

Chapter 9

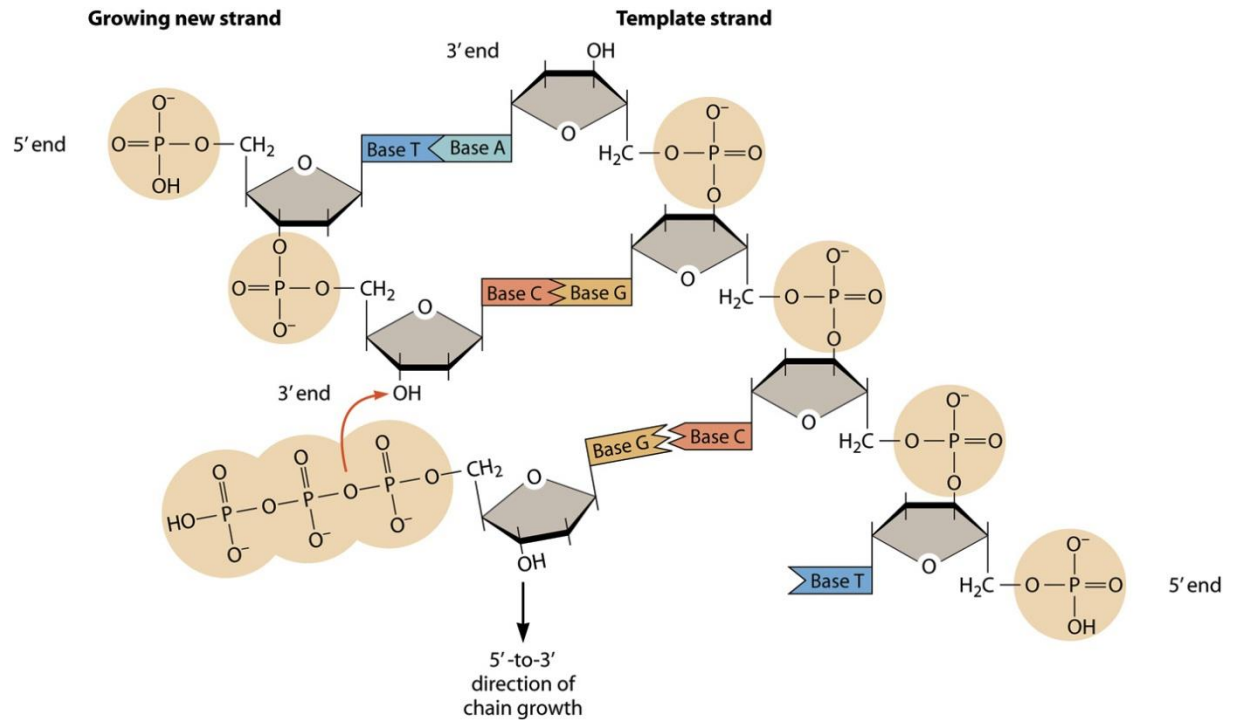
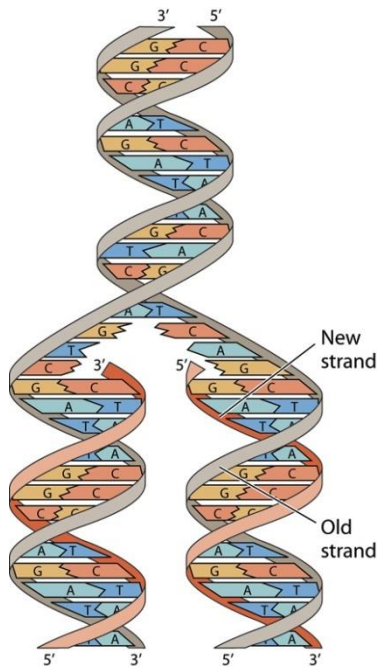
# Cells Grow and Reproduce



# DNA Replication

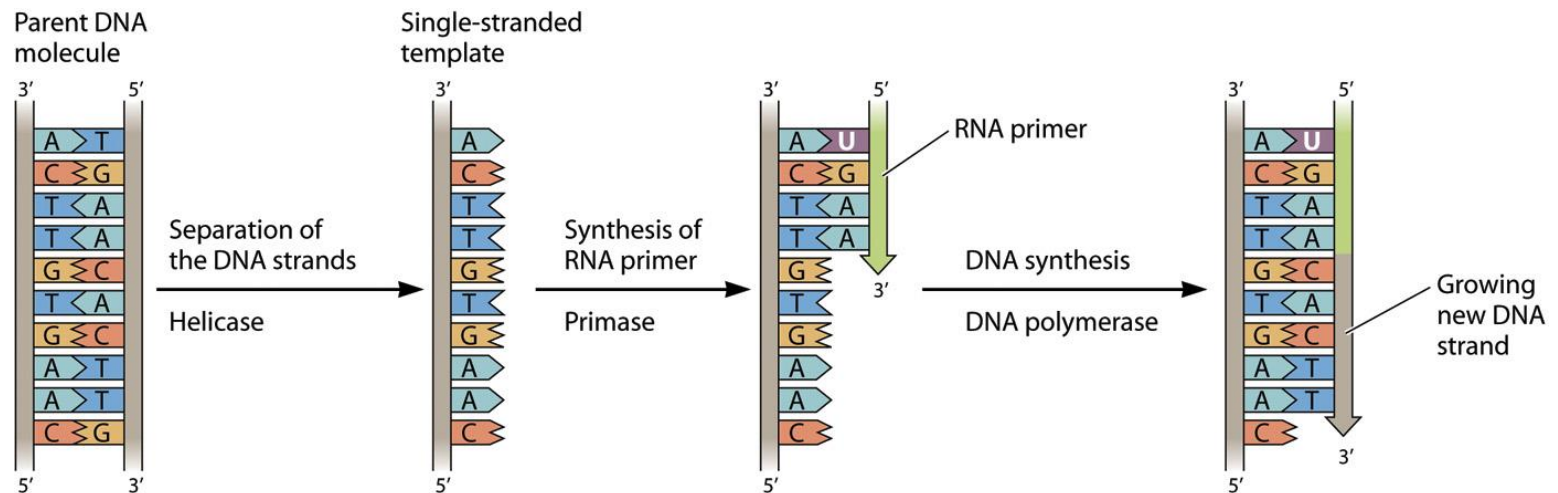
- DNA polymerase

- Addition of a nucleotide to the 3' end of a growing strand
- Use dNTPs as substrate → Release of pyrophosphate



