LEARNING OUTCOME

a) analyse the structural and functional significance of nucleic acids in meiosis and mitosis, their role in cellular functions, and how mutations in nucleotide sequences can contribute to disease (cancer). (u, s, gs, v/a)

KEY AREAS

The genome

The cell cycle and mitosis

Cancer

Meiosis

Nucleic acids

DNA structure

DNA replication

DNA mutation

Transcription

Translation

Genetic code

Mechanism of protein synthesis

Gene regulation

THE GENOME

Collectively, all the DNA found within the cell is called its genome. An organism's genome determines its overall characteristics. Prokaryotic and eukaryotic cells differ in both the quantity and organization of their genomes; therefore, they differ in their characteristics.

Genomic DNA

In prokaryotes, the genome is typically composed of a single chromosome. The chromosome is made of a double-stranded DNA molecule organized in a loop or a circle. The circular chromosome is found in a region called the nucleoid. Some prokaryotes also have smaller loops of DNA called plasmids. Plasmids are not essential for normal growth, but often contain unique genes that confer beneficial properties, such as antibiotic resistance. These plasmids can be exchanged between different bacteria, and therefore, the beneficial properties can propagate.

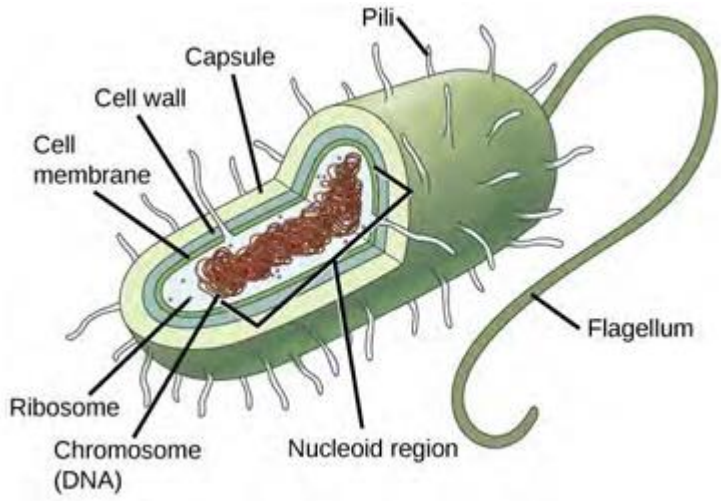


Figure: Prokaryotes, including both Bacteria and Archaea, have a single, circular chromosome located in a central region called the nucleoid.

In eukaryotes, the genome is made up of several linear chromosomes (Figure 8.3). Chromosomes consist of double-stranded DNA molecules wrapped around proteins. Each eukaryotic species has a characteristic number of chromosomes in its nuclei. In humans, all cells (with the exception of our eggs and sperm) contain 46 chromosomes, or 23 pairs of chromosomes

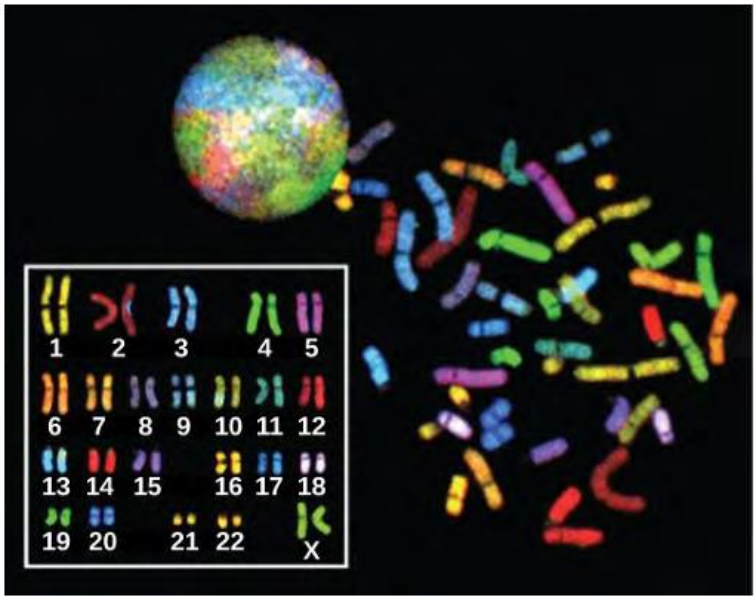


Figure: There are 23 pairs of chromosomes in a female human cell. In this image, the chromosomes were exposed to fluorescent stains to distinguish them.

Eukaryotic Chromosomal Structure and Packaging

If the DNA from all 46 chromosomes in a human cell were laid out end-to-end, it would measure approximately two meters! The average size of a human cell is about 10 µm; this means that the DNA must be packaged or condensed to fit into the cell's nucleus. At the same time, it must also be readily accessible so that it can be used to make proteins. For this reason,

the long strands of DNA are either loosely or tightly condensed with the help of different proteins.

To begin, DNA is loosely condensed by winding it around special proteins called histone proteins. As the DNA is wound around the protein, it forms a long fiber-like strand called chromatin. Within the chromatin fibers, stretches of DNA wind around several histone proteins simultaneously forming beadlike complexes called nucleosomes. The nucleosomes can coil, which condenses the DNA even more.

When a cell divides, the DNA will be condensed even more and individual chromosomes will become visible. Chromosomes are always present in the form of chromatin; however, they cannot be easily seen until the cell is preparing to divide.

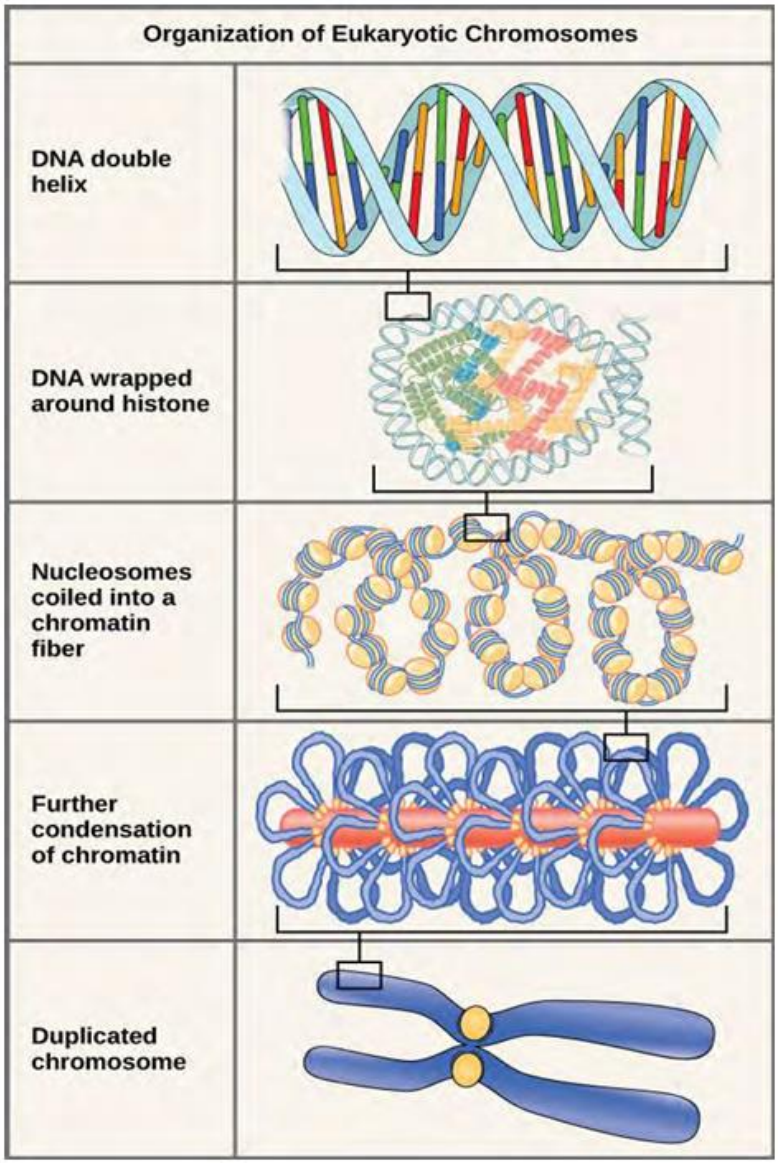


Figure: From top to bottom: The top panel shows a DNA double helix. The second panel shows the double helix wrapped around histone proteins, which makes a nucleosome. The middle panel shows multiple nucleosomes. The fourth panel shows that the chromatin fiber further condenses into the chromosome shown in the bottom panel.

THE CELL CYCLE AND MITOSIS

The cell cycle is a series of events involving both cell growth and division. The cell cycle begins when a cell is first formed and continues until it divides and produces two new daughter cells. When a cell is dividing, it proceeds through a series of carefully timed and regulated stages of growth, DNA replication, and division.

Many multicellular organisms, including humans, reproduce sexually by the completing the process of meiosis. Meiosis is a process that produces specialized reproductive cells called eggs and sperm. Sexual reproduction requires the egg and sperm to come together to form a fertilized egg, also called a zygote. In humans, gametes are produced in the testes of males and the ovaries of females.

Interphase and the Mitotic phase

Once the zygote is formed, it will begin to reproduce or divide through a process called mitosis. Mitosis must occur billions of times to produce the billions of genetically identical cells that make up one multicellular human. All multicellular organisms use mitosis for growth, maintenance, and cell repair.

The cell cycle has two major phases: interphase and the mitotic phase. During interphase, the cell grows, and DNA is replicated. The mitotic phase consists of two subphases: mitosis and cytokinesis. In mitosis, the nucleus breaks down and the genetic material is equally divided. Once the DNA is divided, two new identical nuclei are formed. Cytokinesis then divides the cytoplasm into two new distinct cells.

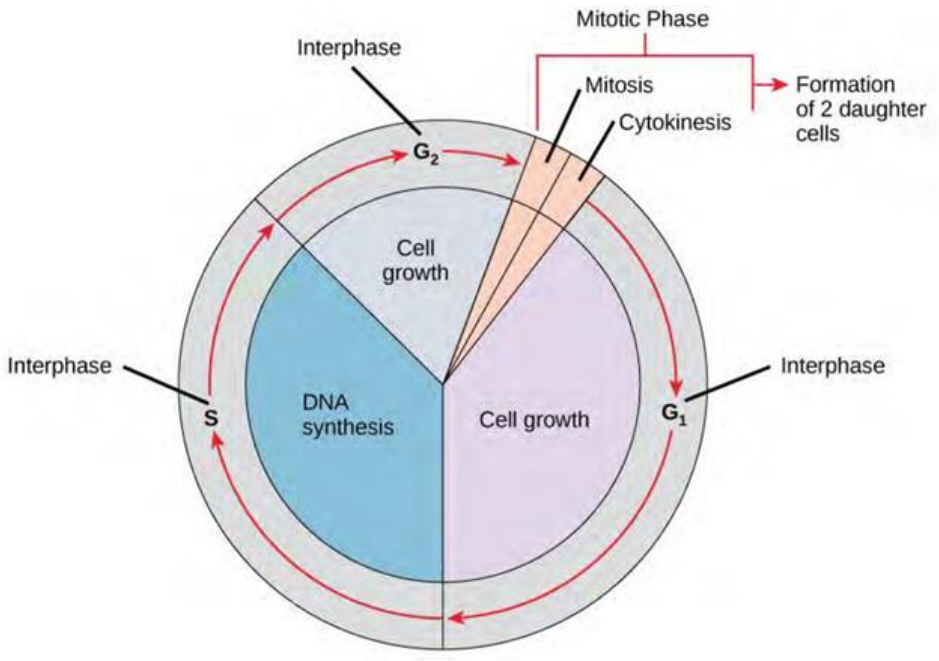


Figure: A cell moves through a series of phases called the cell cycle.

Interphase

Most cells spend the majority of their time in interphase. During interphase, the cell undergoes normal processes while also preparing for cell division. The three stages of interphase are called G1 (gap 1), S (synthesis), and G2 (gap 2).

G1 Phase

The first stage of interphase is called the G1 phase, or gap 1. Although it may not seem like much happens in gap one, especially given its name, the cell is actually very active at the biochemical level. During the G1 phase, the cell is accumulating the materials it will need to replicate its chromosomes. The cell must also generate enough energy to perform the processes of DNA replication and cell division. The cell also continues to carry out its normal cell function.

S Phase

Throughout interphase, chromosomes are in a semi-condensed state, meaning chromatin is visible; however, individual chromosomes are not. In the S phase or synthesis phase, DNA replication occurs. DNA replication involves making an identical copy of each chromosome. It is helpful to refer to chromosomes as being in either the unduplicated state or the duplicated state

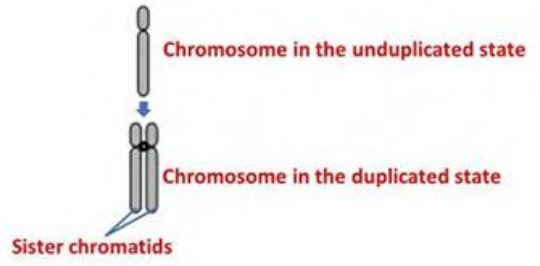


Figure: Chromosome in the unduplicated state versus a chromosome in the duplicated state.

For example, in G1 all chromosomes exist in the unduplicated state. After S phase chromosomes exist in the duplicated state. Chromosomes in the duplicated state each consist of two identical sister chromatids. Sister chromatids are firmly attached to one another at a location called the centromere region

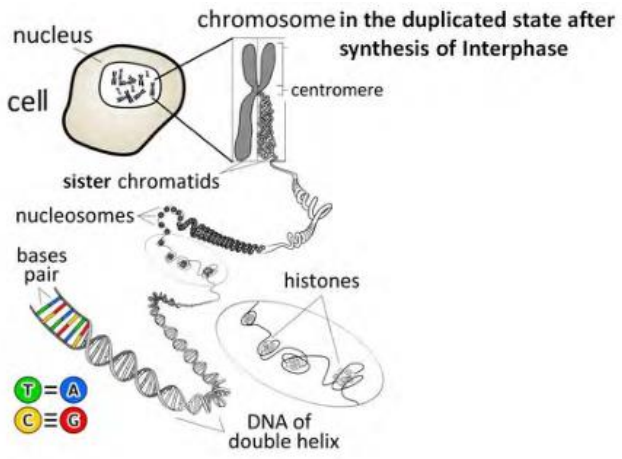


Figure: shows a chromosome in the duplicated state consisting of two identical sister chromatids.

Centrosomes are also duplicated during the S phase. Recall from chapter 4 that centrosomes are mostly microtubule-organizing centers. The two centrosomes give rise to the mitotic spindle, a microtubule network used to physically move the chromosomes during mitosis. The centrosomes consist of a pair of rod-like centrioles at right angles to each other. Centrioles help organize cell division in human cells and different types of animal cells. Neurons found in the brain and spinal cord lack centrioles and are therefore amitotic, meaning they do not divide. Plants and most fungi also do not use centrioles for cell division.

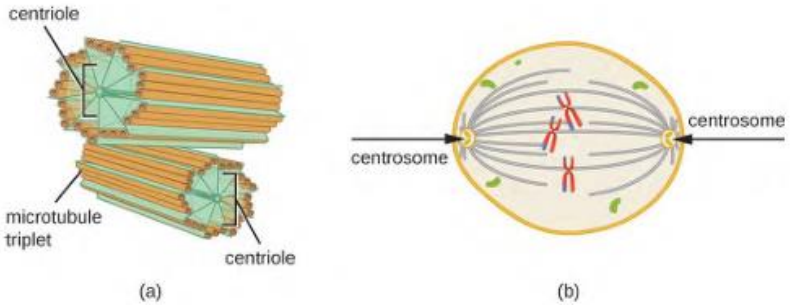


Figure 1 (a) A centrosome is composed of two centrioles positioned at right angles to each other. (b) In animal cells, the centrosomes (arrows) serve as microtubule-organizing centers of the mitotic spindle during mitosis.

