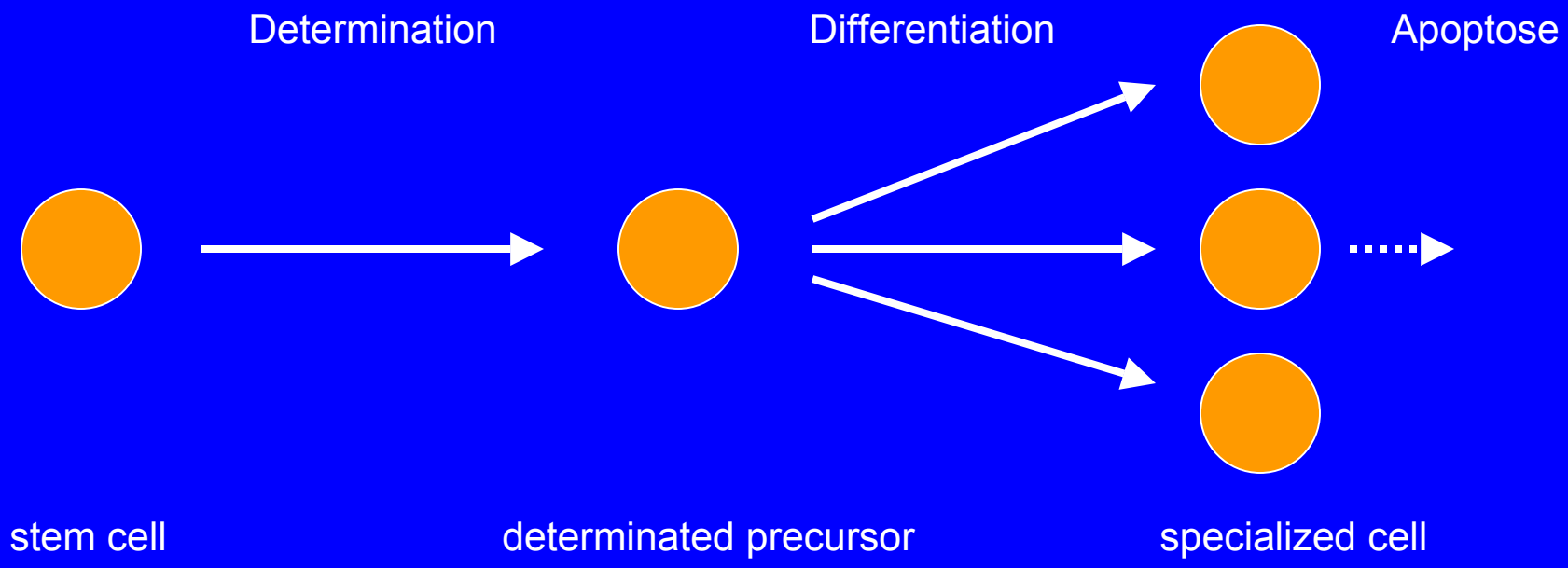
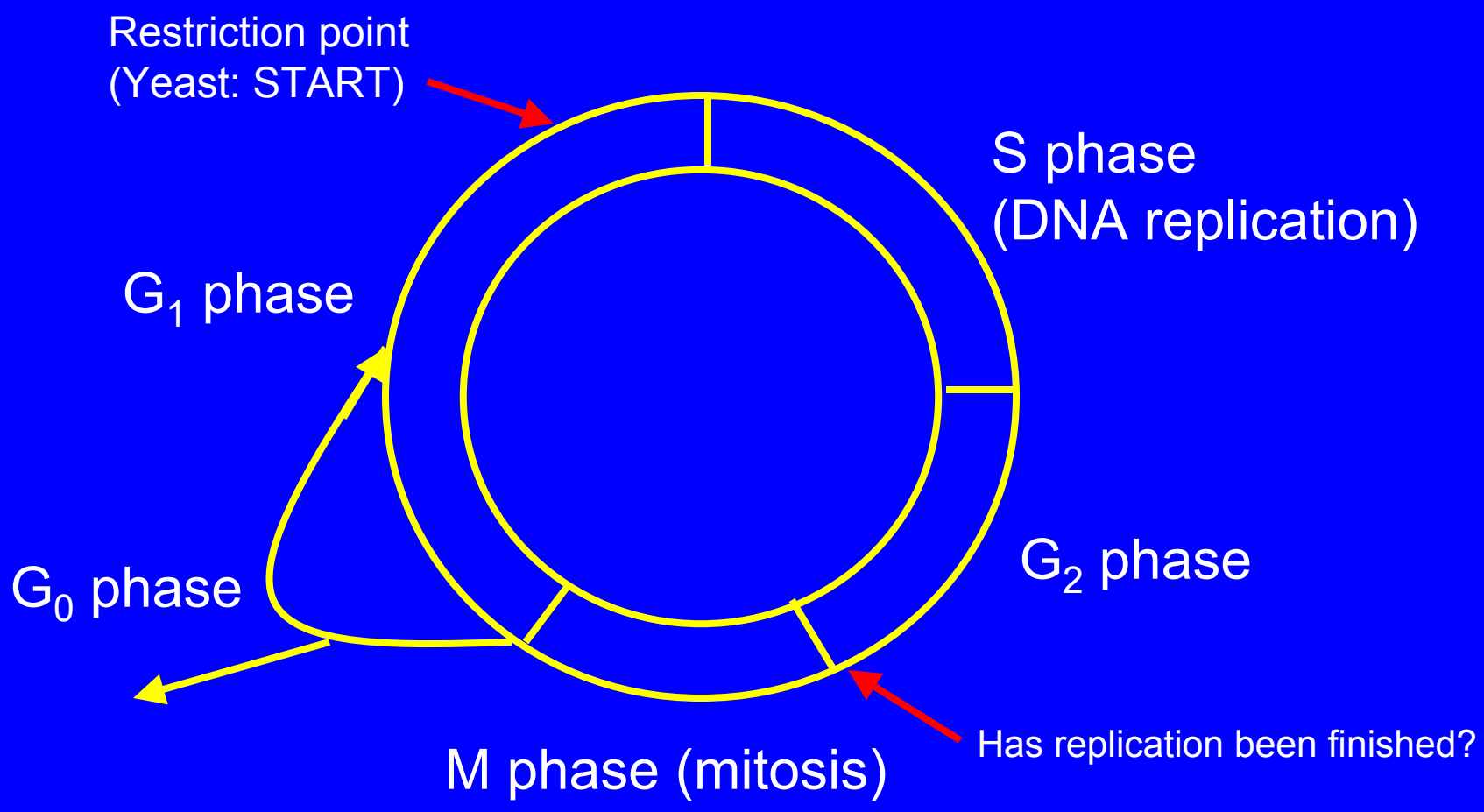
Biology of Cancer

