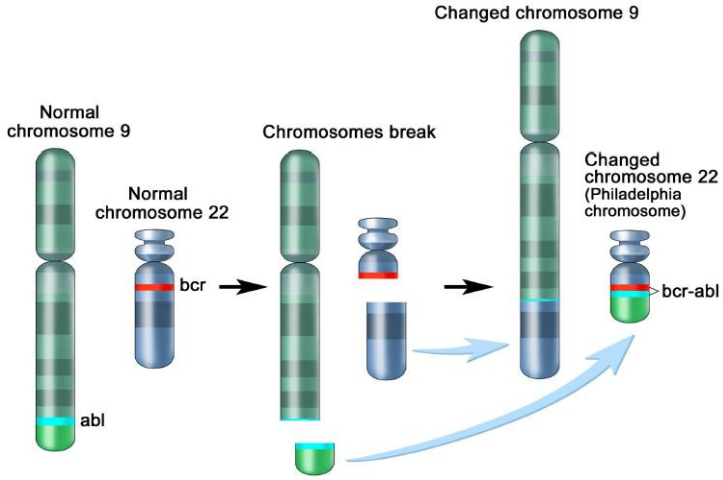
- **RAS:**
  - It is a mutated proto-oncogen.
  - Responsible for colon cancer and pancreatic cancer.
- **MYC**:
  - It is present within the nucleus of the cell.
  - Activated genes which promote cell cycling are: MYC, MYB, JUN and FOS.
  - MYC is amplified/overexpressed in lungs, colon and breasts.
- **Retinoblastoma (Rb) gene:**
  - It is a governor.
  - It maintains control on proliferation.
- **p53:**
  - It is a guardian which sense genomic damage.
  - **Notice that genomic damage results in:**
    - ✓ Senescence (permanent: cells will not divide anymore).
    - ✓ DNA-repair (temporarily).
    - ✓ Apoptosis (programmed cell death).



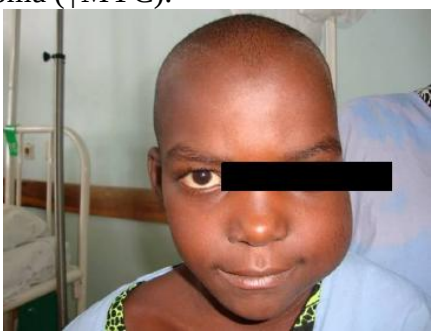
- **APC (Adenomatous Polyposis Coli):**
  - It destroys β-catenin so there are no more proliferation signals to the nucleus.
  - Proliferation initially begins as polyps in the colon which will become malignant later.



- **Activation by mutation:**
  - **Translocation**: from one chromosome to another
    - ✓ t(9,22): Philadelphia leukemia (ABL-BCR).



    - ✓ t(8,14): burkitt lymphoma (↑MYC).



    - ✓ t(14,18): follicular lymphoma.
  - **Amplification:**
    - ✓ N-MYC (neural tumors).
    - ✓ Increase in the number of copies (double minutes) with homogenous-staining regions.
- **microRNAs:**
  - They are single-stranded, containing 22 nucleotides and repressing normal RNAs in the cell.
  - They are reduced with the presence of oncogens → thus resulting in overexpression of oncogens themselves.
  - They are over-activated with the presence of tumor suppressor genes → thus resulting in reduced tumor suppression genes.