G2 Phase

In the G2 phase, or gap 2, the cell replenishes its stored energy and synthesizes the proteins necessary for separating the chromosomes. Some cell organelles are duplicated, and the cytoskeleton is dismantled to provide resources for the mitotic spindle. There may be additional cell growth during G2. The final preparations for the mitotic phase must be completed before the cell can enter the first stage of mitosis.

G_0

Phase Some cells can also enter a resting phase called the G_0 phase. Cells, such as muscle cells and hair follicle cells, can temporarily stop dividing and will not enter the S phase. At that time, these cells are said to be in the G_0 phase. When cued, the cells can enter back into gap one of interphase. Some cells, such as nerve cells or mature cardiac muscle, have permanently stopped dividing and are also said to be in the G_0 phase.

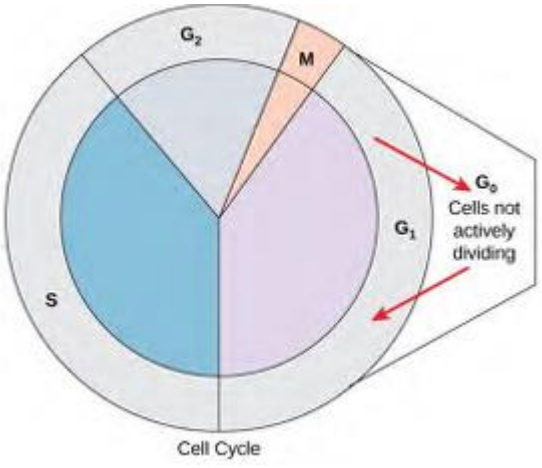


Figure: Cells that are not actively preparing to divide enter an alternate phase called G0.

The Mitotic Phase

The mitotic phase is a multistep process where chromosomes in the duplicated state are aligned, separated, and moved to opposite poles of the cell. The cell is then divided into two new identical daughter cells. The first portion of the mitotic phase, mitosis, is composed of five stages. Each stage has key events which allow for the chromosomes to be equally divided amongst the two daughter cells. The second portion of the mitotic phase, called cytokinesis, is the physical separation of the cytoplasmic components into two new daughter cells.

Mitosis

Mitosis is divided into five phases: prophase, prometaphase, metaphase, anaphase, and telophase. Each of these phases includes important events that allow for equal division of the chromosomes into two new daughter cells.

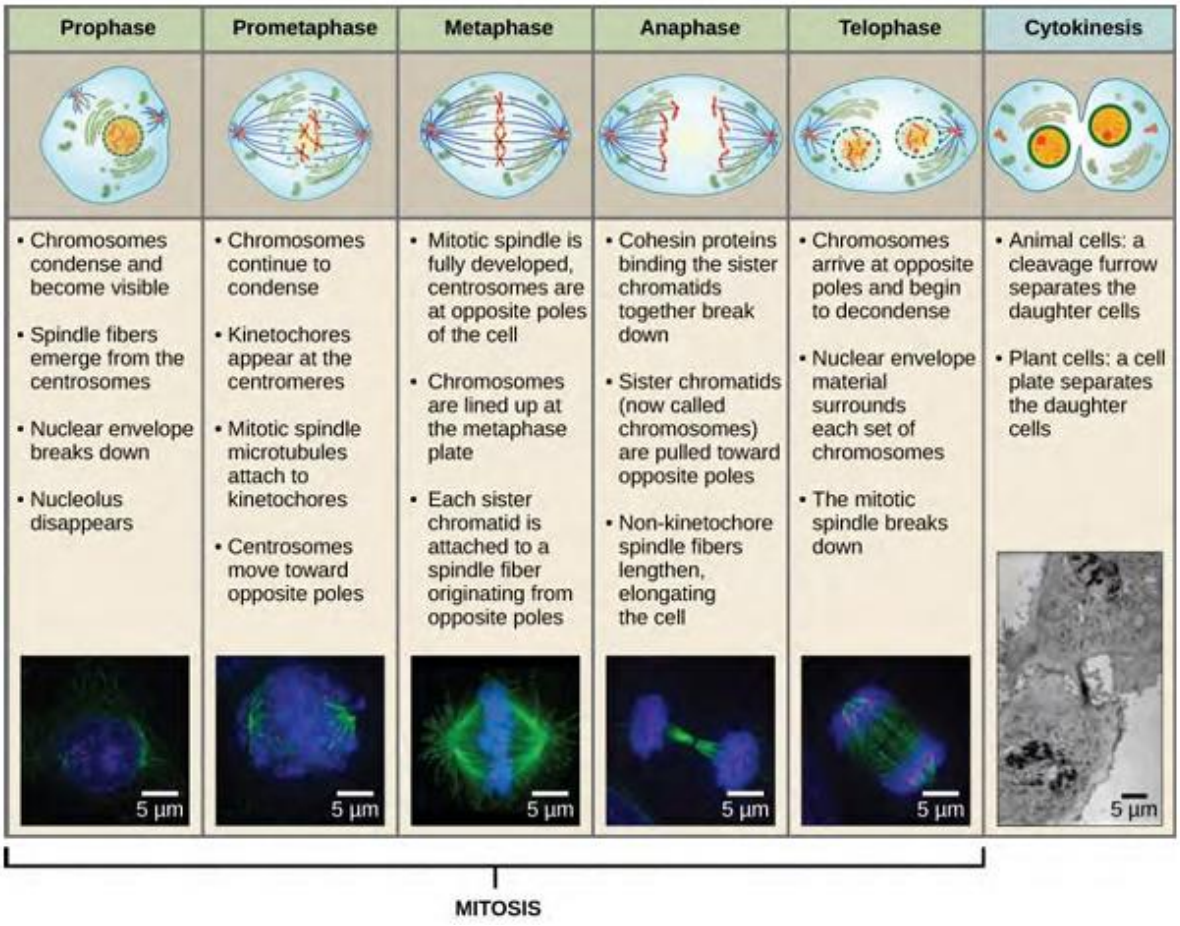


Figure: Animal cell mitosis is divided into five stages—prophase, prometaphase, metaphase, anaphase, and telophase—visualized here by light microscopy with fluorescence.

Prophase

During prophase, the first phase of mitosis, several events occur which will allow chromosomes in the duplicated state to be divide. During this phase, the nuclear envelope starts to breakdown into small vesicles. The Golgi apparatus and endoplasmic reticulum fragment and disperse to the outer edges of the cell, and the nucleolus disappears. The centrosomes begin to move to opposite poles of the cell with the help of microtubules. As the microtubules begin to form the mitotic spindle, they extend between the centrosomes, pushing the centrosomes farther and farther apart. The sister chromatids begin to coil tightly and become visible when using a light microscope.

Prometaphase

During prometaphase, many of the processes that began in prophase continue. The remaining nuclear envelope completely disappears. The mitotic spindle continues to develop as more microtubules are formed and then stretched across the entire length of the cell. Chromosomes become more condensed, and individual chromosomes become more visible. A protein

complex called the kinetochore attaches each sister chromatid to microtubules at the centromere region.

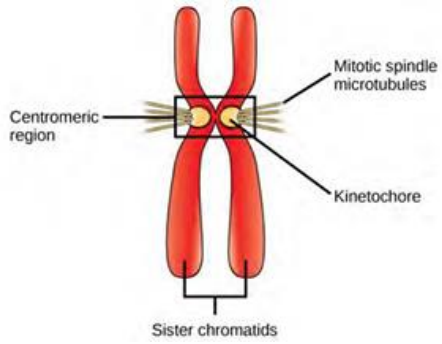


Figure: During prometaphase, mitotic spindle microtubules from opposite poles attach to each sister chromatid at the kinetochore.

Metaphase

During metaphase, all the chromosomes align in a region called the metaphase plate with the help of the mitotic spindle. The metaphase plate is a region midway between the two poles of the cell. The sister chromatids are tightly attached to one another. At this time, the chromosomes are in their most condensed form.

Anaphase

During anaphase, the sister chromatids are split apart with the help of both the kinetochore proteins and the spindle fibers. Each chromatid is now referred to as a chromosome in the unduplicated state. Each chromosome is rapidly pulled toward the centrosome to which its microtubule is attached. The cell becomes visibly elongated as the microtubules slide against each other at the metaphase plate.

Telophase

During telophase, as the chromosomes reach the opposite poles, they begin to decondense or unravel. The mitotic spindles are broken down into amino acid monomers that will be used to assemble the cytoskeleton for each daughter cell. Two nuclear envelopes begin to form around each separated group of chromosomes

Cytokinesis

Cytokinesis is the second part of the mitotic phase. During cytokinesis, cell division is completed when the cytoplasmic components are physically separated into two identical daughter cells. Although the stages of mitosis are similar for most eukaryotes, the process of cytokinesis is very different for eukaryotes that have cell walls, such as plant cells.

In cells that lack cell walls, such as animal cells, cytokinesis begins during anaphase. A contractile ring composed of actin protein filaments forms just inside the plasma membrane at the center of the cell. The microfilaments pull the equator of the cell inward, forming a fissure called the cleavage furrow. The cleavage furrow deepens as the actin ring contracts, and eventually, the membrane and cell are cleaved into two separate identical daughter cells

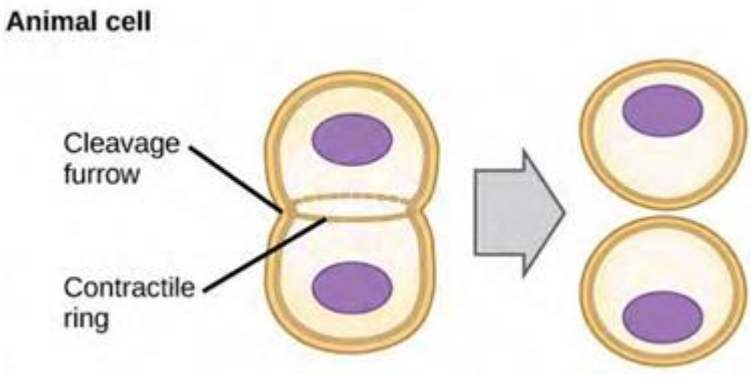


Figure: a cleavage furrow forms at the former metaphase plate in the animal cell.

In plant cells, a cleavage furrow is not possible because of the rigid cell walls surrounding the plasma membrane. A new cell wall must form between the two daughter cells. During interphase, the Golgi apparatus accumulates enzymes, structural proteins, and glucose molecules, which will later be used to build the new cell wall. Once these materials are collected, the Golgi apparatus breaks into vesicles that disperse throughout the dividing cell. During telophase, microtubules move these Golgi vesicles to the metaphase plate. Once there, the vesicles begin to fuse, forming a structure called the cell plate. As more vesicles fuse, the cell plate enlarges until it merges with the cell wall at the periphery of the cell. Enzymes use the glucose that has accumulated between the membrane layers to help build a new cell wall of cellulose.

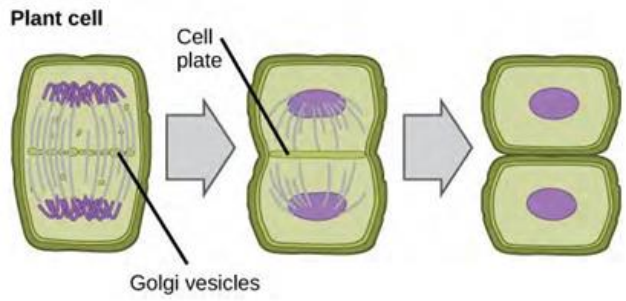


Figure: The cell plate grows from the center toward the cell walls.

Length and Control of the Cell Cycle

The length of the cell cycle varies greatly depending on the organism. Even within a multicellular organism, not all cells will divide at the same rate. In humans, the frequency of

cell division ranges from embryonic cells that divide in just a few hours to cells like the neurons of the brain that never divide. There is also variation in the time that a cell spends in each phase of the cell cycle. When fast-dividing mammalian cells are grown in culture, outside the body under optimal growing conditions, the length of the cycle is approximately 24 hours. The timing of events in the cell cycle is controlled by mechanisms that are both internal and external to the cell.

Regulation at Internal Checkpoints

Daughter cells must be exact copies of the parent cell. Mistakes in the duplication or distribution of the chromosomes lead to mutations that will then be passed on to every new cell produced. To prevent a compromised cell from continuing to divide, there are internal control mechanisms or cell cycle checkpoints at which the cell cycle can be stopped until conditions are favorable. There are three checkpoints where cell division can be stopped; they occur near the end of G1, at the G2–M transition, and during metaphase.

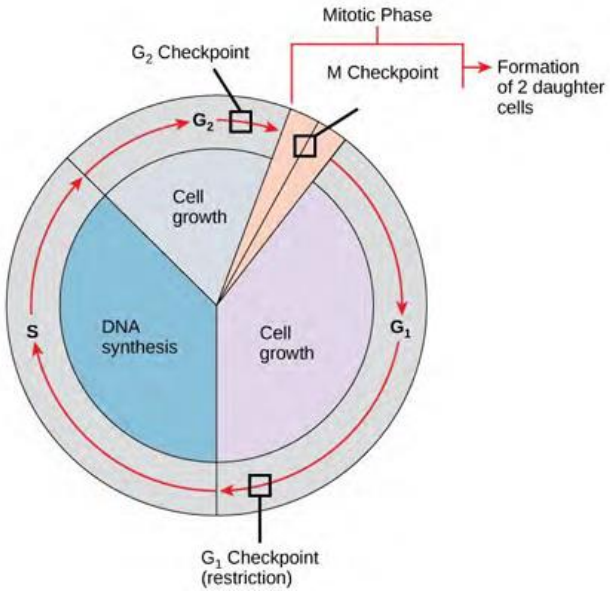


Figure: The cell cycle is controlled at three checkpoints.

The G_1 Checkpoint

The G_1 checkpoint determines whether all conditions are favorable for cell division to proceed. The G_1 checkpoint, also called the restriction point, is the point at which the cell irreversibly commits to the cell-division process. In addition to adequate protein reserves and cell size, there is a check for damage to the genomic DNA at the G_1 checkpoint. A cell that does not meet all the requirements will not enter the S phase.

The G_2 Checkpoint

The G_2 checkpoint prevents the cell from entering the mitotic phase if certain conditions are not met. As in the G_1 checkpoint, cell size and protein reserves are assessed. However, the most

crucial role of the G_2 checkpoint is to ensure that all the chromosomes have been replicated and that the replicated DNA is not damaged.

The M Checkpoint

The M checkpoint occurs near the end of metaphase of mitosis. The M checkpoint is also known as the spindle checkpoint because it determines if all the sister chromatids are correctly attached to the microtubules that make up the mitotic spindle. Because the separation of the sister chromatids during anaphase is an irreversible step, the cycle will not proceed until each pair of sister chromatids is firmly anchored to spindle fibers arising from opposite poles of the cell.

CANCER CONNECTION: The Implication of an Out-of-Control Cell Cycle

Cancer is a collective name used to describe many different diseases caused by uncontrolled cell division. Despite the redundancy of the cell cycle, errors can occur. Proper replication of DNA during the S phase is monitored closely during the cell cycle checkpoints. These checkpoints are controlled by cyclins and cyclin-dependent kinases (CDKs) which act as molecular switches that either allow or halt progression through the cycle. In healthy cells, failure to pass these checkpoints triggers cell cycle arrest, DNA repair, or programmed cell death (apoptosis). However, even with the checkpoints, a small percentage of replication errors, called mutations, can occur and be passed on to the daughter cells. If one of these mutations occurs within a gene, a gene mutation occurs.