# Initiation of Replication

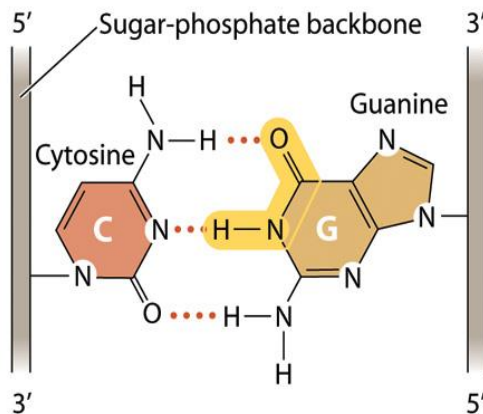
- Replication origin
  - The site where replication starts
  - Binding of several proteins involved in replication
- Helicase
  - Separation of the DNA strands
- Primase
  - Synthesis of RNA primer



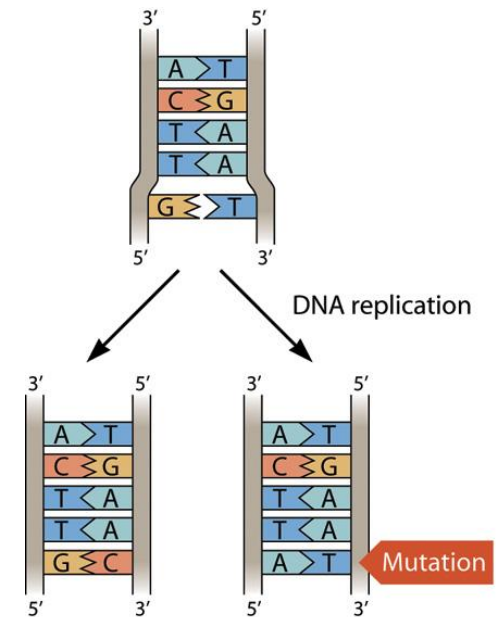
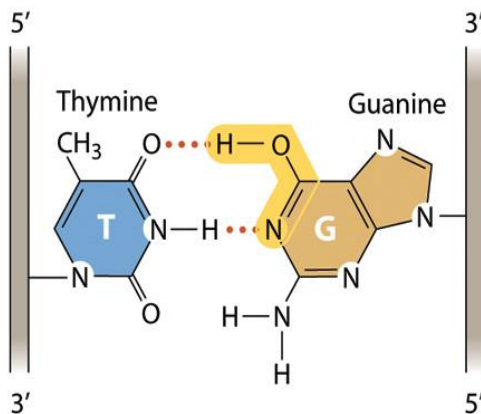
# Incorporation of Wrong Nucleotide

- e.g. alternate form of G base pairs with T
- Mismatch → Induction of mutation

Normal G—C pairing



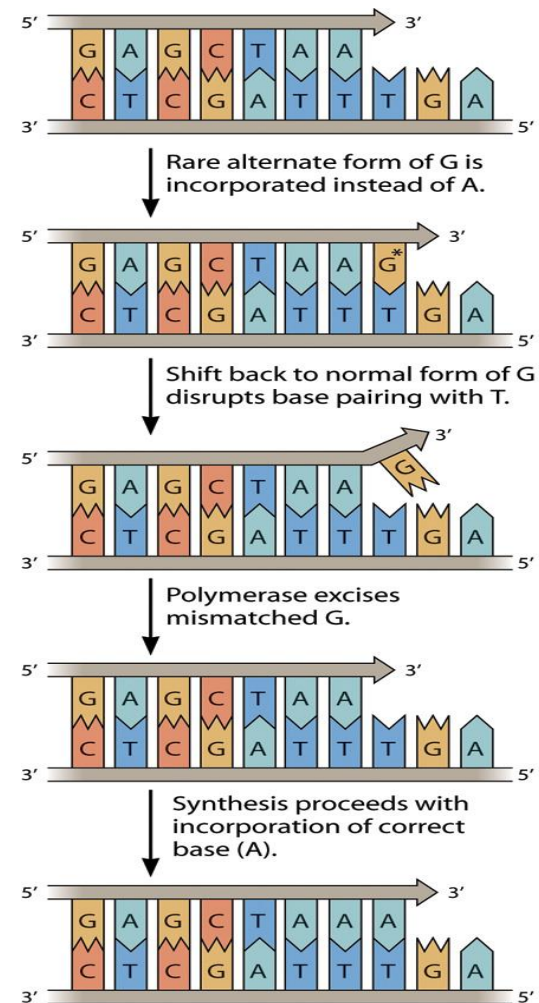
Rare alternate form of G pairs with T



# Preventing Mutation

- Proofreading by DNA polymerase
- Several repair systems for mismatches and DNA damage
- Final guard against mutation

--- “Quality control”: no cell division if damaged DNA is present



# Division of DNA Molecules During Cell Division

- **Bacteria**
  - Attachment of each DNA to two different spots on the membrane
- **Eukaryotes**
  - More complex
  - Two copies of 23 different chromosomes (human)

## BOX 9.1 Mitosis, chromosomes, and amniocentesis

Chromosomes are ordinarily invisible under the microscope because, in their relaxed state, they are such thin structures. When they condense during prophase, however, it becomes possible to see them (under a microscope), and at metaphase they reach the point of greatest condensation. The reason that human chromosomes look like tiny Xs in photographs is that the pictures are taken when chromosomes are in metaphase, so each "chromosome" is really two replicated chromosomes held together at the centromere (see the figure).

