Cycle 2: Cell Cycles and Cell Division

The Cycle of Cell Growth and Division

All cells are descended from previous cells in an unbroken chain of cell division. An **embryonic stem cell** will divide many times to produce all cells that make up a human. Embryonic stem cells differentiate into either **progeny cells** or back to embryonic stem cells (to maintain the stem cell population and prevent depletion).
Progeny cells are needed for:

1. Increasing the population of single celled organisms
2. Multicellular tissue growth
3. Asexual reproduction
4. Replacement of cells lost to wear and tear

Cell Differentiation

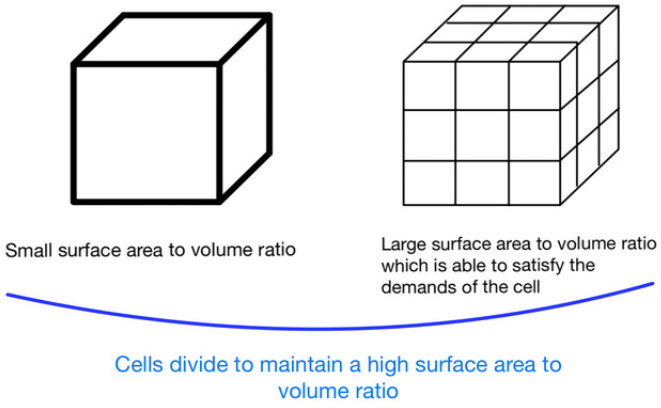
Undifferentiated embryos can differentiate into any cell. Different genes are turned on and off to allow them to differentiate. There are various points of the cell cycle that allow the cell to differentially express their genes and turn into different types of cells in the body. Different cell types have different **turnover rates**.
A turnover rate is the rate at which cells die and produce new cells

- e.g. hair cells and bone marrow cells have rapid turnover rates
- e.g. neurons, heart muscle, liver, adult stem cells and oocytes have very slow turnover rates

Cell division is a very important process that is driven by surface area to volume ratios.

Why cells divide: cell volume vs. surface area

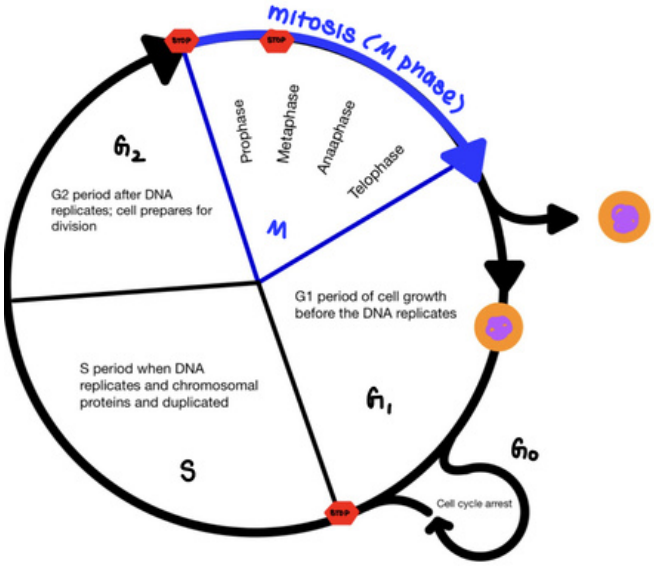
WThe theory of the cell volume to surface area ratio suggests that as a cell grows, its surface area to volume ratio will decrease. This is because the contents inside the cell grow much quicker than the surface area of the cell. Eventually, the surface area is not big enough to allow enough nutrients that is required for the volume of the cell (nutrients will not get in fast enough). Therefore the cell must divide in order to maintain a high surface area to volume ratio. The rate and timing at which cells divide is highly regulated in the cell cycle.



Regulation of the Cell Cycle

The cell cycle must be regulated to ensure that cells do not divide uncontrollably. The cell cycle has various checkpoints that ensure accurate cell division. These cell cycle checkpoints are regulated by **cyclins** and **kinases**. There are three checkpoints that ensure accurate cell division.

