Genetics of Cancer

Alterations in the Cell Cycle and Gene Mutations that Cause Cancer

How do we define cancer?

Cancer is a group of disorders that causes cells to escape normal controls on cell division

-cancer cells divide more frequently

-cancer cells are not inhibited by contact with other cells and can form tumors

-cancer cells can invade other tissues, a process called metastasis

Control of the Cell Cycle

cells grow, divide, mature, and die=Normal

Mechanisms for controlling progress through the cell cycle:

- ✓Checkpoints
- ✓Length of Telomeres(Hayflick time)
- ✓Chemical Signals from within and outside the cell

Failure to Stop at Cell Cycle Checkpoints

Mutation in a gene that usually slows the cell cycle	Rate of cell division is accelerated.
Failure to pause for DNA repair	Faulty DNA leads to unregulated cell growth.
Loss of control over telomere length	Cancer cells have telomerase, an enzyme that elongates telomeres. Cells continue to divide after 50 mitoses.

Chemical Signals that Control the Cell Cycle

1. Cyclin and Kinase

   -proteins that initiate mitosis

   -requires buildup of cyclin to pair with kinase

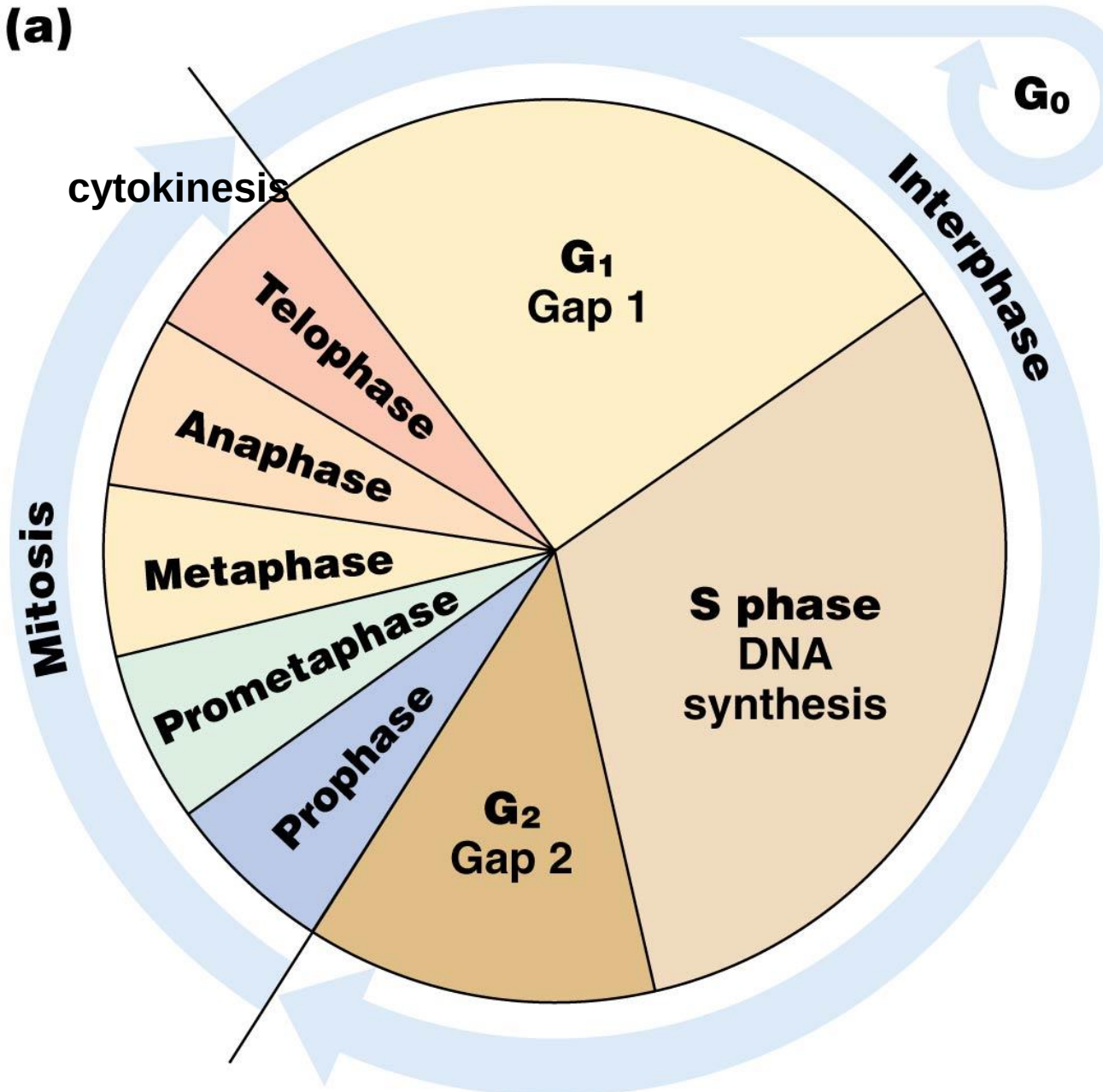
2. Hormones

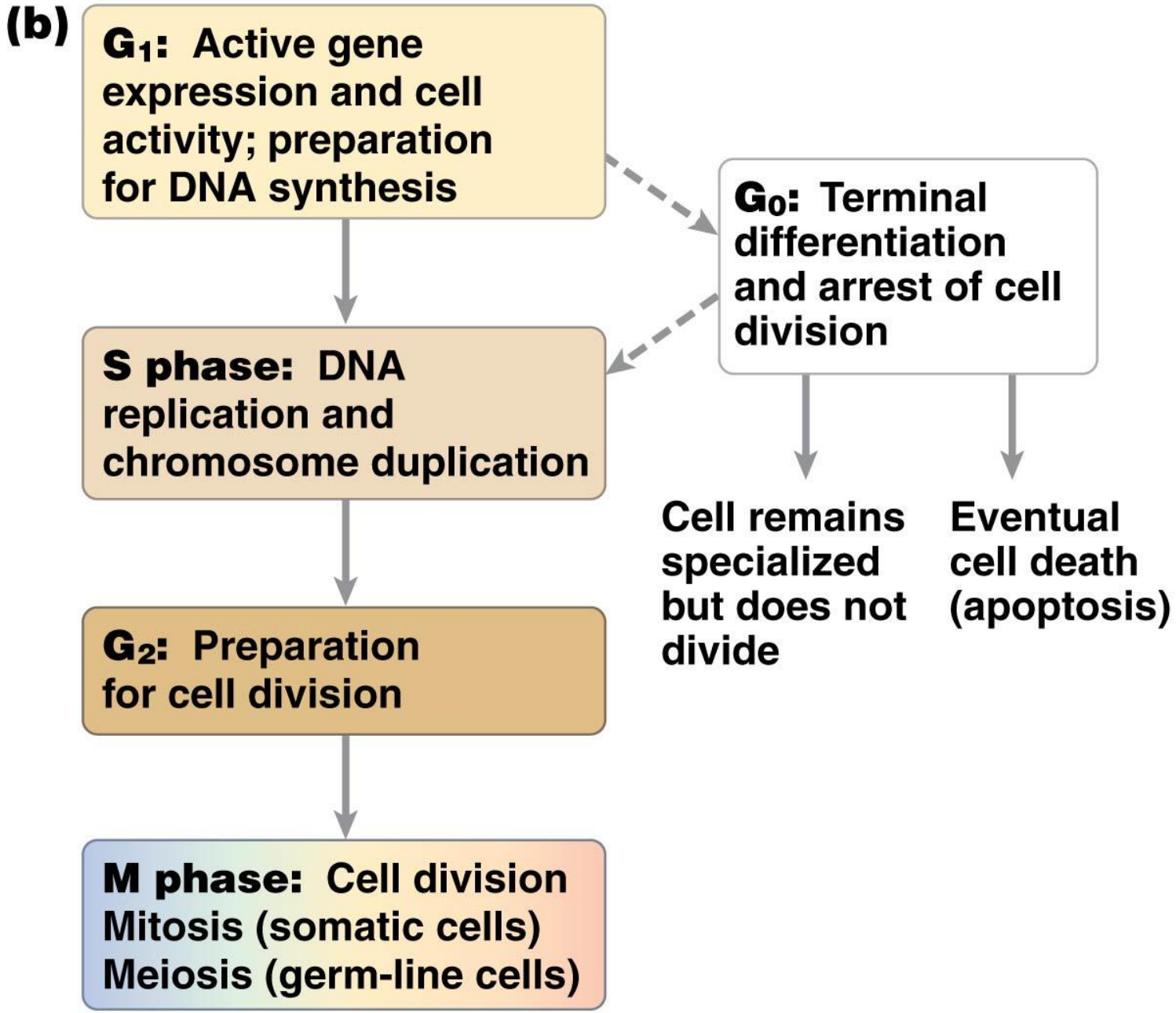
   -chemical signals from specialized glands that stimulate mitosis

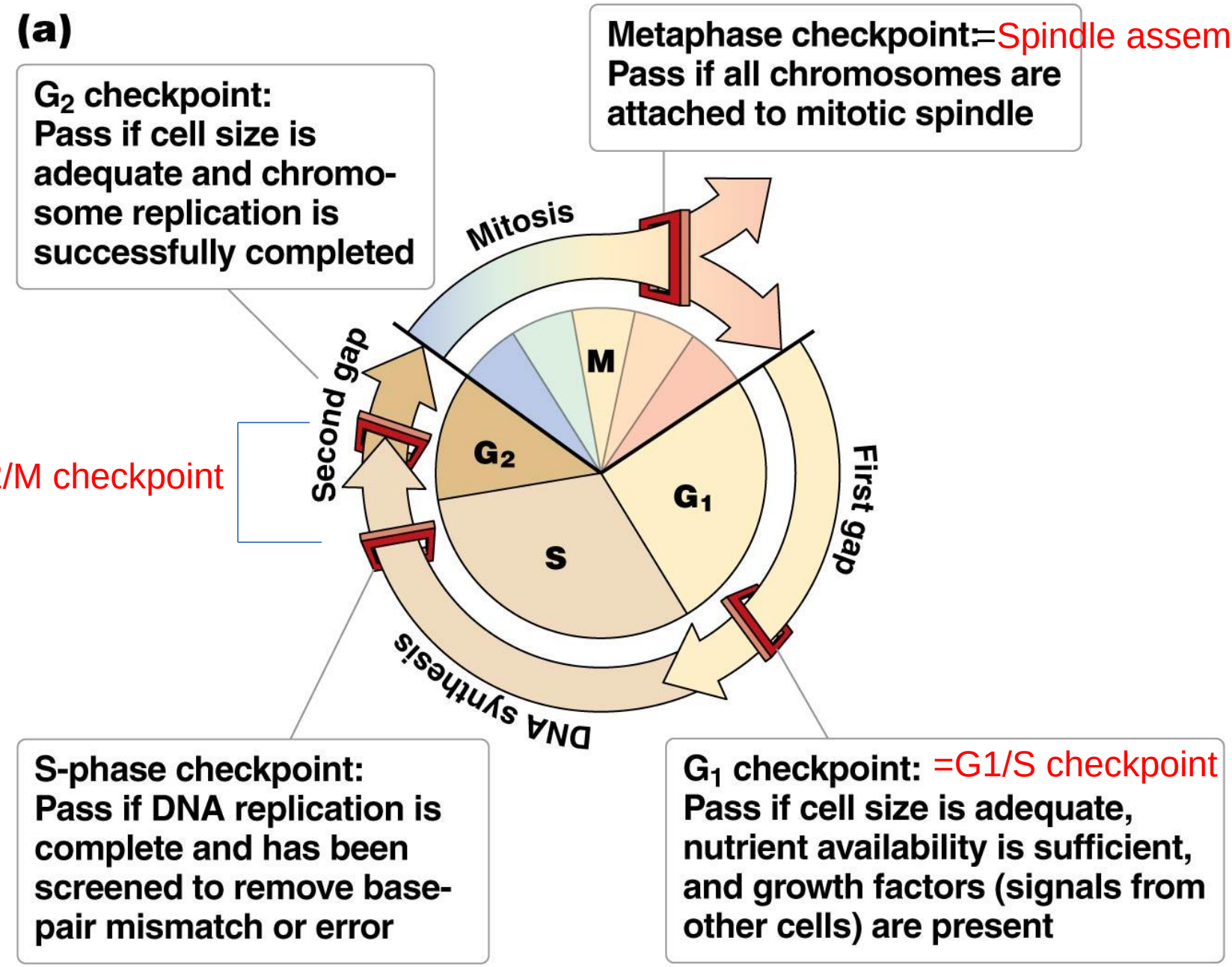
3. Growth Factors

   -chemical factors produced locally that stimulate mitosis

The cell cycle: the genetic information for all characteristics are passed from parent to daughter cells