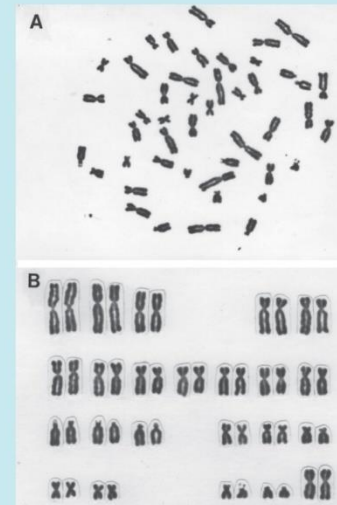
When metaphase chromosomes are stained with various stains or fluorescent dyes, patterns of bands become visible. Each chromosome has a unique pattern that can be used to identify it. In fact, it is possible to detect certain kinds of genetic problems by studying stained metaphase chromosomes and looking for irregularities in the banding patterns.

Pregnant women sometimes undergo a diagnostic procedure called **amniocentesis**, in which technicians examine the banding patterns of chromosomes from fetal cells and screen for certain genetic abnormalities. During amniocentesis, intrauterine fluid is drawn, and fetal cells are isolated from the fluid. These cells are normally present in amniotic fluid and are not forcibly removed from the developing fetus.

The cells are put into a test tube and treated with drugs that halt their divi-

sion process in metaphase, and their chromosomes are stained and photographed. The banding patterns are then used to identify the chromosomes, and the chromosomes are inspected for visible problems. This type of examination does not reveal single-base changes or other small changes in the DNA, but it can show major problems, like chromo-

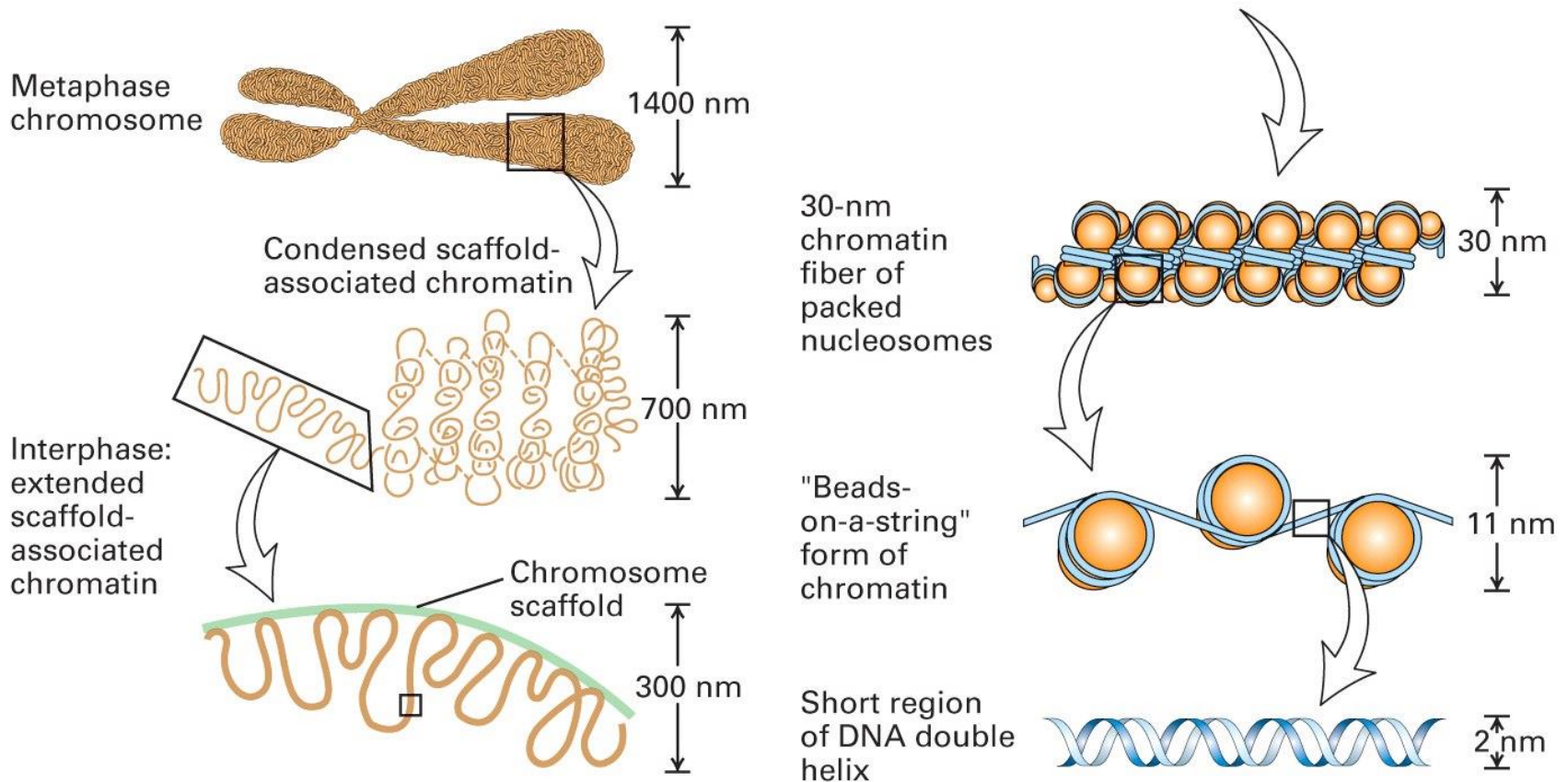
somal rearrangements, missing chromosomes, or extra chromosomes. It also reveals the gender of the baby (see chapter 10). The staining of chromosomes and examination of the resulting banding patterns is called karyotyping, and the pattern obtained from a given individual is that person's **karyotype**.



