HARRISON

EDITION 22nd

ONCOLOGY

Oncology

Molecular Biology Of Cancer Part 1	Completed
Molecular Biology Of Cancer Part 2	Completed
Cancer Genetics	Completed
Cancer Prevention And Screening	Completed
Principles Of Cancer Treatment Part 1	Completed
Principles Of Cancer Treatment Part 2	Completed
Oncological Emergencies	Completed
Cancer Of Skin	Completed
Head And Neck Cancers	Completed
Breast Cancer	Completed
Lower GI Cancers	Completed
Lung Cancer	Completed
Pancreatic Cancer	Completed

Upper GI Tract Tumors

Completed

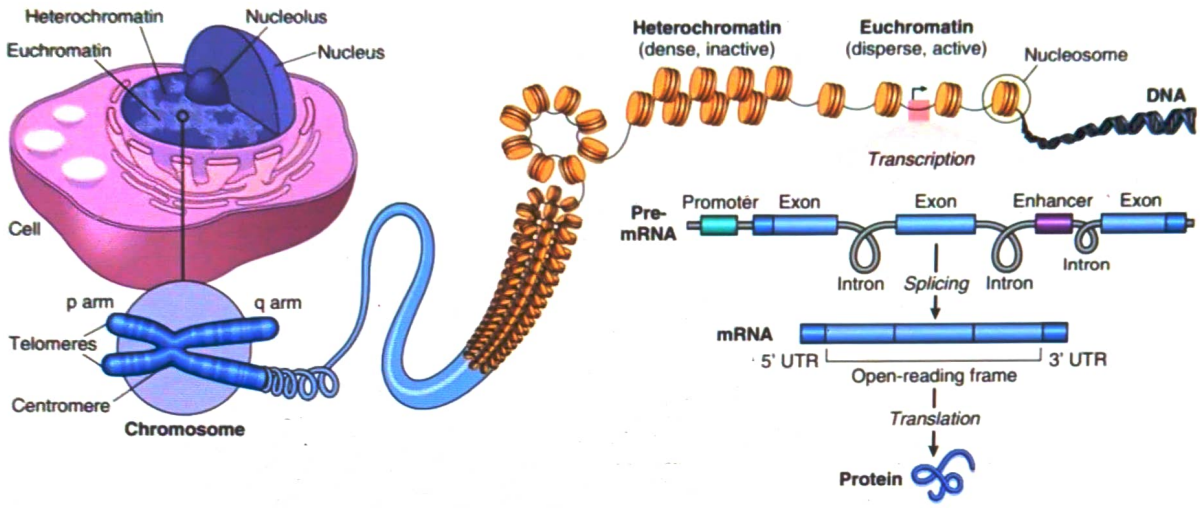
Sub topics

- Introduction and Epigentics
- Cellular activation and Cell cycle
- Molecular basis of cancer
- Hall marks of cancer
  - Hall mark1-Sustaining Proliferative Signalling
  - Hall mark2- Evading Growth Suppressors
  - Hall mark3- Altered Cellular Metabolism- Warburg effect
  - Hall mark4-Evasion of Cell Death
  - Hall mark5-Limitless Replicative Potential (Immortality
  - Hall mark6- Angiogenesis
  - Hall mark7-Invasion and Metastasis
  - Hall mark8-Evading immune destruction
- Cancer enablers-Genomic instability and Chronic infalmmation

Introduction and Epigentics

- The human genome contains about 3.2 billion DNA base pairs but only 20,000 protein-encoding genes approximately-1.5% of the genome
- Noncoding DNA-98.5% (The Dark Matter)(Non-Protein Coding DNA)
  - Promoter and enhancer regions that bind protein transcription factors
  - Binding sites for proteins
  - Noncoding regulatory RNAs—micro-RNAs and long noncoding RNAs
  - Mobile genetic elements -"jumping genes" (Eg: transposans)
  - telomeres and centromeres