All cancers begin when a gene mutation gives rise to a faulty protein that is used during cell division. Even minor mistakes allow subsequent mistakes to occur more readily. Over and over, small, uncorrected errors are passed from parent cell to daughter cells. Eventually, the pace of the cell cycle speeds up as the effectiveness of the control and repair mechanisms decreases. Uncontrolled growth of the mutated cells outpaces the growth of normal cells in the area, and a tumour can result.

Inherited genetic abnormalities may cause loss of cell cycle control. Environmental factors, such as UV light or smoking, can also damage DNA and impact control of the cell cycle. Often, a combination of both genetic predisposition and environmental factors lead to cancer.

The process of a cell escaping its normal control system and becoming cancerous may happen throughout the body quite frequently. Fortunately, specific cells of the immune system are capable of recognizing cancerous cells and destroying them. However, in some instances, the cancerous cells remain undetected and continue to proliferate.

Loss of cell cycle control in cancer

In cancer cells, the normal regulatory mechanisms of the cell cycle are disrupted. Cells ignore growth-inhibitory signals, continue dividing despite DNA damage, and fail to undergo

apoptosis. As a result, abnormal cells accumulate instead of being eliminated. This uncontrolled division leads to genetic instability, where further mutations accumulate, making the cells increasingly abnormal and aggressive. The implication of this loss of control is the formation of tissue that no longer function normally and compete with healthy cells for nutrients and space.

Cell division is regulated by several classes of genes that control growth, repair, and death. The most important among these are proto-oncogenes, tumour suppressor genes, and DNA repair genes. Mutations affecting these genes are central to the development of cancer.

Proto-oncogene are normal genes that promote cell growth and division in a controlled manner. They encode for proteins such as growth factors, growth factor receptors, signal transduction proteins, and transcription factors. Under normal physiological conditions, proto-oncogenes ensure that cells divide only when appropriate, such as during growth or tissue repair. Their activity is tightly regulated so that cell proliferation remains balanced.

When **proto-oncogenes** undergo mutation, they may become **oncogene**. Oncogenes are abnormally active and continuously stimulate cell division, even in the absence of growth signals. Unlike proto-oncogenes, oncogenes are dominant, meaning that a mutation in just one allele is sufficient to cause excessive activity. This results in persistent stimulation of the cell cycle, pushing cells to divide uncontrolled and contributing directly to cancer development.

Tumour suppressor genes act as brakes on the cell cycle. They encode for proteins that slow down cell division, repair damaged DNA, or trigger apoptosis when damage is irreparable. A well-known example is the **p53 gene**, often called the "**guardian of the genome**." p53 detects DNA damage and halts the cell cycle to allow repair or initiates apoptosis if repair fails. Another example is the **RB (retinoblastoma) gene**, which prevents cells from progressing from G_1 to S phase. In cancer, tumour suppressor genes are often inactivated by mutation, meaning the brakes on cell division are lost.

DNA repair genes encode proteins responsible for correcting errors that occur during DNA replication. When these genes are defective, mutations accumulate rapidly throughout the genome. Although mutations in DNA repair genes do not directly cause increased cell division, they greatly increase the likelihood of mutations in proto-oncogenes and tumour suppressor genes. This accelerates the progression from a normal cell to a cancerous one.

Formation of Tumours

A tumour is a mass of abnormal cells formed as a result of uncontrolled cell division. Tumours arise when cancer cells divide repeatedly without the normal limitations imposed on healthy cells. The expanding mass may compress surrounding tissues, interfere with normal organ function, and disrupt blood supply.

Tumours can develop in any organ of the body, but are most commonly found in the lungs, prostate gland (male), breast and ovaries (female), large intestine, stomach, oesophagus and pancreas.

Types of tumours

Not all tumours are cancerous. Those that are cancerous are called malignant while those that are non-cancerous are called benign. A tumour becomes cancerous if it changes from benign to malignant.

Benign tumours

Benign tumours are non-cancerous growths. They consist of cells that divide excessively but remain localized and do not invade surrounding tissues. Benign tumours are usually enclosed in a fibrous capsule and grow relatively slowly. Although they are not malignant, they can still cause harm if they press on vital organs or block ducts or blood vessels.

Malignant tumours

Malignant tumours are cancerous and far more dangerous. Their cells divide rapidly, lack normal adhesion properties and invade surrounding tissues. Malignant cells can enter blood or lymphatic system and spread to distant parts of the body, forming secondary tumours. This invasive and spreading nature is what makes cancer life-threatening.

The main characteristics of benign and malignant tumours are summarized in the table below

Benign tumours	Malignant tumours
Can grow to a large size	Can also grow to a large size
The cell nucleus has a relatively normal appearance	The cell nucleus is often larger and appears darker due to an abundance of DNA
Cells are often well differentiated (specialized)	Cells become de-differentiated (unspecialized)
Cells produce adhesion molecules that make them stick together and so they remain within the tissue from which they arise = primary tumours	Cells do not produce adhesion molecules and so they tend to spread to other regions of the body, a process called metastasis, forming secondary tumours
Tumours are surrounded by a capsule of dense tissue and so remain a compact structure	Tumours are not surrounded by a capsule and so can grow finger-like projections into surrounding tissue
Much less likely to be life-threating but can disrupt functioning of vital organ	More likely to be life-threatening, as abnormal tumour tissue replaces normal tissue
Tend to have localized effects on the body	Often have systematic (whole body) effects such as weight loss and fatigue
Can usually be removed by surgery alone	Removal usually involves radiotherapy and /or chemotherapy as well as surgery

Note:

1. The process by which cancer cells break away from the primary tumour, travel through the bloodstream or lymphatic system, and establish new tumours in other organs is called **Metastasis**. These secondary tumours disrupt normal physiological processes in affected organs, such as respiration in the lungs, detoxification in the liver, or coordination in the brain. Metastasis greatly complicates treatment and is a major cause of cancer-related deaths.
2. Apoptosis or programmed cell death is a vital physiological process that removes damaged or unnecessary cells. In healthy tissues, apoptosis prevents abnormal cells from surviving. In cancer cells, apoptotic pathways are often defective, allowing cells with severe genetic abnormalities to survive and continue dividing. This failure contributes to tumour growth and resistance to treatment.

Cancer causes risk factors

Cancer does not usually result from a single cause but from multiple risk factors acting over time. These factors increase the probability that mutations will occur in proto-oncogenes, tumour suppressor genes, or DNA repair genes. These mutations may arise spontaneously, be inherited, or be induced by the environmental and lifestyle factors. The likelihood of developing cancer is therefore influenced by a combination of biological, environmental, and behavioral risk factors, many of which act by increasing DNA damage or interfering with DNA repair and cell cycle regulation.

Note: i) carcinogens are physical, chemical, or biological agents that increase the risk of developing cancer by promoting uncontrolled cell division.

ii) mutagens are physical, chemical, or biological agents that cause permanent changes (mutations) in the DNA sequence of an organism.

iii) all carcinogens are mutagenic or promote mutation-related processes, but not all mutagens are carcinogenic. A mutagen causes DNA mutation, whereas a carcinogen specifically increases the likelihood that those mutations will result in cancer.

1. Genetic and inherited risk factors

Some individuals inherit mutations in genes that regulate the cell cycle or DNA repair. Such inherited mutations do not directly cause cancer but increase susceptibility. For example, inherited mutations in tumour suppressor genes reduce the ability of cells to control division or repair DNA damage, as a result, fewer additional mutations are required for cancer to develop. Individual with a family history of certain cancers are therefore at higher risk.

2. Age as a risk factor.

Age is a major risk factor for cancer because the longer a person lives, the more cell divisions occur. Each cell division carries a risk of DNA replication errors. Over time, mutations

accumulate, increasing the likelihood that critical control genes will be affected. This explains why cancer is more common in older individuals.

3. Chemical carcinogens

Chemical carcinogens are substances that cause cancer by damaging DNA or interfering with cell cycle regulation. Examples include tobacco smoke, alcohol metabolites, pesticides, industrial chemicals and aflatoxins produced by fungi in poorly stored food. These chemicals may form DNA adducts (chemical modifications where a carcinogen or reactive chemical binds covalently to DNA strand, forming a new, distinct molecule) or cause mutations during replication. Repeated or prolonged exposure increases the risk of permanent genetic damage leading to cancer.

4. Physical carcinogens (radiations)

Radiation is a powerful cause of cancer because it can directly damage DNA. Ultraviolet (UV) radiation from sunlight causes mutations in skin cells by forming thymine dimers, while ionizing radiations such as -rays and gamma rays causes breaks in DNA strands if these breaks are not correctly repaired, mutations accumulate, increasing the risk of malignant transformation.

5. Biological carcinogens (infectious agents)

Some cancers are linked to viral, bacterial or parasitic infections. Certain viruses insert their genetic material into host cells, disrupting normal gene regulation. Chronic infections can also cause prolonged inflammation, increasing cell turnover and mutation rates. Infections therefore contribute indirectly to cancer by increasing DNA damage and altering normal cell cycle control.

6. Life style and behavioral risk factors

Life style and behavioral factors increase cancer risk by increasing DNA damage, promoting chronic inflammation, and altering normal physiological control of cell division.

One of the most significant factors is tobacco smoking which exposes body tissues to numerous chemical carcinogens. These substances enter the lungs and blood stream, forming adducts that interfere with DNA replication and repair mechanisms, leading to mutations in proto-oncogenes and tumour suppressor genes. Smoking also promotes chronic inflammation of tissues, increasing cell turnover and further raising mutation rates.

Excessive alcohol consumption increases cancer risk through its metabolic product acetaldehyde (ethanal), which is toxic and mutagenic. Acetaldehyde damages DNA and proteins involved in cell cycle regulation. Alcohol also increases permeability of cell membranes enhancing the absorption of other carcinogens, and interferes with the metabolism of hormones such as oestrogen, thereby indirectly promoting hormone-dependent cancers.

Dietary habits strongly influence cancer risk. Diets high in processed foods, saturated fats, and low fibre are associated with increased cancer incidence because they promote obesity, oxidative stress, and chronic inflammation. Obesity alters normal metabolism and increases

levels of growth-promoting hormones such as insulin and insulin-like growth factors, which stimulate cell division and inhibit apoptosis. In contrast, diets rich in fruits and vegetables provide antioxidants that reduce oxidative DNA damage.

Physical inactivity contributes to cancer risk by allowing accumulation of excess body fat and reducing immune surveillance. Regular physical activity improves hormonal balance, reduces inflammatory markers, and enhances immune function, all of which help maintain normal physiological control of cell division.

Use of artificial tanning beds is a significant behavioral risk factor, especially for skin cancer. Tanning beds emit high levels of UV radiation, often stronger than natural sunlight. UV radiation penetrates skin cells and causes direct DNA damage, particularly the formation of thymine dimers. If these lesions are not properly repaired, mutations accumulate in genes controlling division, leading to malignant transformation of skin cells.

7. Hormonal and physiological risk factors

Hormones play a critical role in regulating growth and differentiating of tissues. However, prolonged exposure to elevated hormone levels increases cancer risk by stimulating repeated cell division, thereby increasing the probability of replication errors. the most important example is oestogen, a hormone that promotes cell proliferation in tissues such as the breast and uterus.

Oestrogen increases cancer risk by continuously stimulating cells to enter the cell cycle. The more frequently cells divide, the higher the chance that mutations will occur during DNA replication. In addition, some oestrogen metabolites can directly damage DNA, further increasing mutation rates. Prolonged exposure to oestrogen occurs in situations such as early onset of menstruation, late menopause, hormone replacement therapy, or obesity, since adipose tissue can produce oestrogen. These conditions therefore increase the risk of hormone-dependent cancers.

Hormonal contraceptives and hormone therapies may influence cancer risk depending on duration and hormonal composition. Long-term exposure to external hormones may disrupt the body’s normal feedback mechanisms, leading to sustained proliferative signaling in sensitive tissues.

Cancer prevention

Cancer prevention aims to reduce exposure to risk factors, enhance early detection and maintain normal physiological control of cell division. Prevention can be classified into primary and secondary prevention.

Primary prevention

Primary prevention involves reducing or eliminating exposure to carcinogenic factors before cancer develops. This includes avoiding tobacco use, limiting alcohol consumption, maintaining a balanced diet rich in fruits and vegetables and engaging in regular physical

activity. Protection from excessive sun light and avoidance of harmful chemicals also reduce DNA damage and mutation rates. Vaccination from cancer-associated infections further lowers cancer risk by preventing infection-induced genetic disruption.

Secondary prevention (early detection)

Secondary prevention focuses on early detection of cancer or pre-cancerous changes before symptoms appear. Screening methods allow abnormal cell growth to be identified when it is still localized and easier to treat. Early detection significantly improves survival by preventing progression to invasive or metastatic disease.

Management of cancer

Cancer management refers to the treatment and control of cancer with the aim of curing the disease, prolonging life, or improving quality of life. Management strategies target the abnormal physiology of cancer cells particularly their uncontrolled division and survival.

1. Surgery

Surgery involves the physical removal of tumours and is most effective when cancer is detected early and remains localized. By removing the mass of cancerous cells, surgery reduces tumour burden and prevents invasion and metastasis. Surgery may also be combined with other treatments to eliminate remaining cancer cells.

2. Radiotherapy

Radiotherapy uses high-energy radiation to kill cancer cells by causing irreparable DNA damage. Cancer cells are particularly sensitive because they divide DNA repair mechanism. Radiotherapy may be used to shrink tumours before surgery or destroy remaining cells afterward.

3. Chemotherapy

Chemotherapy involves the use of drugs that interfere with cell division. These drugs target rapidly dividing cells by disrupting DNA replication, mitosis or metabolic pathways essential for proliferation. While effective, chemotherapy may also affect normal rapidly dividing cells, leading to side effects, e.g., hair cells, leading to loss of hair by the person.

4. Hormonal therapy

Some cancers depend on hormones for growth. Hormonal therapy works by reducing hormone levels or blocking hormone receptors, thereby removing the proliferative signals that drive cancer cell division. This approach slows tumour growth and may cause tumour regression.

5. Targeted therapy and immunotherapy

Targeted therapies specifically block abnormal proteins produced by oncogenes or mutated signaling pathways in cancer cells.

Immunotherapy enhances the body's immune response, enabling immune cells to recognize and destroy cancer cells that would otherwise evade detection and often cause fewer side effects than traditional treatments.

6. Palliative care

When cancer cannot be cured, palliative care focuses on relieving symptoms and improving quality of life. This includes pain management, nutritional support, and psychological care. Palliative care addresses the physiological, emotional, and social effects of cancer.

MEIOSIS

Sexual reproduction requires fertilization, a fusion between two specialized cells, called gametes. Each gamete is haploid, meaning it contains one set of chromosomes. When gametes unite, they form a zygote, or fertilized egg. Each zygote is diploid, meaning that it contains two sets of chromosomes, one from each biological parent.

Most of the cells that make up the human body are called somatic cells. Each somatic cell, also called a body cell, should contain 46 chromosomes. Germline cells lead to the production of gametes and makeup only a small percentage of our overall cells. In humans, gametes are our sex cells, and should each contain 23 chromosomes. Female gametes are called eggs, whereas male gametes are called sperm.

A typical diploid somatic cell contains two copies of each chromosome, called homologous chromosomes. Homologous chromosomes are the same length and have specific nucleotide sequences called genes in exactly the same location, or locus. Genes, the functional units of chromosomes, determine an organism's specific characteristics.