**Human metaphase chromosomes.** (A) Light micrograph. (B) Paired and sorted. (Photographs copyright Craig Holmes/Biological Photo Service.)

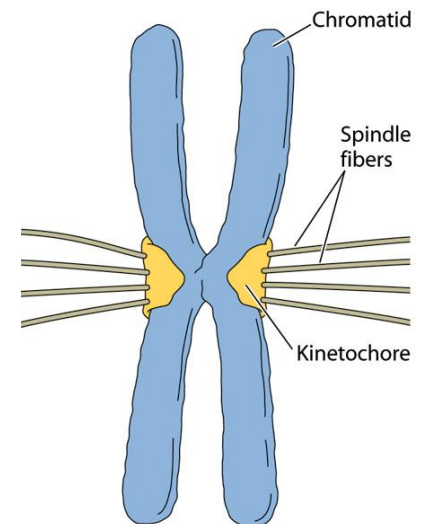
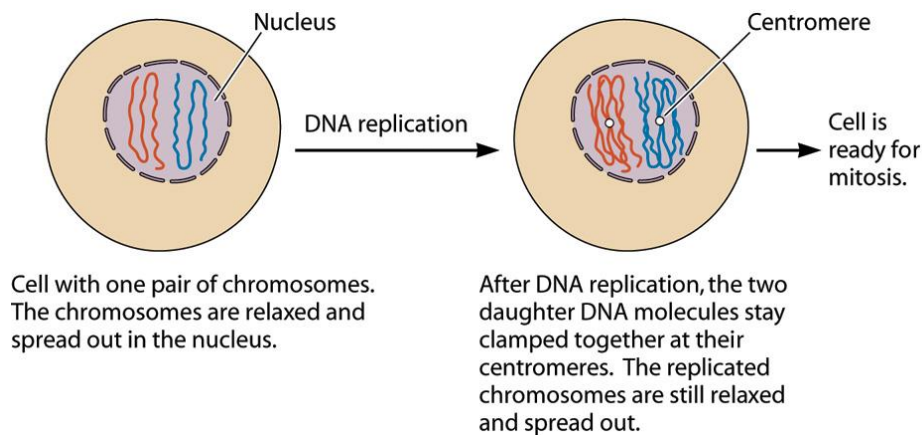
# Chromosome

- Tightly packed complex of DNA and histone proteins



# Mitosis

- Distribution of chromosome to daughter cells
- Mitosis does not begin until DNA replication has already occurred.
- Setting the stage after DNA replication
  - Connected two daughter chromosome after DNA replication
    - Joined at centromere (unique DNA sequence) via a protein clamp
    - Kinetochore:  
centromere + centromere proteins
    - Chromatid  
--- each identical DNA molecule