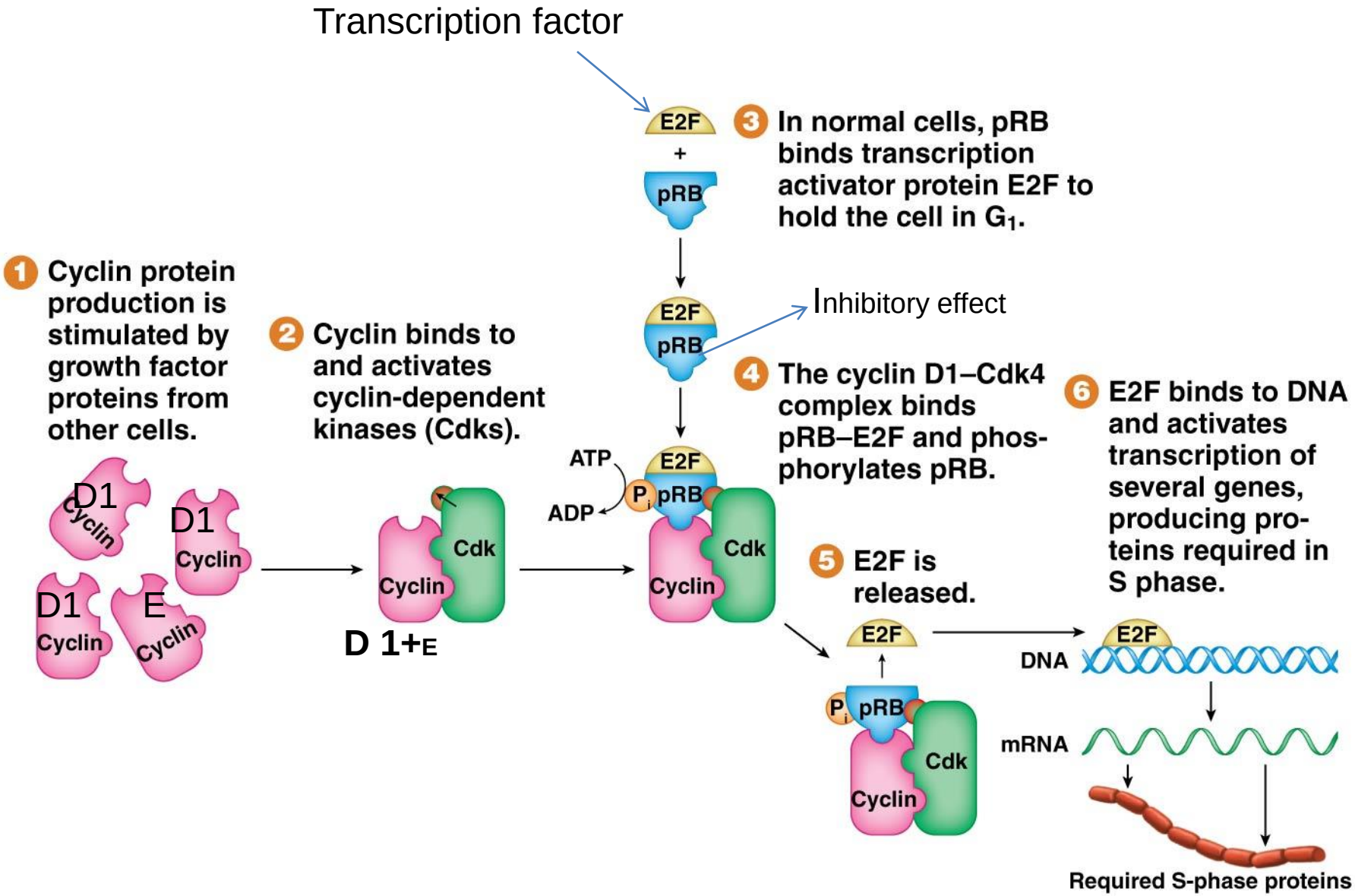

(b)
G1: Active gene expression and cell activity; preparation for DNA synthesis
S phase: DNA replication and chromosome duplication
G2: Preparation for cell division
M phase: Cell division
Mitosis (somatic cells)
Meiosis (germ-line cells)
G0: Terminal differentiation and arrest of cell division
Cell remains specialized but does not divide
Eventual cell death (apoptosis)


(a)
Metaphase checkpoint: Pass if all chromosomes are attached to mitotic spindle
=Spindle assembly
G2 checkpoint: Pass if cell size is adequate and chromosome replication is successfully completed
Mitosis
M
G2
G1
S
Second gap
First gap
DNA synthesis
G2/M checkpoint
S-phase checkpoint: Pass if DNA replication is complete and has been screened to remove base-pair mismatch or error
G1 checkpoint: =G1/S checkpoint
Pass if cell size is adequate, nutrient availability is sufficient, and growth factors (signals from other cells) are present

cyclin-dependent kinases (CDKs)

- Phosphorylation
- functional = associate with another protein called **cyclin.**

G1/S checkpoint: retinoblastoma



The RB1 Gene Is a Tumor Suppressor Gene

- The unphosphorylated pRB acts like a brake on the cell cycle, preventing progression to S phase
- It is one of many proteins known as tumor suppressors, with roles in blocking the cell cycle
- The gene RB1, which produces pRB, is a **tumor suppressor gene**

The Cyclin D1 Gene Is a Proto-Oncogene

- The gene *cyclin D1* leads to formation of the cyclin D1-Cdk4 complex that stimulates the cell cycle to enter S phase

- Cyclin D1 is a **proto-oncogene**, defined as a gene that when expressed stimulates cell cycle progression

Cell Cycle Mutations and Cancer

- Normal cells proliferate only when needed, in response to signals from growth factors

- Cancer is characterized by out-of-control proliferation of cells that can invade and displace normal cells

Mutations Related to Cancer Development

- Two kinds of mutations alter cyclin D1-Cdk4 and pRB interactions
- Some mutations increase the number of copies of *cyclin D1*
- Higher-than-normal levels of cyclin D1 interact with the constantly available Cdk4 to promote uncontrolled entry into S phase, due to constant phosphorylation of pRB

Mutations Related to Cancer Development, continued

- A second kind of mutation affects *RB1;* it produces a pRB that binds weakly or not at all to E2F

- This can cause uncontrolled entry into S phase due to the constant availability of E2F to activate genes needed for S phase progression

- Several types of cancers are associated with RB1 mutations, including retinoblastoma, and bladder, lung, bone, and breast cancers

G2/M checkpoint: mitosis-promoting factor(MPF)

- ↑cyclin B +CDK = inactive complex called MPF
- MPF activated by activating factors (dephosphorylation)

- ↑↑[MPF]= phosphorylates other proteins= many events associated with mitosis:

  nuclear-membrane breakdown, spindle formation, and chromosome condensation.

Keep in Mind

DNA damage= inhibits the activation of MPF; consequently, the cell is arrested in G2 and does not undergo division

Spindle-assembly checkpoint

- cyclin B is degraded=↓ amount of MPF and initiating anaphase

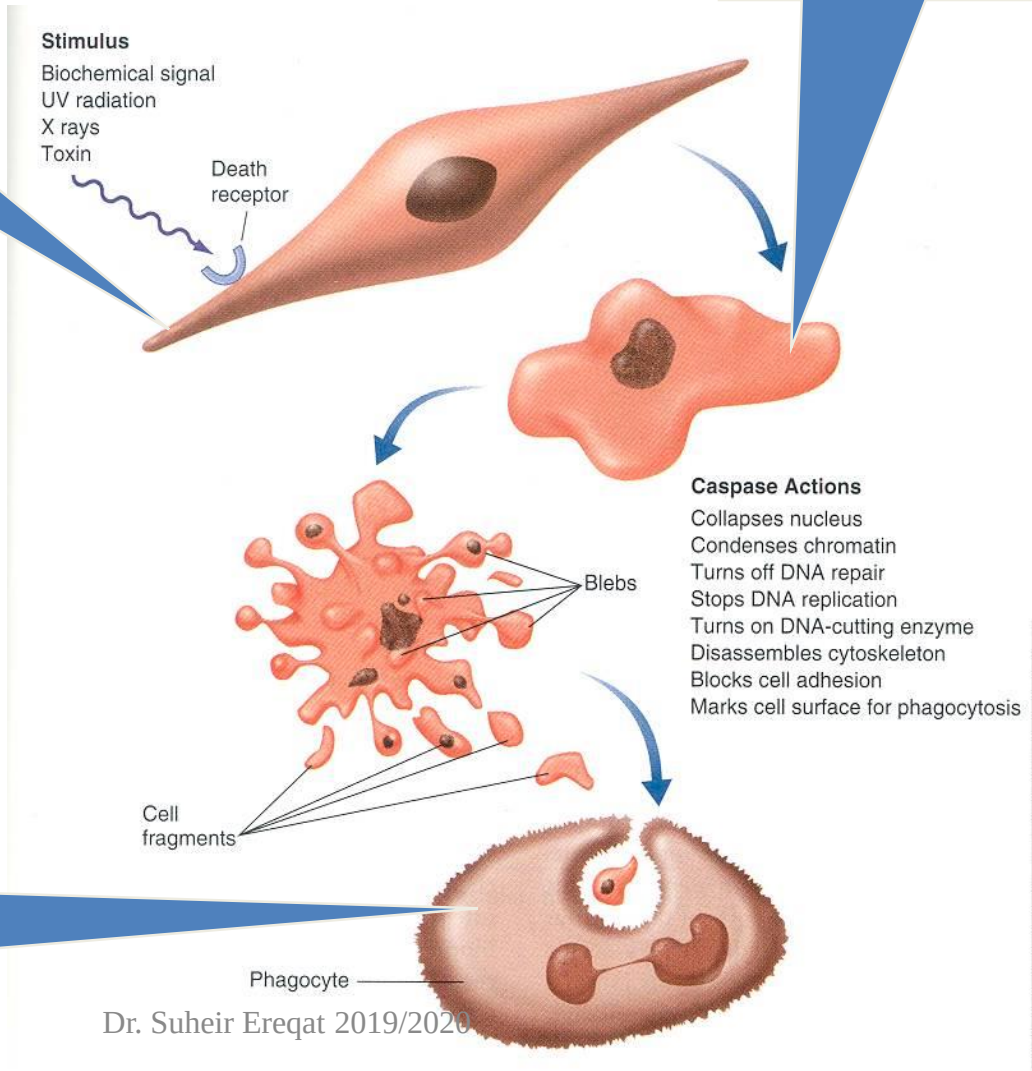
- But this checkpoint delays the onset of anaphase until all chromosomes are aligned on the metaphase plate and sister kinetochores are attached to spindle fibers from opposite poles.

