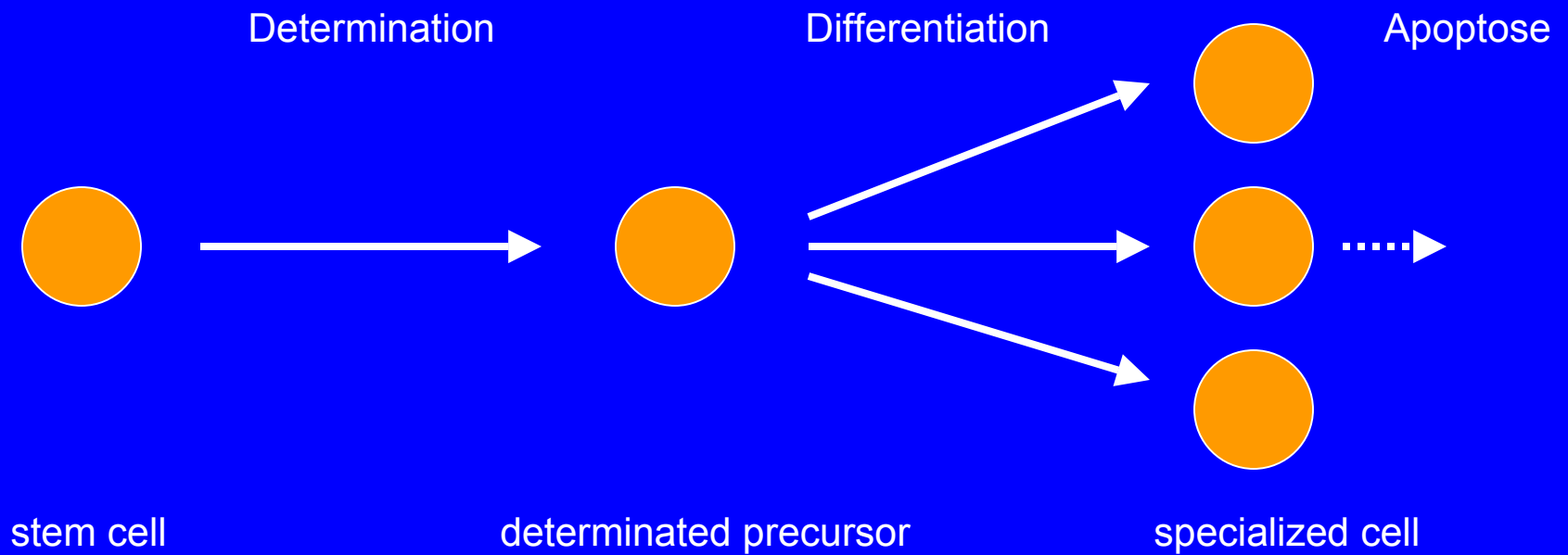


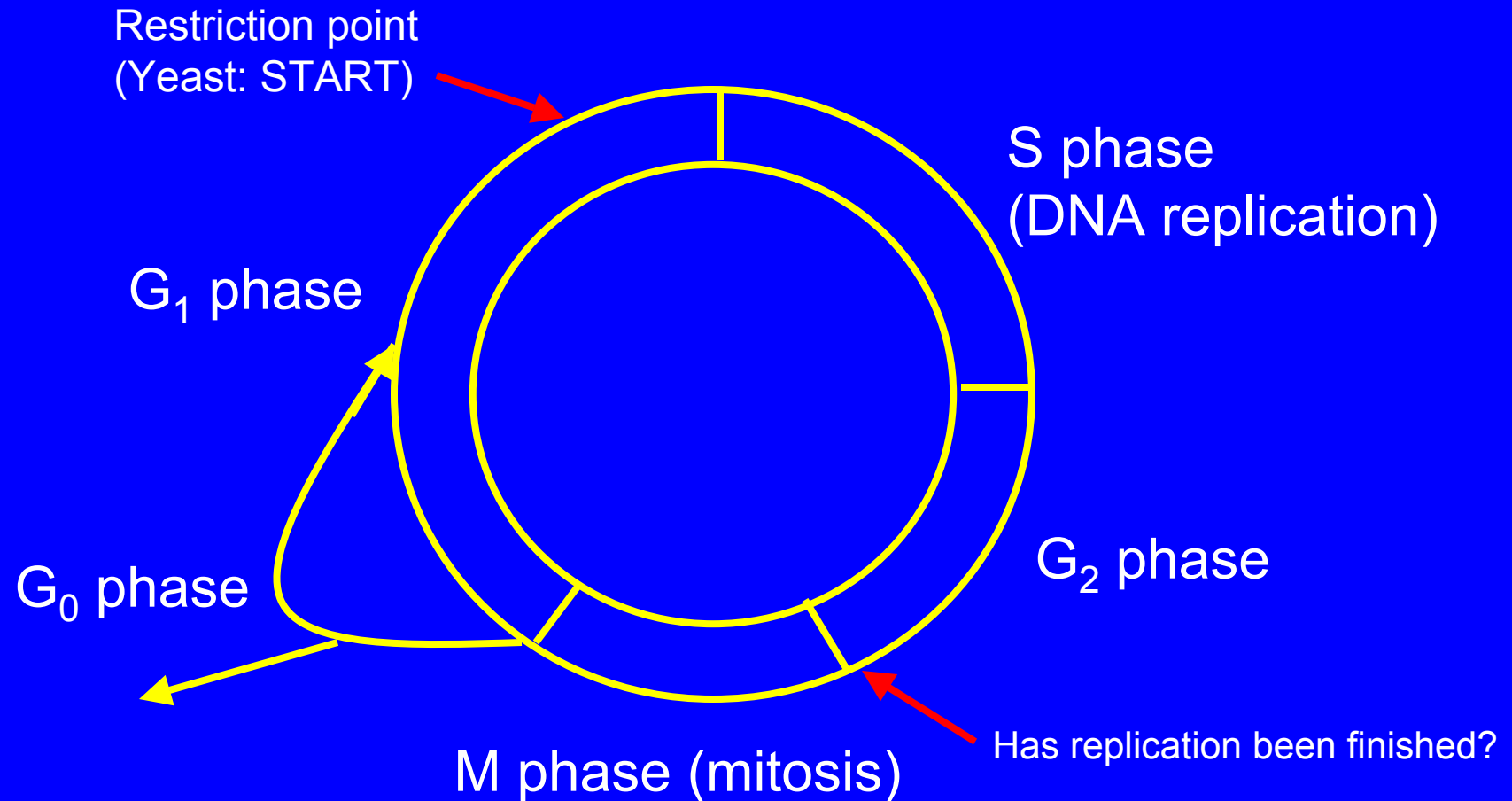
# Biology of Cancer

- Developmental Biology: Determination and Differentiation
- Cell Cycle Regulation
- Tumor genes: Proto-Oncogenes, Tumor suppressor genes
- Tumor-Progression
- Example for Tumor-Progression: Colon cancer
- Chromosome Translocations in Leukemia