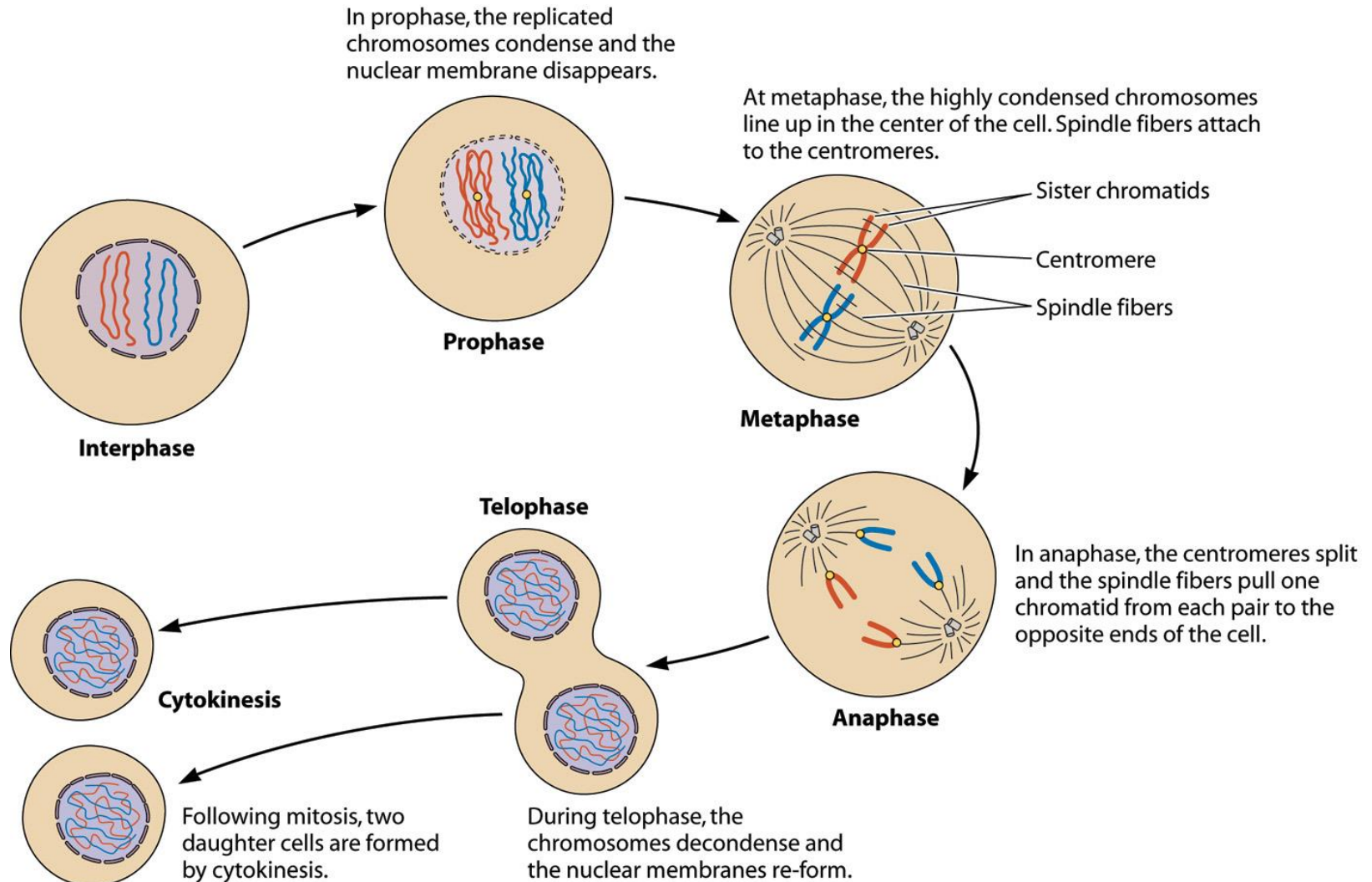




# Mitosis

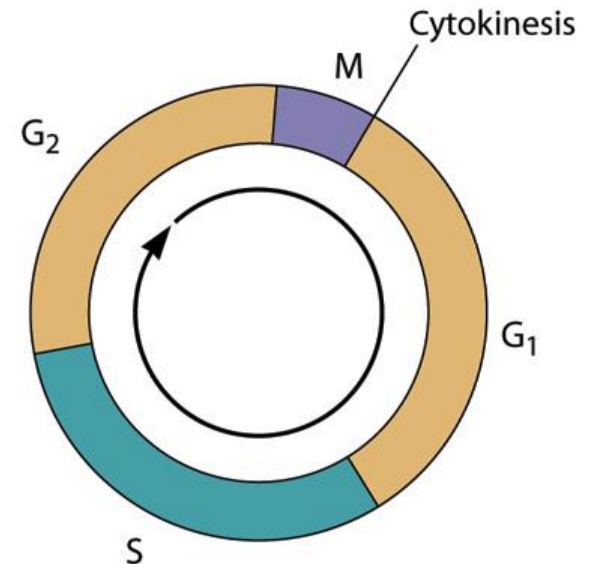
- DNA replication
- Mitosis
  - Prophase
    - Condensation of chromosomes and disappearance of nuclear membrane
  - Metaphase
    - Alignment of chromosome in the center
    - Pulling by spindle fibers attached to the kinetochore
  - Anaphase
    - Splitting of chromatids and pulling to the opposite ends of the cell
  - Telophase
    - Decondensation of chromosome
    - Formation of new nuclear membrane
- Cytokinesis
  - Cell division after mitosis
- Interphase
  - The time between cell division and the next mitosis ( $G_1$ , S,  $G_2$ )

# Mitosis and Cytokinesis



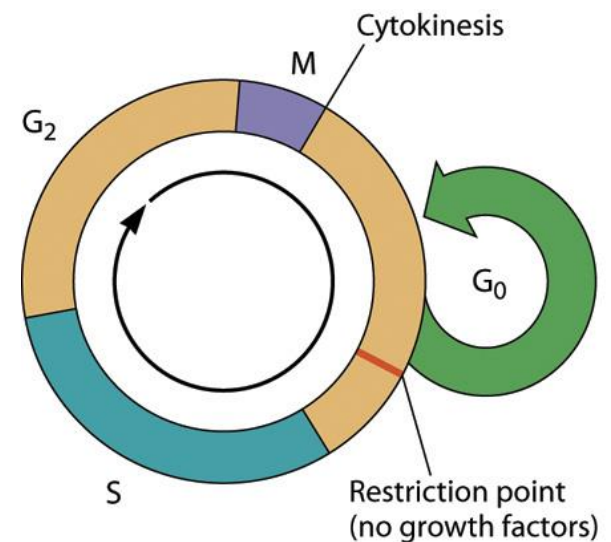
# The Cell Cycle

- Cell Cycle
  - S phase:
    - DNA synthesis  
(DNA replication)
  - M phase:
    - mitosis
  - $G_1$ ,  $G_2$  :
    - G stands for gap  
between S and M phase
    - Cell growth



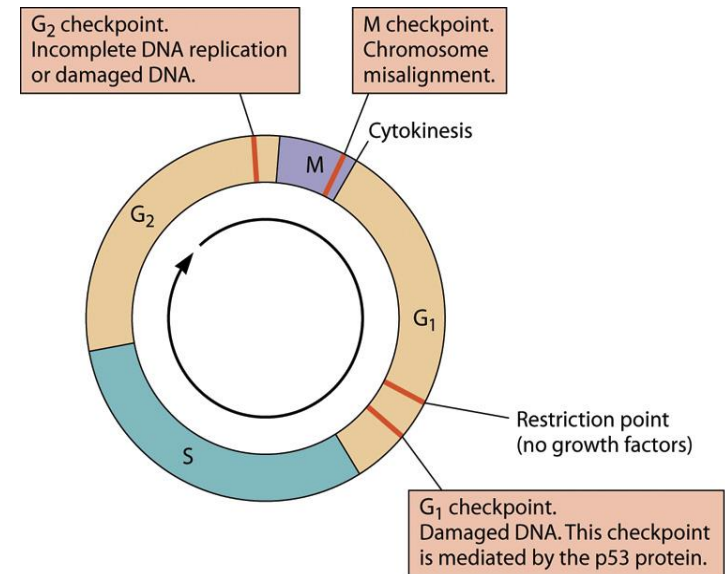
# The Cell Cycle

- Regulation of cell cycle
  - Restriction point : late G1
    - With growth factor → S phase
    - Without growth factor → G<sub>0</sub> : metabolism without growing  
e.g. platelet-derived growth factor during blood clotting  
→ Growth of skin fibroblasts
  - Ras protein
    - Activated by many growth factors
      - Many growth factor receptors transmit their signals through Ras.
    - Signal transduction to induce DNA synthesis