- If all chromosomes are not properly aligned, the checkpoint blocks the destruction of cyclin B.

Apoptosis: Cell Death

Caspase enzymes carry out cell destruction

Signal arrives at “death” receptor on cell



White blood cells destroy cell fragments

Cancer: a genetic disease?

The environment (smoking, radiation), the main cause of cancer=most cancers are preventable.

How many mutant genes are required to produce cancer?

A mutation in a single gene is not enough to produce cancer. Mutations in many important genes are required.

Types of cancer can be hereditable

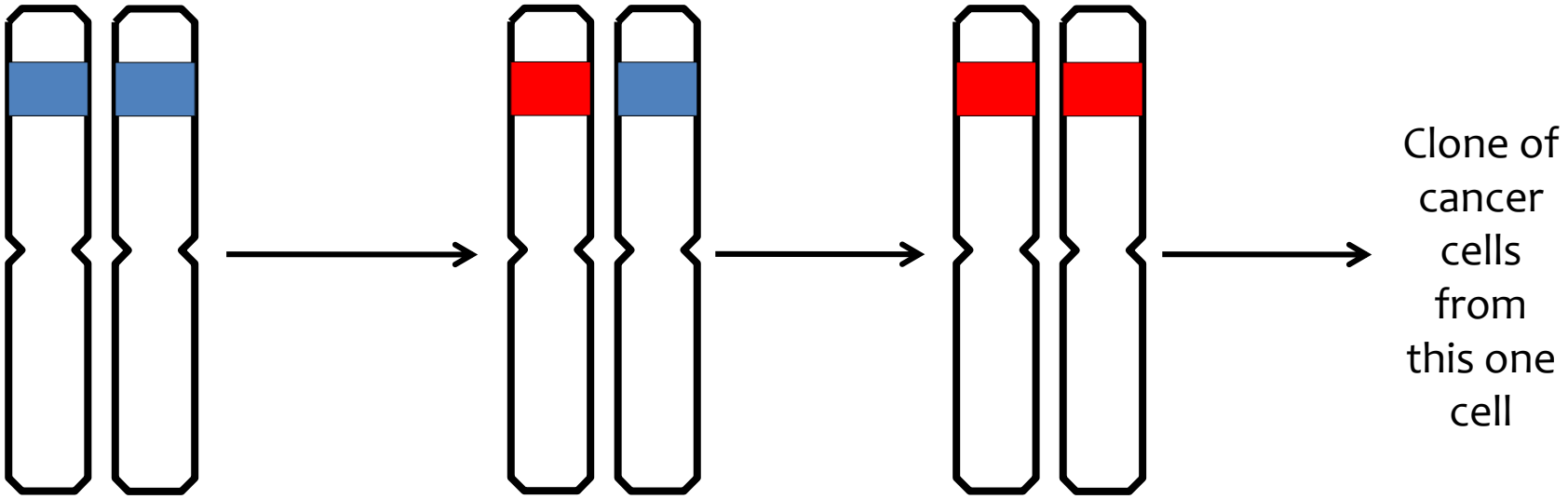
It is now believed that cancer is caused by genetic mutation most often, by a series of mutations, some of may be **inherited**

Some people are more likely to develop certain cancers ,because they have inherted mutations in cancer – related genes. Example:women with BRCA (breast cancer)

Why does cancer tends to strike older people?

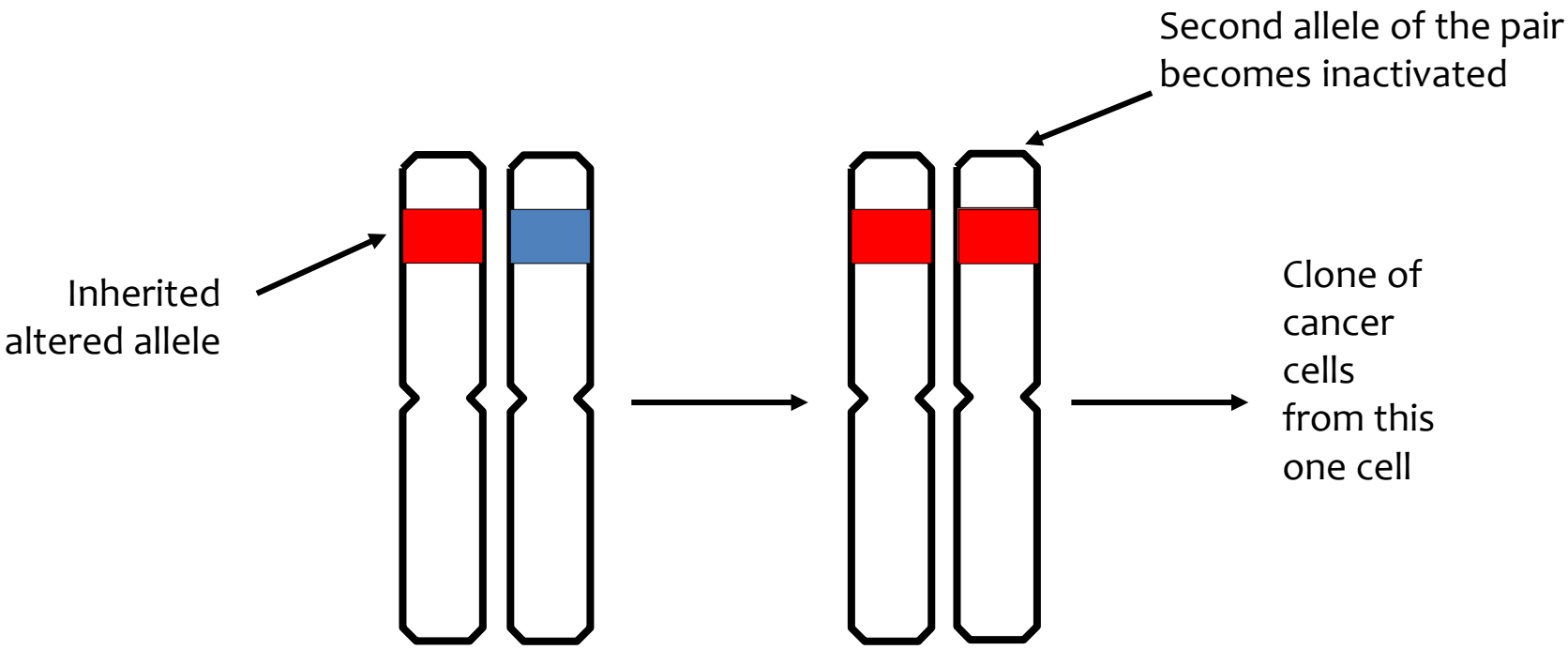
The genetic basis of sporadic cancer

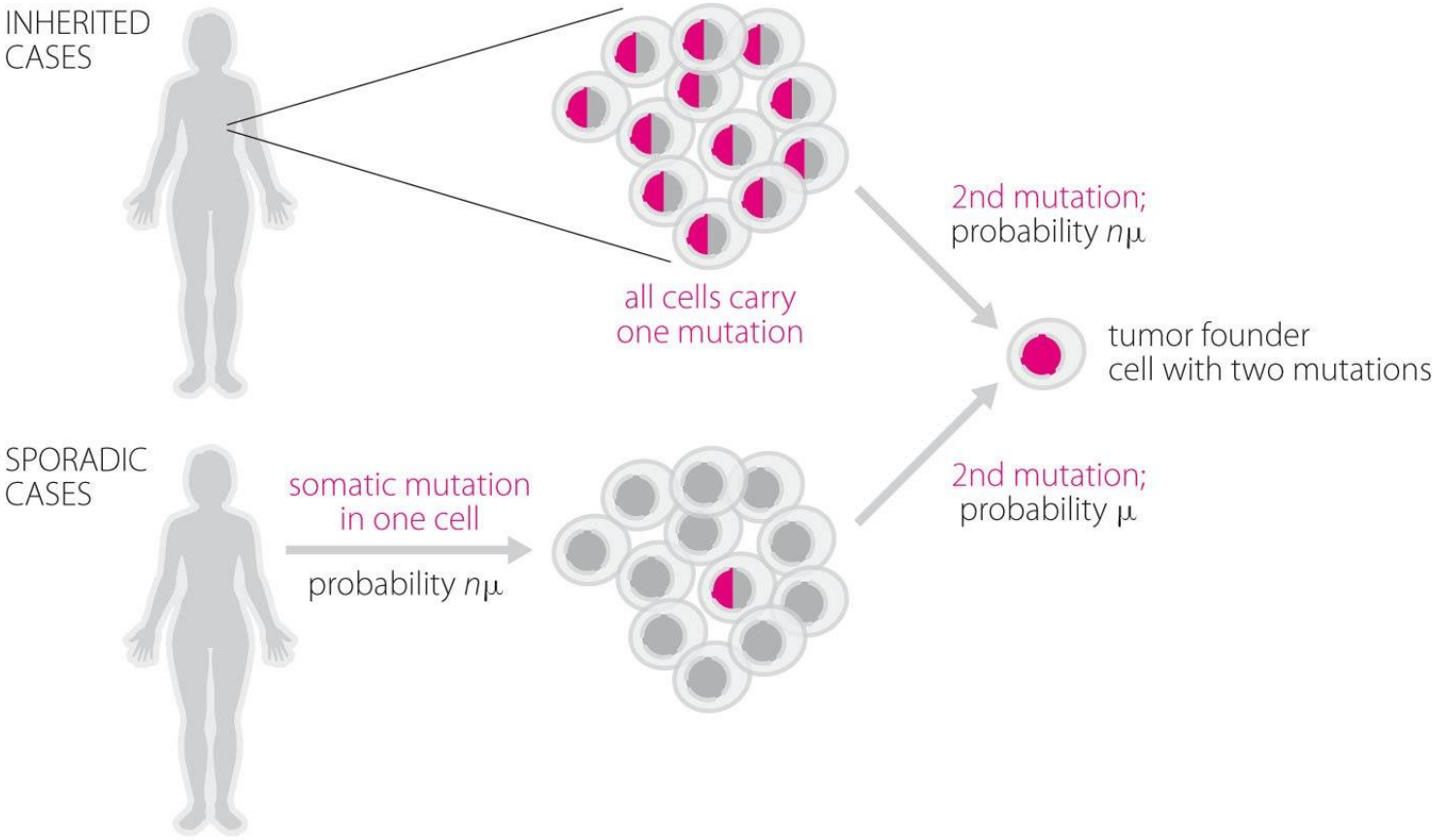
Both alleles of a gene become inactivated *in a particular somatic cell* leading to loss of control of growth and unchecked cell proliferation.