Epigenetics

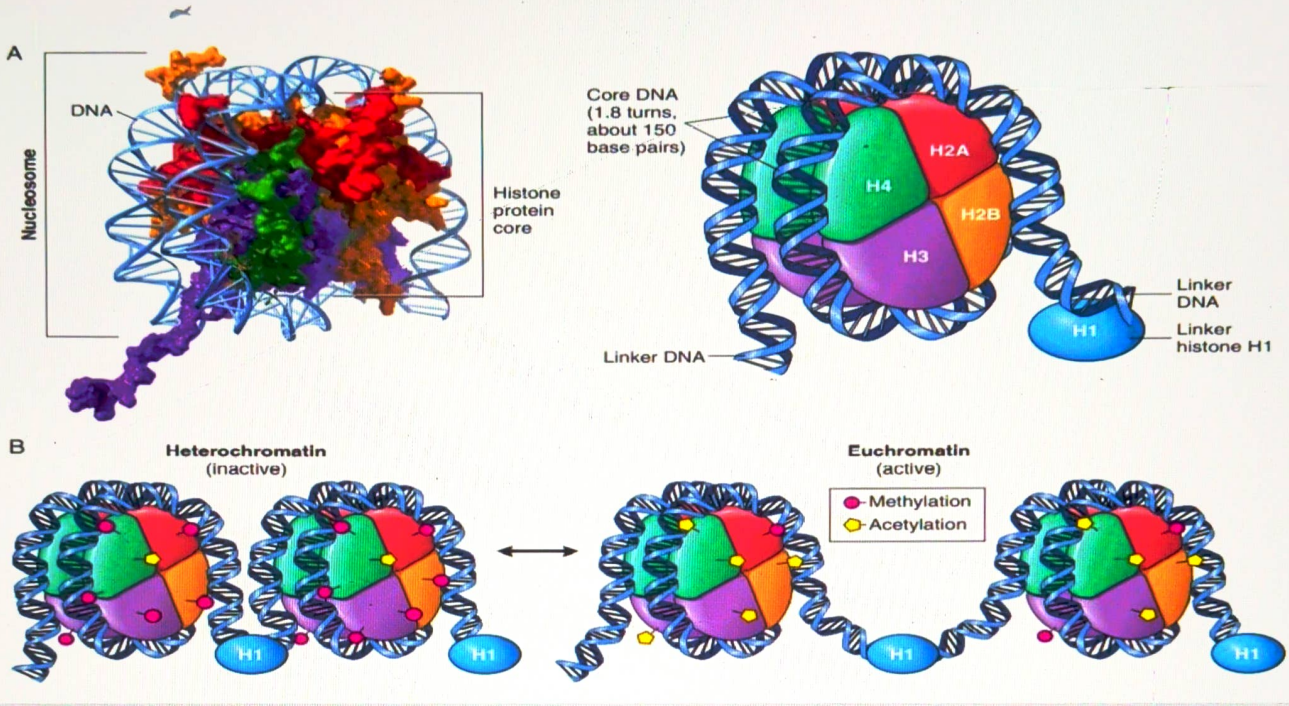


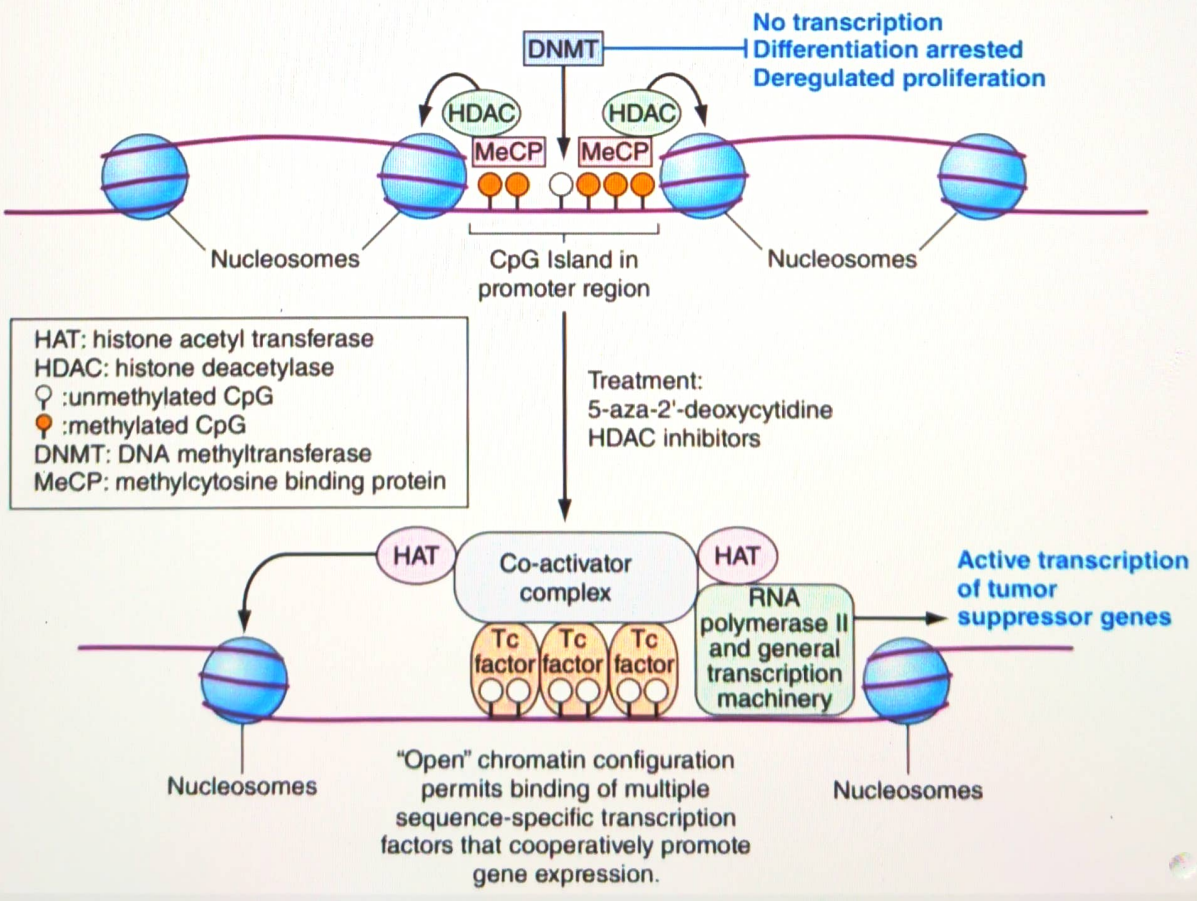
Epigenetics -modification of gene expression

- Chromatin Organization
- DNA Methylation- Regulated by Methyltranferases and Demethylating enzymes and binding proteins.
- Histone Modification- Chromatin writers, readers and erasers

Histone Phosphorylation	Serine	Increase or Decrease
Histone Methylation	Lysine and Arginine	Increase or decrease
Histone Acetylation	Lysine	Increase

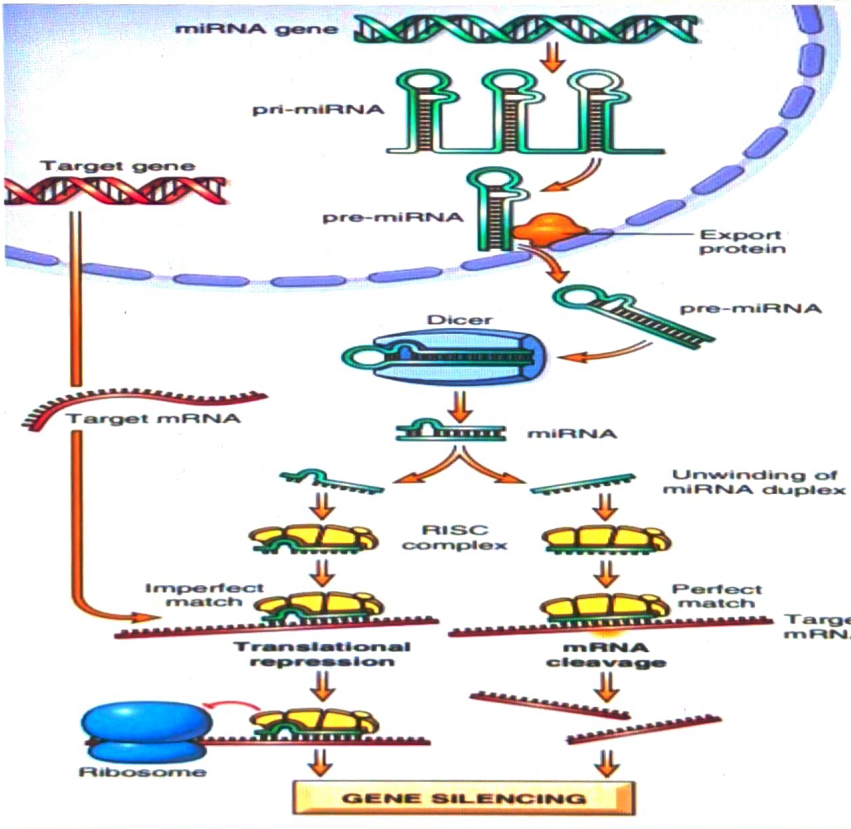
Histone Organisation





Epigenetics -modification of gene expression

- **Noncoding RNAs: MicroRNAs and Long noncoding RNAs**
- Micro-RNAs (miRNAs) (22 nucleotides on average). Posttranscriptional silencing of gene expression by miRNA is in all eukaryotes.
- The human genome contains almost 6000 miRNA genes(protein-coding genes-20000).
- Individual miRNAs regulates multiple protein-coding genes.