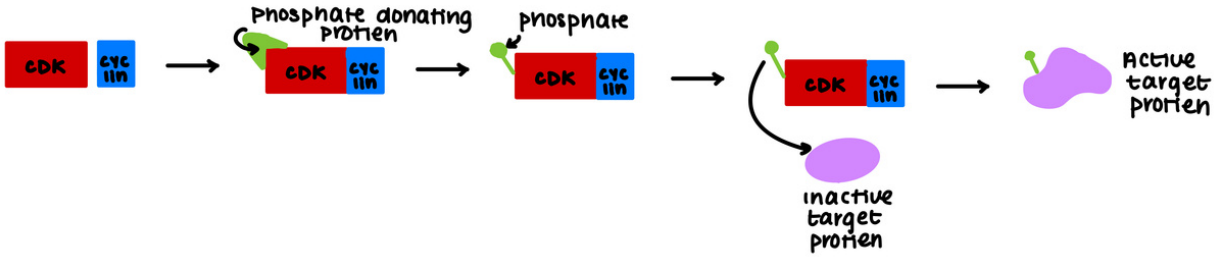
- **G1/S checkpoint** - the checkpoint between G1 and S phase
- **G2/M checkpoint** - passage through this checkpoint commits a cell to mitosis. Cells are arrested in G2/M if the DNA was not fully replicated in S phase or if the DNA was damaged
- **Mitotic spindle checkpoint** - this is during mitosis before metaphase. It assesses whether the chromosomes have been attached properly to the mitotic spindle so they align properly at the metaphase plate



Positive regulation of the cell cycle

CDKs (cyclin dependent kinases) are enzymes that monitor the progression of the cell cycle. The kinases only work in the presence of cyclins. CDKs phosphorylate other proteins to activate them and encourage progression through the cell cycle. There are many different cyclins, however the concentration of particular cyclins increases when it is time for a certain cell cycle phase to occur. For example: S phase cyclins increase in concentration before S phase occurs. The process of activating the cyclin-CDK complex is as follows:

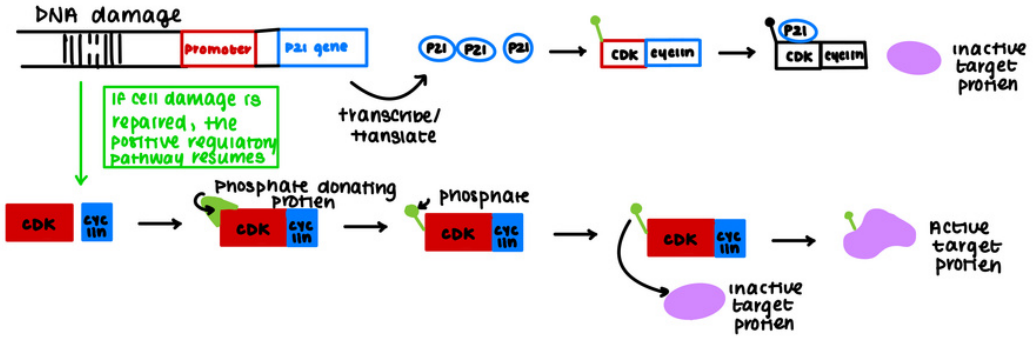
1. The kinase and cyclin need to be binded
2. A phosphate donating protein binds to the CDK, allowing the cyclin-CDK complex to bind together
3. The phosphorylated cyclin-CDK complex is now active
4. The active cyclin-CDK complex will now phosphorylate a target protein by donating its phosphate
5. The phosphorylated target protein will undergo a conformational change (change shape) into its active form
6. The phosphorylated target protein will help drive the cell from one phase to another in the cell cycle