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

Determination and Differentiation



Cell Cycle

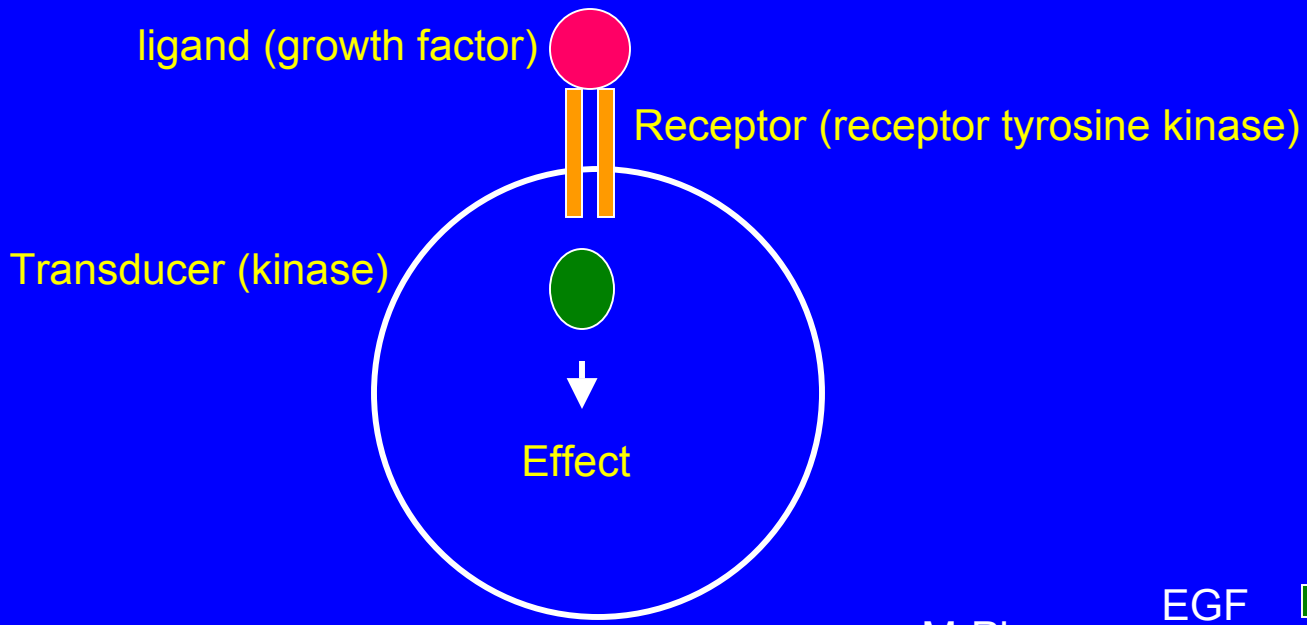

Restriction point
(Yeast: START)
S phase
(DNA replication)
G_1 phase
G_0 phase
G_2 phase
M phase (mitosis)
Has replication been finished?

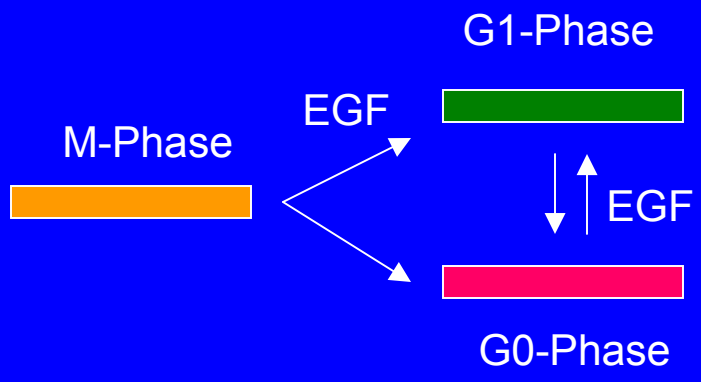
Cell Cycle

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

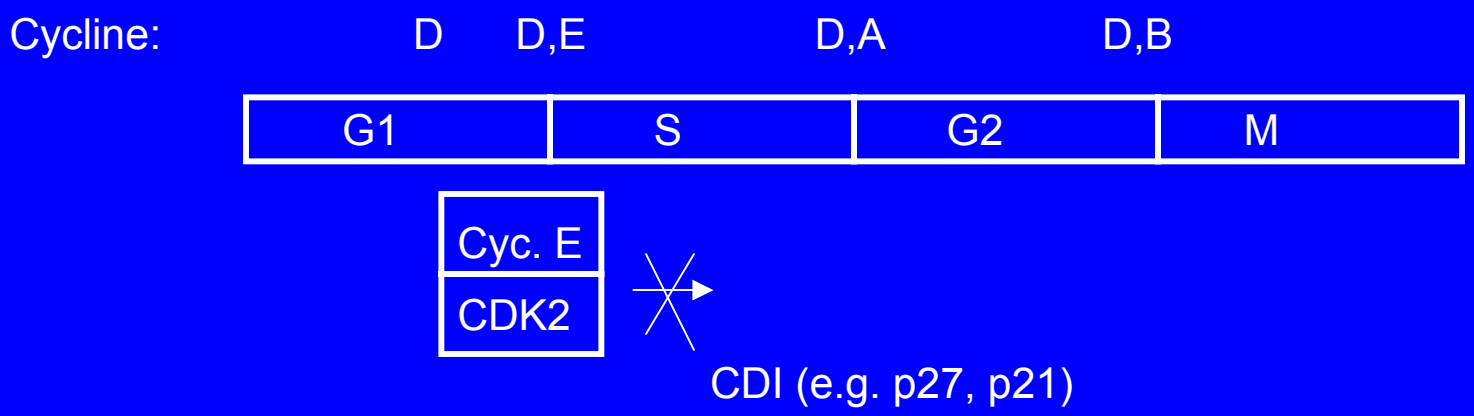




EGF: Epidermal Growth Factor

Cell Cycle: Regulation

Cyclines: regulatory proteins, active at specific stages in the cell cycle
CDK: cycline dependent kinases
CDI: CDK inhibitor