# Determination and Differentiation



# Cell Cycle

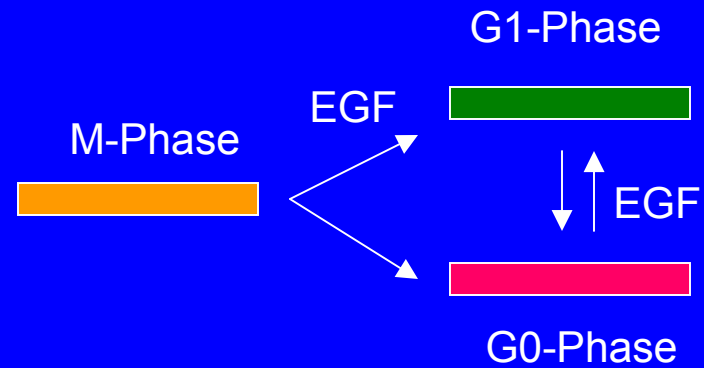
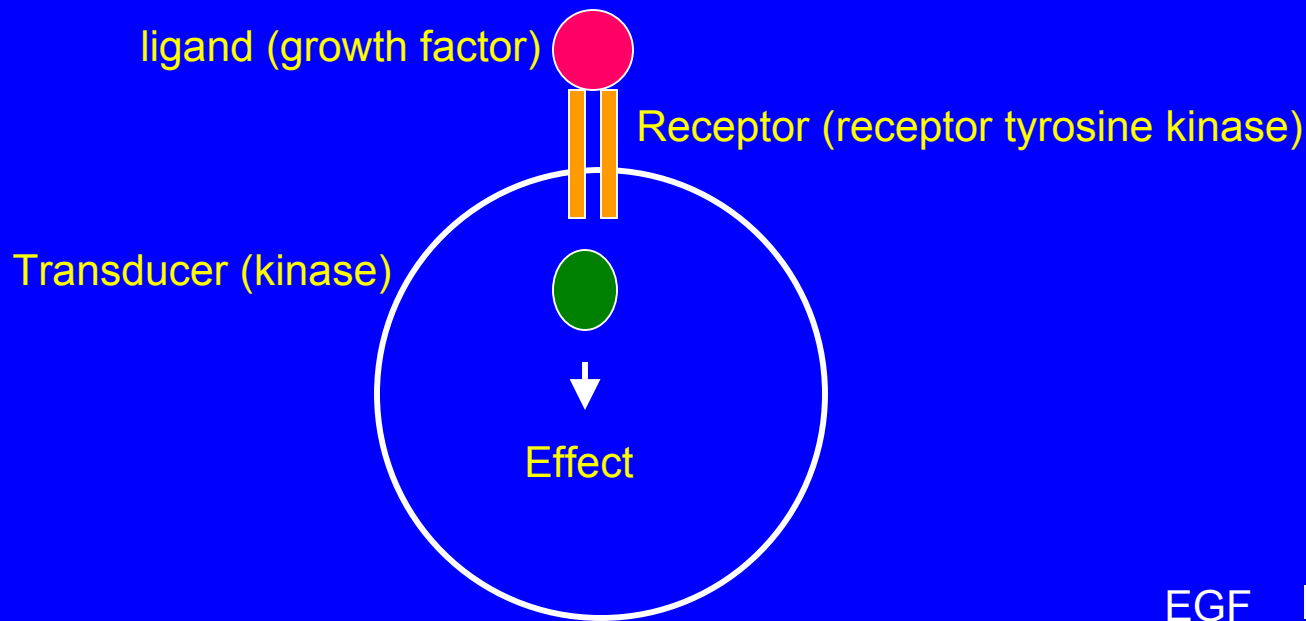


# Cell Cycle

Important barriers in the Cell Cycle:

- G1 → S: transcription has to be stopped
- G1 → S: DNA-repair has to be finished
- G2 → M: replication has to be finished
- G0 ↔ G1: is there any need for proliferation

# Signal Transduction



EGF: Epidermal Growth Factor

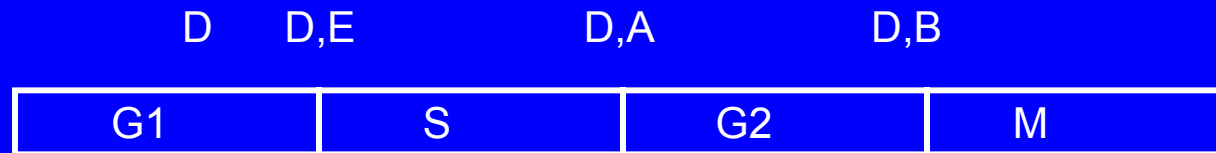
# Cell Cycle: Regulation

Cyclins: regulatory proteins, active at specific stages in the cell cycle

CDK: cycline dependent kinases

CDI: CDK inhibitor

Cycline:



CDI (e.g. p27, p21)

# Tumor genes: Knowledge from Viruses

- Viruses need mechanisms for replication
- many use hosts replication machinery
- Consequence: Viruses have to disable the hosts strict regulation mechanisms

## Possible mechanisms:

- active interaction of a viral protein in the cells regulatory pathways (e.g. v-ras)
- inactivation of a hosts regulatory factor by binding of a viral protein (e.g. T-Antigen from SV40)

# Tumor genes: Knowledge from Viruses



# Oncogenes

## Oncogenes:

viral proteins which interact with the cellular control mechanisms to overcome the strict regulation of proliferation (v-ras, v-myc, v-abl, ...)

## Proto-Oncogenes:

Cellular proteins which correspond to the viral Oncogenes but which are strictly regulated. Mutations in this genes could transform a cell into a tumor cell (c-ras, c-myc, c-abl, ...).

