Genetic Basis of Cancer

Prof.Dr. Selma Yılmazer

&

Prof.Dr. Turgut Ulutin

Genetic Basis of Cancer

- Nonlethal genetic damage lies at the heart of carcinogenesis

Properties of Cancer cells

Cancer cells display abnormalities in the mechanism that regulate **cell proliferation**, **differentiation** and **survival**

Targets of genetic damage in carcinogenesis

(***Normal growth regulatory genes***)

- 1- The growth promoting genes;

Protooncogenes

Mutant Protooncogenes: Oncogenes

Dominant effect

- 2- The growth inhibiting genes;

Tumor-supressor genes

Recessive effect

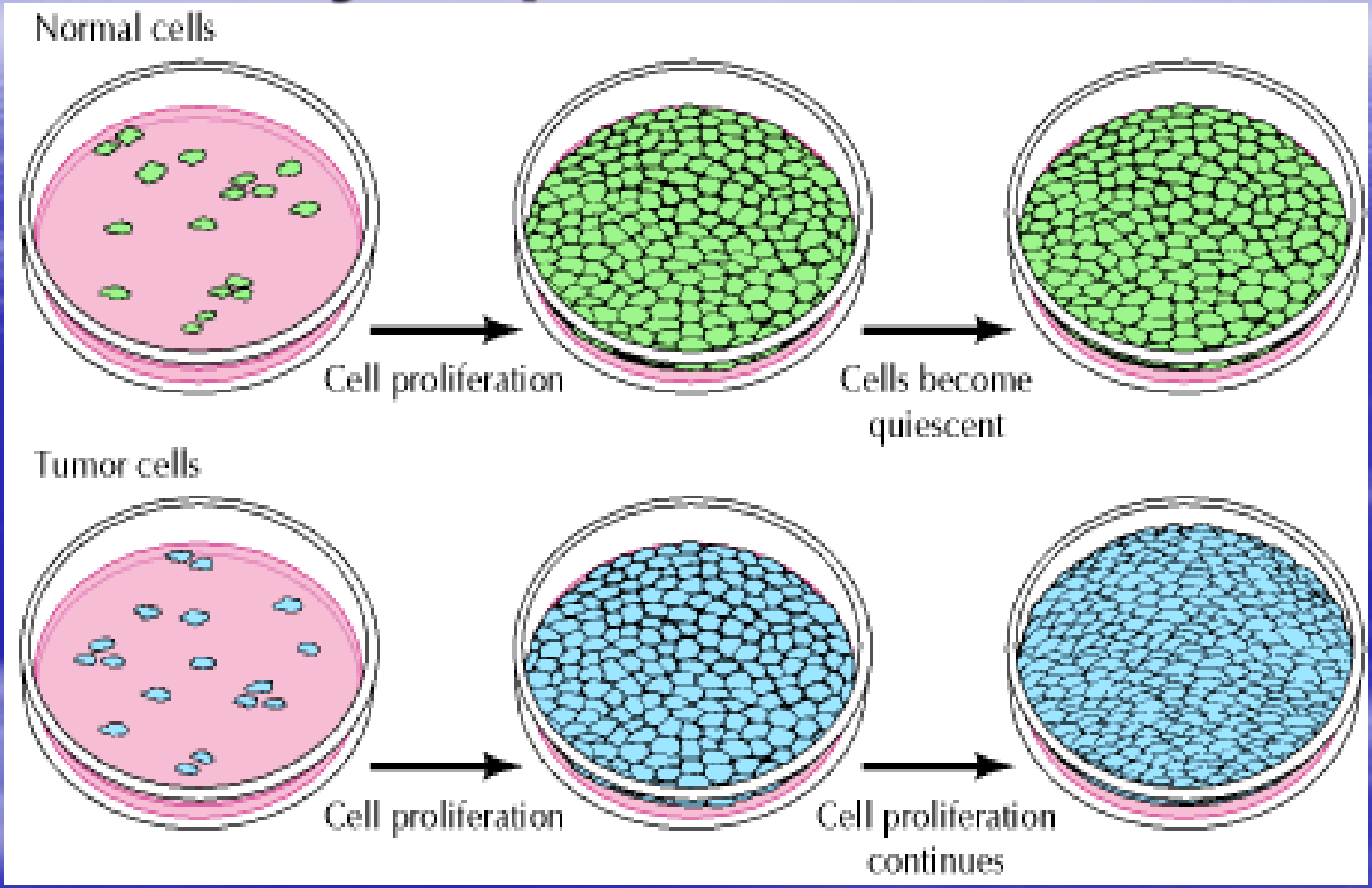
Properties of Cancer cells

Uncontrolled cell division

Cancer cells are **not sensitive to**

- **Density dependent inhibition** of cell proliferation

Density dependent inhibition



Normal cells proliferate in culture until they reach a finite cell density, at which point they become quiescent. Tumor cells, however, continue to proliferate independent of cell density.

Properties of Cancer cells

- **Reduced requirements for Growth factors**
- some produce GFs; autostimulation autocrine GF production
- Abnormalities in intracellular signalling pathways i.e.unregulated activity of
- GF receptors or other proteins (i.e.Ras)

Cancer cells are **insensitive to contact inhibition**

- continue moving after contact with their neighbors,
- migrate over adjacent cells, growing multilayered patterns

Cancer cells loss anchorage dependence

- **less adhesive** than normal cells
- less regulated by cell-cel, cell-matrix interactions
- have spherical shape

(changes in cytoskeleton)

- **Secrete proteases** (i.e collagenase)
- digest extracellular matrix components i.e.basal lamina
- contributes to the ability to invade and metastasize

- **Promote** formation of new blood vessels **(angiogenesis)**

- Fail to undergo **apoptosis** **(immortal)**

  Normal cells divide 50 times in culture.

  Cancer cell divides indefinetely

Metastasis

- Enter blood circulation
- Migrate to distant regions
- Produce secondary tumors

Targets of genetic damage in carcinogenesis

(***Normal growth regulatory genes***)

- The growth promoting genes;

Protooncogenes

Mutant Protooncogenes: Oncogenes

Dominant effect

- The growth inhibiting genes;

Tumor-supressor genes

Recessive effect

- Genes that regulate programmed cell death or **apoptosis**
- The **DNA repair genes**

Mechanisms which convert a proto-oncogene into an oncogene

- Changes in the structure of **proto-oncogenes**

  (point mutation ,translocation,deletion)

  Abnormal gene product
- i.e.Translocation;Philadelphia chromosome (chronic myelogenous leukemia
- Activation **by gene amplification**

  Normal product is overexpressed

N-myc amplification (700 times increase)

