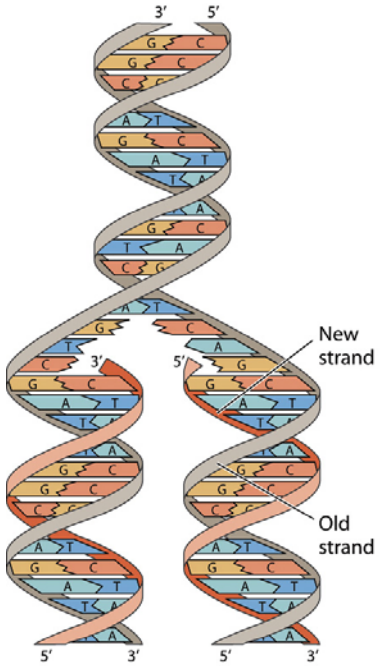
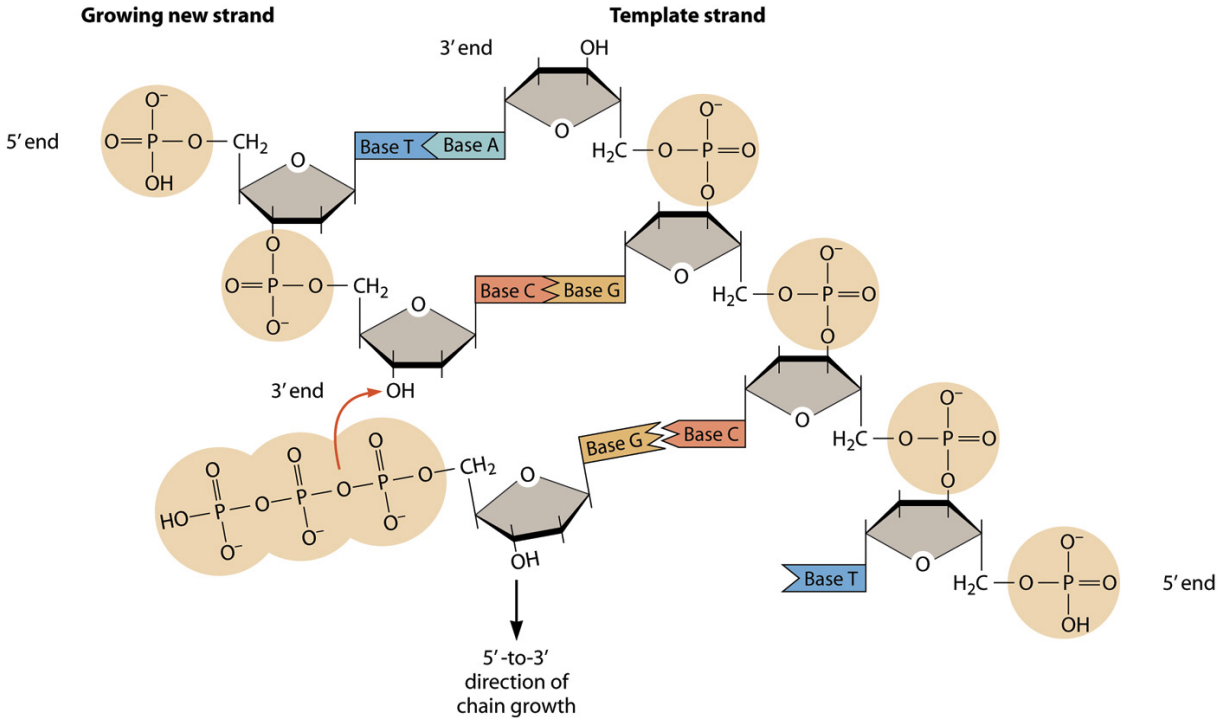
Chapter 9