Negative regulation of the cell cycle

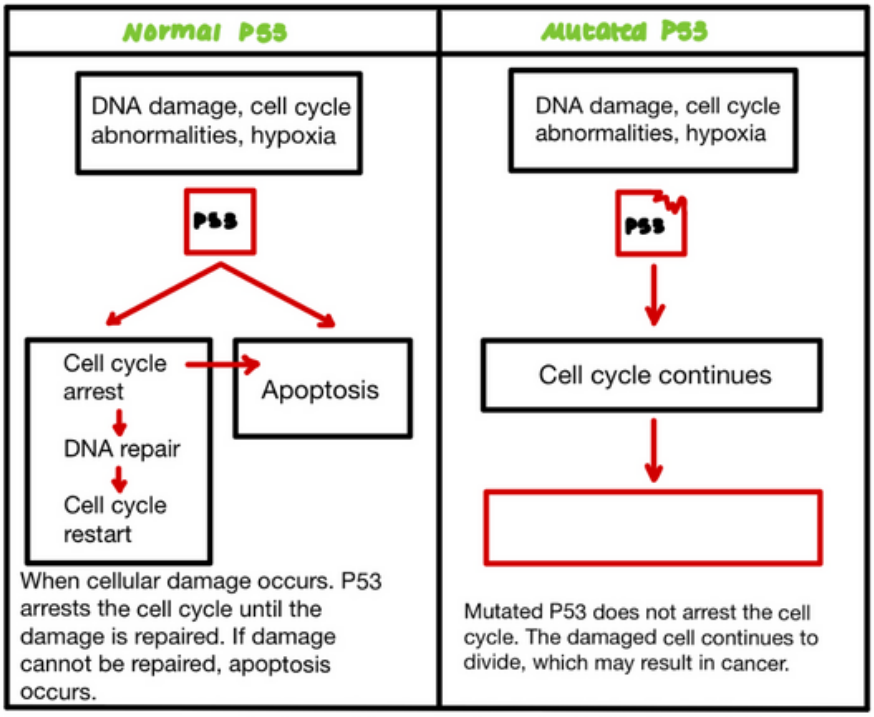
There are also proteins that negatively regulate the cell cycle to prevent the cell from entering a new phase of the cell cycle. This process is crucial to ensure that damaged cells do not continue to divide. Proteins such as **p53, p21 and Rb** are negative regulators that act at the G1/S checkpoint to halt the cell cycle, allow the cell to repair and then let the cell enter the cycle again. P53, p21 and Rb are defective and mutated in cells that divide uncontrollably (cancer cells). These proteins are also referred to as **tumor suppressors** because when they are present, they suppress tumors from arising. The process in which p53 inhibits cell growth in the presence of cellular damage is as follows:

1. P53 will act when it detects DNA damage
2. P53 inhibits cyclin CDKs by targeting p21 production
3. It will bind to the promoter of the p21 gene to activate p21 proteins
4. P21 proteins will bind to the cyclin-CDK complex to inactivate it
5. Since the inactivated cyclin-CDK complex will not be able to activate the target proteins, it will not drive the cell through the cycle
6. If the damaged cell can be repaired, the positive regulation pathway will be stimulated once again



Mutations in p53 or other Cell Cycle Proteins

p53 is known as the “guardian of the genome” because it prevents tumorous cells from forming. Since p53 monitors and repairs damaged cells, it ensures that cancerous cells do not form. p53 is normally mutated in cancerous cells, allowing the cells to divide unchecked. This logic applies for all cell cycle regulating proteins.