in neuroblastoma

Oncogene activation by translocation

1-Philedelphia chromosome

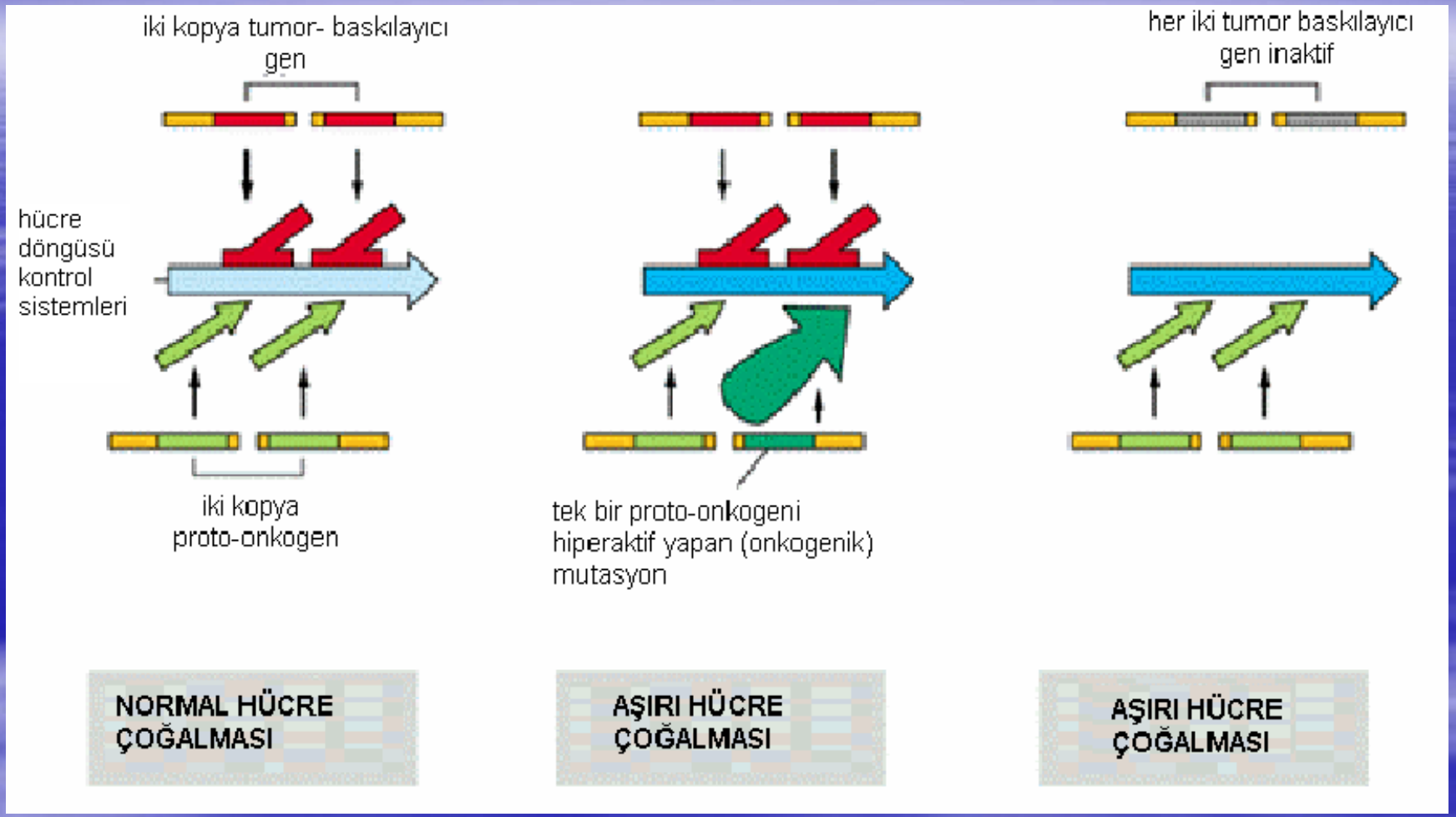
(chronic myelogenous leukemia)