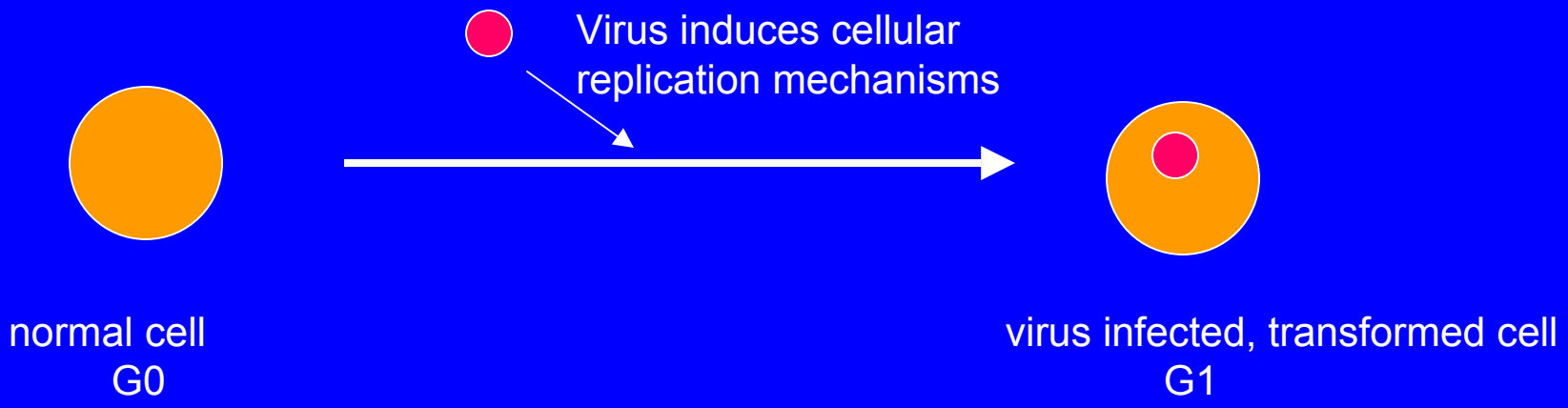


Tumor genes: Knowledge from Viruses

- 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 controll 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, were 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)

