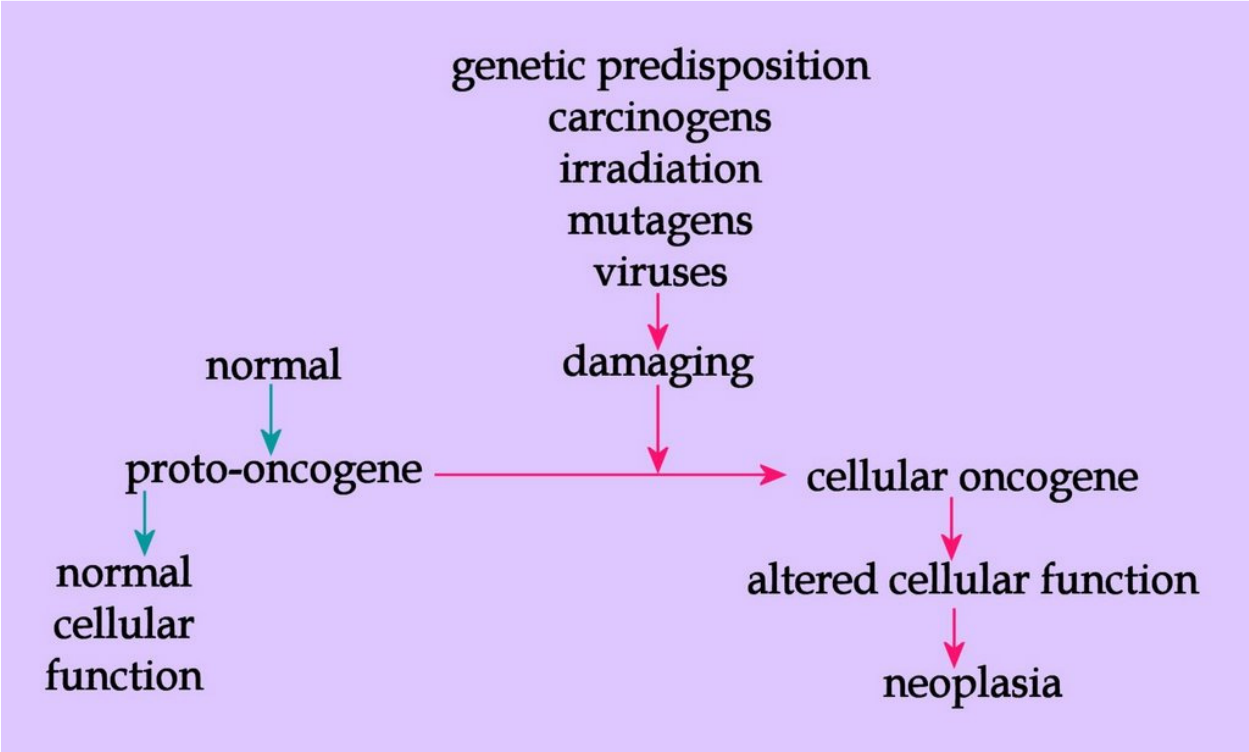
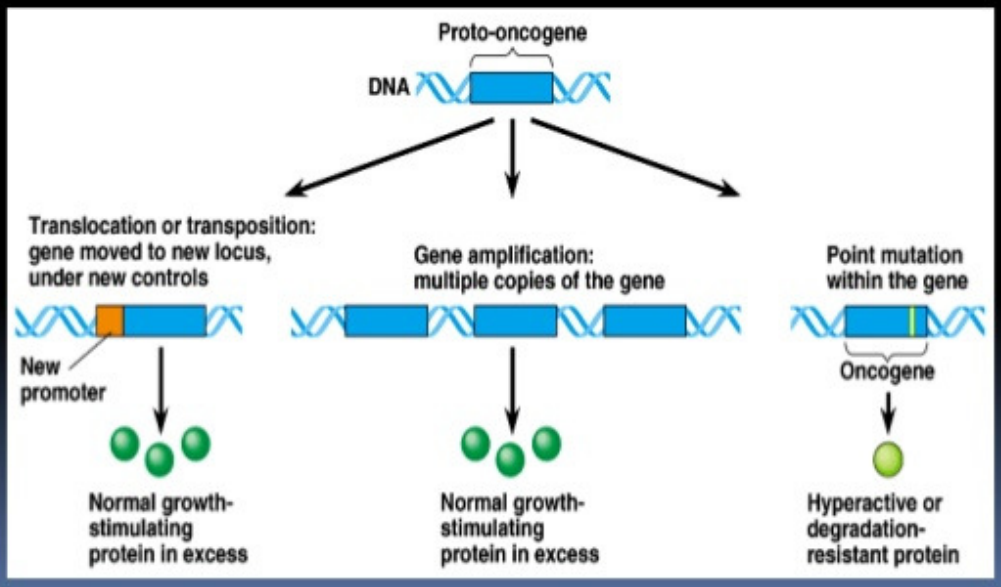
PROTO –ONCOGENES AND ONCOGENES/SDG/UG SEM