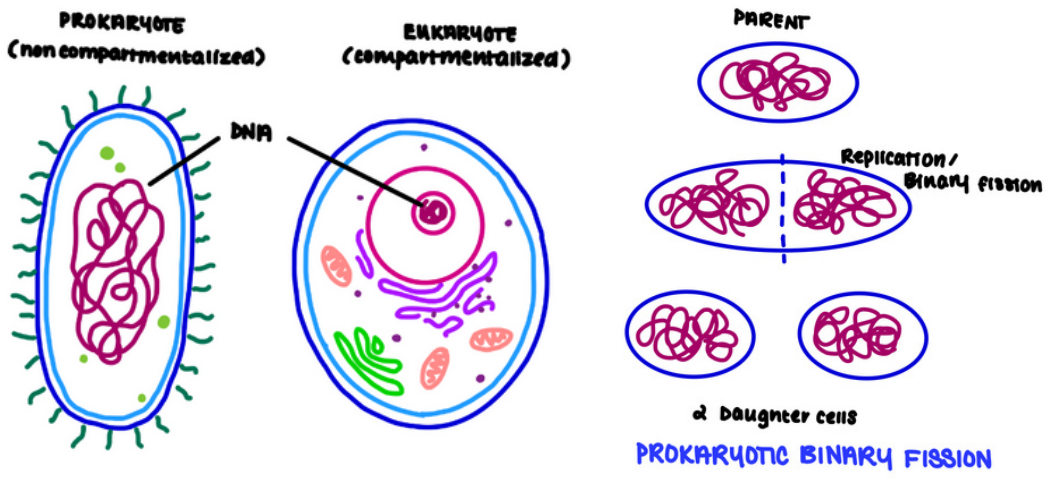


Introduction to Apoptosis

Apoptosis is programmed cell death. Some examples of cells that would normally be signalled to undergo apoptosis include: Damaged cells, Mutated cells, Aging cells

The cell cycle in prokaryotic organisms

Prokaryotic organisms, which are **unicellular**, replicate themselves through a process called **binary fission**. Binary fission is where the cell splits into two parts. All prokaryotes will store their DNA as a compacted chromosome. The DNA is not compartmentalized. As the cell increases in size, it will replicate its circular chromosome beginning at the origin of replication. The two circular chromosomes will then move to opposite ends of the cell. A membrane will then pinch together between them, making two daughter cells.



The cell cycle in eukaryotic organisms

Eukaryotic organisms replicate DNA through mitosis.

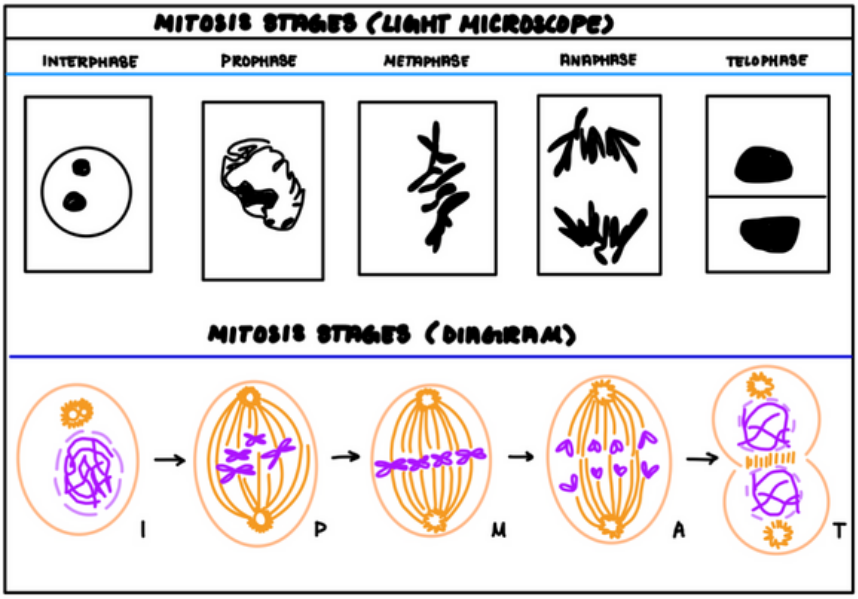
- **Chromosomes**: composed of DNA molecules and their associated proteins
- **Diploid:** eukaryotes have two copies of each type of chromosome in their nuclei, so their chromosome complement is said to be diploid (2n)
- **Haploid**: some eukaryotes may have only one copy of each type of chromosome in their nucleus, and therefore they are haploid (n)
- **Sister chromatids**: sister chromatids are held together along their length by proteins called cohesions. Cohesins are removed and sister chromatids separate with one of each pair going to the daughter nuclei

Prior to mitosis, we have interphase, which is composed of **G1 phase, S phase and G2 phase**.