# Oncogenes: ras

- ras is a small protein involved in Signal Transduction from cell surface receptors (receptor tyrosine kinases) into the nucleus, where Transcription Factors are activated
- active form: ras-GTP/ inactive form: ras-GDP
- is activated through the so called GDP/GTP-exchange factor(GEF,GRF)
- helps to activate a Serine/Threonine Kinase (raf)
- negatively controlled by an intrinsic phosphatase activity which hydrolyses GTP to GDP (induced by a protein called GAP)

# Oncogenes: ras

v-ras (viral form): constitutive activity  
=> Oncogene

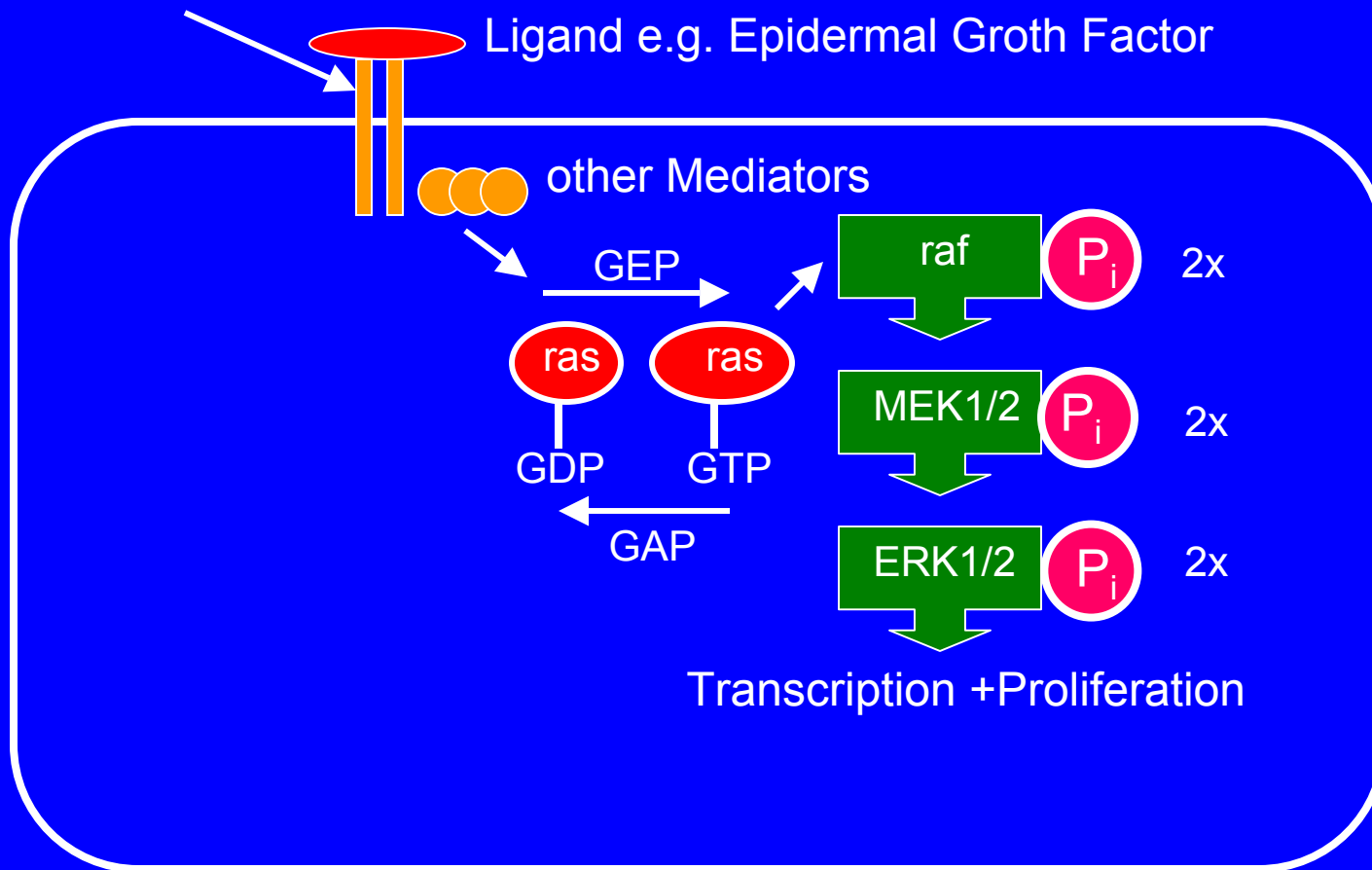


c-ras (cellular form): activity is regulated  