# Cell Cycle Checkpoints

- Roles of cell cycle checkpoints
  - Prevent entry into the next phase before the completion of the previous phase
  - DNA damage checkpoints
- Cell cycle checkpoints
  - G1 check point
    - *p53* : activated by damaged DNA
      - activates the G1 check point
      - stops DNA replication
    - Success in damage repair
      - proceeds DNA replication
    - Fail in damage repair
      - The *p53* induces apoptosis.  
(programmed cell death)
  - G2 check point
    - Activated by damaged DNA and unreplicated DNA
  - M check point
    - Incorrect mitosis



# Unregulated Cell Division : Cancer

- **Cancer: caused by failure in regulation of cell division**
  - Carcinoma
    - Originating from epithelial cells (85% of all cancers)
  - Sarcoma
    - Originating from cells of connective tissue, bone, or muscle tissue
  - Leukemia
    - Originating from white blood cells (leukocytes)
  - Adenocarcinoma
    - Originate from glandular tissue
  - Glioma and astrocytoma
    - Cancers of the nonneuronal cells of the brain
- **Tumor: a mass of cancer cells derived from a single parent cell**
  - Benign: no invasion
  - Malignant: invasion of surrounding tissue
    - Metastasis: migrate to new sites and establish new tumors

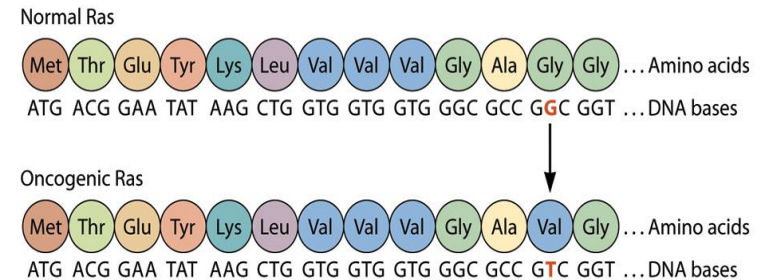
# The accumulation of mutations in a single cell can lead to cancer

## ■ Oncogenes

- Mutant genes that promote cell division
  - Genes in signaling pathway to cell division (e.g. *ras*, platelet-derived growth factor receptor gene)
- Mutation in *ras*
  - constitutively active → cell division
  - 20% of human cancer

## ■ Tumor suppressor genes

- Genes that halt cell replication
  - Mutation causes cancer.
- *p53* : DNA damage check point protein
  - 50% of human cancers including leukemia, brain tumor, breast, colon, and lung cancer
- *BRCA1* and *BRCA2* genes
  - Breast cancer
- *MADR2* and *APC* genes
  - Colon cancer



# Genes Involved in Cancer

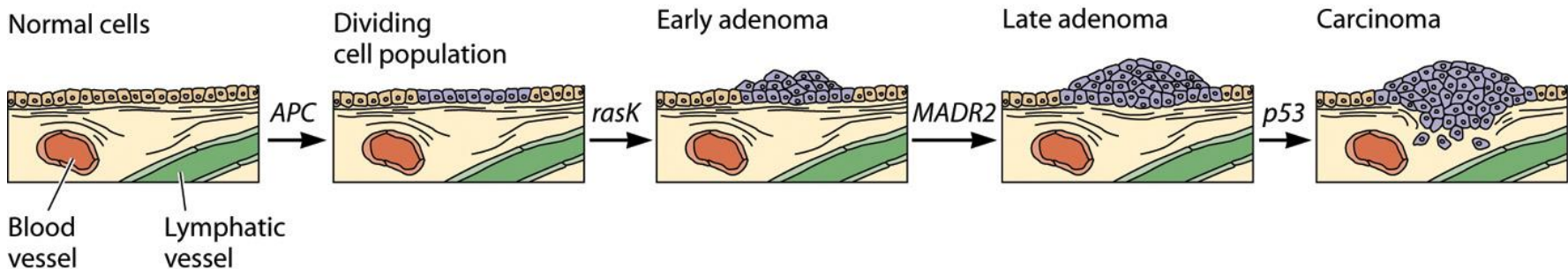
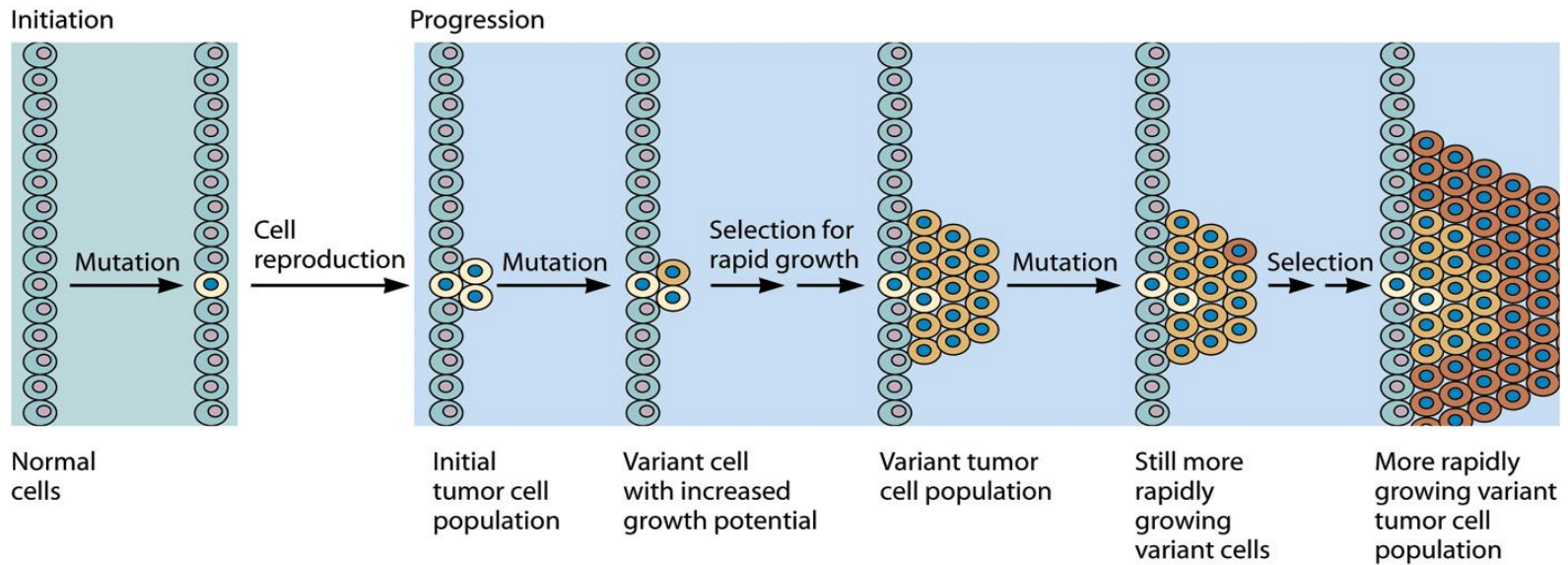
**Table 9.1** Some cancer genes and the normal physiological roles of their products