Cells Grow and Reproduce

DNA Replication

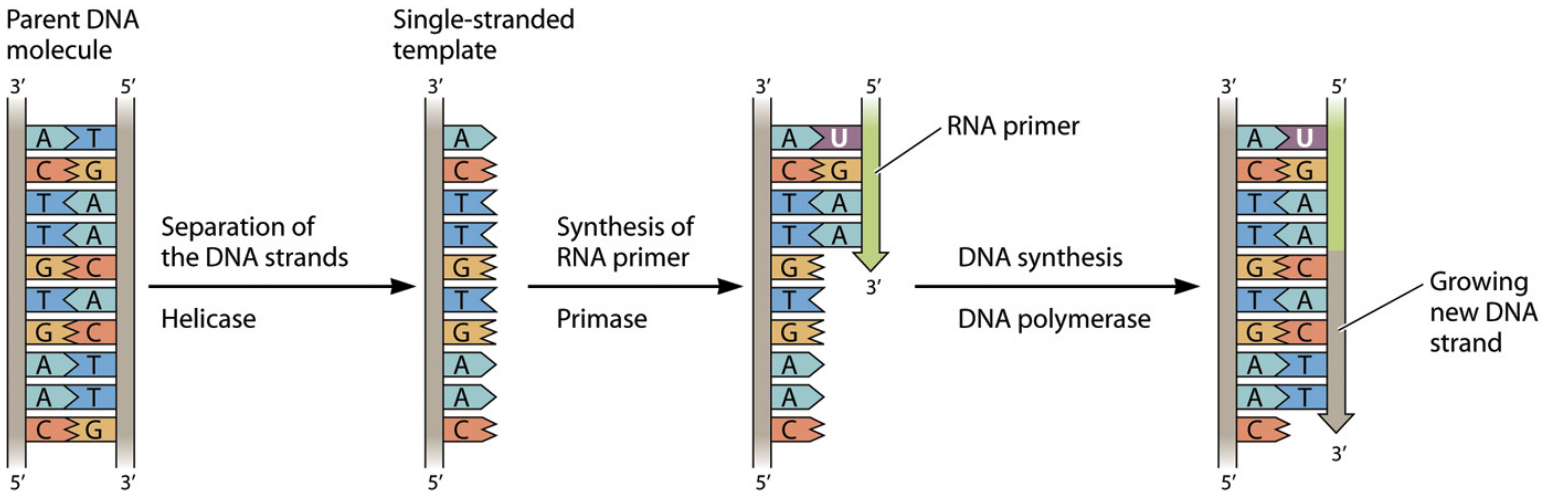
- DNA polymerase
  - Addition of a nucleotide to the 3’ end of a growing strand
  - Use dNTPs as substrate → Release of pyrophosphate





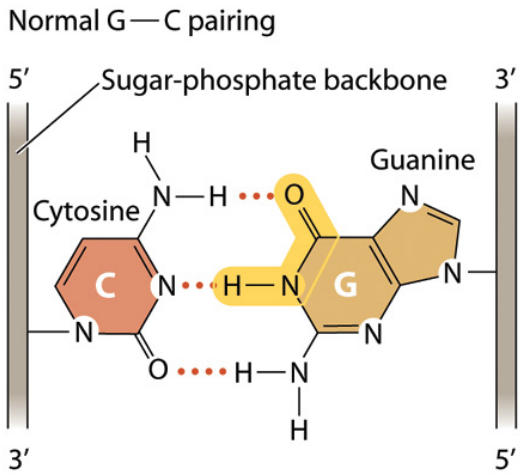
Initiation of Replication

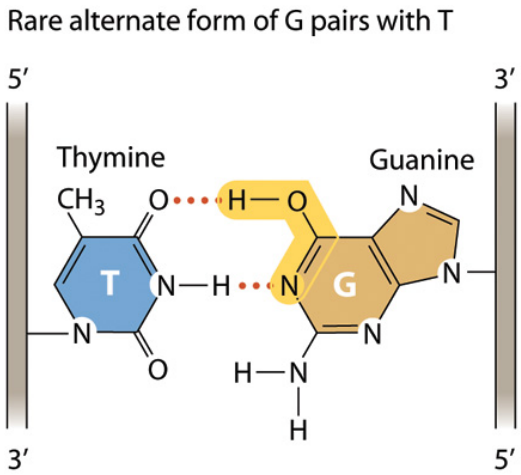
- Replication origin
  - The site where replication starts
  - Binding of several proteins involved in replication
- Helicase
  - Separation of the DNA strands
- Primase
  - Synthesis of RNA primer