- **Interphase** is the longest phase of the cell cycle. Cells spend most of their time in interphase.
  - **G1** - the cell carries out its function and grows
  - **S** - DNA is replicated and chromosomes are duplicated
  - **G2** - cell growth continues and the cell prepares for mitosis and cytokinesis

Mitosis is composed of **prophase, metaphase, anaphase, telophase, and cytokinesis.**

- Mitosis is an important process because it ensures that genetic information from a parental cell is successfully passed onto the daughter cells
  - **Prophase** - chromosomes that were replicated during interphase will condense into a nucleosome composed of DNA and histones. Linker DNA will link one nucleosome to the next. The nuclear envelope breaks down.
  - **Prometaphase** - bundles of spindle microtubules grow from the centromeres at opposing spindle poles towards the center of the cell (the kinetochore). Each chromosome is made up of two sister chromatids, held together by cohesion proteins.
  - **Metaphase** - spindles bound to kinetochores will line chromosomes up at the metaphase plate
  - **Anaphase** - the spindles will pull the chromosomes apart. Sister chromatids travel to opposite ends of the cell
  - **Telophase** - the spindle disassembles, the chromosomes decondense, and the nuclear envelope forms
  - **Cytokinesis** - furrowing in animal and bacteria, cell plate formation in plants
    - Furrowing - spindles spread laterally and the cell is squeezed to furrow
    - Cell plate - vesicles fuse along the metaphase plate to form a cell wall that splits the cells into two



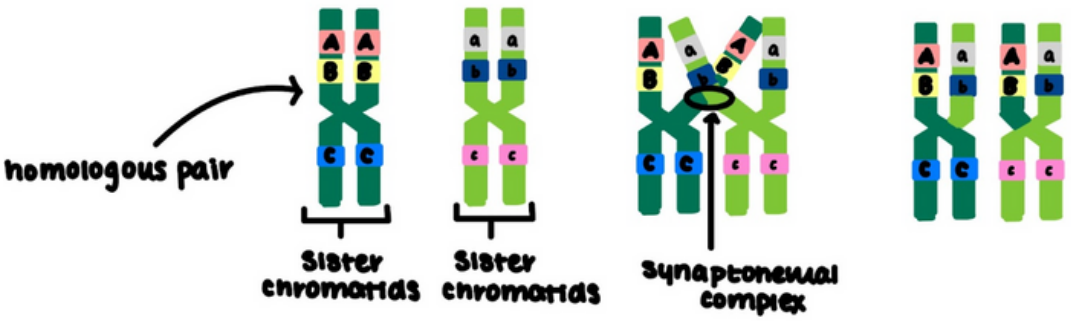
Meiosis

Meiosis is the process of producing more sex cells (gametes). Meiosis is unlike mitosis, where there is an exchange of alleles between homologous chromosomes. Unlike mitosis, meiosis has two sets of divisions, meiosis I and II.

- Meiosis I is **reductional** because the cell is reduced from a diploid to a haploid
- Meiosis II is **equational** because the cell is a haploid and remains haploid after the second division

Genetic Recombination

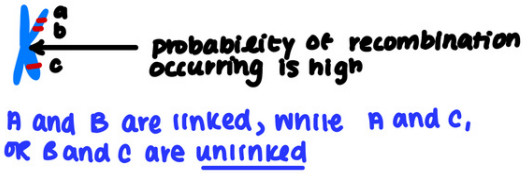
Meiosis involves genetic recombination which is what gives rise to differences among individuals. Genetic recombination gives rise to genetic variability (see page 9 for more information). Genetic recombination is the process of recombining our chromosomes to exchange alleles. During the pairing of the homologous chromosomes into a tetrad, cohesion proteins help the sister chromatids pair with one another. A synaptonemal complex is formed, the protein structure formed between homologous chromosomes during genetic recombination of meiosis.



Linked genes

Genes that are linked tend to be segregated together while unlinked genes will likely be separated

