Cell division

One cell dividing into two cells

- A "mother" cell divides into two "daughter" cells
- This is how cells reproduce
- Nuclear division (splitting of the nucleus) always happens first, followed by cytokinesis (splitting of the membrane and cytoplasm)

Figs 12.9 and 13.5

Mitosis

Nuclear division that produces daughter cells with the same number of chromosomes as the mother cell

- Example: Two diploid (2n) daughter cells from a diploid (2n) mother cell.

Fig 13.5

Meiosis

Nuclear division that produces haploid (n) daughter cells from a diploid (2n) mother cell

Fig 13.5

Before the nucleus divides, the cell must replicate its DNA

- Each chromosome becomes a duplicated chromosome (One centromere holding two identical chromatids)
- Sister chromatids = The two identical chromatids on a duplicated chromosome
- A duplicated chromosome is still considered **one** chromosome

Fig 12.4

DNA Polymerase III

The main enzyme responsible for duplicating each chromosome's DNA

- The double helix separates into two single DNA strands

- DNA Polymerase III makes a complementary DNA strand to each single DNA strand (the "template" strand)

  √ The enzyme must make the complementary strand in the 5' to 3' direction

  √ The enzyme must start at a double-stranded region

  - An enzyme called primase makes short RNAs ("primers") complementary to the template strand, to give DNA Polymerase III a starting point

  - Another enzyme will later replace the RNA primers with DNA

  - An enzyme called ligase will then join ligate (join) the DNA primer to the complementary strand made by DNA polymerase III

- Each new double-stranded DNA contains one old strand and one new strand ("semi-conservative replication")

Figs 16.9 and 16.16

Origins of Replication

Areas of the chromosome where DNA replication starts

- Each origin of replication is a round "bubble" where the two DNA strands have separated

  √ Chromosomes may have hundreds of origins of replication

  √ Replication fork = The sides of the replication bubble, where the double stranded DNA is being separated into two single strands

- As DNA Polymerase III makes the complementary strands in each replication bubble, the bubble expands in both directions along the chromosome

Fig 16.12

Activities at each replication fork

- Leading strand = The new strand that is being made in the direction of the replication fork

  √ DNA polymerase III "chases" the replication fork

  √ The leading strand is made continuously without any break in the DNA

- Lagging strand = The new strand that is being made in the direction away from the replication fork

  √ DNA polymerase III begins the lagging strand at the replication fork but moves away from the fork

  √ Whenever DNA Polymerase III completes 100 – 200 bases of the lagging strand, the enzyme must break away from the template strand, move back to the replication fork (because the fork has opened new single stranded DNA), reattach to the template strand, and begin a new 100 – 200 base segment

  - The lagging strand is therefore made in 100 – 200 bases segments ("Okazaki fragments") that will later be ligated together

Fig16.16

Mutation

A change in the DNA sequence of a gene

- Mutations are infrequent but they do occur

- Mutations can be caused by radiation, exposure to certain chemicals, or by DNA Polymerase III enzyme making an error during DNA replication

- A mutation can cause a random change in the protein that comes from the gene
  - √ Most mutations are harmful to the protein's function
  - √ Very rarely, mutations improve the protein's function or give it a new function.
  - √ Mutations are vital for the evolution of species

Types of mututions

Silent mutation: A nucleotide change that changes a codon into a different codon that encodes the same amino acid

- No amino acids in the protein are changed

Missense mutation: A nucleotide change that changes a codon into a different codon that encodes a different amino acid

- Only one amino acid in the protein is changed

Frameshift mutation: A nucleotide is deleted from or inserted into the gene

- All amino acids following the deletion/insertion are changed

Nonsense mutation: A nucleotide change that changes a codon into a stop codon

- All amino acids following the mutation are missing from the protein

Cell cycle

Alternating periods of interphase (the cell making preparations to divide) and cell division (mitosis nuclear division followed by cytokinesis)

- Interphase has 3 phases:
  - √ G_1 = The first growth phase
  - √ S = DNA synthesis (DNA replication) phase
  - √ G_2 = The second growth phase
- M phase = Mitosis and cytokinesis
- Mitosis (the nucleus dividing) has 4 phases:
  - √ Prophase
  - √ Metaphase
  - √ Anaphase
  - √ Telophase
- Cytokinesis (splitting of the membrane and cytoplasm) has only one phase:
  - √ Cytokinesis

Figs 12.5, 12.6, and 13.5

The 4 phases of mitosis:

	Chromosomes	Nuclear membrane	Spindle apparatus
1) Prophase	Condense	breaking down	Centrosomes at poles. Spindle connects centrosomes to kinetochores
2) Metaphase	Lined up in middle	gone	Kinetochores pull chromosomes to middle of cell
3) Anaphase	Centromeres divide	gone	Kinetochores pull chromosomes to opposite poles
4) Telophase	Uncondensing	reappearing	Disappearing