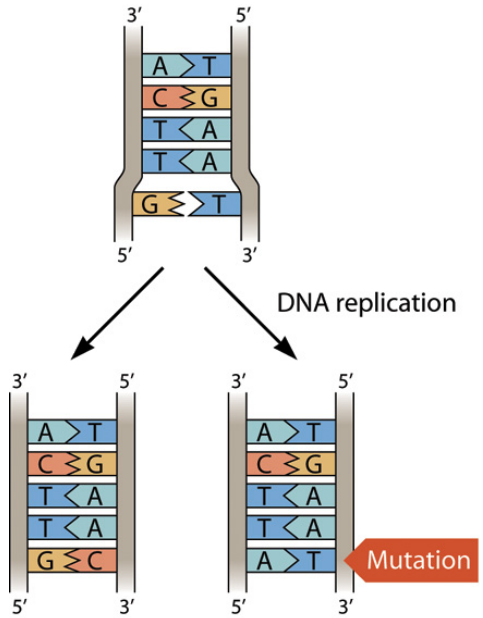


Proofreading of DNA Polymerase

- Incorporation of wrong nucleotide
  - e.g. alternative form of G base pairs with T
  - Mismatch→ Induction of mutation
- Preventing mutation
  - Proofreading by DNA polymerase
  - Repair system for DNA damage
  - Quality control: no cell division if damaged DNA is present