=> Proto-Oncogene

# Proto-Oncogenes: c-ras

Receptor Tyrosine Kinase

Ligand e.g. Epidermal Growth Factor



# Tumor suppressor genes

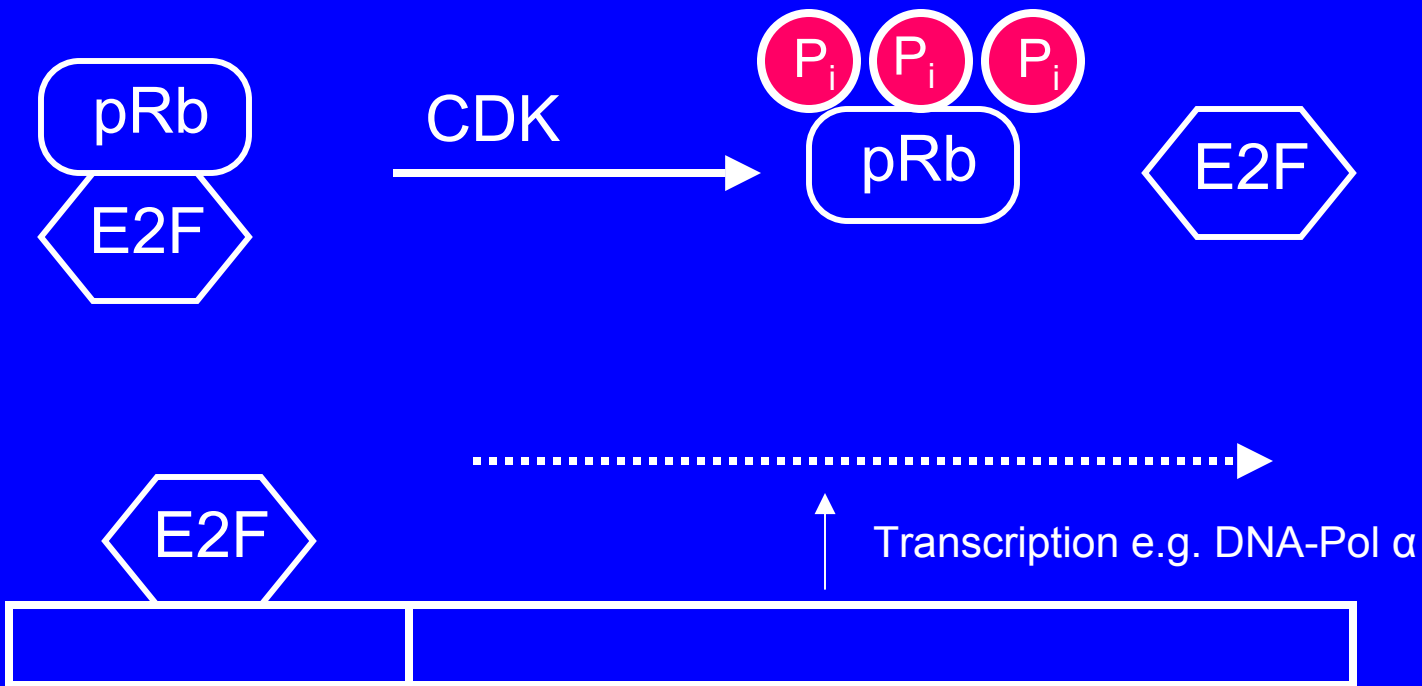
Gene products which are normally responsible for negative control of transcription and proliferation

Examples:

pRb inhibits transcription factors of the E2F-family, which are needed to get into the S-Phase of the cell cycle (Restriction Point)

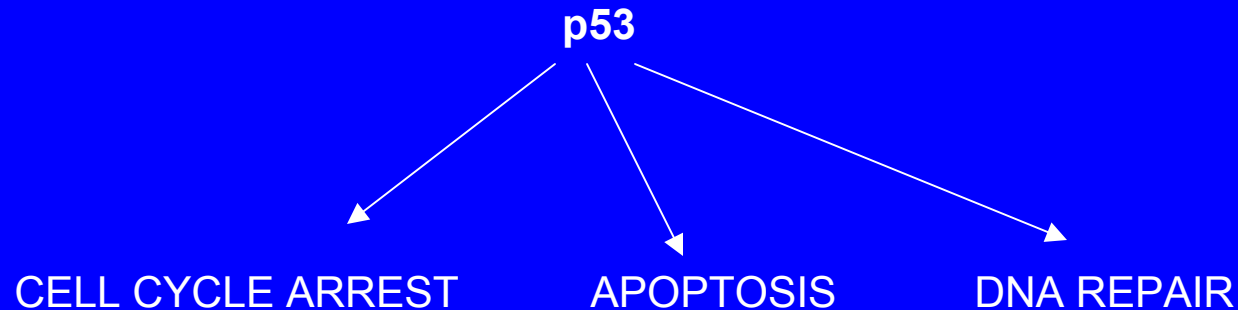
p53 induces transcription of the CDK-inhibitor (CDI) p21 which causes a cell cycle arrest (one function)  
p53 is found upregulated in cells with a high level of DNA-damage