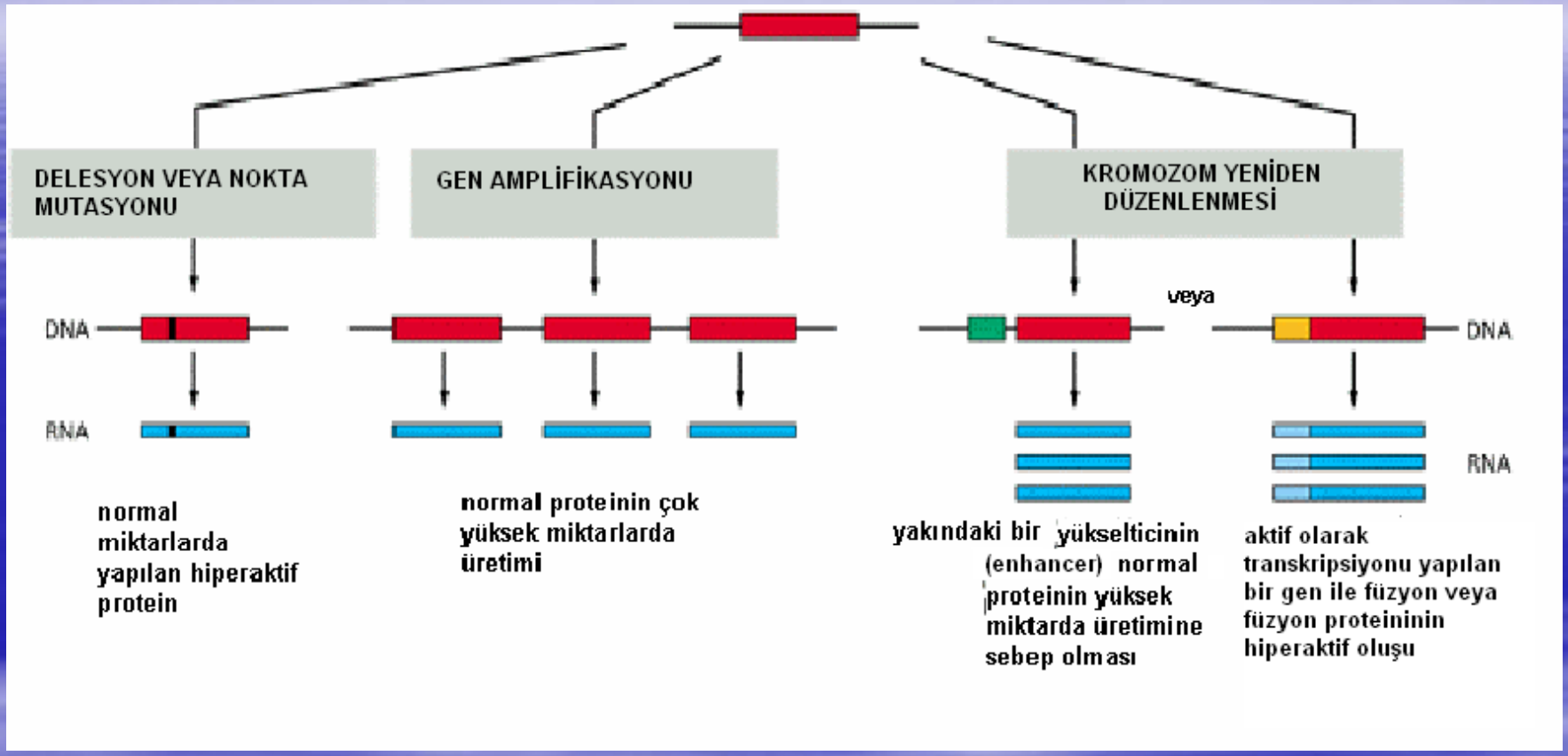
Chromosome 9 (abl) and Chromosome 22(bcr)

Bcr/abl fusion= Oncogene

2-Burkitt lenfoma

Chromosome 8 (c-myc) and Chromosome 14 immunoglobin heavy chain gene


iki kopya tumor- baskılayıcı gen
her iki tumor baskılayıcı gen inaktif
hücre döngüsü kontrol sistemleri
iki kopya proto-onkogen
tek bir proto-onkogeni hiperaktif yapan (onkogenik) mutasyon
NORMAL HÜCRE ÇOĞALMASI
AŞIRI HÜCRE ÇOĞALMASI
AŞIRI HÜCRE ÇOĞALMASI