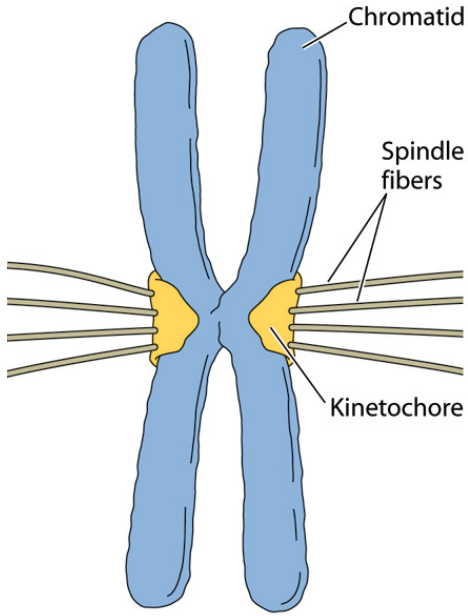






Division of DNA molecules during cell division

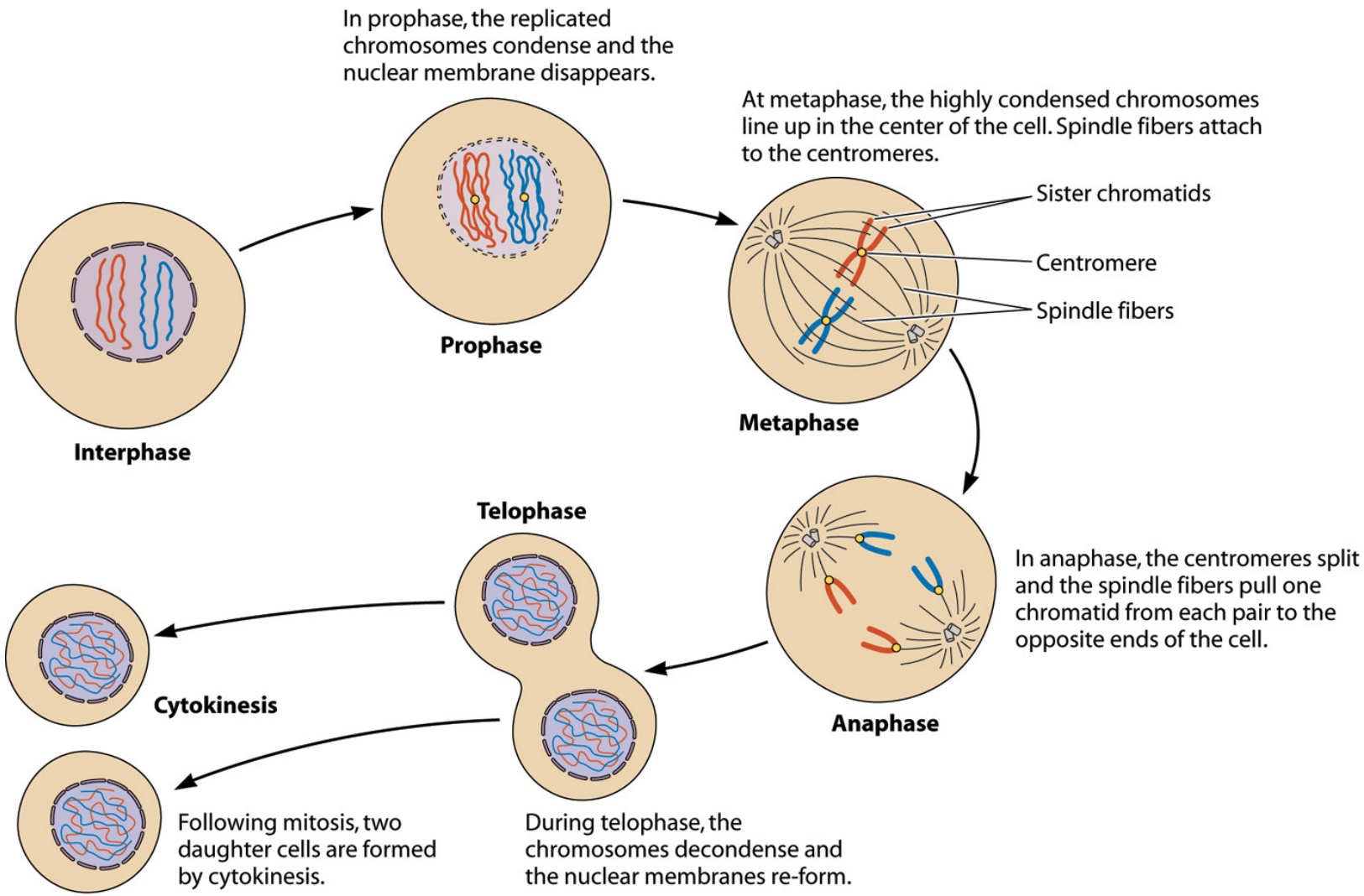
- Bacteria
  - Attachment of DNA to the membrane
- Eukaryotes
  - Two copies of different chromosomes (human: 23)
  - Connected two daughter chromosome after DNA replication
    - Chromatids
    - Joined at centromere
    - kinetochore: centromere + binding proteins
  - Mitosis : Distribution of chromosome to daughter cells