- 5 mechanisms of activation :

1. Promoter insertion
2. Enhancer insertion
3. Chromosomal translocation
4. Gene amplification
5. Point mutations

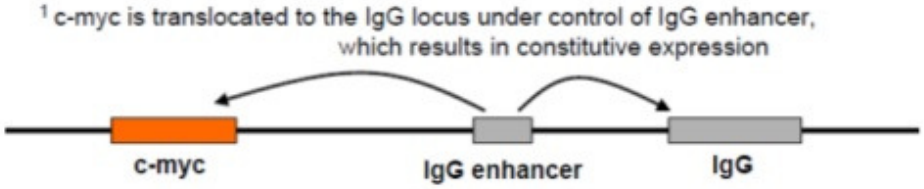


TRANSLOCATIONS

CHROMOSOMAL REARRANGEMENTS OR TRANSLOCATIONS

Neoplasm	Translocation	Proto-oncogene
Burkitt lymphoma	t(8;14) 80% of cases t(8;22) 15% of cases t(2;8) 5% of cases	c-myc[1]
Chronic myelogenous leukemia	t(9;22) 90-95% of cases	bcr-abl[2]
Acute lymphocytic Leukemia	t(9;22) 10-15% of cases	bcr-abl[2]

[1]c-myc is translocated to the IgG locus, which results in its activated expression

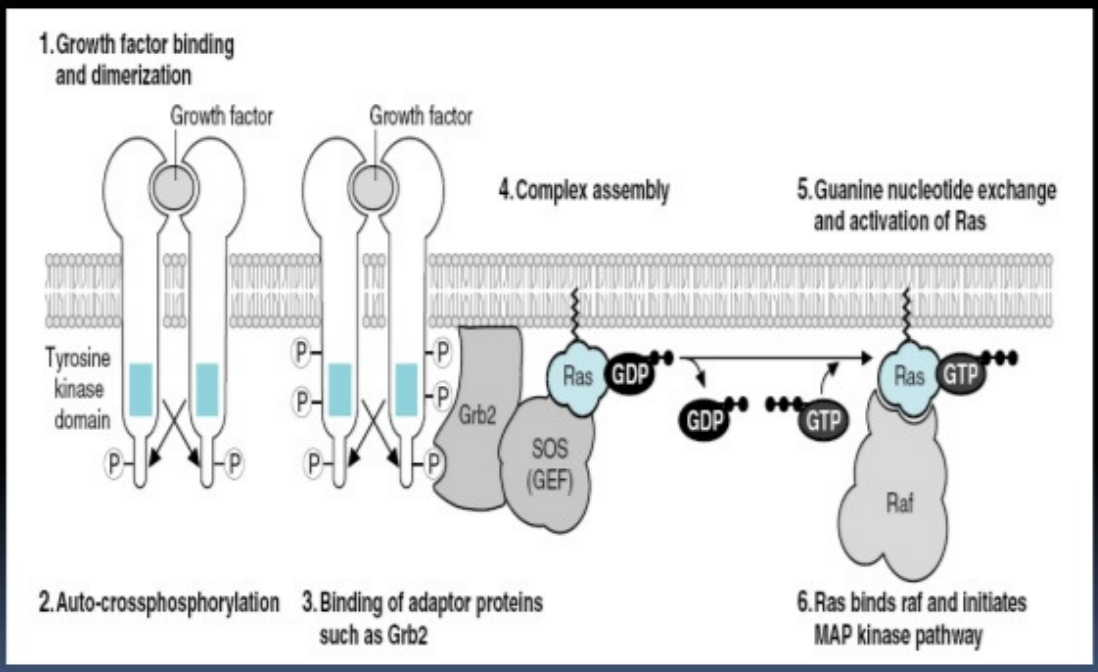


[2]bcr-abl fusion protein is produced, which results in a constitutively active abl kinase