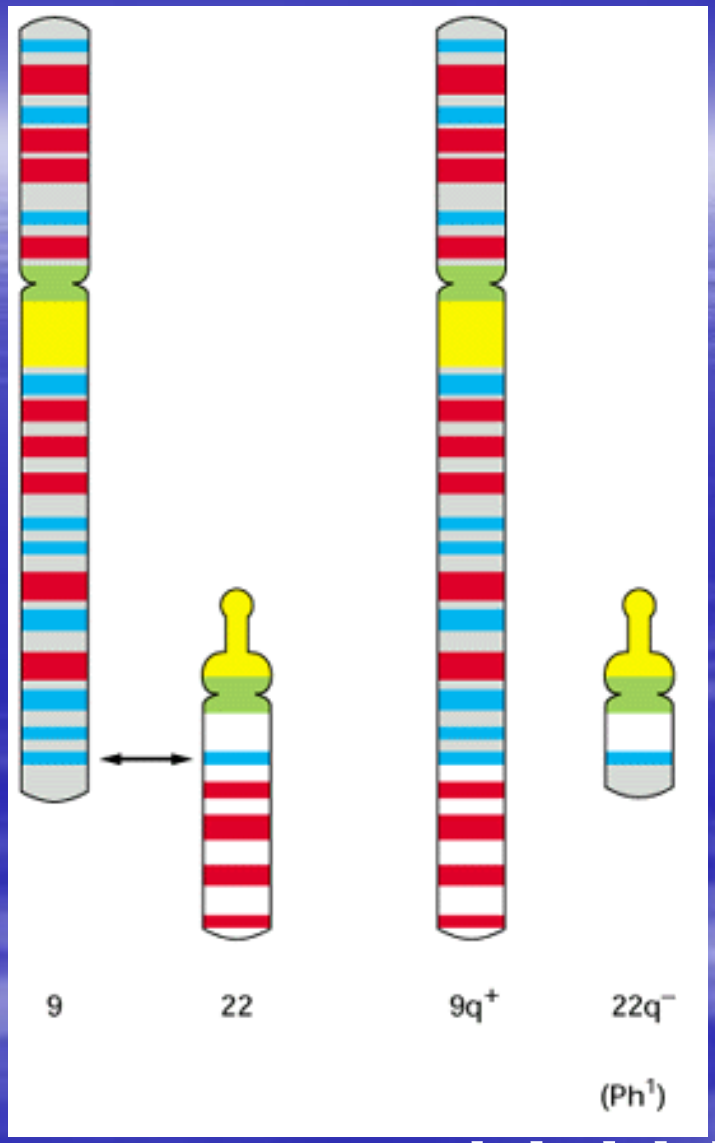
- **Mechanisms which convert a proto-oncogene into an oncogene**