Mitosis

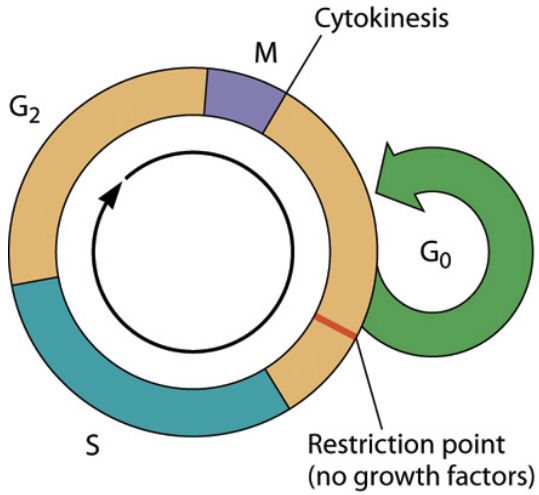
- DNA replication
- Mitosis
  - Prophase
    - Condensation of chromosomes and disappearance of nuclear membrane
  - Metaphase
    - Alignment of chromosome in the center
    - Pulling by spindle fibers attached to the kinetochore
  - Anaphase
    - Splitting of chromatids and pulling to the opposite 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

Mitosis and Cytokinesis



The Cell Cycle

- Cell Cycle
  - S phase: DNA synthesis
  - G_1, G_2 : G strands for gap between S and M phase
  - M phase: mitosis

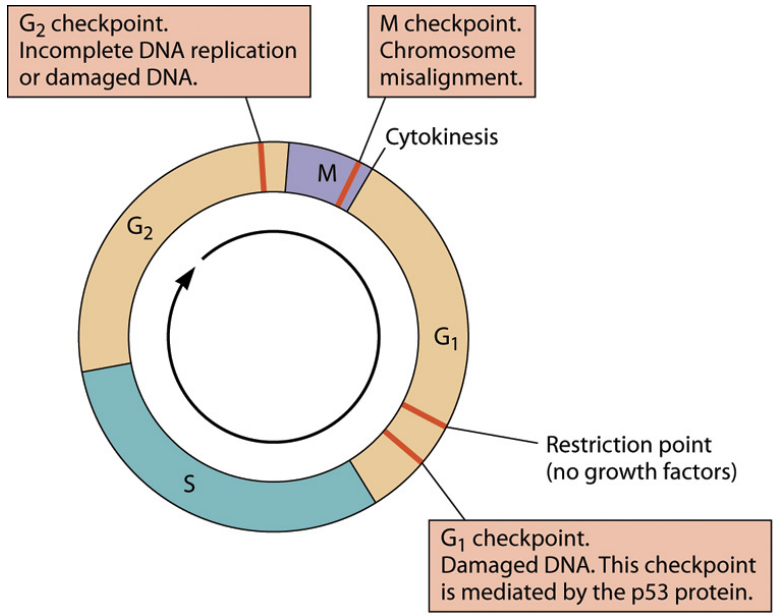


- Regulation of cell cycle
  - Restriction point : late G_1
    - With growth factor → S phase
    - Without growth factor → G_0 : metabolism without growing

    e.g. platelet-derived growth factor during blood clotting → Growth of skin fibroblasts
  - Ras protein
    - Activated by many growth factors
    - 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
  - G_1 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 → Apoptosis : programmed cell death
  - G_2 check point
      - Activated by damaged DNA and unreplicated DNA
  - M check point

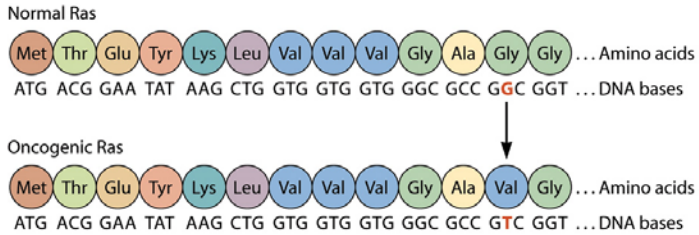


Unregulated Cell Division : Cancer

- Cancer: caused by failure in regulation of cell division
  - Carcinoma
    - Originated from epithelial cells (85%)
  - Sarcomas
    - Originated from cells of connective tissue, bone, or muscle tissue
  - Adencarcinomas
    - Originated from glandular tissue
  - Gliomas and astrocytomas
    - 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