The genetic basis of the dominantly inherited familial cancer syndromes

An altered allele is inherited and so is in all body cells containing genetic material. When the second (previously normal) allele of the gene pair becomes inactivated *in a particular somatic cell* this leads to loss of control of growth and unchecked cell proliferation.




INHERITED CASES
all cells carry one mutation
2nd mutation; probability $n\mu$
tumor founder cell with two mutations
SPORADIC CASES
somatic mutation in one cell
probability $n\mu$
2nd mutation; probability μ

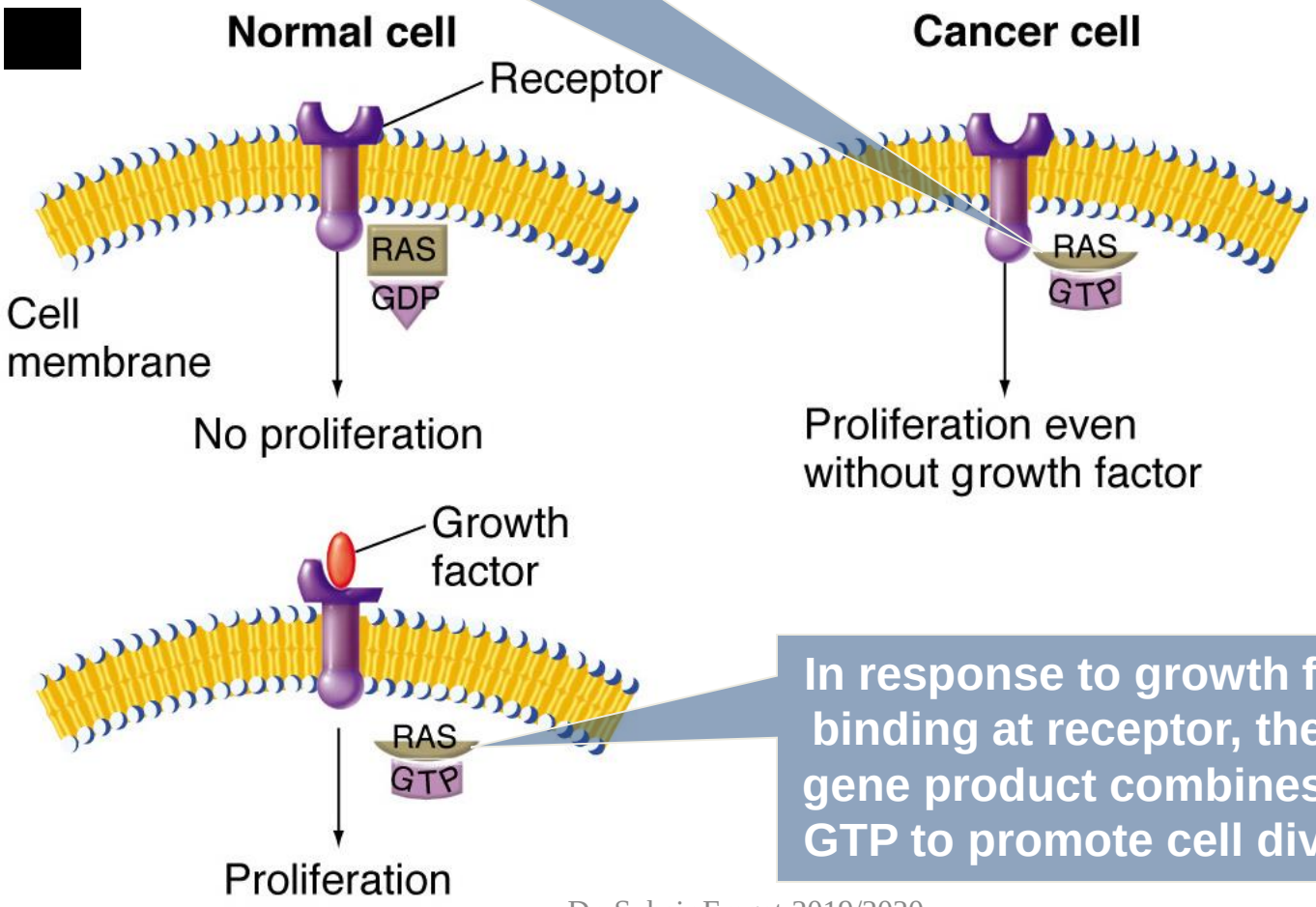
Genetic Mutations That Can Cause Cancer

Oncogenes

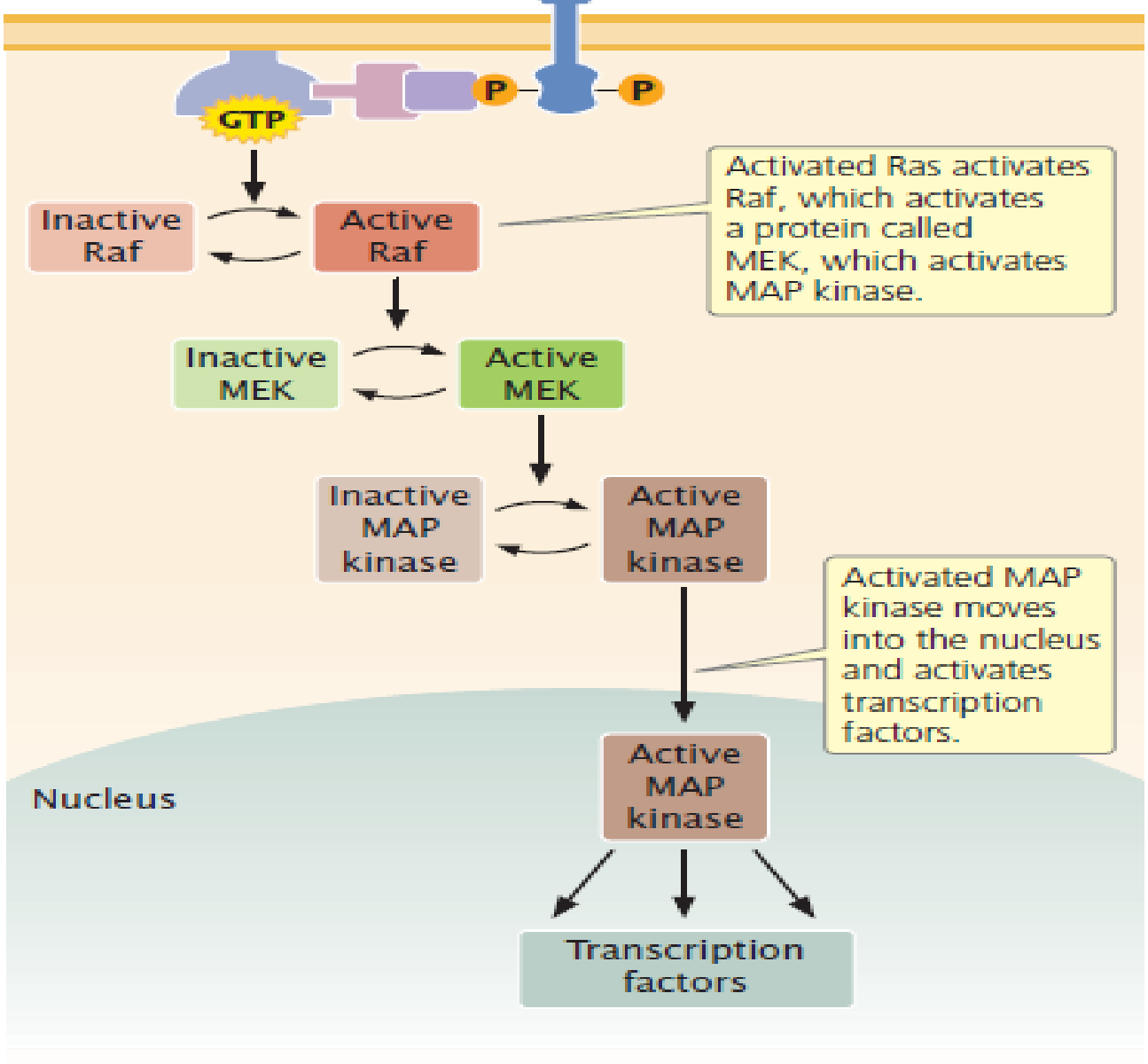
- Formed when proto-oncogenes that promote cell division are improperly activated.
  May lead to
  - increased expression of the gene in a new location
  - production of fusion proteins with new functions

Ras =Proto-Oncogene

In cancer cells, the RAS gene product is locked into its GTP-binding shape and does not require a signal at the receptor in order to stimulate cell division

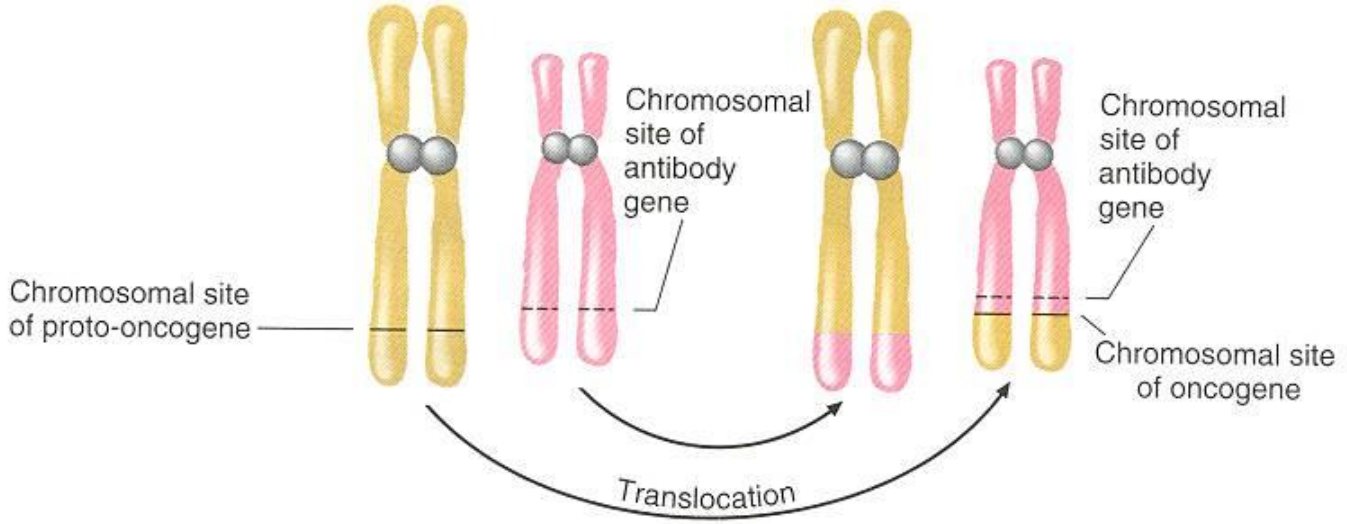


In response to growth factor binding at receptor, the Ras gene product combines with GTP to promote cell division



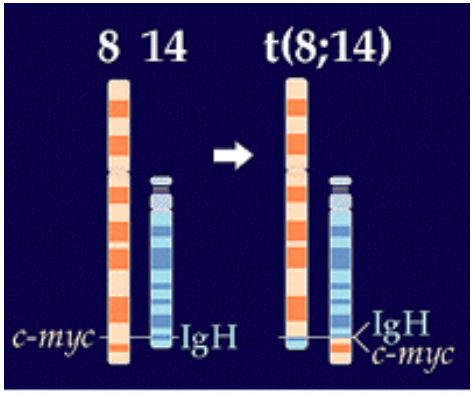
23.9 The Ras signal-transduction pathway conducts signals from growth factors and hormones to the nucleus and stimulates the cell cycle. Mutations in this pathway often contribute to cancer.

chromosome rearrangements are associated with certain types of cancer



Movement of a proto-oncogene on chromosome 8 to the vicinity of a highly active gene on chromosome 14 causes Burkitt's lymphoma.