- Oncogene activation

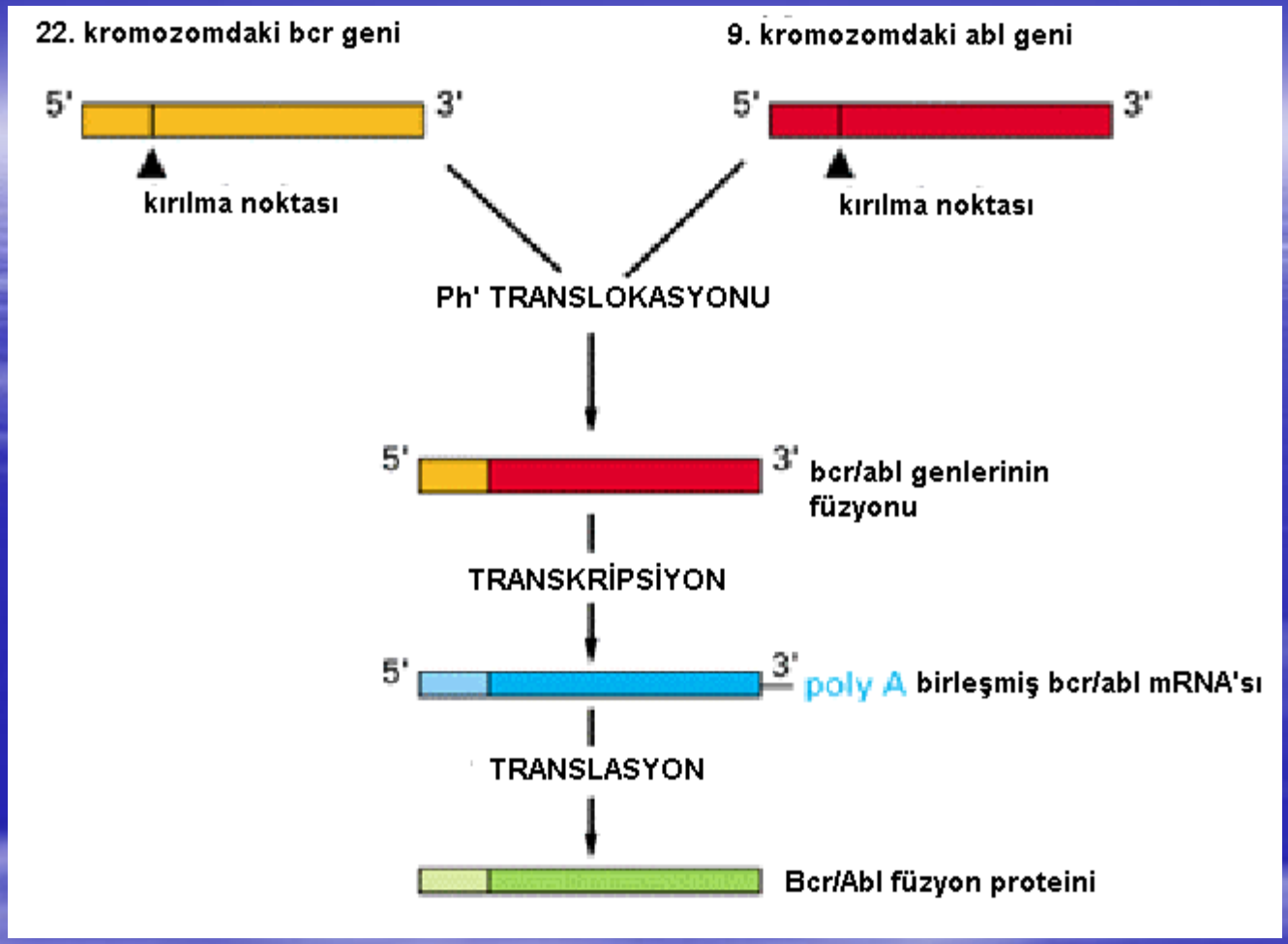
by chromosome