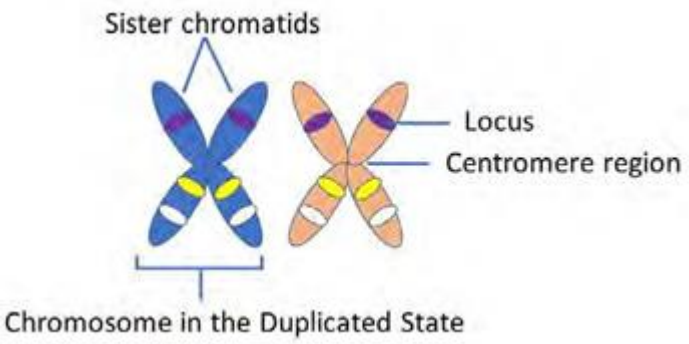


Figure: Homologous chromosomes. Each chromosome is in the duplicated state.

Homologous chromosomes may have different variations of the same gene at the same location. For example, on a homologous pair of chromosomes, one of the chromosomes may have a gene for attached earlobes at a specific location. On the other chromosome, at the same

location, there may be a gene that causes earlobes to be unattached. In the end, it is the genes on the chromosome pairs that determine the physical characteristics of an individual.

Both human males and females have twenty-two pairs of homologous chromosomes called autosomes. Autosomes are chromosome pairs one through twenty-two and do not determine a person's biological sex. The twenty-third pair of chromosomes are referred to as the allosomes.

Humans contain the allosomes X and Y. Some resources use the term "sex chromosomes" instead of allosomes. "Sex chromosome" is misleading. Many non-sex determining genes are found on the X chromosome and autosomes do contain genes involved in sex determination. In phenotypic females, the twenty-third pair of chromosomes are homologous, X and X. Phenotypic males, however, have a twenty-third pair, X and Y, that are not homologous. The genes found on the X and Y chromosomes do not code for the same characteristics. For example, on the Y chromosome, there is a set of genes called the SRY genes that allow males to develop testes. Those genes are not typically located on the X chromosome; thus, this pair is not homologous.

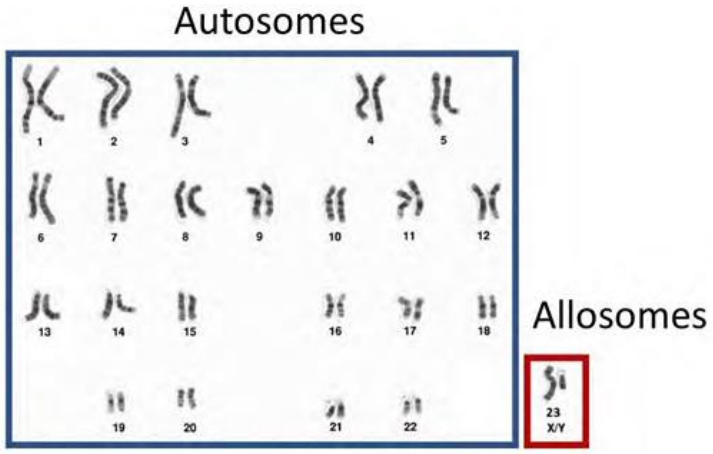


Figure: shows a human karyotype.

If the reproductive cycle is going to occur, specialized diploid cells called adult stem cells must carry out a process called **meiosis**. In males, the adult stem cells are called spermatogonia and lead to the production of gametes called sperm. In females, these cells are called oogonia and lead to the production of female gametes called eggs or ova.

Plants do not reproduce the same way as animals; however, they still produce two separate and distinct gametes. In flowering plants, the male gametes form in the anthers and are enclosed within a pollen grain. Flowering plants make their female gametes in a structure called the ovary and the gametes are called ovules.

Meiosis is the process that produces haploid gametes by reducing the number of chromosome pairs by half. If this did not occur, the number of chromosomes would double with every future round of fertilization. Meiosis includes many of the same cellular events as mitosis. However, mitosis produces daughter cells who are genetically identical to one another. In mitosis, both the parent and the daughter cells should have the same genetic material and, therefore, the same chromosome number. Both the parent cell and the daughter cells are said to have the same

“ploidy level.” This means that a diploid parent cell will produce daughter cells that are also diploid. The process of mitosis should result in the ploidy level remaining the same.

In meiosis, the starting adult stem cell is always diploid. The daughter cells that are produced are haploid; therefore, with meiosis, the ploidy level changes. To achieve this reduction in chromosome number, meiosis consists of one round of chromosome replication followed by two rounds of chromosome division. Because the events that occur during each of the stages are similar to the events of mitosis, the same stage names are assigned. However, because there are two rounds of division, the major processes and the stages are designated with a “I” or a “II.” Thus, meiosis I is the first round of meiotic division and consists of prophase I, prometaphase I, and so on. Likewise, meiosis II, during which the second round of meiotic division takes place, includes prophase II, prometaphase II, and so on. Let's take a closer look at the stages that make up meiosis

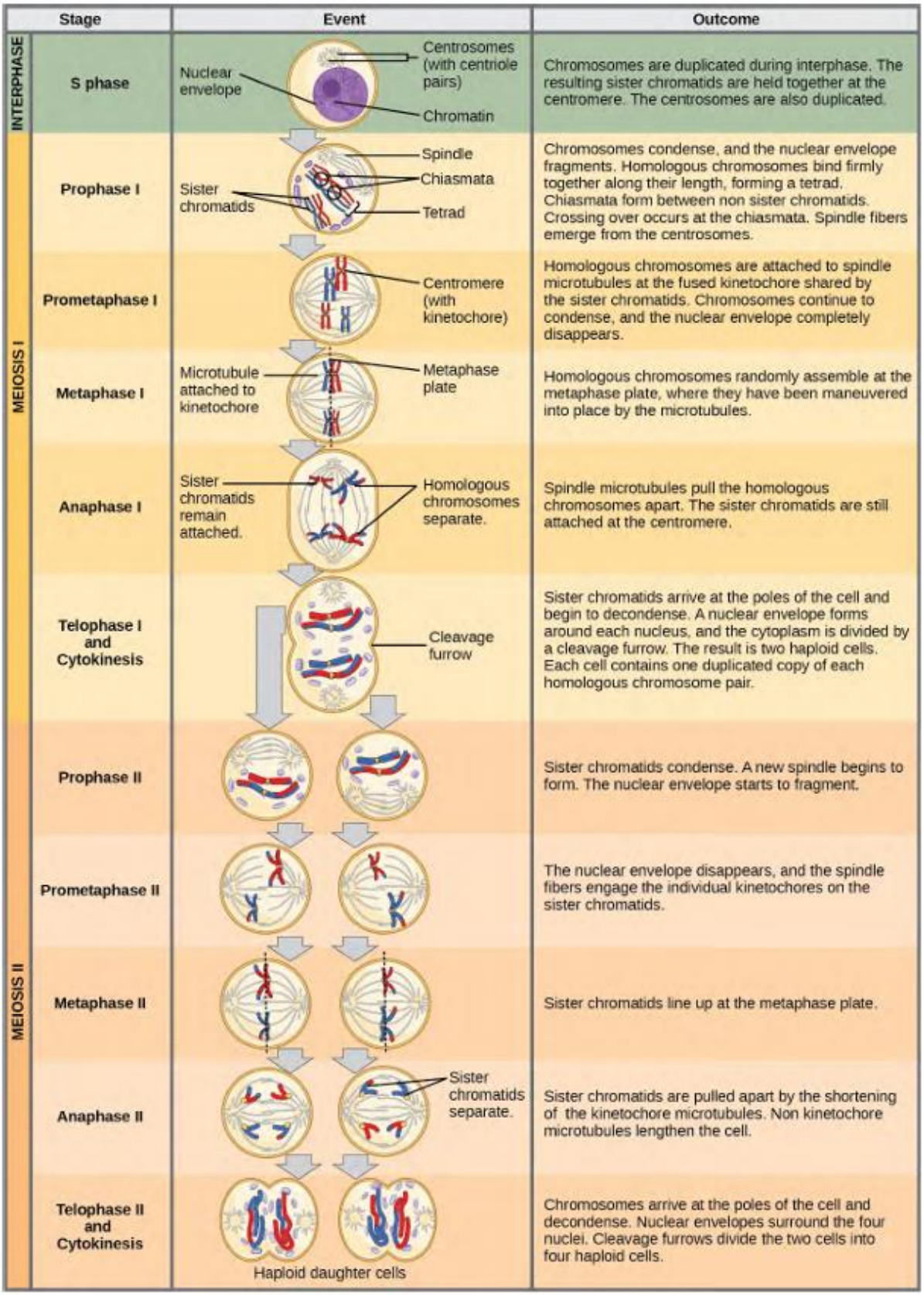


Figure: An animal cell with a diploid number of four (2n = 4) proceeds through the stages of meiosis to form four haploid daughter cells.

Interphase

Meiosis is preceded by an interphase consisting of the G1, S, and G2 phases, which are nearly identical to the phases preceding mitosis. The G1 phase is the first phase of interphase and is focused on cell growth. In the S phase, the DNA of the chromosomes is replicated. Finally, in the G2 phase, the cell undergoes the final preparations for meiosis.

During DNA duplication of the S phase, each chromosome becomes composed of two identical copies called sister chromatids. Once this occurs, the chromosomes are said to be in the duplicated state. Chromosomes in the duplicated state are held together at the centromere until they are pulled apart during meiosis II. In an animal cell, the centrosomes that organize the microtubules of the meiotic spindle also replicate during interphase. This prepares the cell for the first meiotic phase.

Meiosis I

Prophase I

Prophase I is the first phase of meiosis. Early in prophase I, the chromosomes begin to condense, and the nuclear envelope begins to break down. Homologous chromosomes are brought together with the help of unique proteins. Each homologous chromosome pair is held together by proteins forming a tetrad, a complex consisting of four sister chromatids. Recall that in mitosis, homologous chromosomes do not pair together.

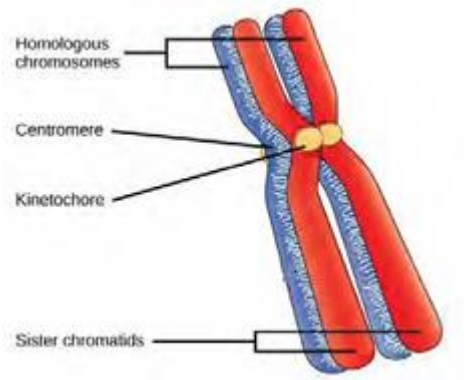


Figure: Homologous chromosomes pair together during prophase I to form a tetrad.

When the tetrad is formed, the genes on the non-sister chromatids of the homologous pair are precisely aligned with each other. This alignment allows for chromosome segments to be exchanged between non-sister chromatids; a process called crossing over or recombination. Crossing over occurs at precise locations called chiasmata (singular = chiasma)

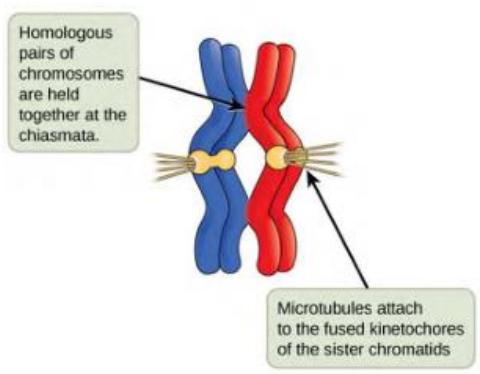


Figure: Chiasmata hold the homologous chromosomes together.

Crossover events are the first source of genetic variation produced during meiosis. A single crossover event between homologous non-sister chromatids results in chromosomes that differ from the two parents. The recombinant sister chromatid has a combination of maternal and paternal genes that did not exist before the crossover. Crossover events can occur almost anywhere along the length of the chromosomes; therefore, each gamete produced will have unique combinations of both maternal and parental genes.

In humans, even though the X and Y allosomes are not considered homologous in that most of their genes differ, there is a small region of homology that allows the X and Y chromosomes to pair up during prophase I.

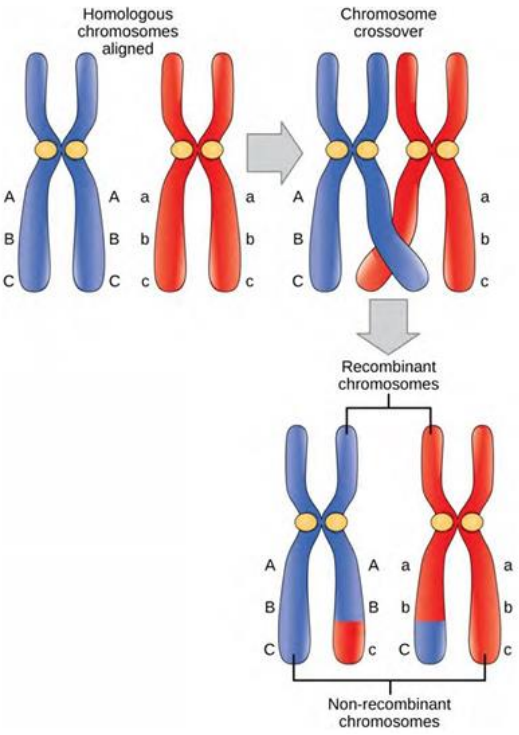


Figure: shows the effects of crossing over; the blue chromosome came from the individual's father, and the red chromosome came from the individual's mother.

Prometaphase I

The key event in prometaphase I is the attachment of the microtubules to each sister chromatid's kinetochore proteins. The microtubules assemble from centrosomes at opposite poles of the cell and grow toward the middle of the cell. Homologous chromosomes are still held together at the chiasma. In addition, the nuclear membrane has broken down entirely.

Metaphase I

During metaphase I, the homologous chromosomes are arranged in the center of the cell, a region called the metaphase plate. Each tetrad is attached to microtubules from both poles. Within the tetrad, one homologous chromosome is attached at one pole, and the other homologous chromosome is attached to the opposite pole. The orientation or arrangement of each homologous pair on the metaphase plate is random.

This randomness of how the chromosomes align at the metaphase plate, called independent assortment, also generates genetic variation in offspring. Using humans as an example, the female provides one set of 23 maternal chromosomes via the egg or ova. The male provides the other set of 23 paternal chromosomes in the sperm which fertilizes the egg. In metaphase I, these pairs line up at the midway point between the two poles of the cell. The arrangement of the tetrads at the metaphase plate is random. This is because a microtubule is just as likely to attach to a maternal chromosome as it is to attach to a paternally inherited chromosome. Thus, any maternally inherited chromosome may face either pole. Likewise, any paternally inherited chromosome may also face either pole. The orientation of each tetrad is independent of the orientation of the other 22 tetrads.