Burkitt Lymphoma



In Burkitt lymphoma, Myc, which is normally found on chromosome 8, is transferred to chromosome 14. This is known as chromosome translocation and can be characteristic of a cancer type. [image credit: Gregory Schuler, NCBI, NLM, NIH.]

Translocation of the *Myc* gene on chromosome 8

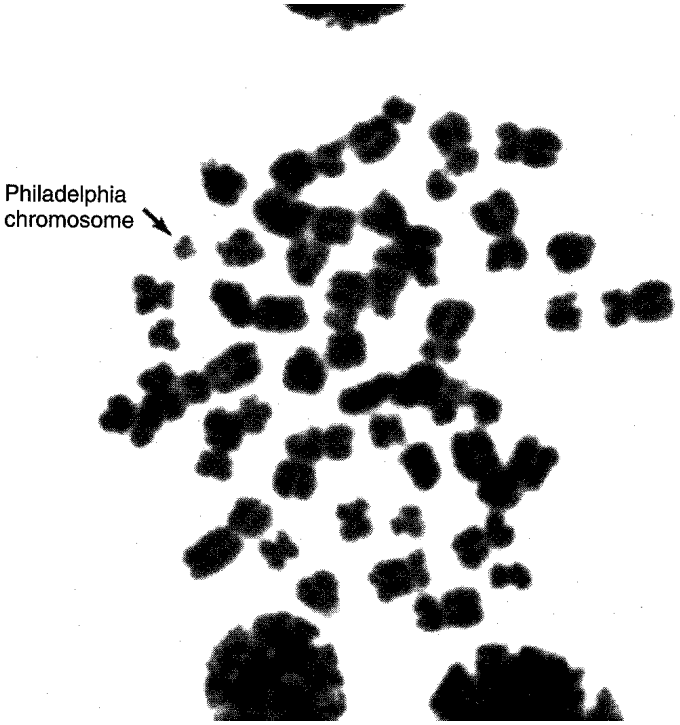
Normal Myc genes control cell growth and division

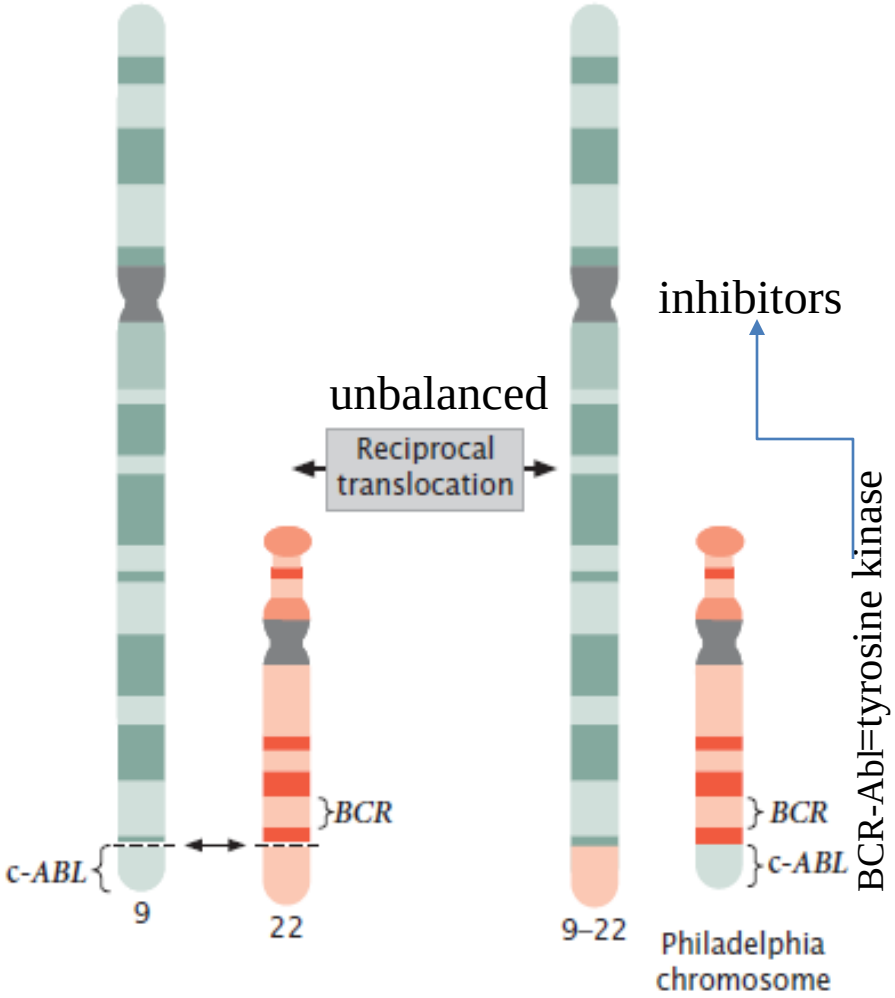
•Translocated *Myc* genes don't function properly

(under control of regulatory sequences that normally activate the production of Igs)

•Leads to cancer of the lymph nodes

CML



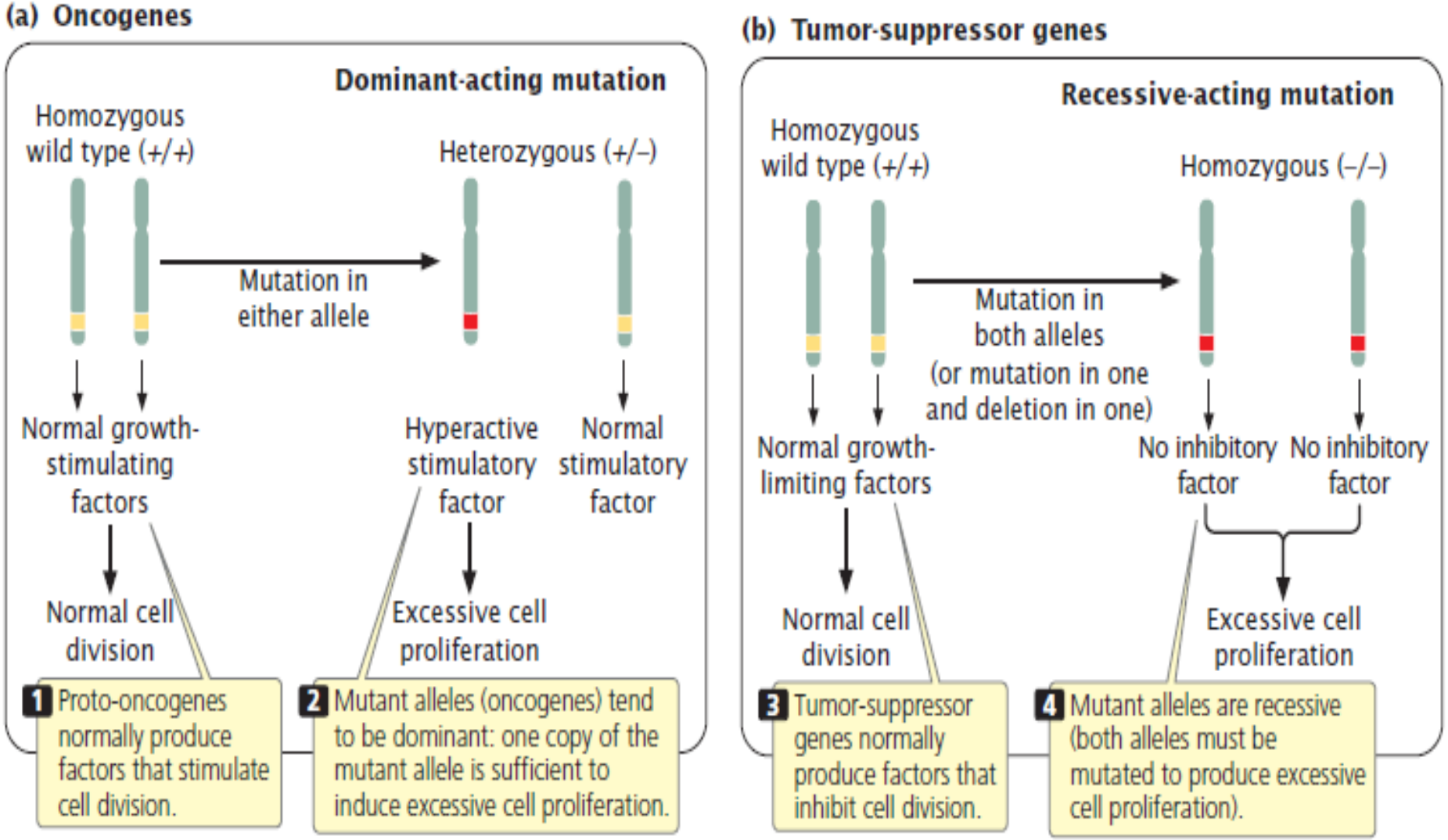


The Philadelphia Chromosome found in patients with Chronic Myeloid Leukemia causes a fusion protein to be made from a combination of genes on chromosomes 9 and 22.

Genetic Mutations That Can Cause Cancer

Tumor Suppressor Genes

- Genes that inhibit cell division are inactivated.
  - Mutation in a gene that halts the cell cycle in G1 causes retinoblastoma.
  - Mutation in p53, a gene that promotes apoptosis if a cell has damaged DNA, leads to a variety of cancers.
  - Mutation in BRCA1, involved in tumor suppression and DNA repair, leads to inherited breast cancer.