translocation

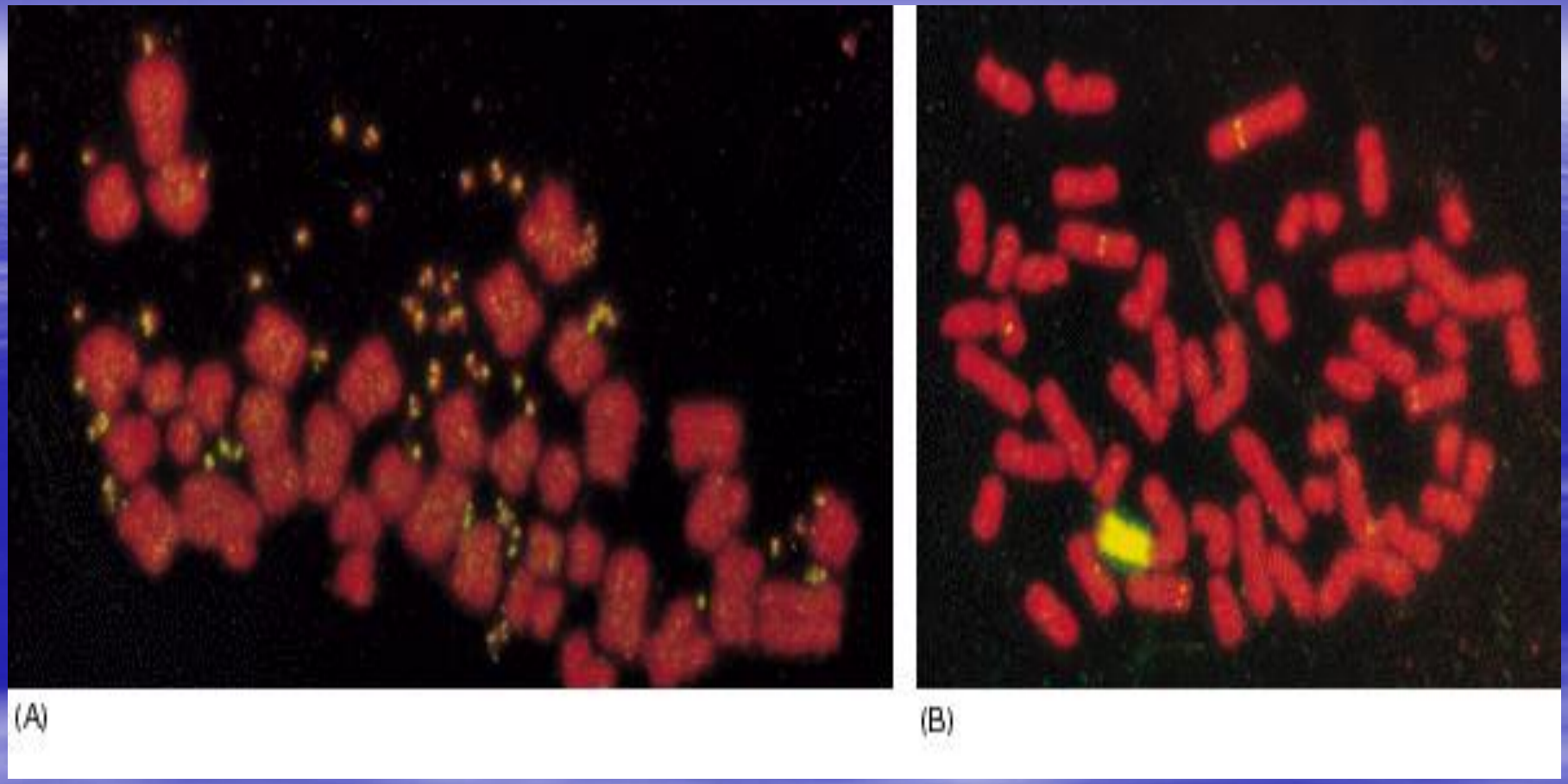
(chronic myelogenous leukemia)