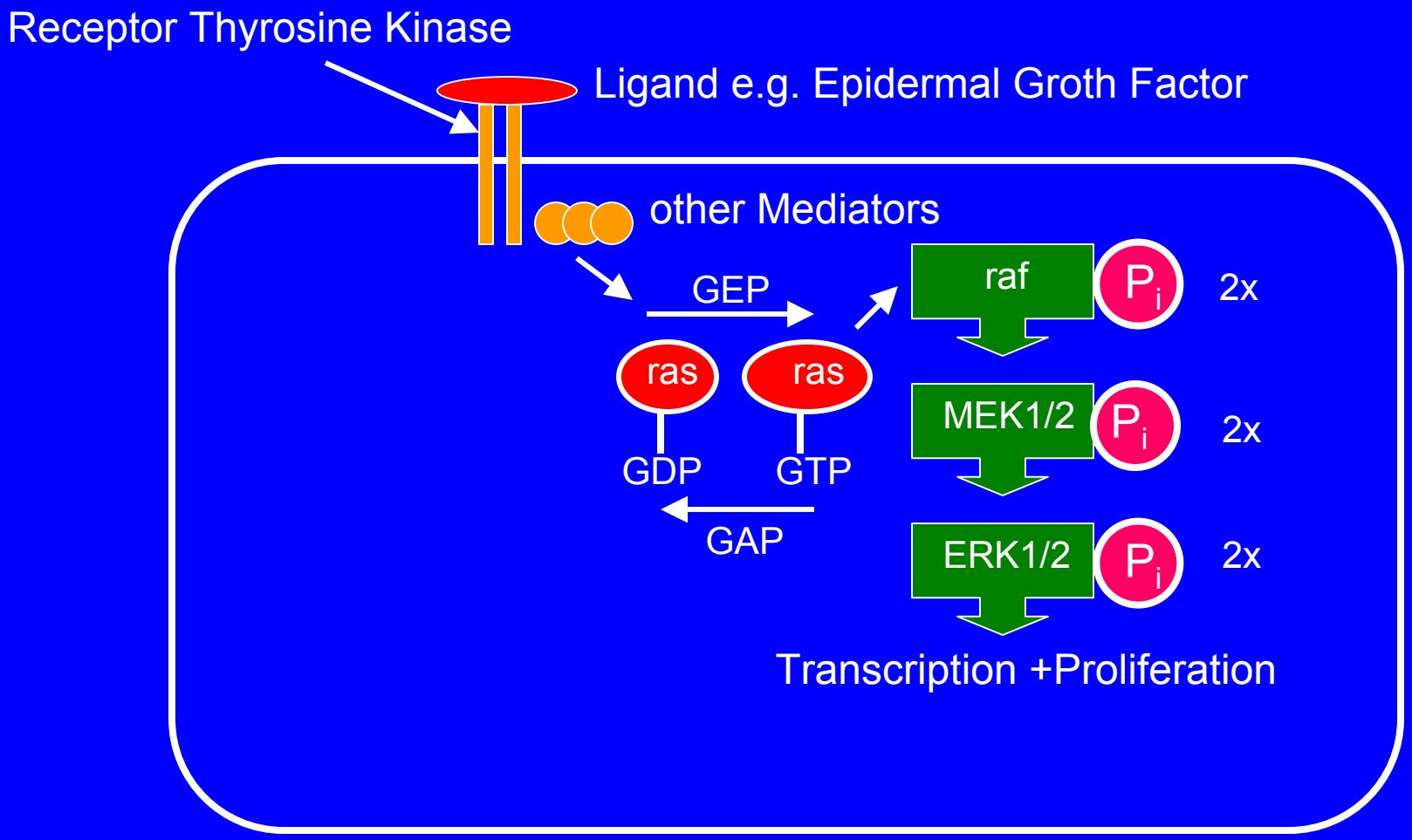
- negatively controlled by an intrinsic phosphatase activity which hydrolyses GTP to GDP (induced by a protein called GAP)

Oncogenes: ras

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