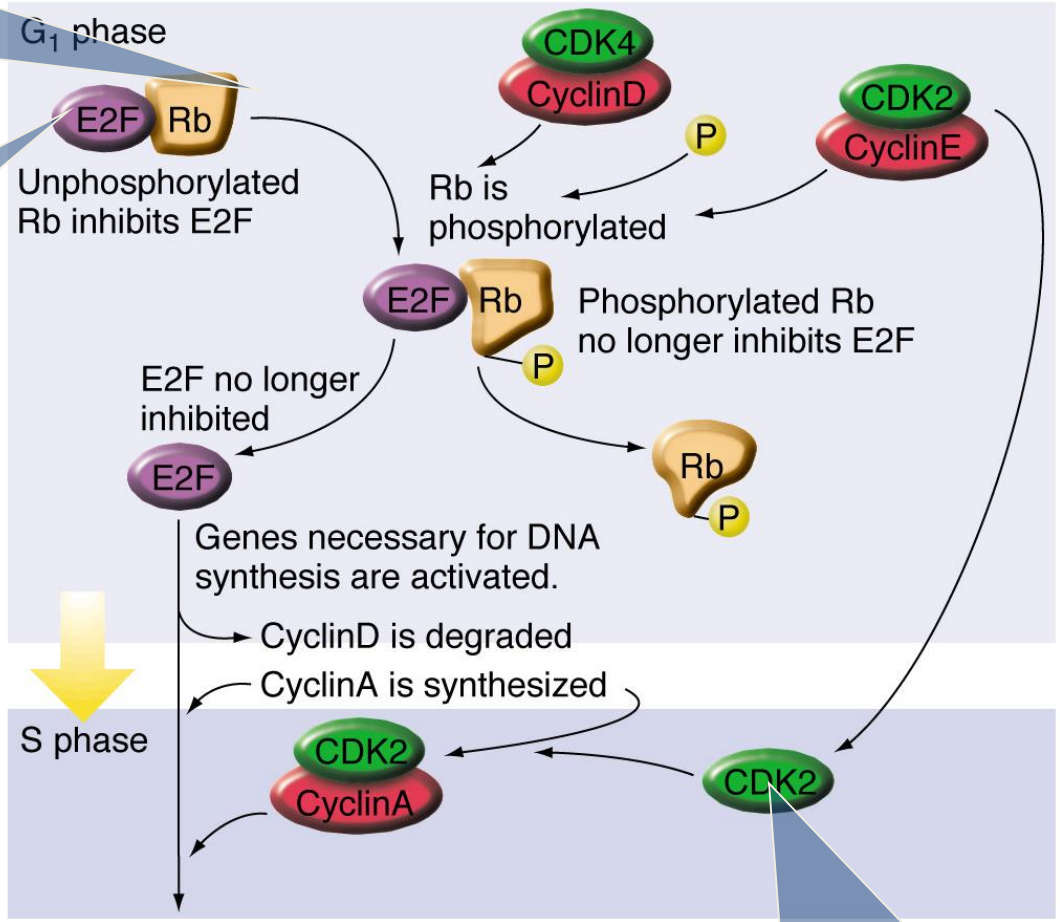


23.5 Both oncogenes and tumor-suppressor genes contribute to cancer but differ in their modes of action and dominance.

In Normal Cells, the Rb Gene Product Controls the G1→ S Transition

Rb = product of Retinoblastoma gene, inhibits action of E2F until chemically modified

E2F = transcription factor required to activate genes for DNA synthesis

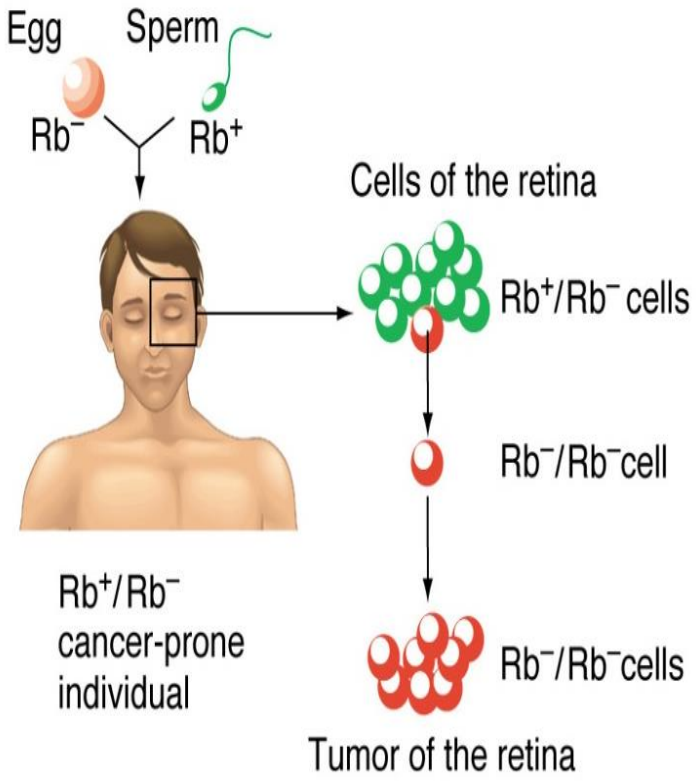


CDK-cyclin (intracellular signal) modifies Rb so the E2F can mediate the G1→S transition

What is Retinoblastoma?

- Tumor of the eye that can occur at a high frequency in children and sporadically at an older age.
- Occurs in hereditary and non-hereditary forms (sporadic).
- Caused by a deletion on chromosome 13 with a locus of 13q14.

RB gene



People prone to retinoblastoma have one mutated copy of the Rb gene (Rb-) and one normal copy (Rb^+). Conversion of the Rb^+ copy to Rb^- by mutation leads to uncontrolled growth of retinal cells.

Hereditary Retinoblastoma

- Inherited as a dominant genetic trait.
- Members of high-risk families inherit one normal allele and one abnormal allele.
- Children that inherit an abnormal allele inherit a strong disposition for developing the disease.
- After retinal cell undergoes one spontaneous mutation, it is left with two mutated alleles.
- Cell divides uncontrollably giving rise to retinal tumor.
- Develops at a young age and affects both eyes.

Sporadic Retinoblastoma

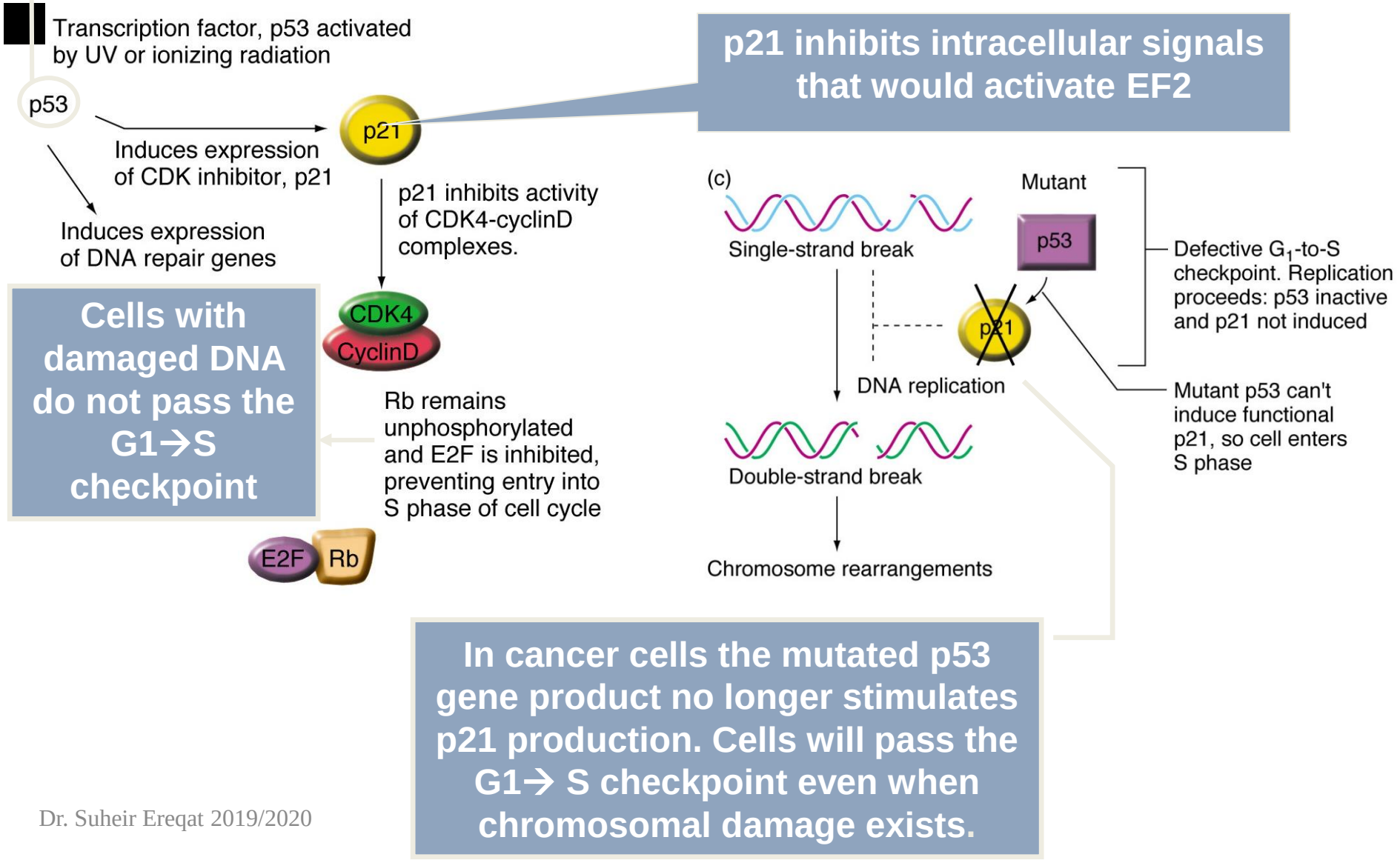
- Very rare.
- Requires that **two separate spontaneous** mutations must occur in the RB gene.
- Retinoblastoma occurs only after both alleles carry the mutation.
- Cell divides uncontrollably giving rise to retinal tumor.
- Develops at an older age and affects only one eye.