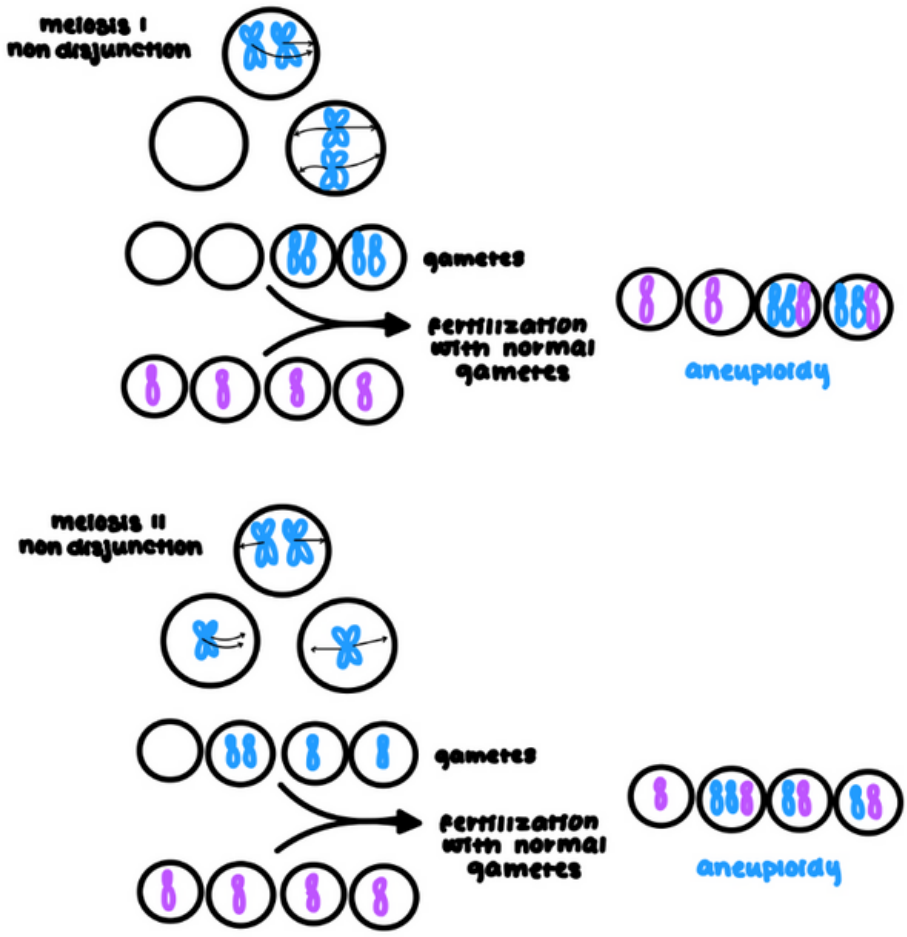
- Linked genes - genes that are very close together on the chromosome and will likely be inherited together
- Unlinked genes - genes that are far apart on the chromosome and there is a high probability of a recombination event occurring between them



Aneuploidy

Aneuploidy can arise if there are issues during genetic recombination. Aneuploidy is when there is an abnormal number of chromosomes in the gametes. This arises from non disjunction events in meiosis I or II. This can result in issues such as:

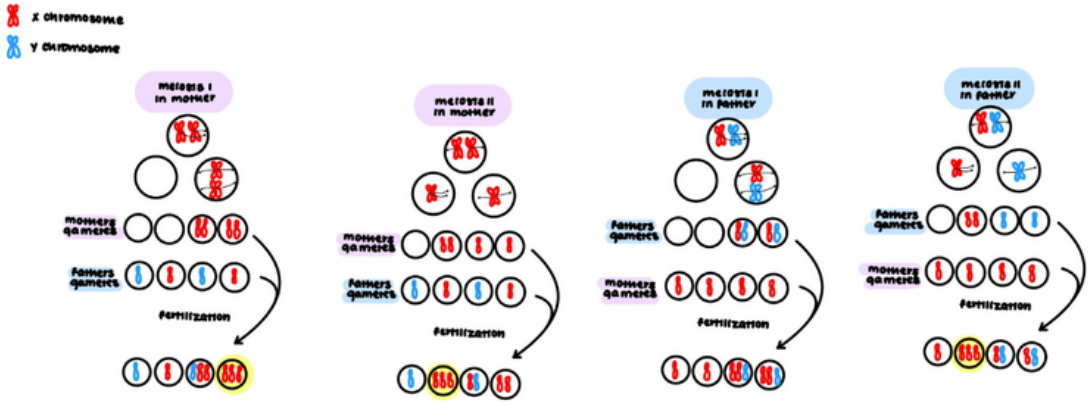
1. Down syndrome - 3 chromosome 21s in a gamete
    - It is often found that the older the oocyte (maternal eggs), the greater the susceptibility of offspring obtaining trisomy 21
2. Turner syndrome - only one X chromosome
3. Klinefelter syndrome - XXY
4. Triplex syndrome - XXX
5. Non viable - Y



Example 1: XXX syndrome is a genetic condition called Triple X Syndrome where an individual has three X chromosomes. Assuming the XXX karyotype resulted from a single error in chromosome partitioning, in which of the following stages of meiosis might the error have occurred?