<b>Gene</b>	<b>Normal physiological role</b>
<b>Oncogenes</b>	
<i>sis</i>	Growth factor
<i>erbB, fms, neu</i>	Growth factor receptors
<i>ras, src, abl</i>	Signal transmission within the cell
<i>bcl2</i>	Blocks programmed cell death
<i>myc, fos, myb</i>	Regulators of transcription
<b>Tumor suppressor genes</b>	
<i>rb</i>	Regulation of replication and transcription
<i>p53</i>	Regulation of cell division cycle; stops cells from dividing if their DNA is damaged, allowing time for repair; initiates programmed cell death if DNA is not repaired



# Development of Cancer

- Accumulation of mutations during cancer development

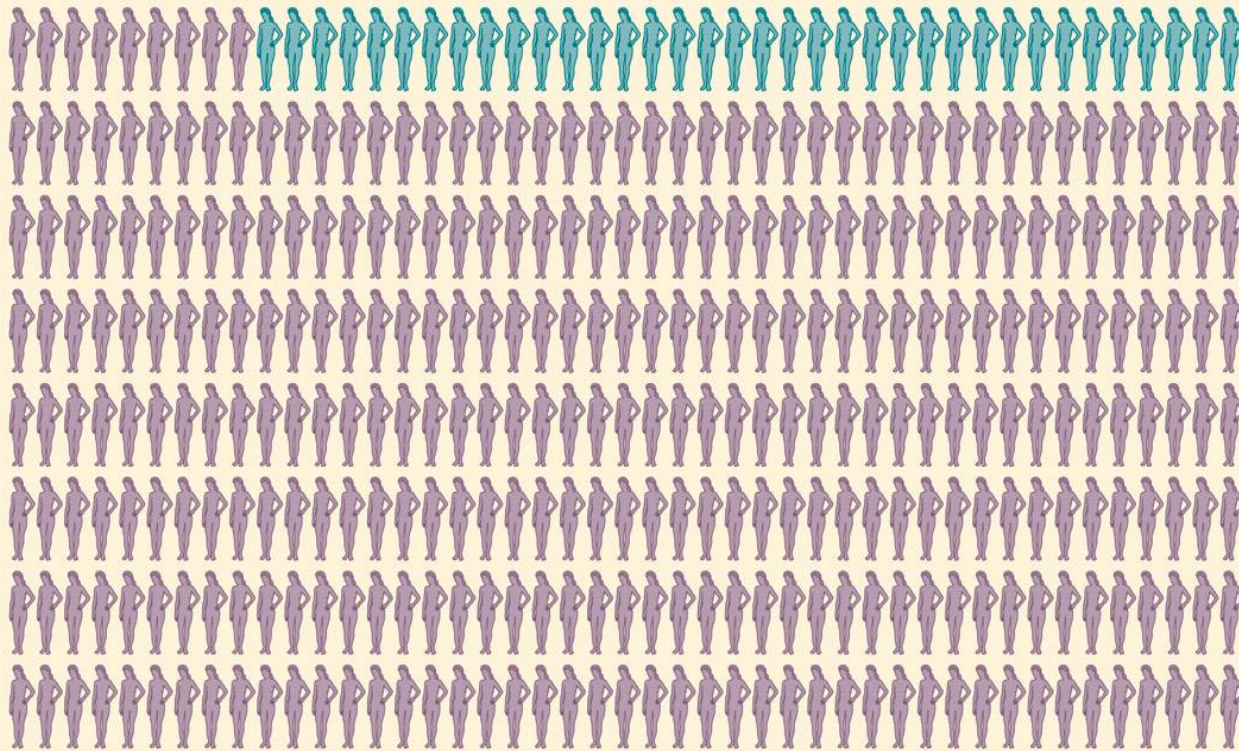


# Inherited Mutation in Tumor Suppressor Genes

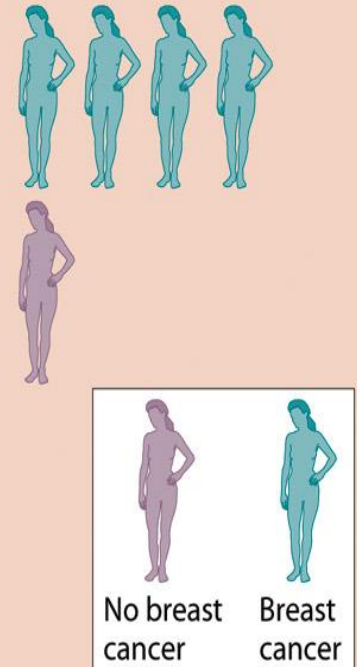
- Mutation and inheritance
  - Mutations in somatic (soma, body) cells
    - No inheritance
  - Mutations in reproductive cells (eggs, sperm)
    - Inheritance
- Inherited mutations and cancer
  - Breast tumor suppressor genes
    - *BRCA1*: involved in DNA repair
    - Mutant *BRCA1* gene
      - 80% chance of developing breast cancer (normal gene: 10%)
      - 40% chance of developing ovarian cancer
    - Inherited mutations of *BRCA1* and *BRCA2* are involved in only 5 to 10% of breast cancers → sporadic mutations are the major cause

# Breast Cancer

Women without inherited mutations in *BRCA1* or *BRCA2*

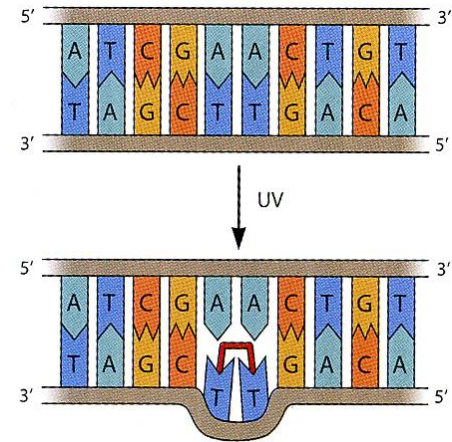