P53- The guardian of the genome

- The most gene studied ever. More than 62,800 scientific publication.
- The most mutated gene ever.
- Determine the fate of the cell when exposed to DNA damage or stresses.
- It’s a transcription factor.
- Cancer cant withstand functional p53 pathway.
- All cancers have mutations in p53 or its signaling pathways.

p53 = transcription factor that causes p21 to be produced

In Normal Cells, the p53 Gene Product
Acts at the G1→ S Checkpoint Preventing Entry Into S Phase If DNA Is Damaged

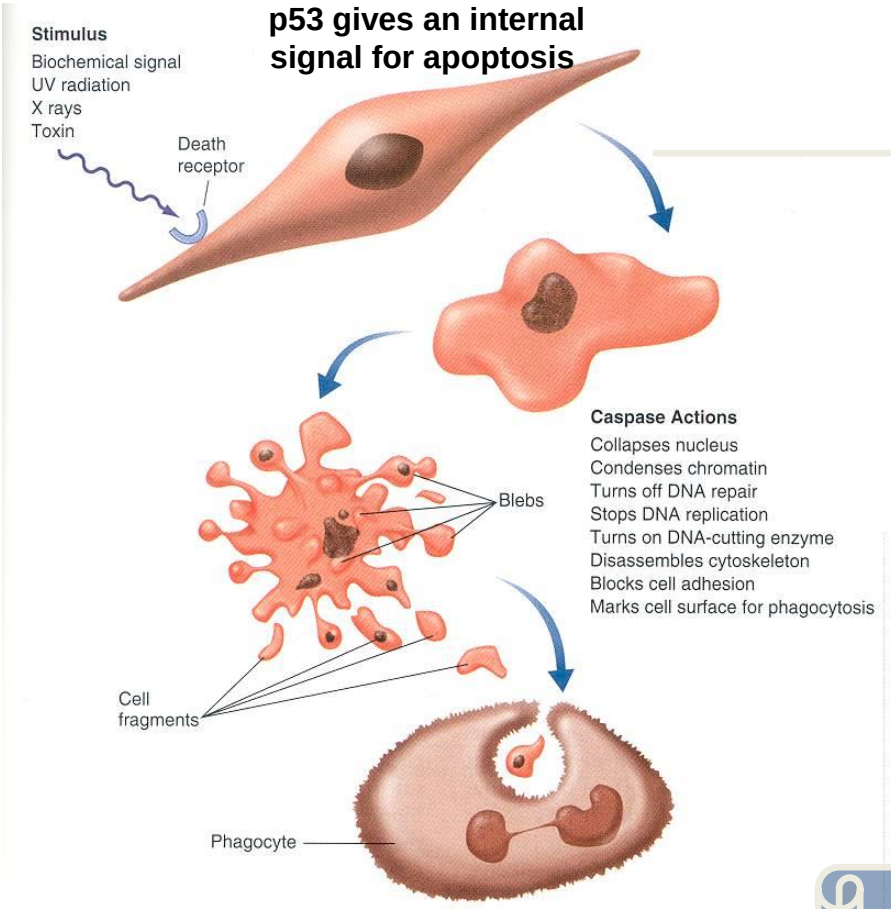


p21 inhibits intracellular signals that would activate EF2

Cells with damaged DNA do not pass the G1→S checkpoint

In cancer cells the mutated p53 gene product no longer stimulates p21 production. Cells will pass the G1→ S checkpoint even when chromosomal damage exists.

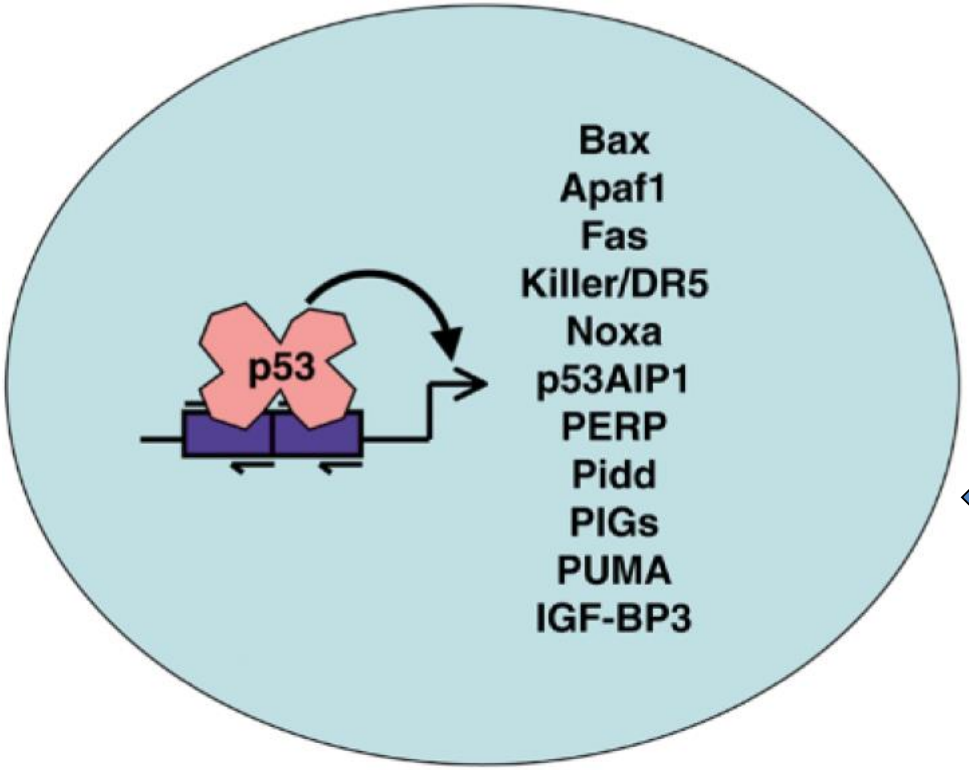
In Normal Cells, the p53 Gene Product Stimulates Apoptosis If DNA Damage Cannot Be Repaired



In cancer cells, a mutated p53 gene product no longer initiates self-destruction. Cells with damaged DNA can divide and more DNA damage can be accumulated.

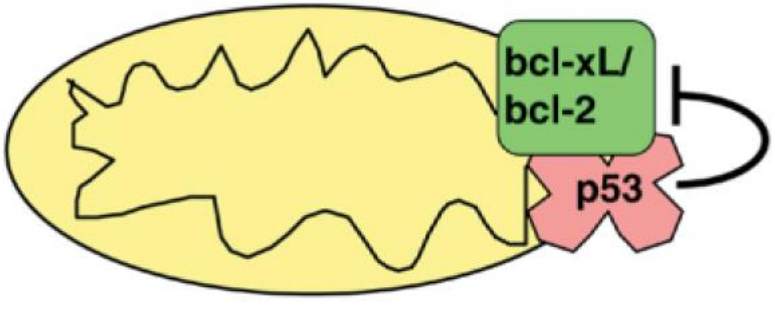
p53 is the most frequently mutated of all known cancer-causing genes, contributing to many types of cancer.

How p53 effect apoptosis



P53 transcribes pro-apoptotic factors

APOPTOSIS

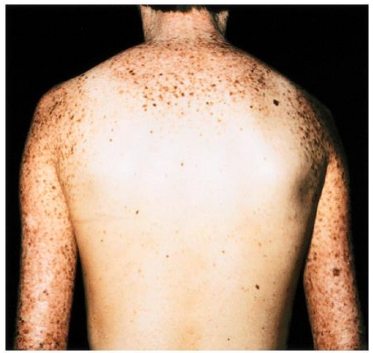


P53 inhibits survival factors

Genetic Mutations That Can Cause Cancer

DNA Repair Genes

- Genes that promote DNA repair are inactivated.
  - BRCA1 is a tumor suppressor involved in DNA repair. Faulty copies of BRCA1 cause inherited breast cancer.
  - The disease Xeroderma Pigmentosum results from a defect in N-excision repair.
  - Hereditary nonpolyposis colorectal cancer =HNPCC(missmatch repair defect)



Applying Your Knowledge

Indicate whether each statement is TRUE or FALSE:

- Oncogenes are formed by mutations of genes that normally stimulate cell division.
- Cancer-causing mutations in tumor suppressor genes inhibit cell division

A typical progression of cancer

Oncogene

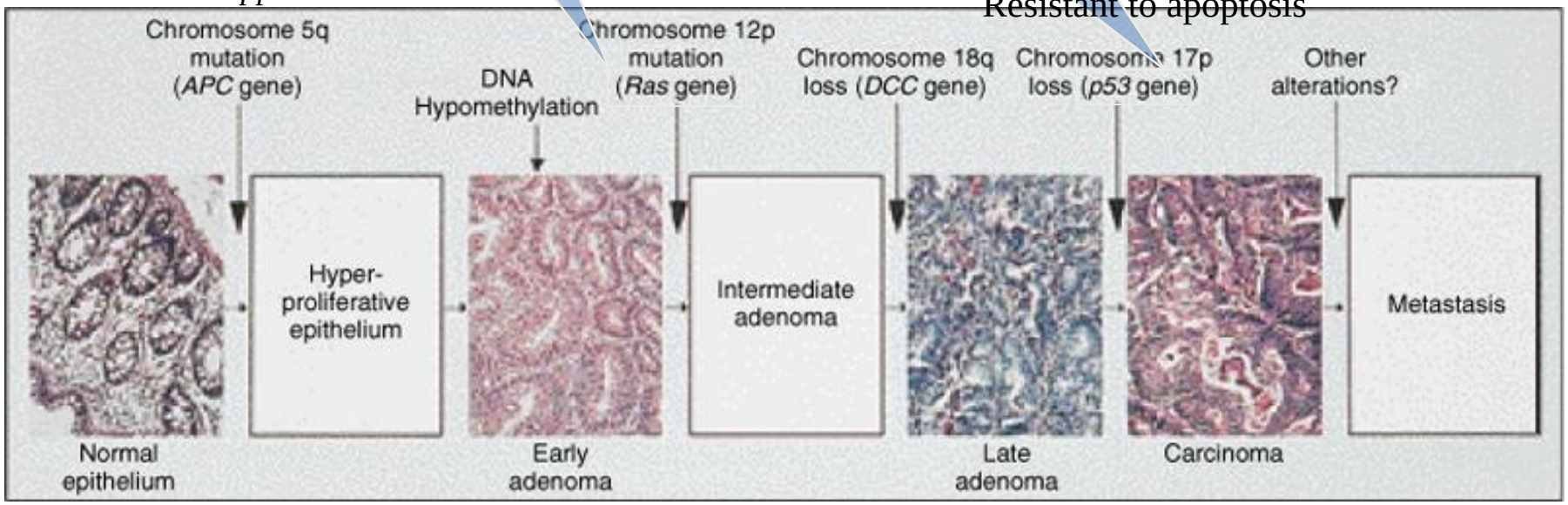
Tumor Suppressor Gene

80%

Tumor suppressor

50-60%

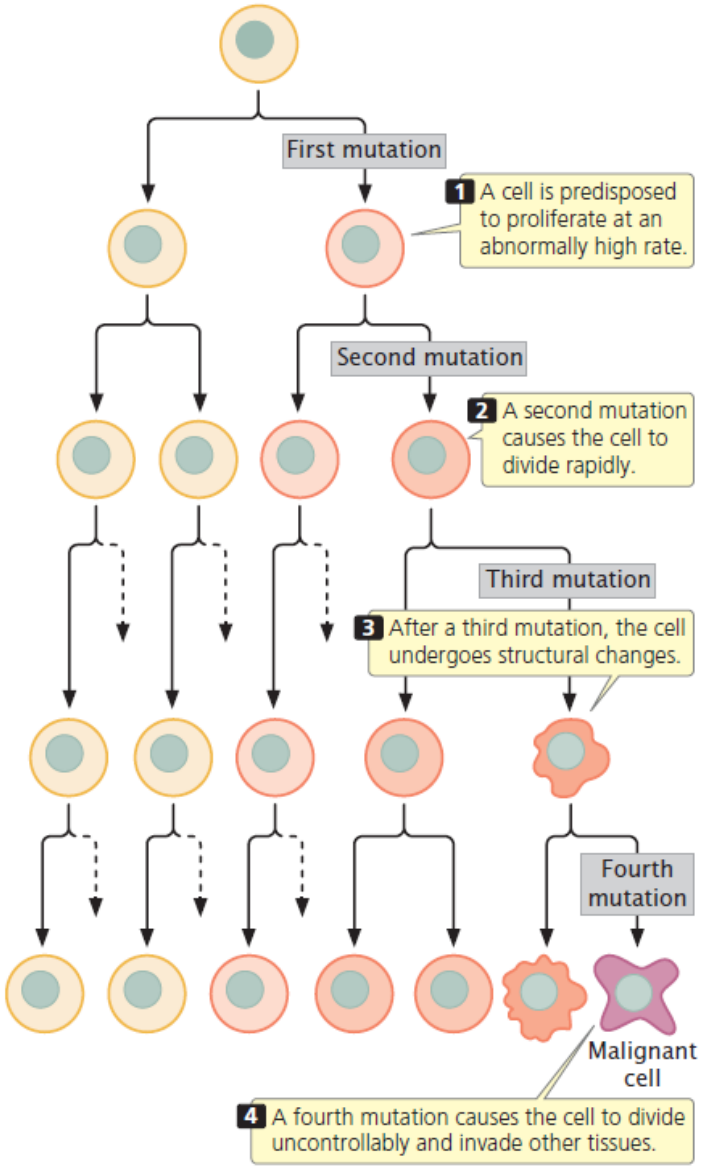
Resistant to apoptosis



Loss of contact inhibition

angiogenesis

A series of mutations is responsible for the development of colon cancer.