•Philedelphia chromosome



Chromosome translocation converts abl protooncogene into oncogene



Activation by gene amplification (myc amplification)

ONCOGENES

Growth Factor Genes

- c-sis (PDGF heavy chain) , v-sis mutant

astrositoma,osteosarcoma.

(PDGF expression) Autostimulation

GF receptors

- erbB ; EGF receptor (Breast carcinoma)

Intracellular signal transduction proteins

- Ras (GTP binding protein) mutant in colon Ca, pancreas Ca

Nuclear Regulatory Proteins

- Myc,Jun,Fos

p53 (Tumor supressor gene)

- Safety device in G1 check point
- In the presence of DNA damage p53 increase and stop cell division
- Allow time to repair DNA

- Most frequent mutation in human cancers
- İncrease genetic instability

Tumor supressor genes

- Loss of function mutations
- Loss of both of the alleles (recessive)
- Most frequent mutation in human cancers
- İncrease genetic instability

Retinoblastoma (Rb) gene

- İnherited childhood eye tumor
- Rb protein is phosphorylated by cdk4,6/cyclin D
- Loss of function results in tumor development

Tumor supressor genes

- Wilms Tumor Gene (WT)

  (Kidney Tumor)

  Transcription factor

  expressed in Fetal Kidney

- Mammary cancer
  - BRCA1
  - BRCA2

  (DNA repair)

Causes of genetic damage (mutation)

1- **Acquired mutations**

Environmental agents

a-***Carcinogenic chemicals***

- Tobacco smoke (cause of 80 to 90 % of lung cancers)

  smoking is responsible for ~ 1/3 of all cancer deaths
- Aflatoxin (A potent liver carcinogen produced by some molds that contaminate improperly stored grains etc.)

Causes of genetic damage (mutation)

b- ***Radiation***

solar ultraviolet radiation major cause of skin cancer

c- ***Viruses***

tumor viruses:

- Hepatitis B virus ; liver cancer)
  100 fold increased risk of liver cancer)
- papilloma virus ;cervical cancer

2- **inherited mutations**