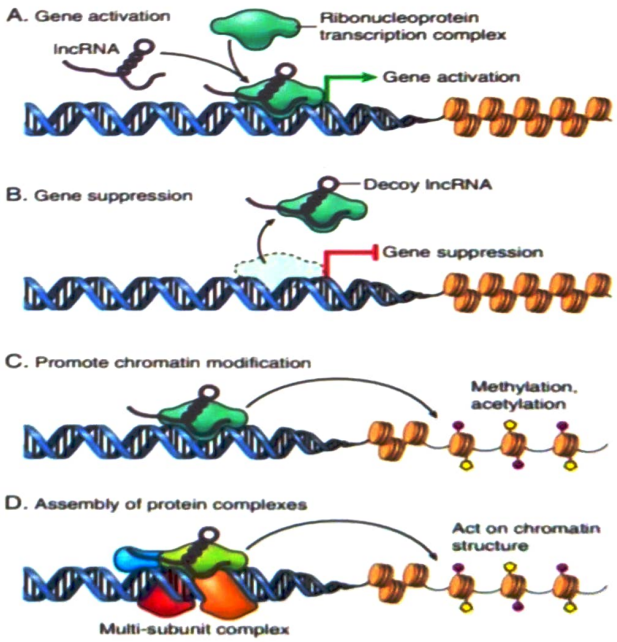
RISC: RNA-induced silencing complex

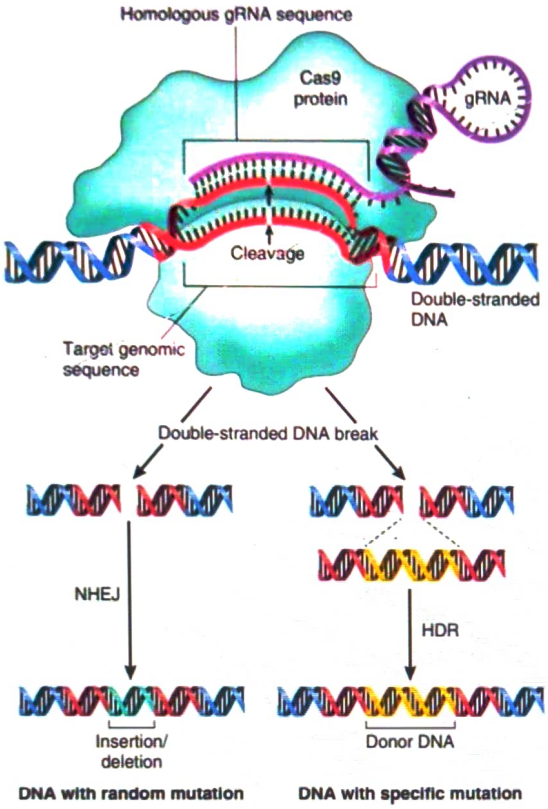
Epigenetics -modification of gene expression

- Small interfering RNAs (siRNAs) are short Synthetic RNA sequences analogous to mi RNA can be introduced into cells.
- These serve as substrates for Dicer and interact with the RISC complex.
- Used to target specific mRNA species are therefore powerful laboratory tools to study gene function (so-called knockdown technology); they also are promising as therapeutic agents to silence pathogenic genes.

Epigenetics -modification of gene expression

- Long noncoding RNA (lncRNA). The human genome also contains a very large number of lncRNAs—at least 30,000





- **Bacterial origin**: defense against viral components
- gRNA (constant + variable ~20 bases) & Cas9 nuclease (DNA-cutting enzyme)
- **Process**:gRNA binds Cas9 -Variable region pairs with target DNA-Cas9 introduces double-strand DNA break (DSB)
- **DNA Repair & Applications**
- **Repair pathways**:
  - **NHEJ** → error-prone, causes indels → gene disruption
  - **HDR** → uses donor DNA → precise gene correction or insertion
- **Applications**:
  - Correct inherited genetic defects
  - Create pathogenic mutations for study
  - Gene editing in crops, microbes, animals
  - Basis for potential therapeutic strategies

Epigenetic Changes in Cancer

- **p16Ink4a** promoter methylation → ↑ CDK4/Cyclin D → ↓ pRb function → Uncontrolled cell cycle
- **Gene silencing by methylation:**
  - **VHL** → Renal cancer
  - **BRCA1** → Breast cancer
  - **STK11** → Colon cancer
- **MSH2 inactivation:**
  - Caused by EPCAM (TACSTD1) 3'-end deletion
  - Accounts for **20-25% of MSH2 cases** and **1-6% of LS cases**

- **t(15;17) in APL** → PML-RARα fusion binds retinoic acid response elements → recruits **HDACs** → blocks gene expression
- **HDAC inhibitors (FDA-approved):**
  - **Vorinostat, Romidepsin** → Cutaneous T-cell lymphoma
  - **Romidepsin, Belinostat** → Peripheral T-cell lymphoma
  - **Panobinostat** → Multiple myeloma

- **DNA Demethylating Agents**
- **5-aza-2-deoxycytidine (Decitabine)** → Restores expression of silenced tumor suppressor genes
- **Azacytidine & Decitabine** → Approved for **Myelodysplastic Syndrome (MDS)** treatment