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

Proto-Oncogenes: c-ras



Tumor suppressor genes

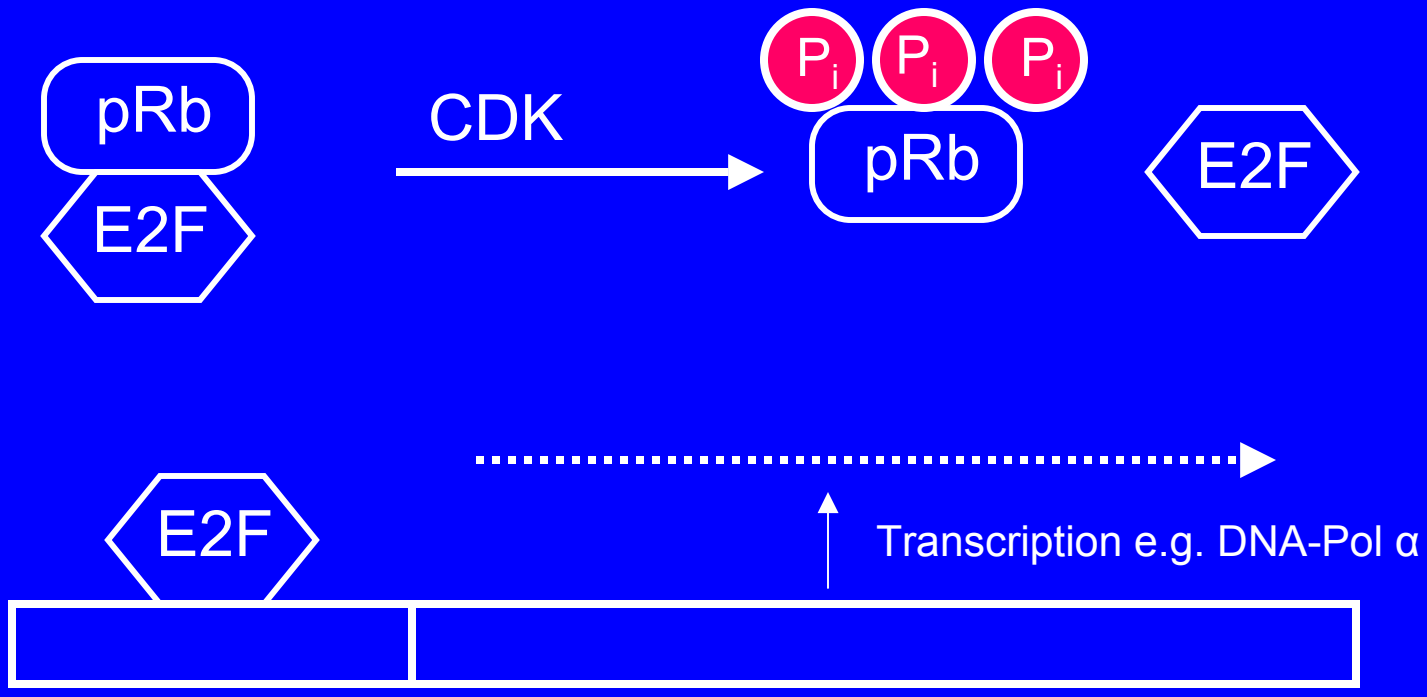
Geneproducts which are normaly responsible for negative controll of transcription and proliferation