# Tumor suppressor genes: rb



# Tumor suppressor genes: p53

DNA damage  
hypoxia  
nucleotide depletion  
heat shock  
viral oncoprotein



# Neoplastic transformation

- a tumor has a monoclonal origin
- a single mutation of a proto-Oncogene or Tumor suppressor gene is not enough for a Neoplastic Transformation
- mutations of a proto-Oncogene have a dominant effect
- mutations of a Tumor suppressor gene are recessive
- only a chain of multiple genomic changes leads to a Neoplastic Transformation (Tumor Progression)

# Neoplastic transformation

spontaneous or induced DNA damage



primary molecular lesion



genomic instability

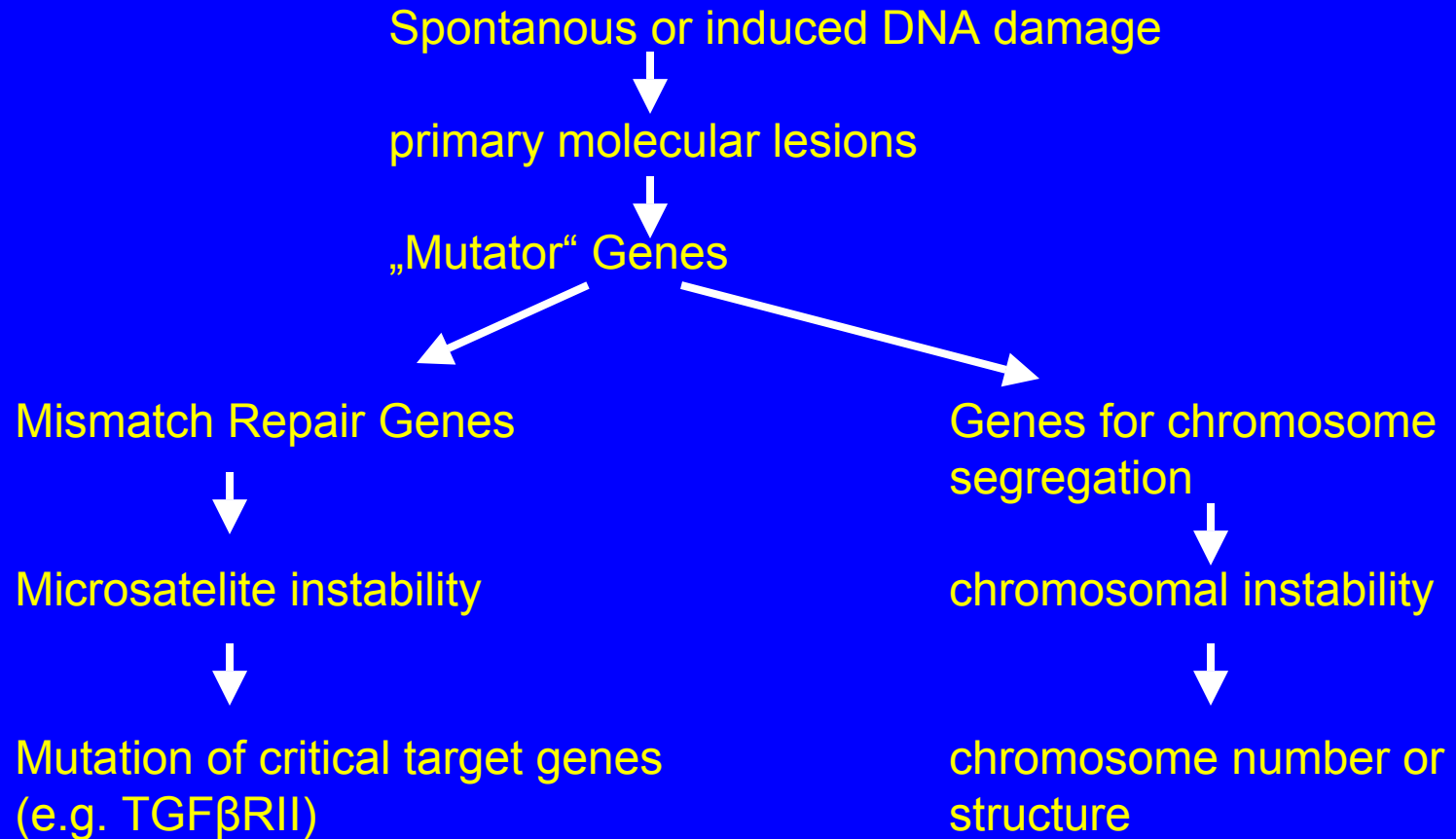


transforming molecular lesion



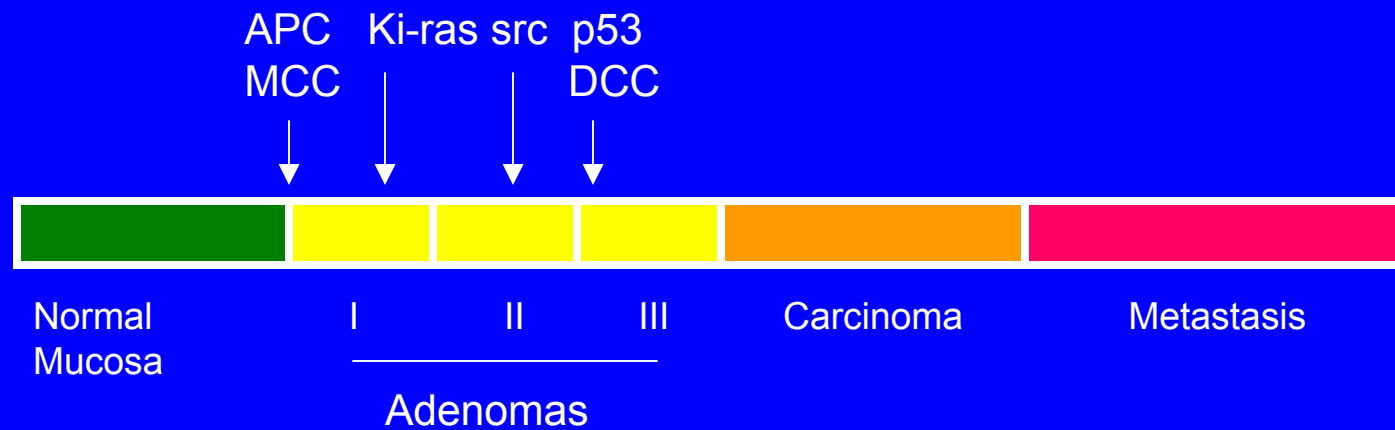
**Neoplastic Transformation**

# Neoplastic transformation



# Neoplastic transformation

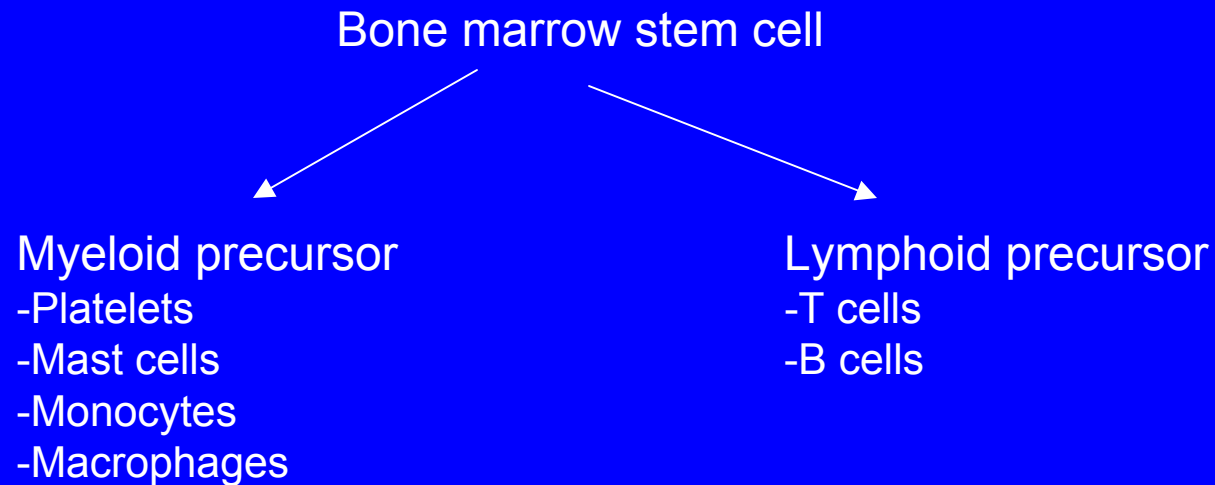
Genetic alterations during the Familial Adenomatous Polyposis Syndrome (FAP)