In each cell that undergoes meiosis, the arrangement of the tetrads is different. The number of variations depends on the number of chromosomes making up a set. Each tetrad has two possible orientations; thus, the potential number of alignments equals 2n, where n is the number of chromosomes per set. Humans have 23 chromosome pairs, which results in over eight million (223) possibilities. This number does not include the variability previously created in the sister chromatids by crossing over. Given these two mechanisms, it is highly unlikely that any two haploid cells resulting from meiosis will have the same genetic composition

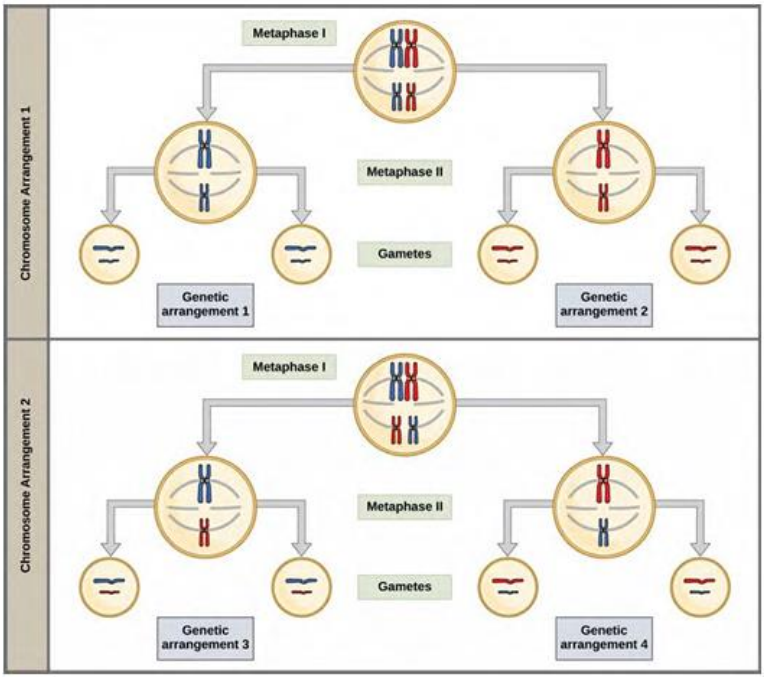


Figure: demonstrates independent assortment in metaphase I.

Anaphase I

In anaphase I, the spindle fibers pull the linked homologous chromosomes apart. Once the homologous chromosomes are separated, one chromosome, in its duplicated state, is slowly pulled towards one pole while the other is pulled to the opposite pole. The sister chromatids that make up each chromosome remain tightly bound together at the centromere.

Telophase I

In telophase I, the separated chromosomes arrive at opposite poles. Other events that may occur in telophase depend on the species. In some organisms, including animal cells, the chromosomes decondense and the nuclear envelopes reform in telophase I. In other organisms, such as some protists, cytokinesis occurs without the reformation of the nuclei.

Cytokinesis I

In nearly all species, cytokinesis I separate the cell contents by either a cleavage furrow in animals and some fungi, or a cell plate in plant cells. The cell plate will ultimately lead to the formation of a cell wall between the two new plant cells. At this point, each daughter cell is considered haploid; each cell contains only one set of chromosomes. Each of the chromosomes found in the daughter cells is in the duplicated state, meaning each chromosome consists of two sister chromatids that are still attached to each other. Although in interphase, the sister chromatids were exact copies of one another, they are no longer identical at this stage because of the process of crossing over.

In some species, cells enter a brief interphase, or interkinesis, before entering meiosis II. Interkinesis lacks an S phase, so chromosomes are not duplicated. The two haploid cells produced in meiosis I go through the events of meiosis II in synchrony. During meiosis II, the

sister chromatids within the two daughter cells separate, forming four new haploid gametes. The mechanics of meiosis II are similar to mitosis, except that each dividing cell has only one set of homologous chromosomes, each consisting of two sister chromatids.

Meiosis II

In meiosis II, the connected sister chromatids will be split and separated into four haploid cells. Let's take a closer look at the events of meiosis II, which begins with prophase II.

Prophase II – Prometaphase II

In prophase II, if the chromosomes decondensed in telophase I, they condense again. If nuclear envelopes were formed, they once again break down. The centrosomes once again move away from each other toward opposite poles, and new spindles are formed. In prometaphase II, the nuclear envelopes are completely broken down, and the spindle is fully formed. Each sister chromatid's kinetochore attaches to microtubules from the opposite poles.

Metaphase II – Anaphase II

In metaphase II, the sister chromatids are completely condensed and align on the metaphase plate. In anaphase II, the sister chromatids are pulled apart by the spindle fibers and move toward opposite poles.

Telophase II – Cytokinesis II

In telophase II, the chromosomes, now in the unduplicated state, arrive at opposite poles and begin to decondense. Nuclear envelopes now form around the chromosomes. Cytokinesis II separates the two cells into four genetically unique haploid cells. At this point, the newly produced cells are haploid and genetically unique because of the crossing over and independent assortment.

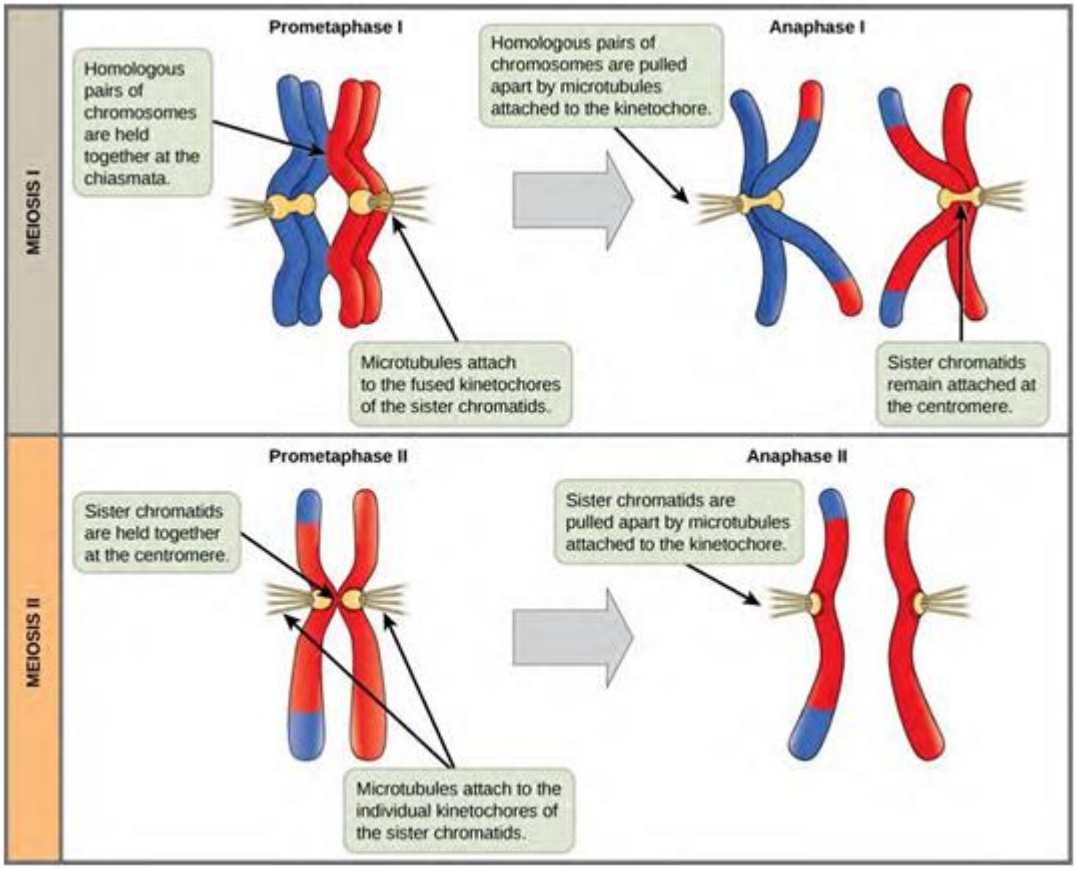


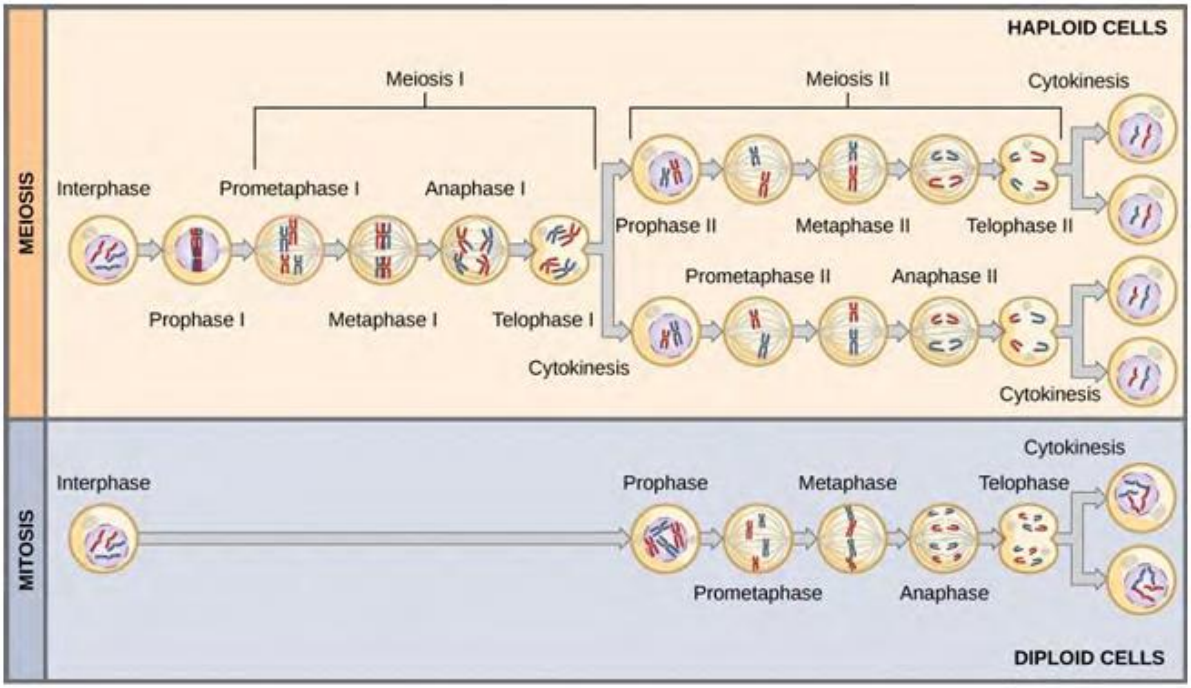
Figure: In prometaphase I, microtubules attach to the fused kinetochores of homologous chromosomes. In anaphase I, the homologous chromosomes are separated. In prometaphase II, microtubules attach to individual kinetochores of sister chromatids. In anaphase II, the sister chromatids are separated.

Comparing Meiosis and Mitosis

Mitosis and meiosis are both necessary processes of the eukaryotic cell cycle. These processes share some similarities, but also exhibit several important and distinct differences that lead to very different outcomes.. Mitosis is a process where one single diploid cell divides and produces two new genetically identical daughter cells.

On the other hand, meiosis is a process that begins with one diploid cell, which then goes through two rounds of chromosome divisions. The four daughter cells produced at the end of meiosis are genetically unique because of processes like crossing over and independent assortment. Each of the daughter cells produced during meiosis is haploid. Keep in mind haploid cells each contain only one chromosome set, which is half of the original chromosome number.

In humans, cells produced by mitosis will function in different parts of the body and are essential for growth and/or replacing dead or damaged cells. Cells produced by meiosis are used for organismal reproduction.



						OUTCOME
PROCESS	DNA synthesis	Synapsis of homologous chromosomes	Crossover	Homologous chromosomes line up at metaphase plate	Sister chromatids line up at metaphase plate	Number and genetic composition of daughter cells
MEIOSIS	Occurs in S phase of interphase	During prophase I	During prophase I	During metaphase I	During metaphase II	Four haploid cells at the end of meiosis II
MITOSIS	Occurs in S phase of interphase	Does not occur in mitosis	Does not occur in mitosis	Does not occur in mitosis	During metaphase	Two diploid cells at the end of mitosis

Figure: Meiosis and mitosis are both preceded by one round of DNA replication; however, meiosis includes two nuclear divisions.

Errors in meiosis

Inherited chromosomal disorders can occur when mistakes happen during meiosis. Chromosome disorders can be divided into two categories: abnormalities in chromosome number and chromosome structural rearrangements. Chromosomal disorders are characteristically noticeable and often fatal. We will look at how errors occur during meiosis and the impact this has on an individual's health and homeostasis.

Disorders in Chromosome Number

Chromosomal abnormalities in humans can be detected by first isolating chromosomes and then observing them using a microscope**. A karyotype** is the number and appearance of an individual's chromosomes, including their length, banding pattern, and centromere position.

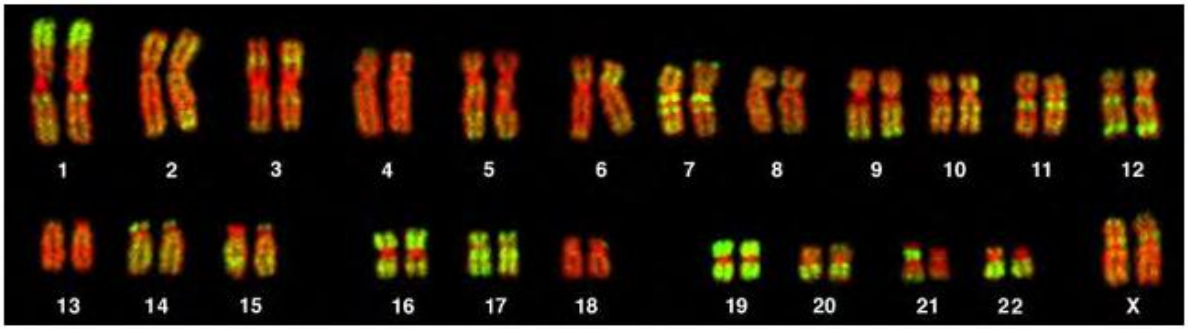


Figure: This karyogram shows the chromosomes of a female human immune cell during mitosis.

To observe an individual's karyotype, a person's cells, such as their white blood cells, are first collected from a blood sample or other tissue sample. The isolated cells are stimulated to begin mitosis. A chemical is then applied to the cells to arrest mitosis during metaphase, and the cells are then fixed to a slide. Chromosomes are stained with one of several dyes to better visualize the distinct and reproducible banding patterns of each homologous chromosome pair. An experienced medical professional can identify each band, size, and centromere location. To generate the karyogram, the chart that shows an individual's karyotype, homologous pairs of chromosomes are manually aligned in numerical order from longest to shortest.

Chromosomal Number Disorders

Of all chromosomal disorders, abnormalities in chromosome number are the most obvious when looking at a karyogram. Duplicating or losing entire chromosomes can occur through a process called nondisjunction. Nondisjunction occurs when homologous chromosome pairs or sister chromatids fail to separate during meiosis I or meiosis II. Misaligned chromosomes, chromosome pairs not forming tetrads, or failure of the microtubules to attach and then move chromosomes to opposite poles can all cause nondisjunction to occur. The risk of nondisjunction occurring increases with the parents' age.

Nondisjunction can occur during either meiosis I or II. If homologous chromosomes fail to separate during meiosis I, 100% of the gametes will be affected. In this case, two gametes will lack a particular chromosome, and two gametes will have additional copies of that particular chromosome. If sister chromatids fail to separate during meiosis II, there is a chance that 50% of the gametes will contain the correct number of chromosomes.

Regardless of whether nondisjunction happens in meiosis I or II, some gametes, if not all, will have the wrong chromosome number. If those gametes participate in fertilization, it will result in an individual that has a genetic condition.