Examples:

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

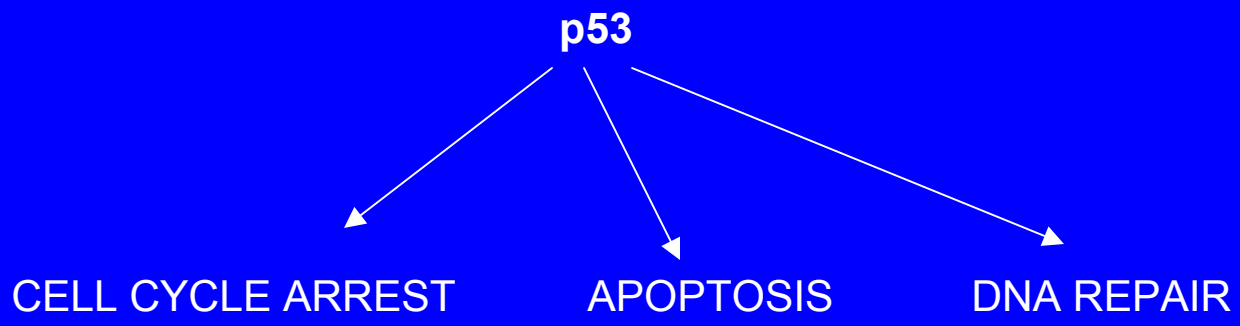
p53 induces transcription of the CDK-inhibitor (CDI) p21 which causes a cell cycle arrest (one function)
p53 is found upregulated in cells with a high level of DNA-damage

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 leeds to a Neoplastic Transformation (Tumor Progression)