Fig 12.6

Structures involved in moving the chromosomes

- Spindle = Microtubules (made expressly for cell division) that maneuver the chromosomes

- Centrosome = Structures where the spindle begins to form

    √ Each centrosome contains two centrioles

    √ Dividing cells contain one centrosome at each pole

- Kinetorchore = Structures on the centromere that bind to the spindle

    √ The kinetochores contain proteins that pull the chromosome along the spindle, toward the centrosome

Checkpoints

Points in the cell cycle where the cell can halt the cycle

- There are three checkpoints: At the end of G_1, at the end of G_2, and at the end of metaphase

- Halting at the checkpoints happens because the enzymes that carry out the cycle phase after the checkpoint ("mitosis phase enzymes") are not in an activated state

  √ Examples: The enzymes that replicate the DNA, the enzymes that condense the chromosomes, the enzymes that break down the nuclear membrane, the enzymes that form the spindle fibers

- The G_1 checkpoint (the "restriction point") is the major stopping point for cells in the body

  √ Cells halted at this checkpoint are in "G_0" phase

  √ A few cell types divide continuously, but most cells halt in G_0

  √ Some cells in G_0 cells are permanently in G_0 and can never re-enter the cell cycle

  √ Many cells in G_0 can re-enter the cell cycle (move passed the G_1 checkpoint) when a receptor on the cell binds a growth factor (a mitosis signal molecules from outside the cell)

  √ Cells automatically return to G_o if the growth factor is no longer present. This ensures that mitosis occurs in a controlled manner (only when and to the extent needed)

- The G_2 checkpoint halts the cell cycle if the DNA is damaged or not replicated

- The Metaphase checkpoint halts the cell cycle if the spindle fibers are not attached to all chromosomes

Re-entering the cell cycle from G_0

To re-enter the cell cycle from G_0 (to move passed the G_1 checkpoint) a receptor on the cell must bind the correct growth factor for that cell type

- Binding the growth factor starts a mitosis signal transduction pathway

  √ The S-phase enzymes are the cellular output response enzymes of the pathway

  √ RAS is the first relay protein in many mitosis signal transduction pathways

  √ Many relay proteins in the pathway are kinases that activate the next relay protein by phosphorylation

  √ Some relay proteins activate the next relay protein by removing a mitosis inhibiting protein (a "tumor supressor protein") from the next relay protein

- Mitosis is activated in a controlled manner (only when growth factor is present, only for as many divisions as are needed)

  √ Contact inhibition = Cells exit the cell cycle when they become crowded together, even if growth factor is present

Proto-oncogenes

The genes of the proteins of the mitosis signal transduction pathway

- Examples: Genes for growth factor receptors, RAS, and relay proteins of the mitosis signal transduction pathway

Cancer cells

Cells that divide in a continuous and uncontrolled manner

- Cancer cells can kill by spreading into and damaging multiple organs

  √ Metastasis = Cancer cells spreading throughout the body

- Cancer is caused by mutations in genes involved in mitosis

  √ Gain of function mutations (mutations that cause a protein to be constantly active) in proto-oncogenes.

  - The mutated proto-oncogene is now called an oncogene (cancer-causing gene)

  √ Loss of function mutations (mutations that cause a protein to become non-functional) in tumor supressor genes.

Tumor suppressor genes

Genes that, when they have a loss of function mutation, cause a cell to become a cancer cell

- Many tumor suppressor genes encode inhibitors of mitosis relay proteins

  √ Example: Retinoblastoma protein inhibits a mitosis relay protein

- Some tumor suppressor genes encode DNA repair enzymes

- Some tumor suppressor genes encode proteins that halt the cell cycle at mitosis checkpoints

  √ p53 protein halts the cell cycle at the G_2 checkpoint until damaged DNA is repaired

Cancer summary and facts:

• Cancer is caused by mutations in protooncogenes and tumor surpressor genes

√ Mutagens = Anything that causes mutations in the DNA

√ Carcinogens = Anything that causes cancer. Almost all carcinogens are mutagens

• Cancer rates increase exponentially with age because mutations accumulate in the genome as we age

• There are over 100 known proto-oncogenes and tumor suppressor genes

√ RAS is the most common oncogene in cancer cells

√ The p53 and Retinoblastoma genes are the two most commonly mutated tumor suppressor genes in cancer cells

• The three most common causes of cancer are:

1) Diet
- Meats, especially burnt meats, contain many mutagens

- Vegetables, especially colorful ones, contain anti-cancer compounds

2) Smoking
- Cigarette smoke contains at least 40 known carcinogens

3) Exposure to ultraviolet rays in sunlight
- UV rays directly mutate nucleotides

- Skin cancer is the most common form of cancer