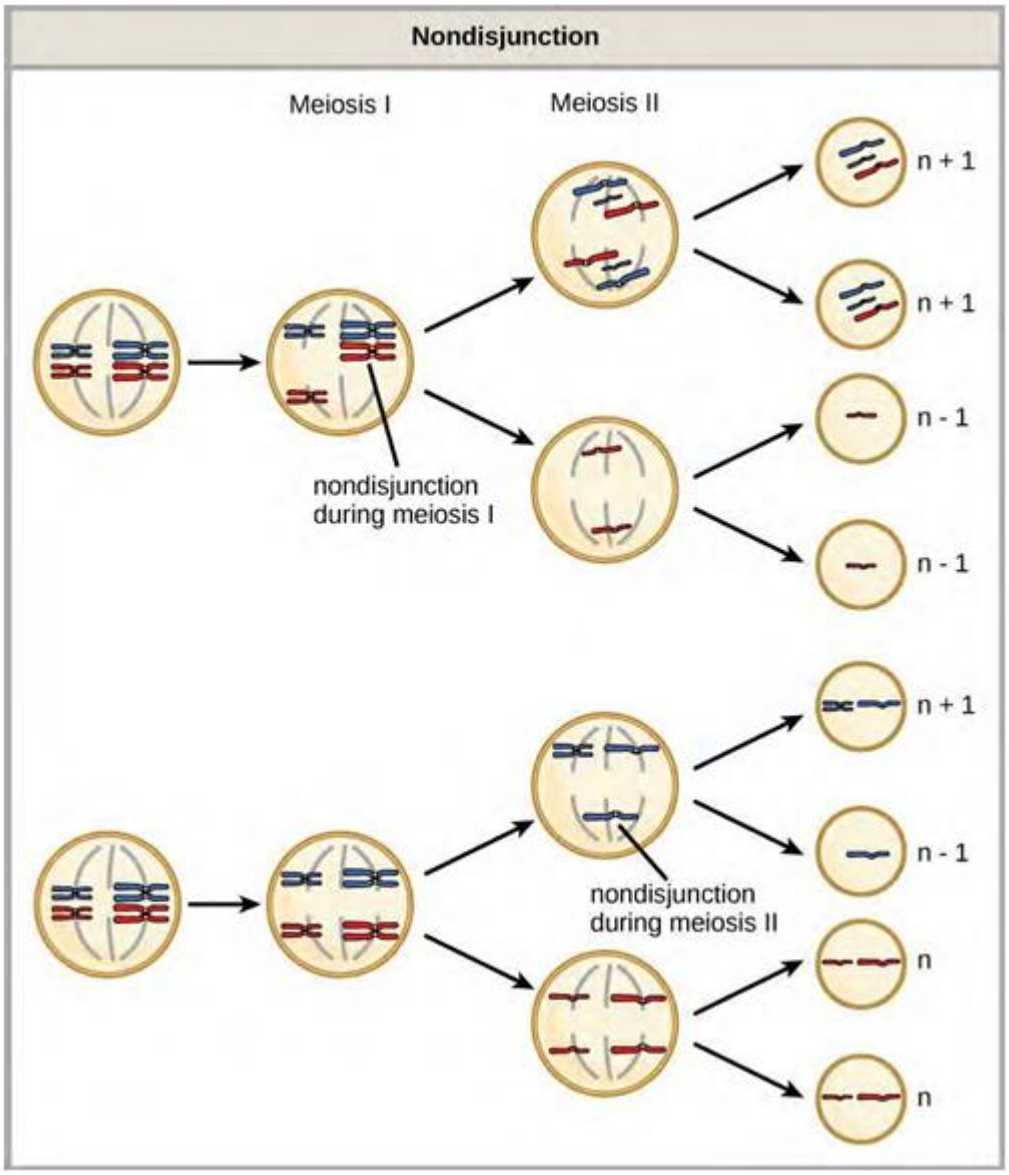


Figure: Following meiosis, each gamete has one copy of each chromosome. Nondisjunction occurs when homologous chromosomes (meiosis I) or sister chromatids (meiosis II) fail to separate during meiosis.

Aneuploidy

Scientists call an individual with the appropriate number of chromosomes for their species euploid. In humans, euploidy corresponds to 22 pairs of autosomes and one pair of allosomes. An individual with an error in chromosome number is described as aneuploid, a term that includes monosomy, losing one chromosome, or trisomy, gaining an extra chromosome.

Trisomy 21, or Down syndrome, is a condition that occurs when an individual has a third copy of chromosome 21. Down syndrome is characterized by short stature, stunted digits, facial distinctions that include a broad skull and large tongue, and significant developmental delays. The occurrence of Down syndrome can be correlated with parental age. Older parents are more likely to produce fetuses carrying the trisomy 21 genotype. Turner syndrome, which is

characterized by the presence of only one X allosome, is an example of a monosomy condition. Females that have Turner syndrome are typically sterile and cannot reproduce.

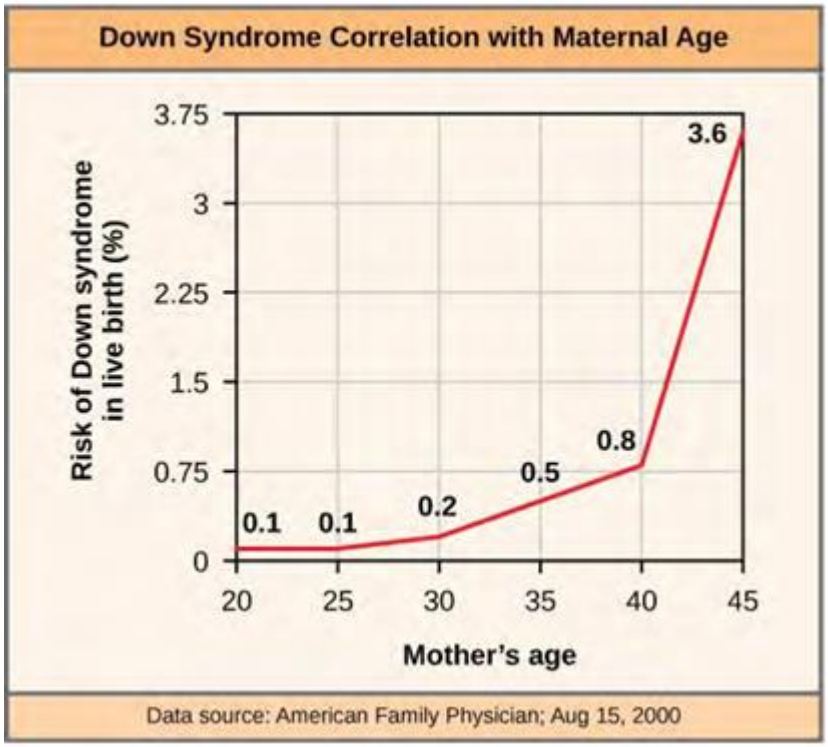


Figure: The incidence of having a fetus with trisomy 21 increases dramatically with maternal age.

Polyploidy

We call an individual with more than the correct number of chromosome pairs a polyploid. For instance, fertilizing an abnormal diploid egg with a normal haploid sperm would yield a polyploid. Polyploid animals are extremely rare, with only a few examples including some flatworms, crustaceans, amphibians, fish, and lizards. Polyploid animals are sterile because meiosis cannot occur normally. Rarely, polyploid animals can reproduce asexually when an unfertilized egg divides mitotically to produce offspring. In contrast, polyploidy is very common in plants, and polyploid plants tend to be larger and more robust than the euploids of their species.

Chromosomal Structural Rearrangements

In addition to errors in chromosome number, numerous structural chromosomal rearrangements can occur. These include duplications, deletions, inversions, and translocations.

Duplications and Deletions

In chromosomal duplications, a part of a chromosome is duplicated. The duplicated DNA can then either be inserted into a different position on the same chromosome or a completely different chromosome.

In chromosomal deletions, a part of the chromosome is lost or removed

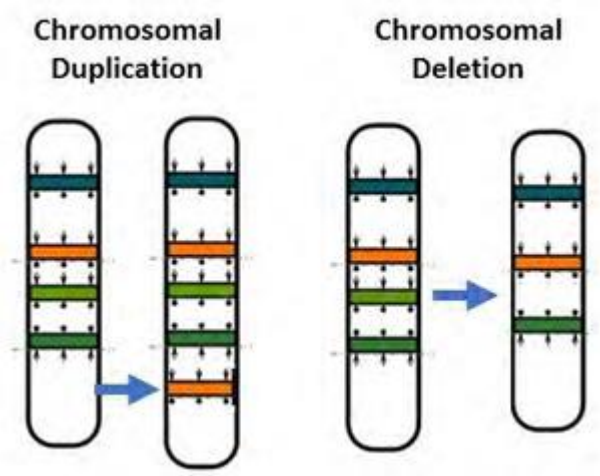


Figure: Chromosomal arrangements include both duplications and deletions.

Both duplications and deletions often produce offspring that survive but exhibit physical and mental abnormalities. A deletion of a region on chromosome 11 leads to a condition called 11q terminal deletion disorder or Jacobsen syndrome. Jacobsen syndrome involves distinct changes to facial features as well as heart and bleeding defects. A gene duplication on chromosome 17 leads to a condition known as Hereditary motor and sensory neuropathy or Charcot-Marie-Tooth (CMT) disorder. CMT results in individuals that have nervous system issues involving nerves that carry and deliver information to an individual's legs, arms, hands, and feet.

Inversions

A chromosome inversion is a detachment, 180° rotation, and reinsertion of part of a chromosome. Inversions may occur in nature as a result of damaged or cut DNA or from transposable elements, special DNA sequences capable of rearranging chromosome segments. Unless a gene sequence is disrupted, inversions are likely to have minor effects. However, inversions that disrupt genes can result in abnormally high or low levels of specific proteins.

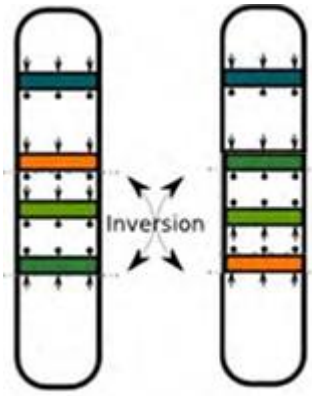


Figure: An inversion is an example of a chromosomal arrangement.

Translocations

A translocation occurs when a segment of genetic material breaks from one chromosome and reattaches to another chromosome or a different part of the same chromosome. Translocations can either have minimal to no impact or have devastating effects depending on how the positions of genes are altered. Notably, specific translocations have occurred with several cancers and with schizophrenia. Reciprocal translocations result from exchanging chromosome segments between two nonhomologous chromosomes such that there is no genetic information gain or loss.

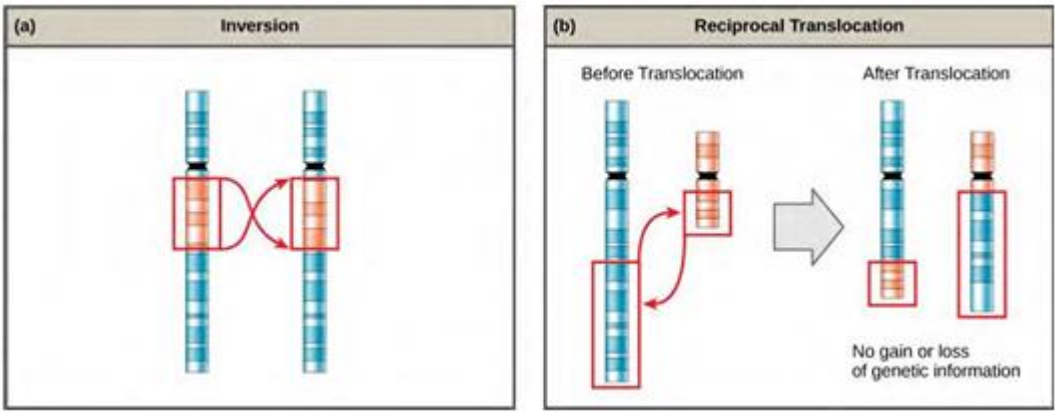


Figure 2 (a) chromosomal inversion (b) reciprocal translocation

NUCLEIC ACIDS

Nucleic acids are polymers made of sub units called nucleotides. A nucleotide is made up of three molecules i.e., phosphate group, pentose sugar and nitrogen bases. Nucleotides are then in turn arranged to form extremely long molecules called polynucleotides.

Structure of nucleotide

Individual nucleotides are made up of three components:

• a pentose sugar (so called because it has five carbon atoms)

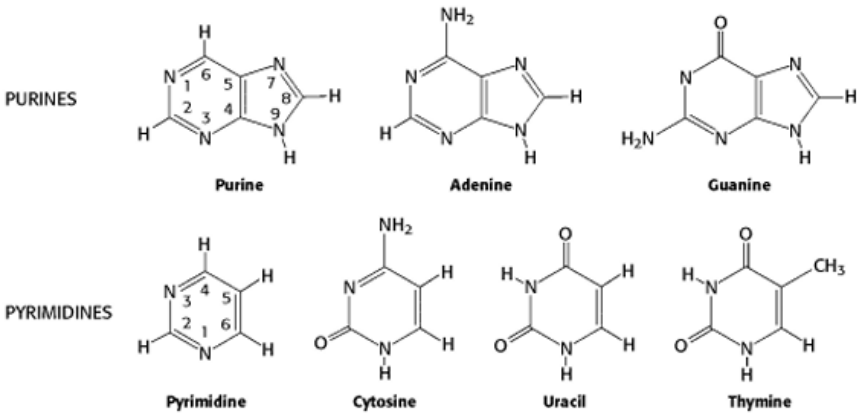
• a phosphate group

• a nitrogen-containing organic base. These are: cytosine C, thymine T, Uracil U, adenine A and guanine G.

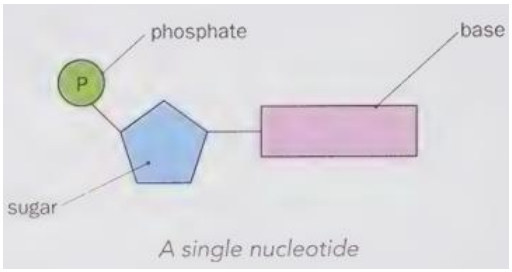
The five organic bases are divided into two groups. i.e.;

Pyrimidines, which are made up of a single six ring, include cytosine, thymine and uracil

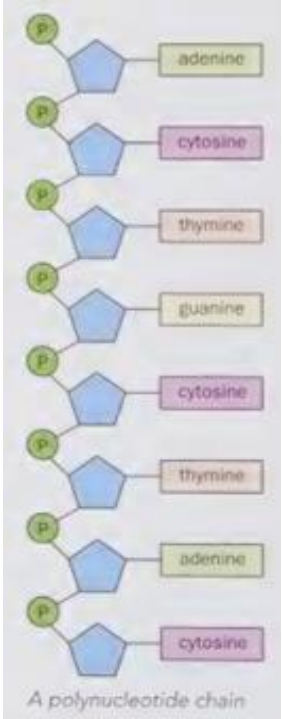
purines, which are made up of a six-sided ring joined to a five sided one, include adenine and guanine.



The pentose sugar, phosphate group and organic base are joined, as a result of condensation reactions, to form a single nucleotide (mononucleotide).



Two mononucleotides may, in turn, be joined as a result of a condensation reaction between the ribose sugar of one mononucleotide and the phosphate group of another. The bond formed between them is called a phosphodiester bond. The new structure is called a dinucleotide. The continued linking of mononucleotides in this way forms a long chain known as a polynucleotide, such as RNA and DNA.



Note:

1. In addition to DNA and RNA, some other biologically important molecules contain nucleotides; e.g., Adenosine triphosphate (ATP) is also a nucleotide derivative. It consists of a molecule of ribose, a molecule of adenine and three phosphate groups. ADP is also a phosphorylated nucleotide
2. For simplicity the various components of nucleotides are represented by symbols, as shown in Table.

NAME OF MOLECULE	REPRESENTATIVE SHAPE
Phosphate	
Pentose sugar	
Adenine (a purine)	Adenine
Guanine (a purine)	Guanine
Cytosine (a pyrimidine)	Cytosine
Thymine (a pyrimidine)	Thymine
Uracil (a pyrimidine)	Uracil

Figure 2 *Molecules found in nucleotides*

3. There are two important polymers of nucleic acids, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Although both DNA and RNA are made up of nucleotides, they function differently within the cell. DNA stores the genetic information needed to build proteins required for maintaining homeostasis. RNAs, on the other hand, are molecules that are involved in protein synthesis. Currently, cells use DNA as a template to assemble RNA.