Neoplastic transformation

spontaneous or induced DNA damge

↓

primary molecular lesion

↓

genomic instability

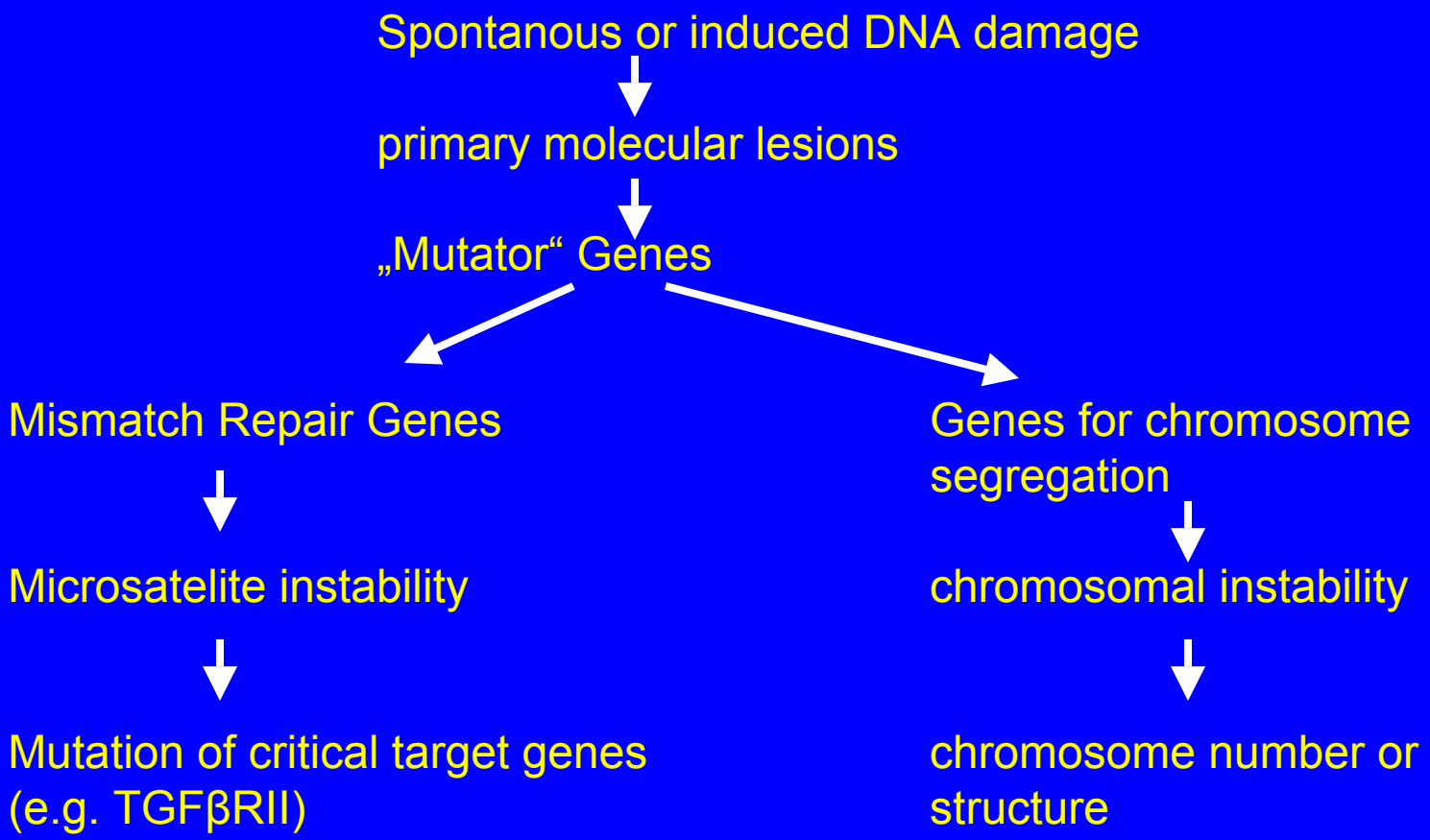
↓

transforming molecular lesion

↓

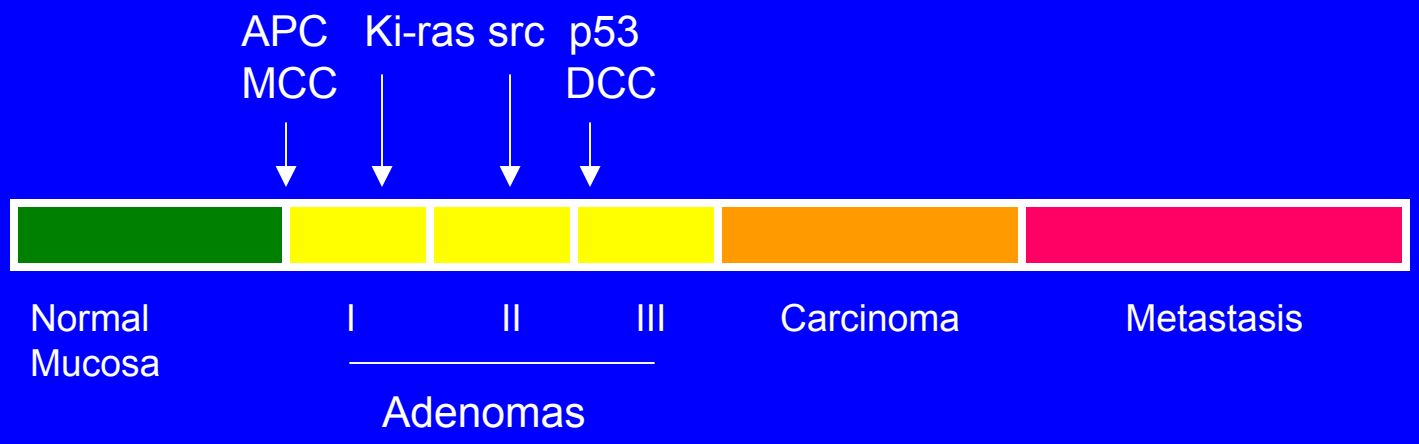
Neoplastic Transformation

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 thyrosine kinase

Leukemia

Myeloid precursor
-Platelets
-Mast cells
-Monocytes
-Macrophages

Lymphoid precursor
-T cells
-B cells