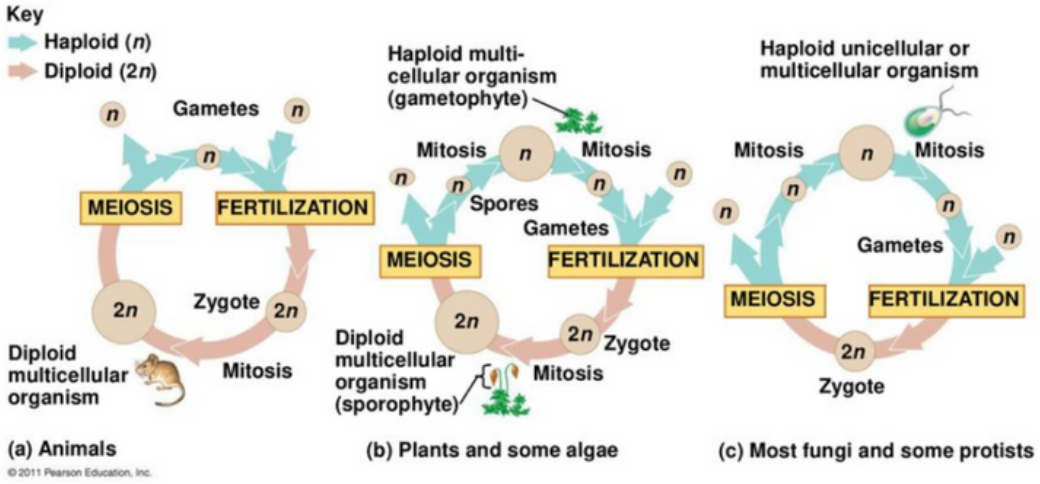
1. Meiosis I in the mother
2. Meiosis I in the father
3. Meiosis II in the mother
4. Meiosis II in the father

a. 1, 3, and 4
b. 1 and 3
c. 2 and 4
d. 4 only
e. All of 1, 2, 3, and 4 are correct



Answer: A

Eukaryotic Life Cycle



Animal life cycle

Animals live most of their life in a diploid phase.

- A 2n animal undergoes meiosis to produce gametes that are n
- Gametes (sperm and egg) fuse to create a 2n zygote
- Mitosis in the zygote allows it to grow into an adult

Diploid phase dominates the life cycle.

Plant and most fungi life cycle

- Fertilization of n gametes create a 2n zygote
- The 2n zygote will then divide by mitosis to make a plant (a sporophyte)
- The sporophyte has cells that will undergo meiosis to make spores
- The spores will then divide by mitosis to produce a gametophyte
- The gametophyte divides by mitosis to produce gametes
  - Therefore: gametes are produced by mitosis and spores are produced by meiosis
- Both the haploid and diploid phases dominate

Algae and some fungi life cycle

In other fungi and algae, a 2n zygote is created by the fertilization of two n gametes.

- The 2n zygote divides by meiosis to produce a haploid spore
- The haploid spore then divides by mitosis to grow and create a haploid gametophyte
- The haploid gametophyte undergoes mitosis to create haploid gametes
  - The haploid phase dominates the life cycle

Genetic Variability

Genetic variability is an important factor of a population. Genetic variability can arise in many ways throughout mitosis and meiosis.

- **Random segregation** - genetic variability can arise through random segregation in mitosis and meiosis, randomly distributing different alleles
- **Genetic recombination** - genetic variability can arise from random genetic recombination events during meiosis that will randomly segregate different alleles
- **Random fertilization** - genetic variability can arise from the random event of any one sperm fertilizing any one egg