Cellular activation and Cell cycle

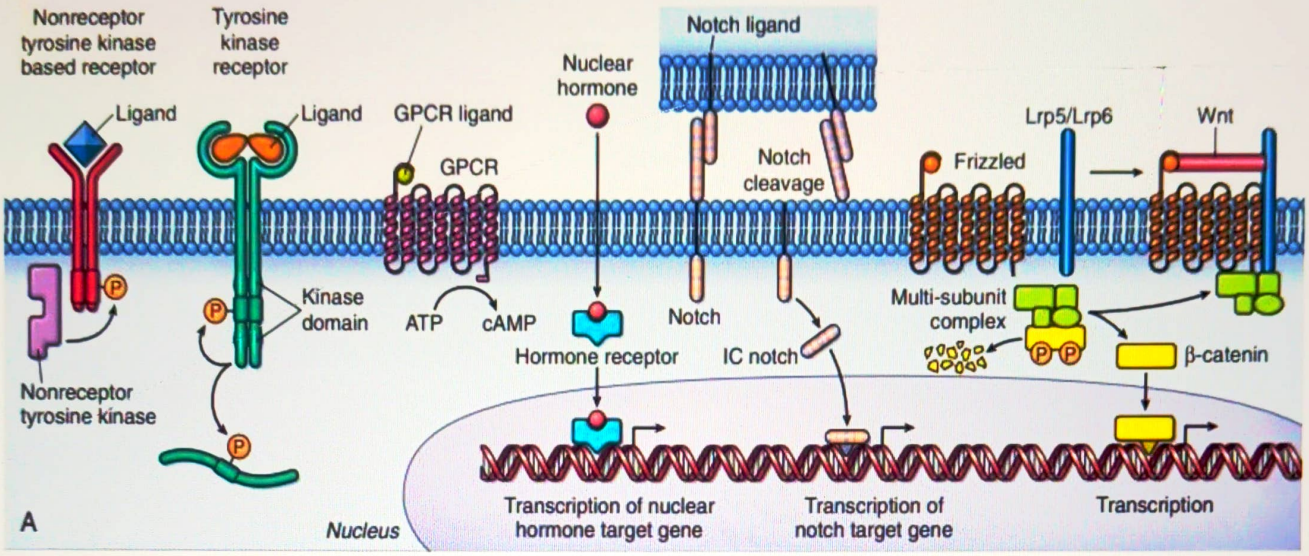
CELLULAR ACTIVATION

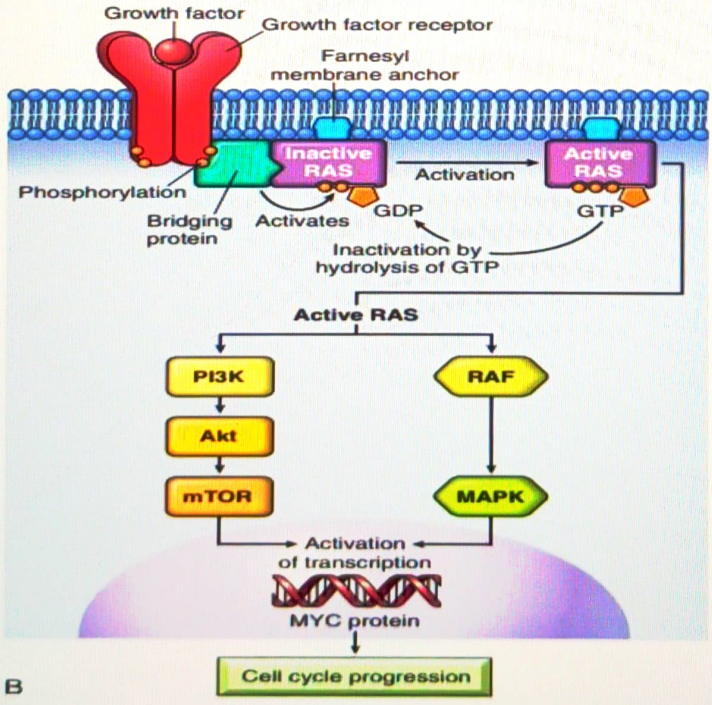
Growth Factor	Sources	Functions
Epidermal growth factor (EGF)	Activated macrophages, salivary glands, keratinocytes, and many other cells	Mitogenic for keratinocytes and fibroblasts; stimulates keratinocyte migration; stimulates formation of granulation tissue
Transforming growth factor-α (TGF-α)	Activated macrophages, keratinocytes, many other cell types	Stimulates proliferation of hepatocytes and many other epithelial cells
Hepatocyte growth factor (HGF) (scatter factor)	Fibroblasts, stromal cells in the liver, endothelial cells	Enhances proliferation of hepatocytes and other epithelial cells; increases cell motility
Vascular endothelial growth factor (VEGF)	Mesenchymal cells	Stimulates proliferation of endothelial cells; increases vascular permeability
Platelet-derived growth factor (PDGF)	Platelets, macrophages, endothelial cells, smooth muscle cells, keratinocytes	Chemotactic for neutrophils, macrophages, fibroblasts, and smooth muscle cells; activates and stimulates proliferation of fibroblasts, endothelial, and other cells; stimulates ECM protein synthesis
Fibroblast growth factors (FGFs), including acidic (FGF-1) and basic (FGF-2)	Macrophages, mast cells, endothelial cells, many other cell types	Chemotactic and mitogenic for fibroblasts; stimulates angiogenesis and ECM protein synthesis
Transforming growth factor-β (TGF-β)	Platelets, T lymphocytes, macrophages, endothelial cells, keratinocytes, smooth muscle cells, fibroblasts	Chemotactic for leukocytes and fibroblasts; stimulates ECM protein synthesis; suppresses acute inflammation
Keratinocyte growth factor (KGF) (i.e., FGF-7)	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation

ECM, Extracellular membrane.

CELLULAR ACTIVATION

- Cell signaling pathways- autocrine, paracrine, endocrine and synaptic signaling.
- Always via receptor- Intracellular or Extracellular
  - Intracellular – Steroid hormones and Vitamin D
  - Cell surface receptors-

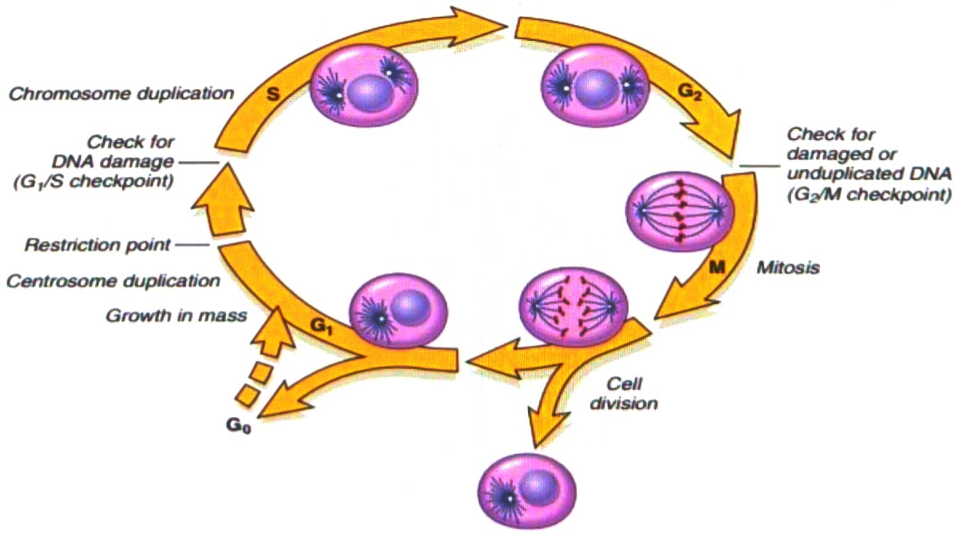

Nonreceptor tyrosine kinase based receptor
Tyrosine kinase receptor
Notch ligand
Nuclear hormone
Ligand
Ligand
GPCR ligand
GPCR
Notch cleavage
Lrp5/Lrp6
Wnt
Frizzled
Kinase domain
ATP
cAMP
Notch
Multi-subunit complex
Hormone receptor
IC notch
β-catenin
Nonreceptor tyrosine kinase
Transcription of nuclear hormone target gene
Transcription of notch target gene
Transcription
A
Nucleus