Deoxyribonucleic acid (DNA)

DNA nucleotides contain the 5-carbon sugar deoxyribose and four types of nitrogenous bases: adenine (A), guanine (G), cytosine (C), and thymine (T). Long polymers of DNA are formed when the phosphate group of one nucleotide bonds covalently with the sugar molecule of the next nucleotide. The sugar–phosphate groups line up and form a "backbone" for each strand of DNA. The nitrogenous bases stick out from each backbone and the bases on opposite DNA strands can base pair through hydrogen bonding

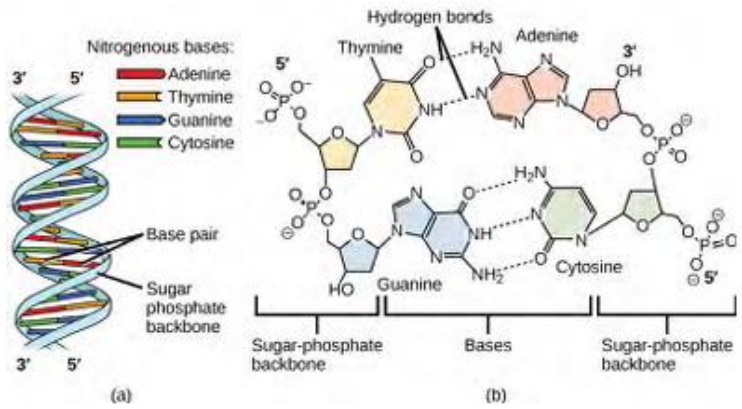


Figure: DNA (a) forms a double stranded helix, and (b) adenine pairs with thymine and cytosine pairs with guanine.

The carbon atoms of the five-carbon sugar are numbered clockwise from the oxygen as 1', 2', 3', 4', and 5' (1' is read as "one prime"). The phosphate group is attached to the 5' carbon of one nucleotide and the 3' carbon of the next nucleotide. Each DNA strand has a 5' carbon at one end and a 3' carbon at the other end. In its natural state, each DNA molecule is composed of two single DNA strands held together by hydrogen bonds between the nitrogenous bases.

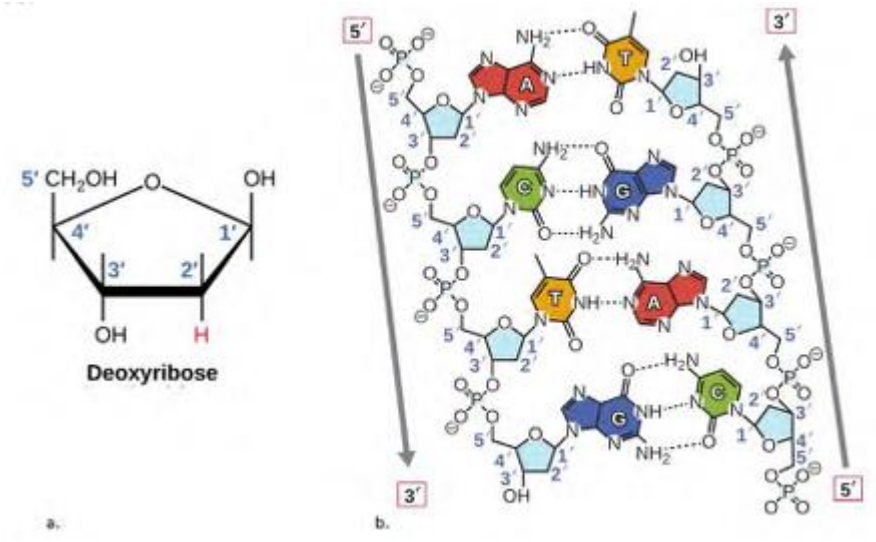


Figure: a. The carbon atoms of the five-carbon sugar are numbered clockwise from the oxygen as 1', 2', 3', 4', and 5' (1' is read as "one prime"). b. The direction of each strand is identified by numbering the carbons (1 through 5) in each sugar molecule.

It has long since been confirmed that base-pairing takes place between specific purines and pyrimidines. Adenine always base pairs with thymine and cytosine always base pairs with guanine. Adenine and thymine are connected by two hydrogen bonds, and cytosine and guanine are connected by three hydrogen bonds, as was suggested by Chargaff's Rules. The two strands of DNA are anti-parallel in nature; that is, one strand will have the 3' carbon of the sugar in the "upward" position, whereas the other strand will have the 3' carbon in the "downward" position.

Note: Chargaff was an Austrian biochemist who examined the content of DNA in different species and found that the amounts of pyrimidines (cytosine and thymine) were not found in equal quantities. Likewise, purines (adenine and guanine) were also not found in equal quantities. He also discovered that the amount of adenine equalled the amount of thymine, and the amount of cytosine equalled the amount of guanine; that is, A = T and G = C. These observations became known as Chargaff's rules. However, the ratio of adenine and thymine to guanine and cytosine varies from species.

The structures of DNA coils to form a double helix, whereby the two polynucleotide strands which are extremely long, they are wound around one another

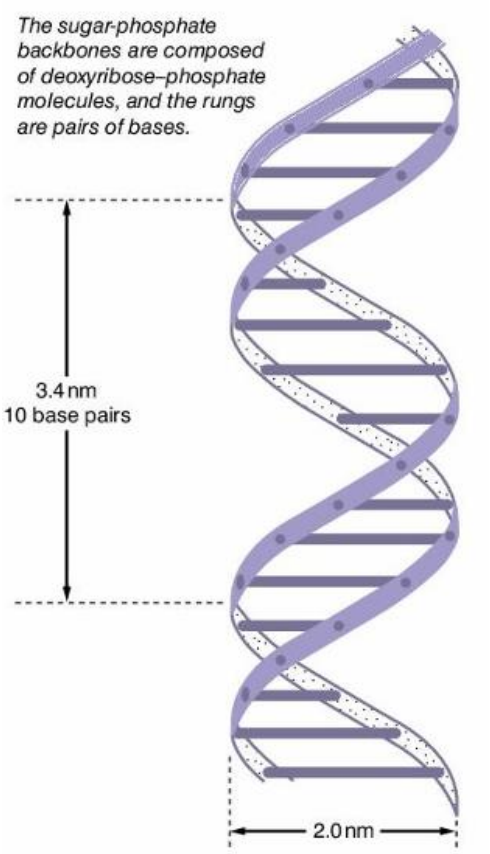


Figure 2 *The DNA double helix structure*

Properties/adaptations of DNA as a suitable hereditary material

Possession of a specific sequence of nitrogen bases for storage of information.

Double stranded for replication to occur semi-conservatively since strands act as templates.

Weak hydrogen bonds enable unzipping/separation of strands to occur readily.

Double helical structure makes the molecule compact to fit in the nucleus.

Sugar-phosphate back bone is held together by strong covalent phosphodiester bonds for stability.

The two sugar-phosphate back bones are antiparallel which enables the purines and pyrimidine nitrogen bases to project towards each other for complimentary base pairing.

Long and large molecule for storage of much information.

Ability to mutate adds to infinite forms of DNA therefore there is no limit on the different genes that can be formed from a single gene.

Many hydrogen bonds which increase stability of the DNA molecule.

The Structure of RNA

Like DNA, RNA is also a polymer composed of nucleotides. RNA nucleotides also contain a 5 carbon sugar, a phosphate group, and a nitrogenous base. RNA nucleotides are made of the five carbon sugar ribose, unlike the deoxyribose found in DNA. Ribose has a hydroxyl group at the 2' carbon, unlike deoxyribose, which has only a hydrogen atom

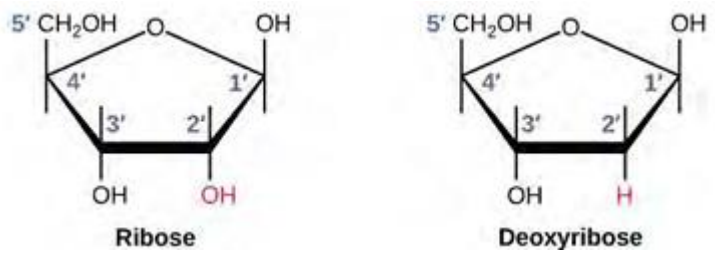


Figure The difference between the ribose found in RNA and the deoxyribose found in DNA is that ribose has a hydroxyl group at the 2' carbon.

RNA nucleotides also have a nitrogenous base; however, the four types of RNA nitrogenous bases are: adenine (A), uracil (U), cytosine (C), and guanine (G). Note, RNA does not use the nitrogenous base thymine, which is found in DNA. RNA is also different than DNA in that it is a single-stranded molecule rather than a double-stranded helix.

Molecular biologists have named several different kinds of RNA based on their function. These include messenger RNA (mRNA), transfer RNA (tRNA), and ribosomal RNA (rRNA). All three types of RNA molecules are involved in protein synthesis and will be discussed later.

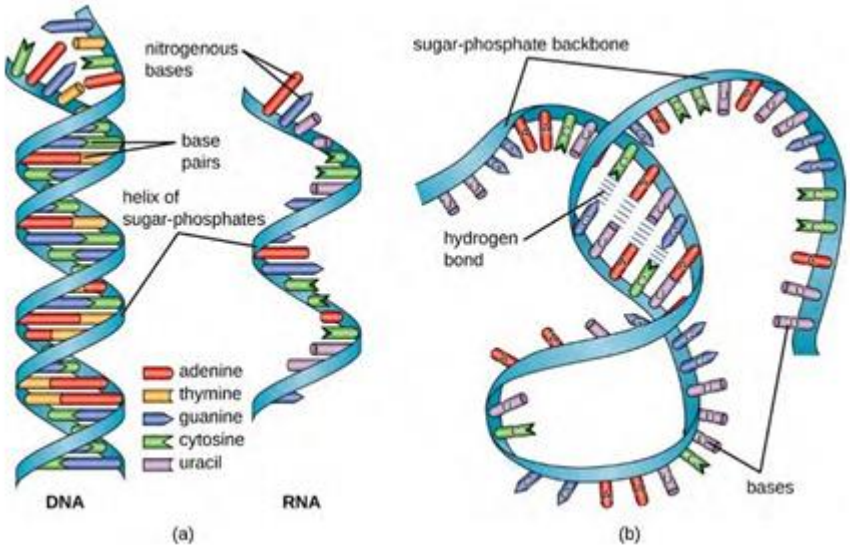


Figure: DNA is typically double stranded, whereas (b) RNA is typically single stranded. Although it is single stranded, RNA can fold upon itself, with the folds stabilized by short areas of complementary base pairing within the molecule, forming a three-dimensional structure.

DNA REPLICATION

When a cell divides, it is important that each daughter cell receives an identical copy of the DNA. This is accomplished by the process of DNA replication. The replication of DNA occurs during the synthesis phase, or S phase, of interphase in the cell cycle, before the cell enters mitosis or meiosis.

The structure of the double helix provided a hint as to how DNA is copied. Recall that adenine nucleotides pair with thymine nucleotides, and cytosine with guanine. This means that the two strands are complementary to each other. For example, a strand of DNA with a nucleotide sequence of AGTCATGA will have a complementary strand with the sequence TCAGTACT

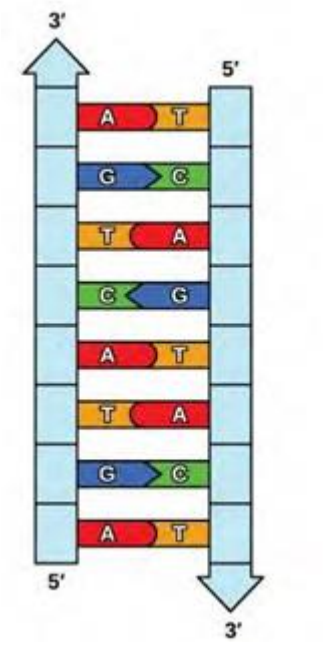


Figure: The two strands of DNA are complementary, meaning the sequence of bases in one strand can be used to create the correct sequence of bases in the other strand.

Because of the complementarity of the two strands, having one strand means that it is possible to recreate the other strand. The double-helix model suggests that the two strands of the double helix separate during replication, and each strand serves as a template from which the new complementary strand is copied. What was not clear was how the replication took place. There were three models suggested i.e., conservative, semi-conservative, and dispersive.

In conservative replication, the "old" parental DNA strands remains together, and the newly formed DNA strands come together to form the second helix.
The semi conservative method suggests that each of the two "old" parental DNA strands acts as templates. The two "new" complement strands of DNA are synthesized using the "old" template strands; after replication, each DNA helix consists of one parental or "old" strand and one "new" complement strand.
In the dispersive model, both DNA helices have double stranded segments of parental DNA and newly synthesized DNA interspersed.

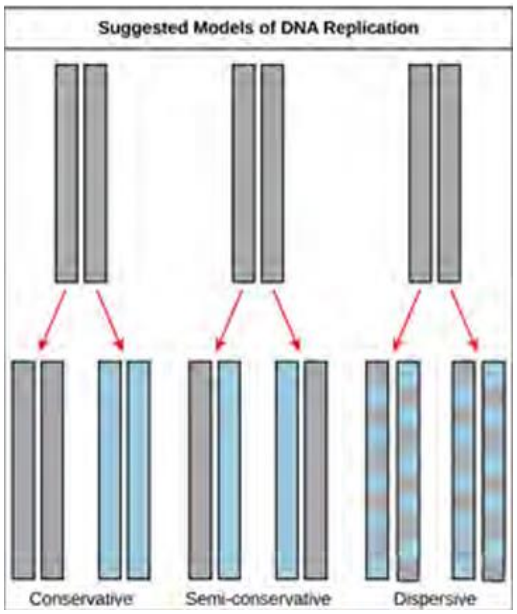
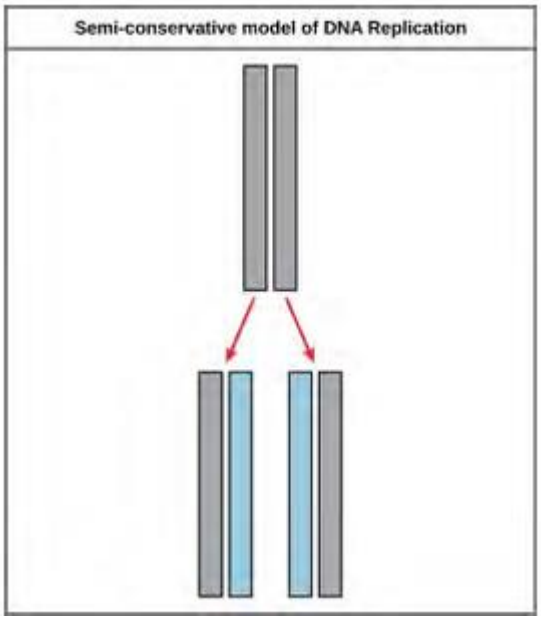


Figure: The three suggested models of DNA replication. Gray indicates the original DNA strands, and blue indicates newly synthesized DNA.

To address these different models, scientists Matthew Meselson and Franklin Stahl carried out experiments using E. coli grown in different environments containing different isotopes of nitrogen. Recall that each nucleotide has a nitrogenous base, therefore nitrogen is necessary for DNA replication. Their work provided the necessary data that supported the semi conservative replication model **(read about their experiment!!!)**

Based on the research of Meselson and Stahl and several others, it is understood that during DNA replication, each of the two "old" parental DNA strands serve as templates from which two "new" complement DNA strands are made. The two "new" strands will be complementary to the parental or "old" strands. Once DNA replication is complete, each new helix will consist of one "old" template strand and one "new" complement strand



DNA Replication in Eukaryotes

Because eukaryotic genomes are very complex, DNA replication is a very complicated process that involves several enzymes and additional proteins. It occurs in three main stages: initiation, elongation, and termination.