Genes Involved in Cancer

- Oncogenes
  - Mutant genes that promote cell division
    - Genes in signaling pathway to cell division
    - Ras, PDGF receptor
  - Mutant ras
    - constitutively active → cell division
    - 20% of human cancer



- Tumor suppressor genes
  - Genes that halt cell replication
    - Mutation cause cancer
  - P53 : DNA damage check point protein
    - 50% of human cancers; leukemias, brain tumors, breast, colon, and lung cancer
  - BRAC1, and BRAC2
    - Breast cancer
  - MADR2 and APC
    - Colon cancer

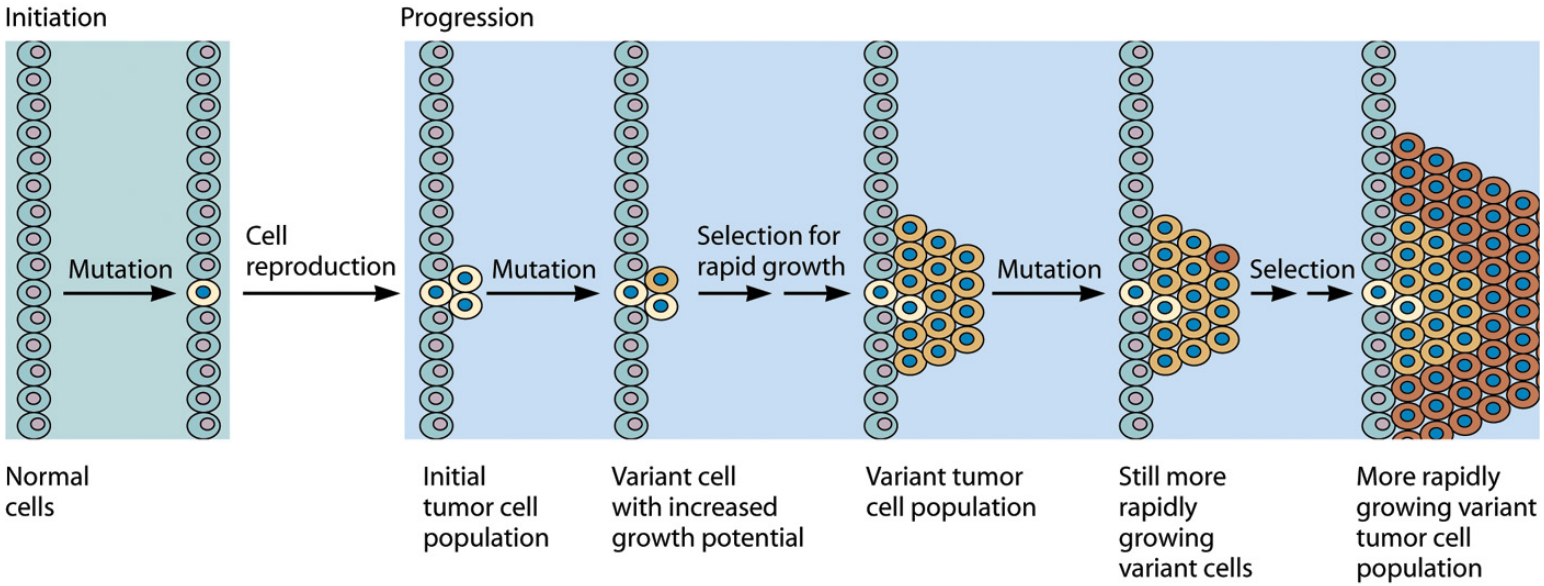
Genes Involved in Cancer

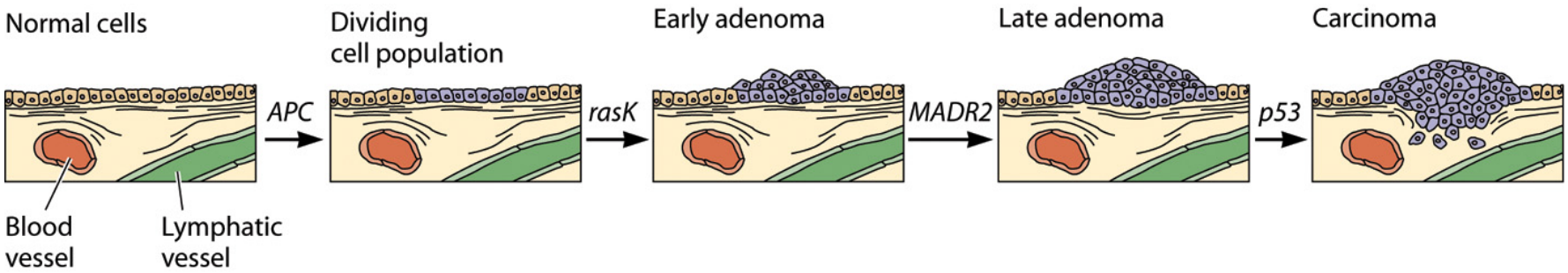
Table 9.1 Some cancer genes and the normal physiological roles of their products

Gene	Normal physiological role
Oncogenes	
sis	Growth factor
erbB, fms, neu	Growth factor receptors