APC: aden polyp. Coli  
MCC: mutated in colon cancer  
DCC: deleted in colon cancer

src: gene for a protein tyrosine kinase

# Leukemia



Lymphoblastic Leukemia: Transformation of a lymphoid determined stem cell (acute or chronic, ALL, CLL)

Myeloid Leukemia: Transformation of a myeloid determined stem cell (acute or chronic, AML, CML)

# Leukemia

Different Leukemias are mostly characterized through simple Translocations between different chromosomes (=> fusion genes)

**best known example: Philadelphia Chromosome t(9;22)(q34;q11) (CML,ALL)**

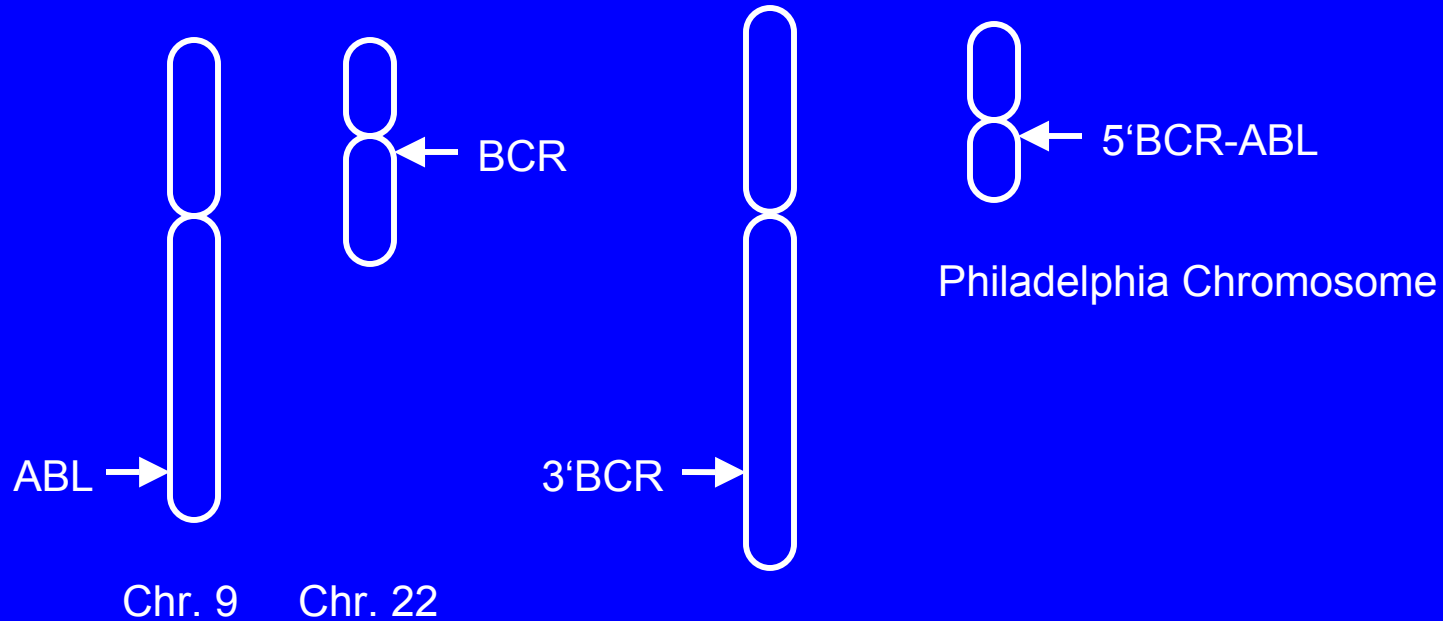
⇒ **Fusion gene: BCR-ABL**

**c-abl:** tyrosine kinase which probably is involved in cell cycle regulation

**bcr(breakpoint cluster region):** maybe involved in signal transduction

**Fusion gene:** constitutive tyrosine kinase activity contributed by c-abl

# Leukemia



Other examples:  $t(8,14)$ ,  $t(2,8)$ ,  $t(8,22)$  => fusion of the proto-Oncogene c-myc on chromosome 8 with one immunoglobulin-locus => overexpression of c-myc

# Summary

- Cancer arises from a wrong cell cycle regulation
- one monoclonal mutation leads to genomic instability
- Neoplastic Transformation is the consequence of the following multiple genetic alterations