Growth factor
Growth factor receptor
Farnesyl membrane anchor
Inactive RAS
Activation
Active RAS
Phosphorylation
Bridging protein
Activates
GDP
GTP
Inactivation by hydrolysis of GTP
Active RAS
PI3K
RAF
Akt
mTOR
MAPK
Activation of transcription
MYC protein
Cell cycle progression
B

CELLULAR ACTIVATION

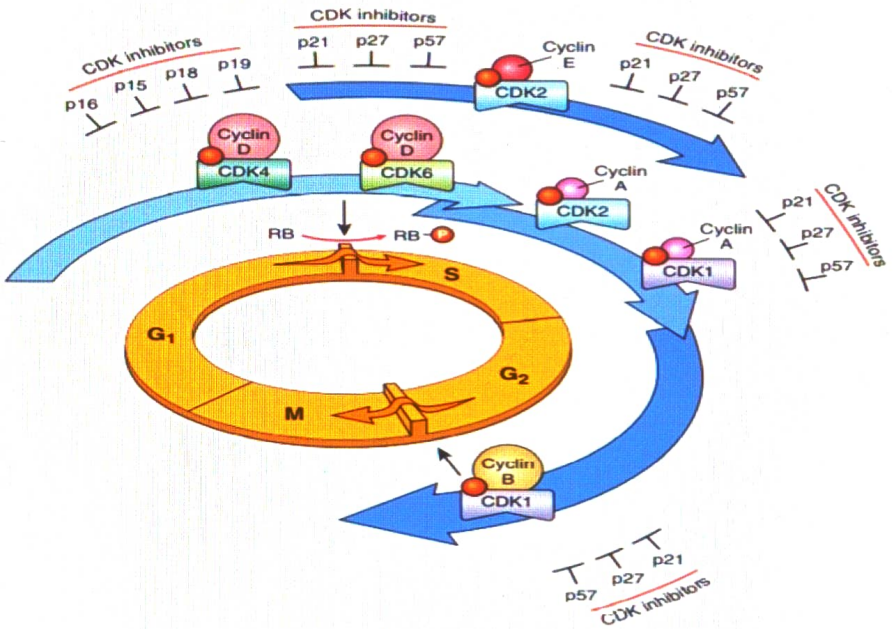
- Transcription Factors-Most signal transduction pathways ultimately influence cellular function by modulating gene transcription through the activation and nuclear localization of transcription factor
- Growth promoting -MYC and JUN
- Growth arrest -p53

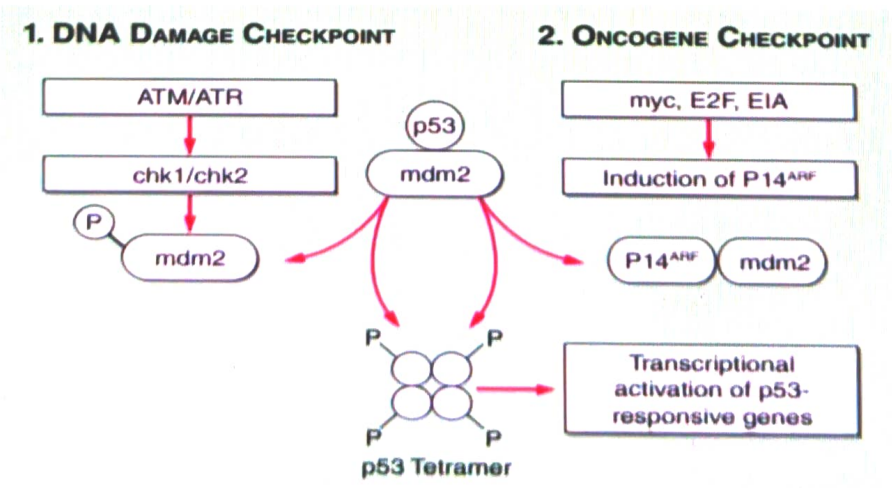
Cell Cycle



Cell Cycle

- Cyclins
- CDK- Cyclin dependent kinases
- CDKI- Cyclin dependent kinase inhibitors
  - One family of CDKIs—composed of three proteins -p21 (CDKN1A), p27 (CDKN1B), and p57 (CDKN1C)— broadly inhibits multiple CDKs
  - Another family of CDKIs has selective effects on cyclin CDK4 and cyclin CDK6; p15 (CDKN2B), p16 (CDKN2A), p18 (CDKN2C), and p19 (CDKN2D)





Question:
Which statement accurately describes the role of the retinoblastoma protein (Rb) and the G1 checkpoint in the context of cancer cell cycle regulation?

- **Options:**
- A. Rb protein is continuously active in cancer cells, preventing the progression from the G1 to the S phase irrespective of DNA damage.
- B. In the G1 phase, Rb protein acts as a checkpoint by halting the cell cycle until the cell is ready for DNA replication, and defects in this checkpoint are rare in cancer.
- C. The phosphorylation of Rb leads to its inactivation, releasing E2F/DP1 for S-phase progression, and nearly every cancer has defects in the G1 checkpoint, allowing progression despite DNA abnormalities.
- D. Rb protein's role in the G1 checkpoint is to enhance the expression of genes required for S-phase progression without assessing the cell's readiness for DNA replication.