ras, src, abl	Signal transmission within the cell
bcl2	Blocks programmed cell death
myc, fos, myb	Regulators of transcription
Tumor suppressor genes	
rb	Regulation of replication and transcription
p53	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

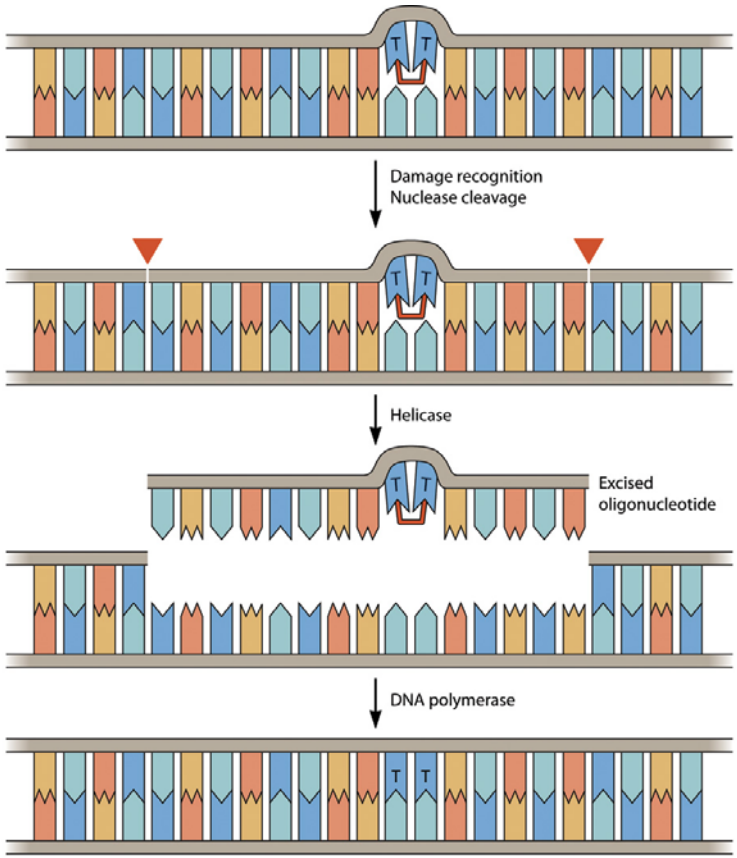
- Mutation and inheritance
  - Mutations in somatic (soma, body) cells
    - No inheritance
  - Mutations in reproductive cells (eggs, sperm)
    - Inheritance
- Inherited mutations and cancer
  - Breast cancer genes
    - BRCA1: involved in DNA repair
      - 80% chance of developing breast cancer (normal;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

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
- 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)
    - Mutation in excision repair system
    - 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