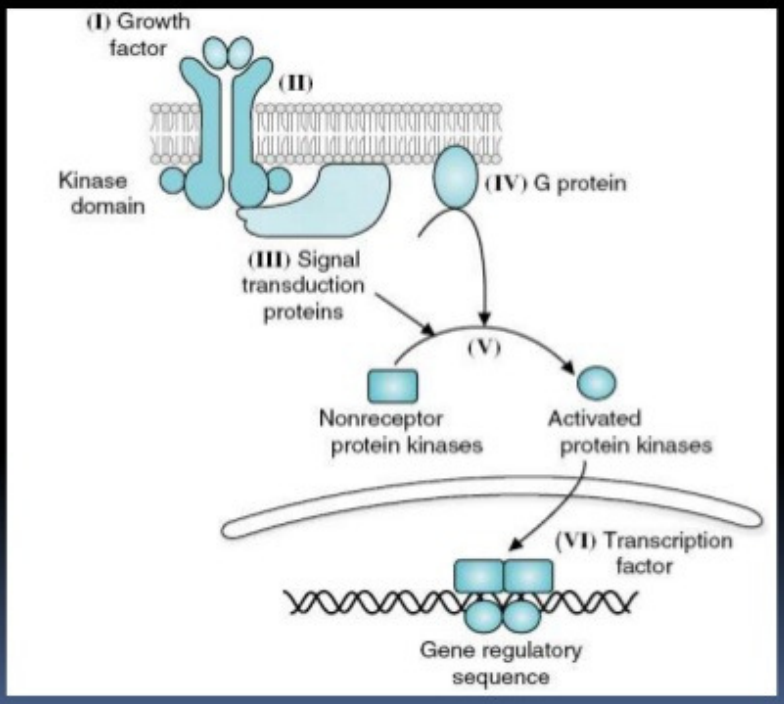
GENE AMPLIFICATION

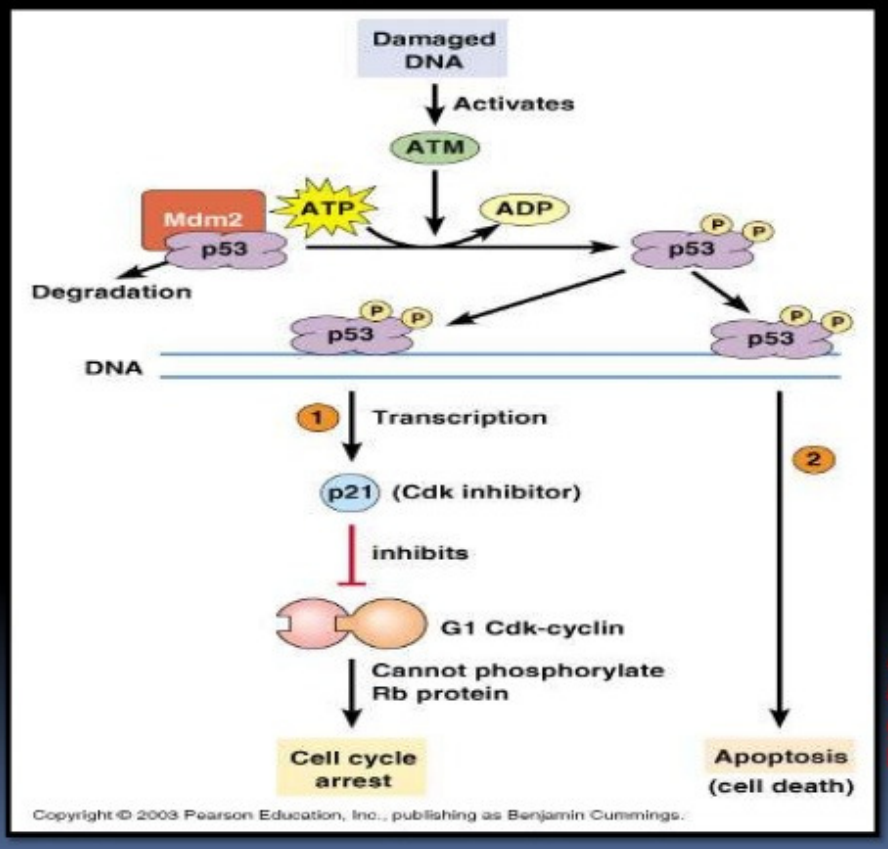
GENE AMPLIFICATION

Oncogene	Amplification	Source of tumor
c-myc	~20-fold	leukemia and lung carcinoma
N-myc	5-1,000-fold	neuroblastoma retinoblastoma
L-myc	10-20-fold	small-cell lung cancer
c-abl	~5-fold	chronic myoloid leukemia
c-myb	5-10-fold	acute myeloid leukemia colon carcinoma
c-erbB	~30-fold	epidermoid carcinoma
K-ras	4-20-fold 30-60-fold	colon carcinoma adrenocortical carcinoma


1. Growth factor binding and dimerization
Growth factor
Growth factor
4. Complex assembly
5. Guanine nucleotide exchange and activation of Ras
Tyrosine kinase domain
P
Grb2
SOS (GEF)
Ras
GDP
GDP
GTP
Ras
GTP
Raf
2. Auto-crossphosphorylation
3. Binding of adaptor proteins such as Grb2
6. Ras binds raf and initiates MAP kinase pathway

Mechanism of action of oncogens





GADD (Growth Arrest DNA Damage)

Activates two apoptotic gene bax and IGFBP3