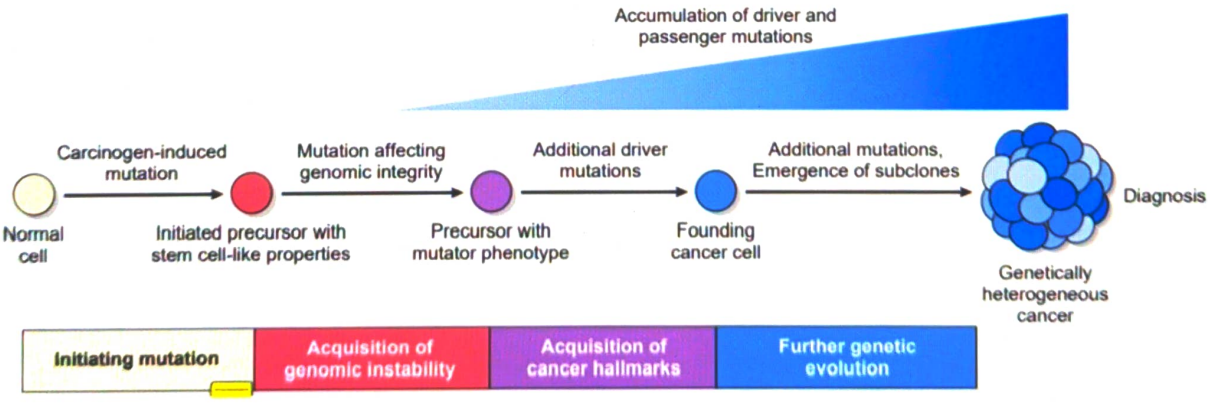
In the context of cell cycle regulation and cancer, which statement accurately describes the intricate mechanisms and consequences of p53 pathway activation?

- Options:
- A. The p53 pathway, once activated by the ATM pathway due to DNA damage, exclusively triggers apoptosis, with no role in cell cycle arrest or DNA repair.
- B. Activation of p53 involves dissociation from mdm2 due to ATM phosphorylation in response to DNA damage, leading to either DNA repair or apoptosis, with mutations in p53 gene being rare in human cancers.
- C. p53 is activated by hyperproliferative signals from oncogenes like Myc, leading to increased mdm2 production and enhanced cell cycle progression into the S phase.
- D. Oncogene activation can induce p14ARF, which competes with p53 for mdm2 binding, leading to p53 accumulation and activation of CDK inhibitors or apoptosis, and mutations in the p53 gene are common in various cancers.

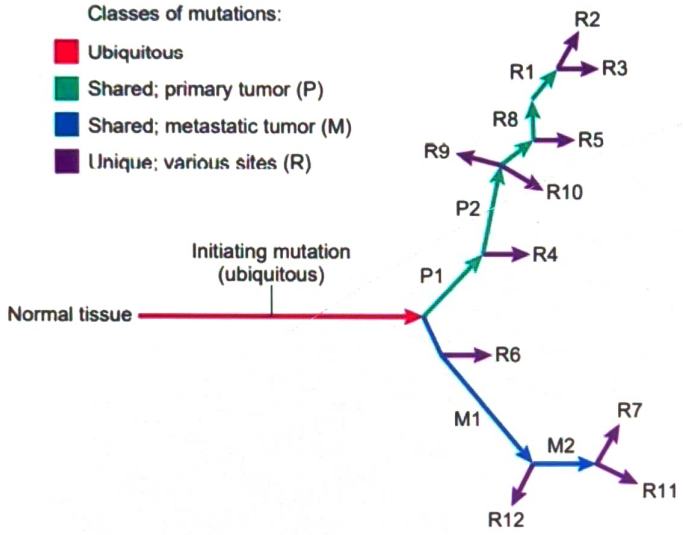
Molecular basis of cancer

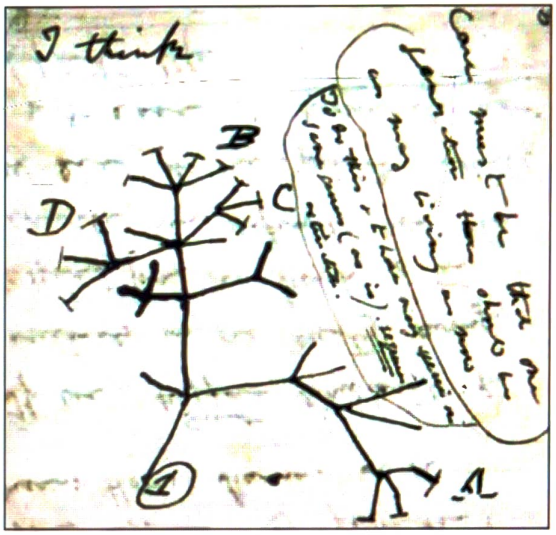
Molecular basis of cancer

- Non-Lethal damage
- Clonal expansion of a single precursor
- Principal targets- Protooncogenes, tumor suppressor genes, genes involved in Apoptosis and DNA repair



- Driver mutation- Initiating mutation
- Passenger mutation-





Tumor Kinetics

- **Gompertzian Kinetics**
- Tumor growth rate = cell growth rate – cell loss rate
- **Growth fraction:**
  - Starts at **100%** in first malignant cell
  - Falls to **<10%** by time of clinical detection
- Varies across cancer types & individuals
- Similar growth fraction as **bone marrow** & **intestinal epithelium** (fastest-growing normal tissues)

Question-

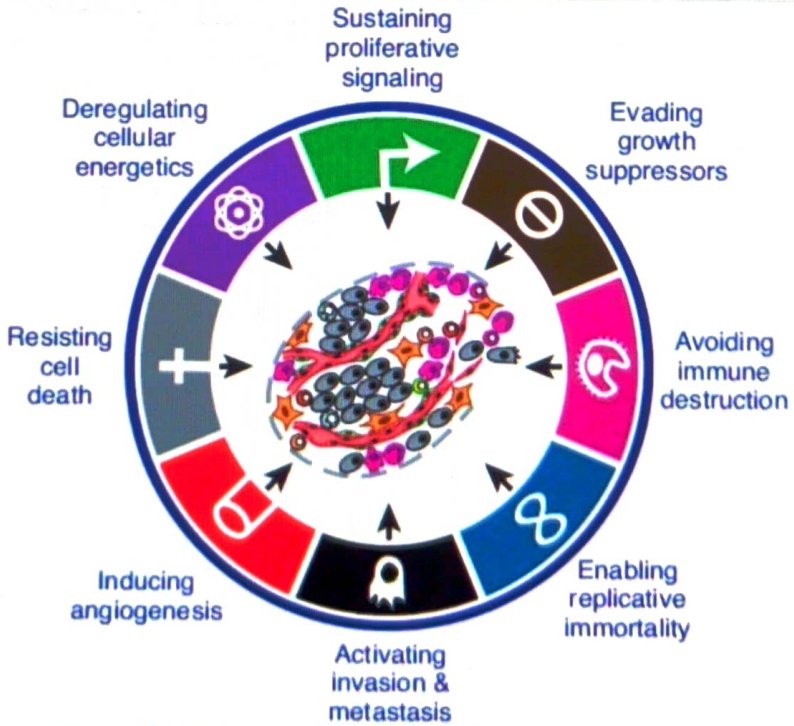
Which of the following statements accurately reflects the dynamics of tumor growth and microenvironment as described in the text about cancer behaving as an organ that ignores its niche?