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

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

Leukemia

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

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

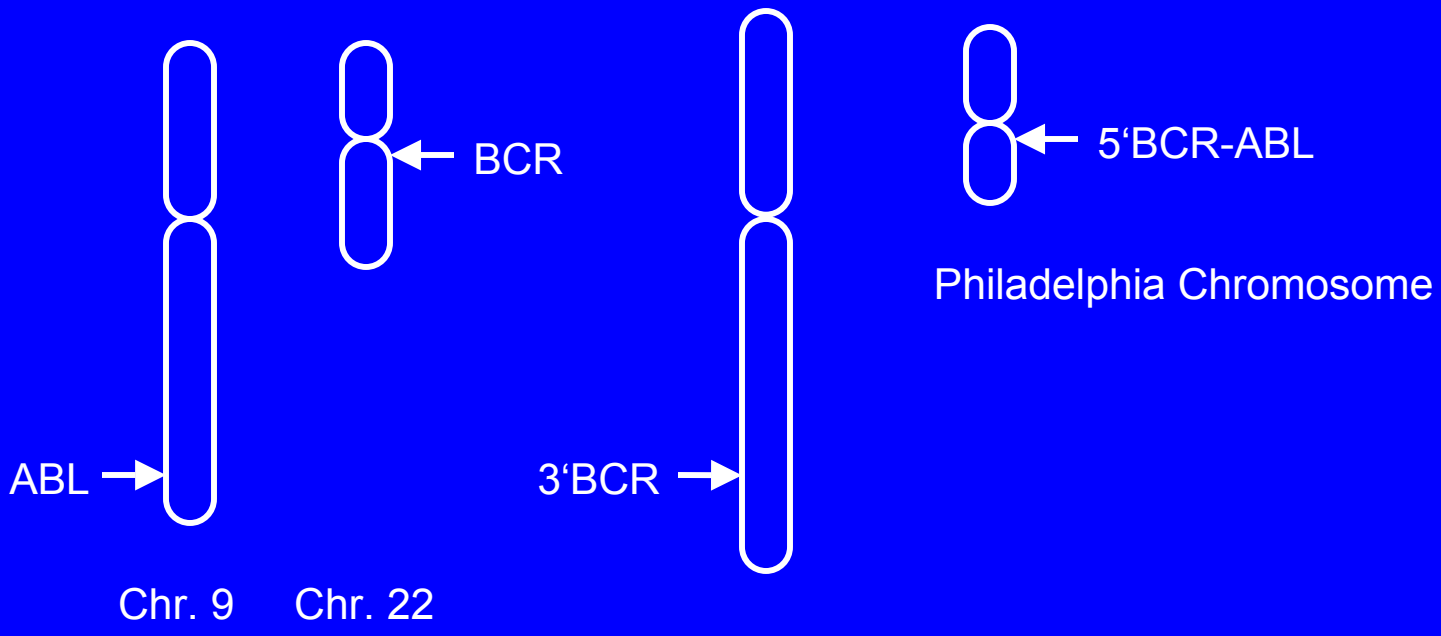
⇒**Fusion gene: BCR-ABL**

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 leeds to genomic instability

-Neoplastic Transformation is the consequnce of the following multiple genetic alterations