Women with inherited mutations in *BRCA1* or *BRCA2*



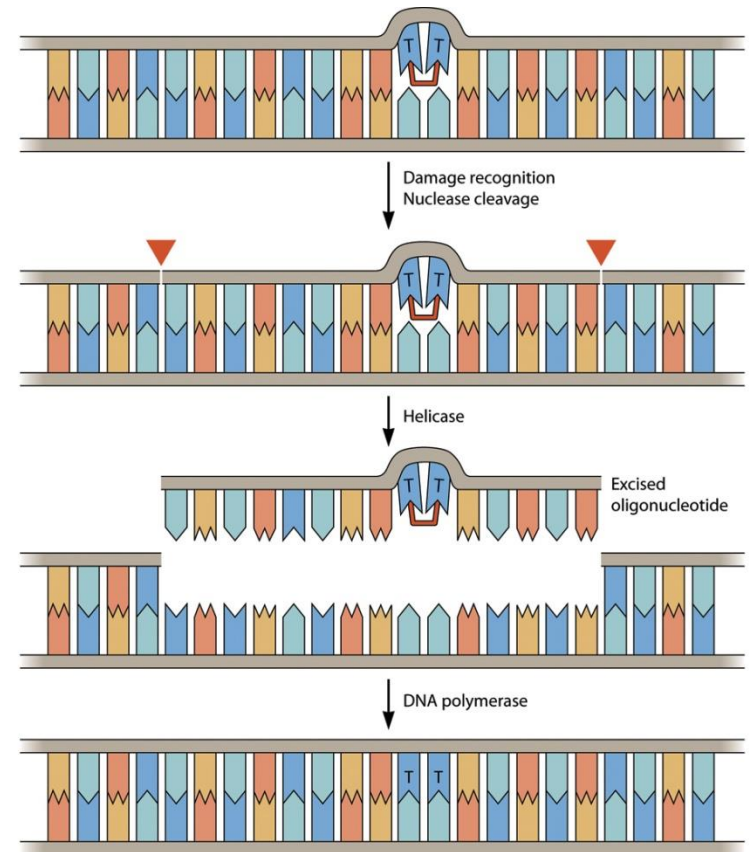
# DNA Damage and Repair

- DNA damaging agents
  - Mutagens : mutation-promoting agents
  - Carcinogen : cancer-inducing agents
- Environmental carcinogens
  - UV
    - Thymine dimer formation  
→ blocking transcription and DNA replication
  - DNA-binding chemicals
    - Benzopyrene
      - Smoke from cigarette, burning leaves, diesel exhaust etc.
      - Bind to DNA G residue and induce mutation



# Repair System

- Mismatch repair
  - as described before
- Excision repair
  - Repair distorted DNA (T-T, benzopyrene binding)
  - Excision of damaged region by nuclease and helicase, and repair by DNA polymerase
  - Xeroderma pigmentosum (XP)
    - Disease
      - Mutation in excision repair system
      - Can not repair T-T
    - Extreme sensitive to UV → skin cancer



# Cancer Drugs

- Classic anticancer treatment
  - Targeting rapidly dividing cells
  - Side effects to other fast growing cells
    - Blood cell progenitors, cells lining the digestive tract, hair follicle cells
- Cancer-specific drugs
  - Tamoxifen
    - Mimic estrogen : binding to estrogen receptor of estrogen-sensitive cancer cells
  - Herceptin
    - Binding to and inactivate Her2 (receptor for EGF): inhibit the growth of Her2-overproducing breast cancer cells
  - Greevec
    - Inhibition of Abl in chronic myelogenous leukemia