Options:

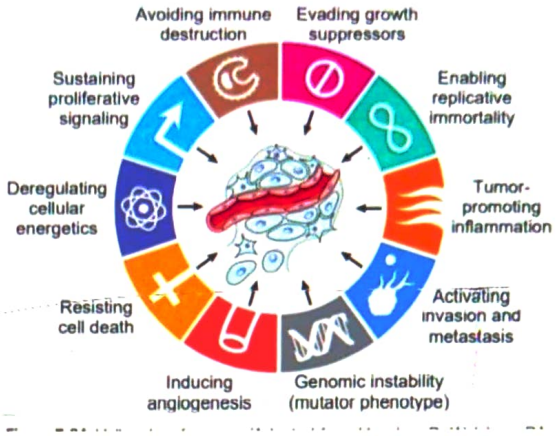
- A. Tumors invariably maintain a constant growth fraction from their initial development to the point of clinical detection, demonstrating uniform cell division rates across different cancer types.
- B. Human tumors grow by Gompertzian kinetics, meaning that the growth fraction of the tumor declines with time, largely influenced by the tumor microenvironment, with a growth fraction less than 10% at the time of clinical presentation.
- C. Tumor cells consistently show increased proliferation over time, unaffected by factors in the microenvironment, with the growth rate remaining constant from the onset of the tumor to its clinical detection.
- D. The growth fraction of a tumor is highest at the point of clinical detection, primarily due to the tumor's resistance to hypoxemia and an adequate supply of nutrients.

Hall marks of cancer

Introduction



- Genomic instability
- Cancer promoting inflammation

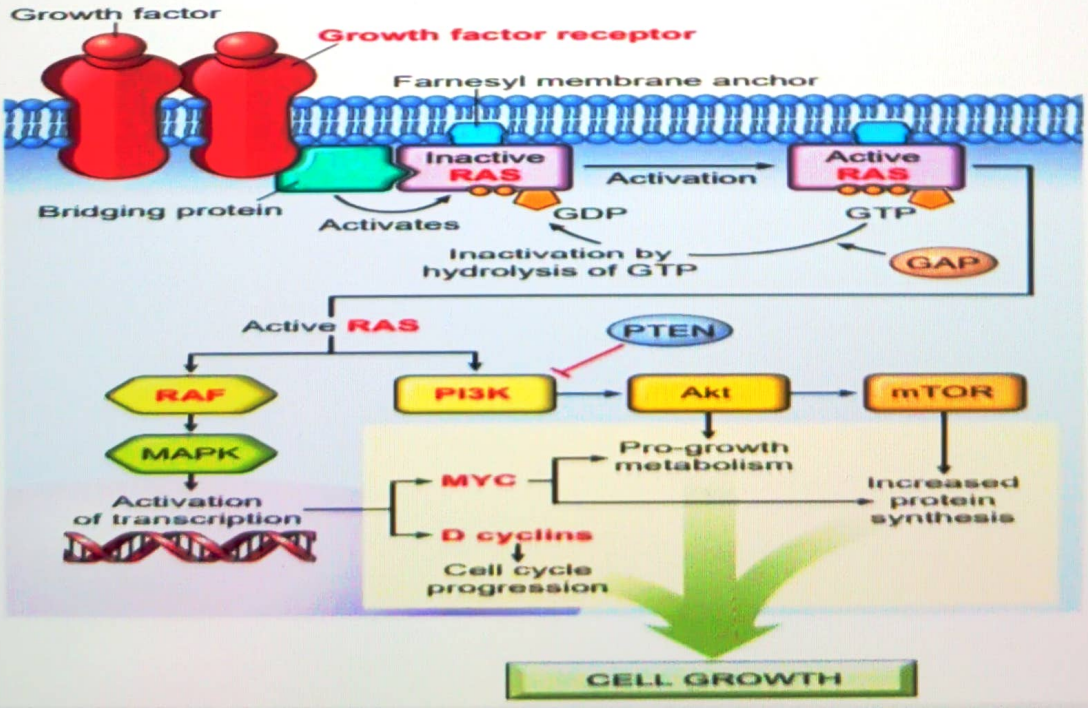


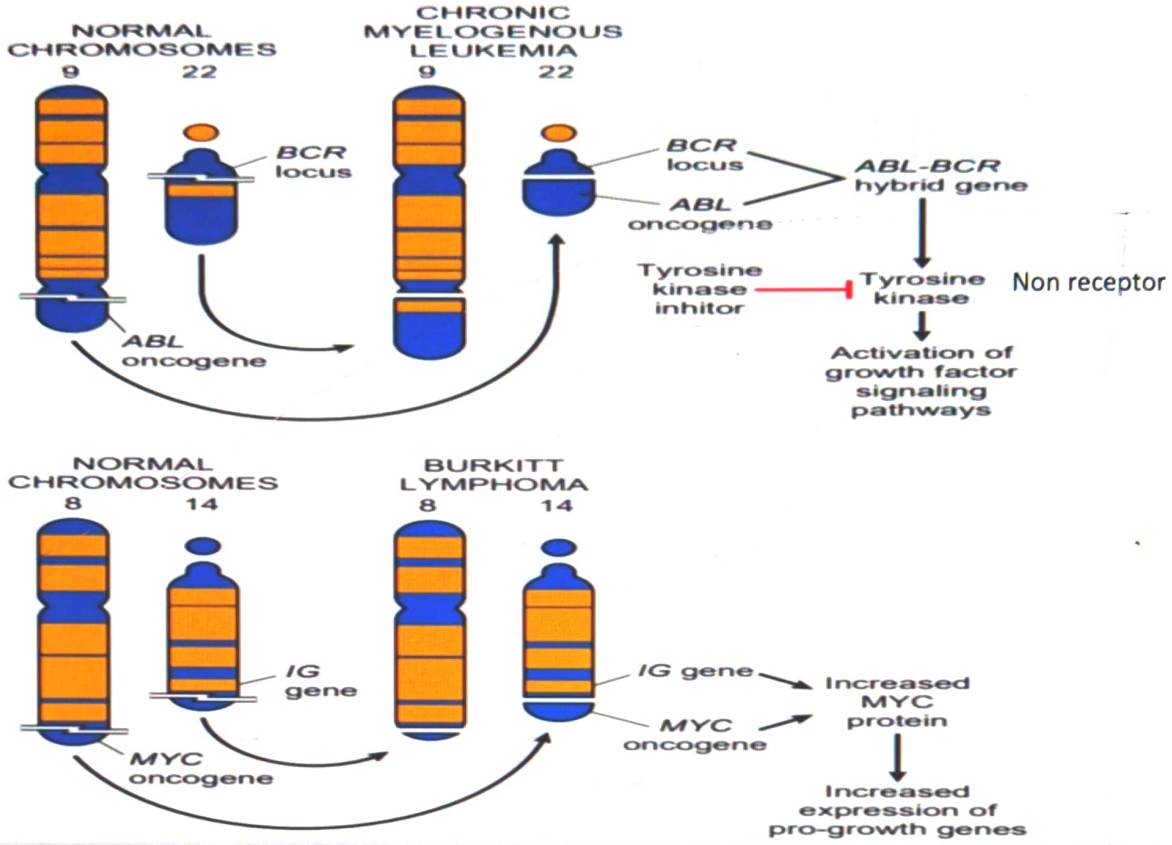
Hall mark1-Sustaining Proliferative Signalling