23.4 Through clonal evolution, tumor cells acquire multiple mutations that allow them to become increasingly more aggressive and proliferative. To conserve space, a dashed arrow is used to represent a second cell of the same type in each case.

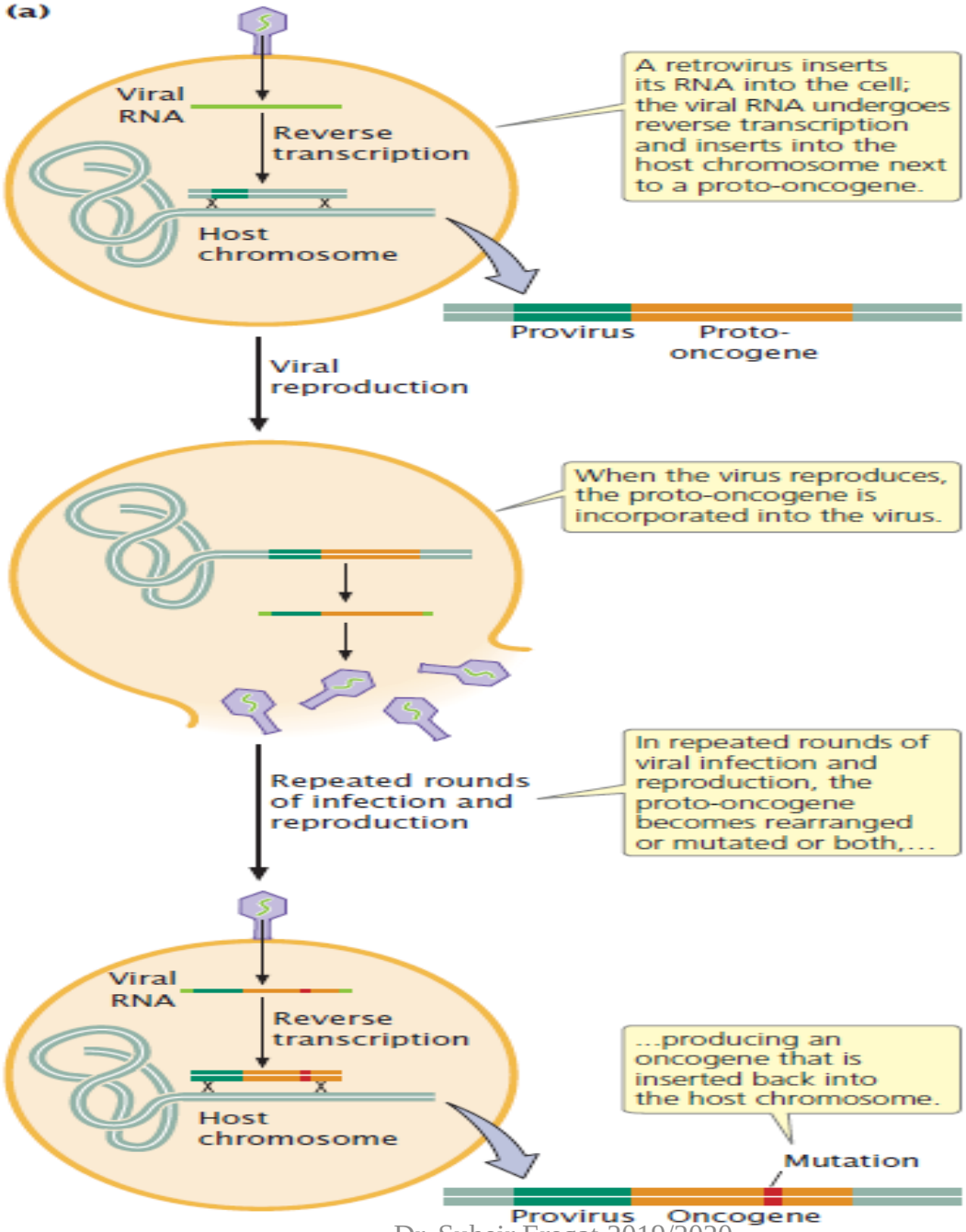
clonal evolution,

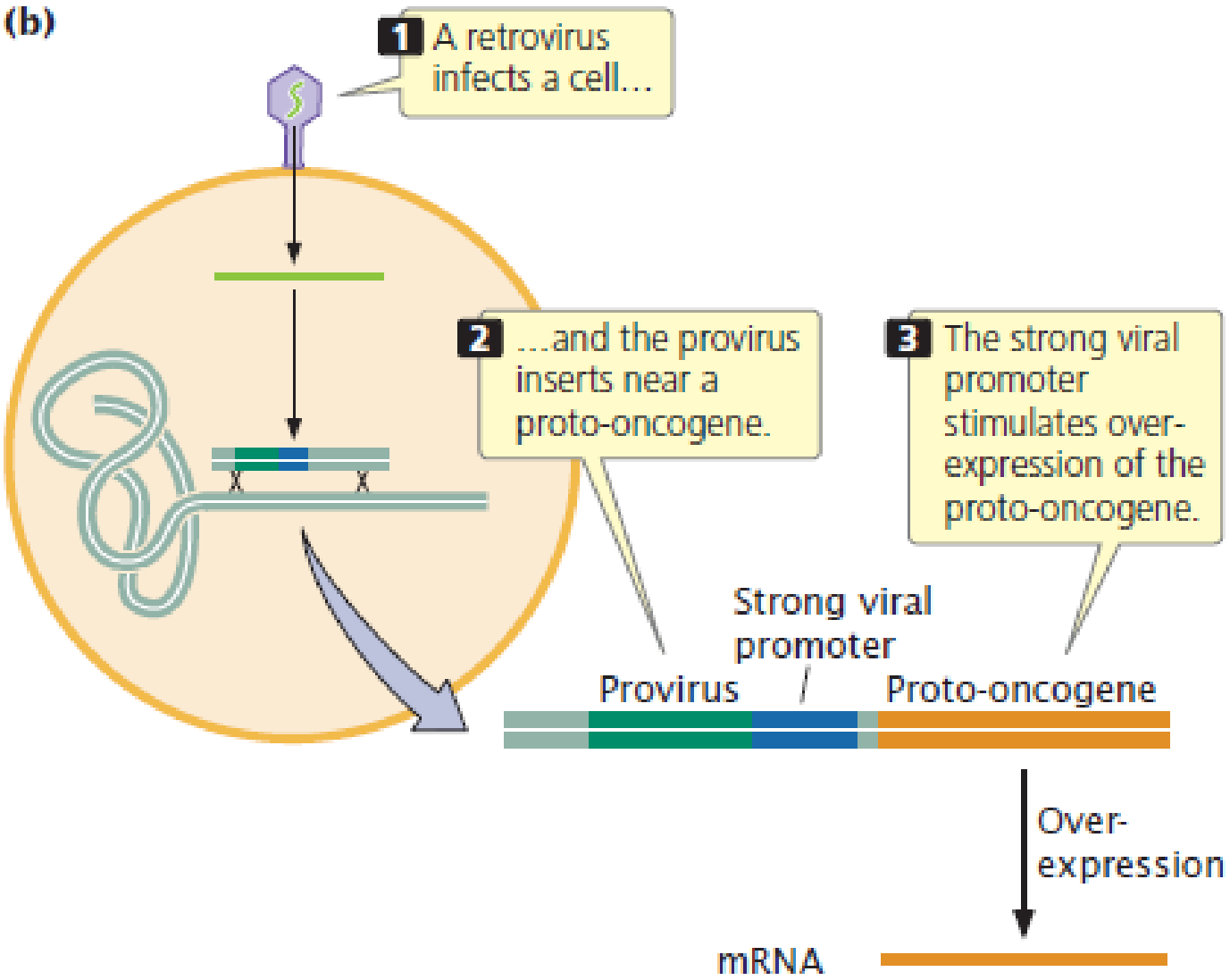
Viruses are associated with some cancers

Table 23.5 Some human cancers associated with viruses

Virus	Cancer
Human papilloma viruses (HPVs)	Cervical, penile, and vulvar cancers
Hepatitis B virus	Liver cancer
Human T-cell leukemia virus 1 (HTLV-1)	Adult T-cell leukemia
Human T-cell leukemia virus 2 (HTLV-2)	Hairy-cell leukemia
Epstein–Barr virus	Burkitt lymphoma, nasopharyngeal cancer, Hodgkin lymphoma
Human herpes virus	Kaposi sacrcoma

Note: Some of these associations between cancer and viruses exist only in certain populations and geographic areas.


(a)
Viral RNA
Reverse transcription
Host chromosome
A retrovirus inserts its RNA into the cell; the viral RNA undergoes reverse transcription and inserts into the host chromosome next to a proto-oncogene.
Provirus
Proto-oncogene
Viral reproduction
When the virus reproduces, the proto-oncogene is incorporated into the virus.
Repeated rounds of infection and reproduction
In repeated rounds of viral infection and reproduction, the proto-oncogene becomes rearranged or mutated or both,...
Viral RNA
Reverse transcription
Host chromosome
...producing an oncogene that is inserted back into the host chromosome.
Mutation
Provirus
Oncogene


(b)
1 A retrovirus infects a cell...
2 ...and the provirus inserts near a proto-oncogene.
3 The strong viral promoter stimulates over-expression of the proto-oncogene.
Strong viral promoter
Provirus
Proto-oncogene
Over-expression
mRNA

summary

Cancer can be caused by

-Environmental factors (increase mutation rate)
-Mutations in genes that control the cell cycle (CDK/cyclins)
- Mutations in tumor suppressor genes (act in a recessive manner) and oncogenes(act in a dominant manner).
- Genes in signal-transduction pathways
-Defects in DNA-repair genes
-Genes activate telomerase (allow cells to divide indefinitely)
-reduction in the expression of miRNAs
-chromosome mutations(deletions, inversions, and translocations)
-Mutations in some genes cause or allow the missegregation of chromosomes(aneuploidy)
-Viruses
-Epigenetic changes (Hypermethylation contributes to cancer by silencing the expression of tumor-suppressor genes).