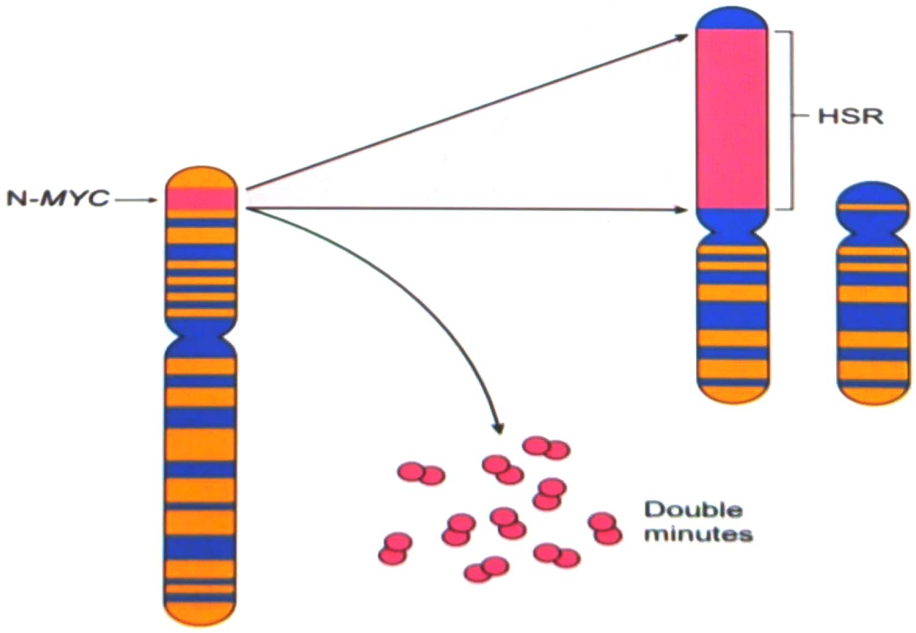
Sustaining Proliferative Signaling

- Oncogenes vs Protooncogenes
- Promotes cell growth in the absence of normal growth promoting signal
- How ??
  - Somatic Mutations Activate Additional Downstream Pathways- Eg: KRAS, BRAF and PIK3 mutation
  - Disruptions of Negative-Feedback Mechanisms that Attenuate Proliferative Signaling- Eg: GTPase(GAP-NF1) and PTEN
- Defensive mechanism
  - Excessive Proliferative Signaling Can Trigger Cell Senescence

Category	Proto-Oncogene	Mode of Activation in Tumor	Associated Human Tumor
Growth Factors			
PDGF-β chain	*PDGFB*	Overexpression	Astrocytoma
Fibroblast growth factors	*HST1* *FGF3*	Overexpression Amplification	Osteosarcoma Stomach cancer Bladder cancer Breast cancer Melanoma
TGF-α	*TGFA*	Overexpression	Astrocytomas
HGF	*HGF*	Overexpression	Hepatocellular carcinomas Thyroid cancer
Growth Factor Receptors			
EGF-receptor family	*ERBB1 (EGFR)* *ERBB2 (HER)*	Mutation Amplification	Adenocarcinoma of lung Breast carcinoma
FMS-like tyrosine kinase 3	*FLT3*	Point mutation	Leukemia
Receptor for neurotrophic factors	*RET*	Point mutation	Multiple endocrine neoplasia 2A and B, familial medullary thyroid carcinomas
PDGF receptor	*PDGFRB*	Overexpression, translocation	Gliomas, leukemias
Receptor for KIT ligand	*KIT*	Point mutation	Gastrointestinal stromal tumors, seminomas, leukemias
ALK receptor	*ALK*	Translocation, fusion gene formation Point mutation	Adenocarcinoma of lung, certain lymphomas Neuroblastoma
Proteins Involved in Signal Transduction			
GTP-binding (G) proteins	*KRAS* *HRAS* *NRAS* *GNAQ* *GNAS*	Point mutation Point mutation Point mutation Point mutation Point mutation	Colon, lung, and pancreatic tumors Bladder and kidney tumors Melanomas, hematologic malignancies Uveal melanoma Pituitary adenoma, other endocrine tumors
Nonreceptor tyrosine kinase	*ABL*	Translocation Point mutation	Chronic myelogenous leukemia Acute lymphoblastic leukemia
RAS signal transduction	*BRAF*	Point mutation, Translocation	Melanomas, leukemias, colon carcinoma, others
Notch signal transduction	*NOTCH1*	Point mutation, Translocation Gene rearrangement	Leukemias, lymphomas, breast carcinoma
JAK/STAT signal transduction	*JAK2*	Translocation	Myeloproliferative disorders Acute lymphoblastic leukemia
Nuclear Regulatory Proteins			
Transcriptional activators	*MYC* *NMYC*	Translocation Amplification	Burkitt lymphoma Neuroblastoma
Cell Cycle Regulators			
Cyclins	*CCND1* (Cyclin D1)	Translocation Amplification	Mantle cell lymphoma, multiple myeloma Breast and esophageal cancers
Cyclin-dependent kinase	*CDK4*	Amplification or point mutation	Glioblastoma, melanoma, sarcoma




NORMAL CHROMOSOMES
9
22
CHRONIC MYELOGENOUS LEUKEMIA
9
22
BCR locus
ABL oncogene
BCR locus
ABL oncogene
ABL-BCR hybrid gene
Tyrosine kinase inhitor
Tyrosine kinase
Non receptor
Activation of growth factor signaling pathways
NORMAL CHROMOSOMES
8
14
BURKITT LYMPHOMA
8
14
IG gene
MYC oncogene
IG gene
MYC oncogene
Increased MYC protein
Increased expression of pro-growth genes


N-MYC
HSR
Double minutes