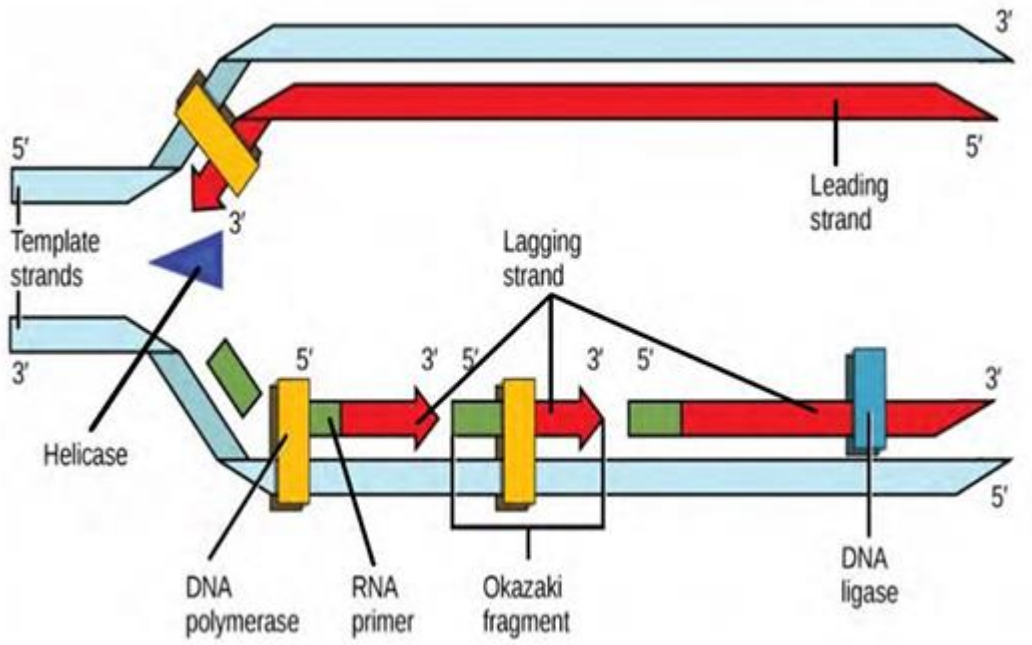


Figure: Helicase opens the DNA double helix and exposes replication forks. RNA primers are added by RNA polymerase. DNA polymerase then starts attaching DNA nucleotides to the 3' end of the primers. For the leading strand, DNA polymerase will continue adding nucleotides to make a single, uninterrupted strand. The lagging strand is constructed in short segments called Okazaki fragments as helicase exposes more of the template strand. DNA ligase then connects the fragments.

Recall that eukaryotic DNA is wound around histone proteins that then coil and form structures called nucleosomes. During initiation, DNA must be unwound in order to make it accessible to binding proteins and enzymes necessary for DNA replication.

How does the replication machinery know where on the DNA double helix to begin?

It turns out that there are specific nucleotide sequences called origins of replication where replication begins. Replication binding proteins attach to the origin of replication and an enzyme called helicase unwinds and opens the DNA helix. As the DNA double-helix opens, Y-shaped structures called replication forks are formed. Two replication forks are formed at the origin of replication, and these extend in both directions. There are multiple origins of replication on eukaryotic chromosomes. This allows replication to occur simultaneously from several places within the genome.

Once initiation has occurred with the help of helicase, the DNA is now accessible. The next step of DNA replication, elongation, can now occur.

During elongation, an enzyme called DNA polymerase adds nucleotides one-by-one to the growing DNA strand which is complementary to the "old" parent template strand. DNA polymerase has two important restrictions. First, DNA polymerase can only add nucleotides in the 5' to 3' direction. This means, new DNA strands can only be extended or made in the 5' to 3' direction. Second, DNA polymerase requires a free 3'-OH group to which it can add nucleotides.

Where does the free 3'-OH group come from?

An enzyme called RNA primase adds a small five to ten nucleotide RNA segments, which provides the necessary free 3'-OH end. Because this RNA sequence primes the DNA synthesis, it is appropriately called the RNA primer. DNA polymerase can now extend the RNA primer, adding nucleotides one by-one that are complementary to the template strand. This primer is later removed, and the RNA nucleotides are replaced with DNA nucleotides.

The two template DNA strands have opposing orientations: one strand is in the 5' to 3' direction and the other is oriented in the 3' to 5' direction. Only one new DNA strand, the one that is complementary to the 3' to 5' parental DNA strand, can be synthesized continuously towards the replication fork. This continuously synthesized strand is known as the leading strand. The other strand, complementary to the 5' to 3' parental DNA, is extended away from the replication fork, in small fragments known as Okazaki fragments.

Each Okazaki fragment requires an RNA primer to start the DNA synthesis. Okazaki fragments are named after the Japanese scientists, Tsuneko and Reiji Okazaki, who first discovered them. The strand with the Okazaki fragments is known as the lagging strand. As synthesis proceeds, each RNA primer is removed and replaced with DNA nucleotides.

Gaps between the Okazaki fragments are filled in and sealed by an enzyme called DNA ligase. Termination is said to have occurred when each of the two original strands are bound to their own, finished, complementary strands.

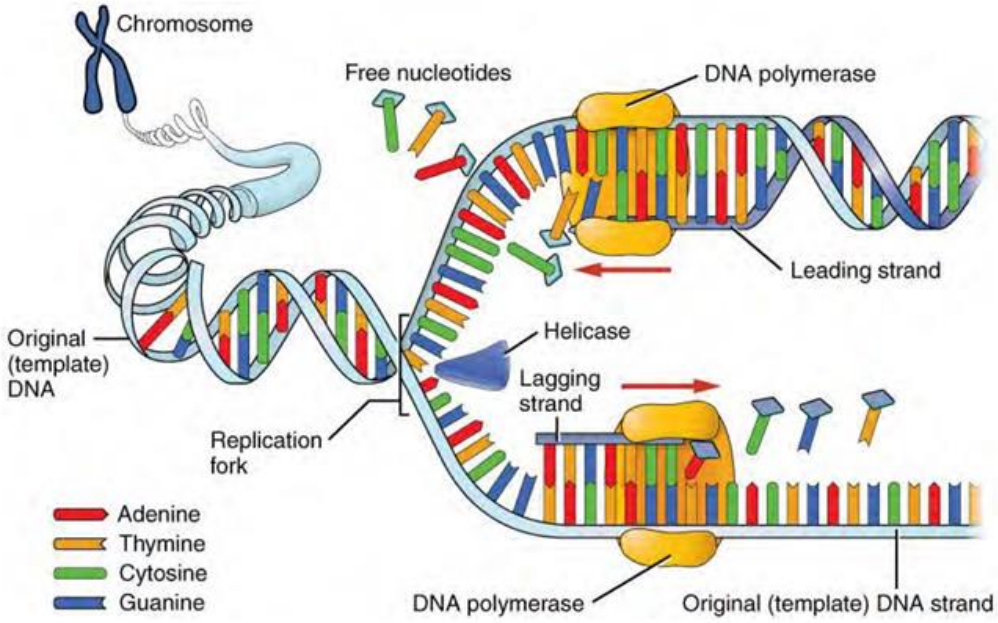


Figure In DNA replication, DNA polymerase adds complementary base pairs.

The process of DNA replication can be summarized as follows:

1. DNA unwinds at the origin of replication with the help of specialized binding proteins.

2. Helicase opens up the DNA, forming replication forks. Each replication fork is extended in one direction.

3. RNA Primase synthesizes RNA primers complementary to the DNA strand.

4. DNA polymerase adds new nucleotides complementary to the DNA strand. The leading strand is made continuously, while the lagging strand is made in segments called Okazaki fragments.

5. RNA primers are removed, new DNA nucleotides are put in place of the RNA primers and the backbone is sealed by DNA ligase.

Telomere Replication

As you have learned, the DNA polymerase can add nucleotides in only one direction. In the leading strand, synthesis continues until the end of the chromosome is reached. However, on the lagging strand, once the end of the chromosome is reached there is no place for a RNA primer to be added. This presents a problem for the cell because the ends remain unpaired, and over time these ends get progressively shorter as cells continue to divide.

The ends of the linear chromosomes are known as telomeres. Telomeres have repetitive sequences that do not code for a gene. They are important because they prevent chromosomes from arbitrarily fusing with one another and protect the DNA from becoming damaged.

It is the telomeres that are shortened with each round of DNA replication instead of genes. For example, in humans, a six base-pair sequence, TTAGGG, is repeated 100 to 1000 times. The discovery of the enzyme telomerase helped explain how chromosome ends are maintained. The telomerase carries its own RNA primer which can base pair to the end of the DNA strand.

The telomerase can then add DNA nucleotides to the end of the chromosome, elongating it. Once the template strand is sufficiently elongated, DNA polymerase can then add nucleotides that are complementary to the ends of the chromosomes. Thus, the ends of the chromosomes are maintained in germline cells, adult stem cells, and some cancer cells.

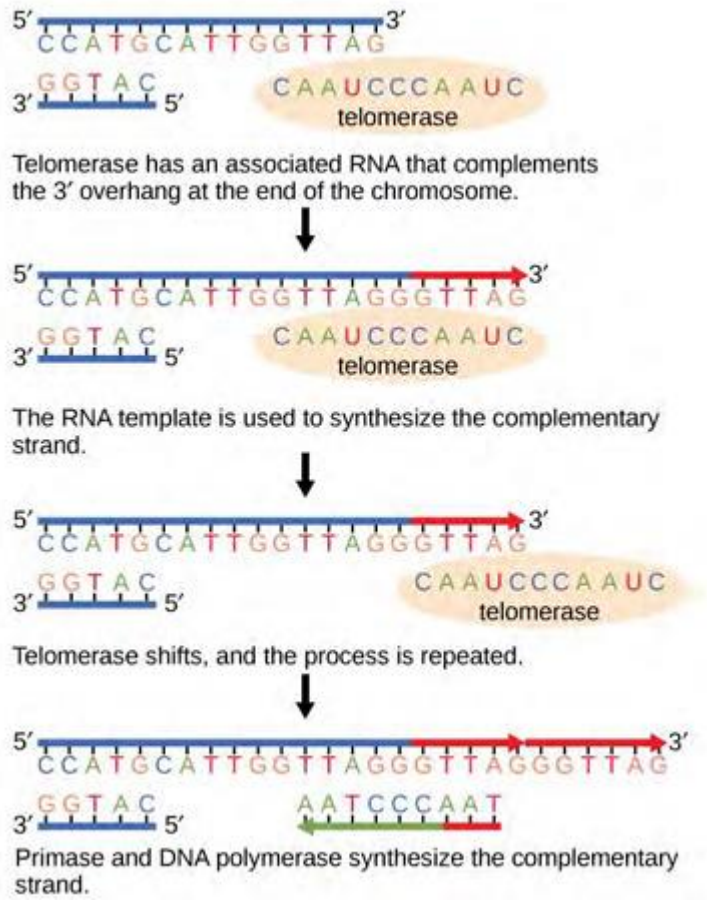


Figure: The ends of linear chromosomes are maintained by the action of the telomerase enzyme.

Telomerase is not active in adult somatic cells. Adult somatic cells that undergo cell division continue to have their telomeres shortened. This essentially means that telomere shortening is associated with aging. For her discovery of telomerase and its action, Elizabeth Blackburn received the Nobel Prize for Medicine and Physiology in 2009.

Figure: Elizabeth Blackburn, 2009 Nobel Laureate, was the scientist who discovered how telomerase works.

DNA Repair

Because DNA polymerase can make mistakes while adding nucleotides, it is important that the enzyme goes back and edits the DNA by proofreading every newly added base. Incorrect bases are removed and replaced by the correct base before the process continues (figure a). Most mistakes are corrected during replication, but some are not.

When mismatched bases are not caught, the mismatch repair mechanism is employed. Mismatch repair enzymes recognize the wrongly incorporated base and cuts it from the DNA. The enzymes then replace the mismatched base with the correct base (Figure b).

In yet another type of repair, nucleotide excision repair, the DNA double strand is unwound and separated. The incorrect bases are removed along with a few bases on the 5' and 3' end, and these are then replaced with the help of the DNA polymerase (Figure c).

Nucleotide excision repair is particularly important in correcting thymine dimers, which are primarily caused by ultraviolet light. A thymine dimer occurs when two thymine nucleotides adjacent to one another, covalently bond to each other rather than their complementary bases. If the dimer is not removed and repaired, it will lead to a mutation. Individuals with flaws in their nucleotide excision repair genes show extreme sensitivity to sunlight and often develop skin cancers early in life.

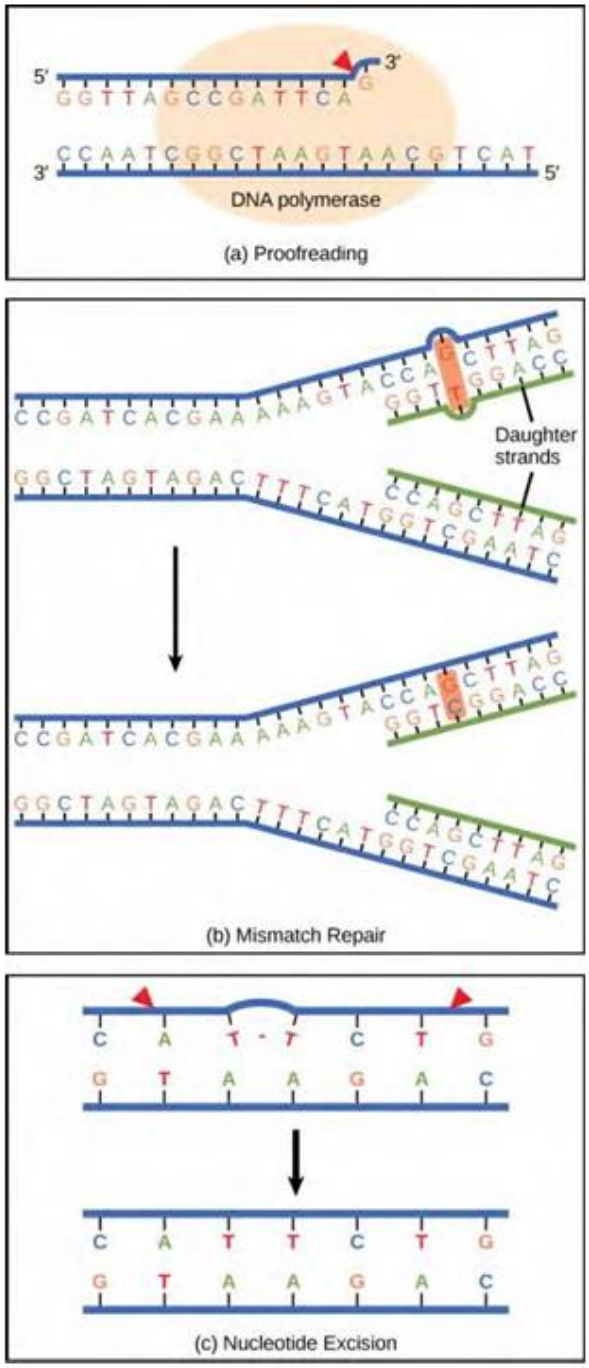


Figure: Proofreading by DNA polymerase (a) corrects errors during replication. In mismatch repair (b), the incorrectly added base is detected after replication. Nucleotide excision (c) repairs thymine dimers. When exposed to UV, two thymines lying adjacent to each other can form thymine dimers. In normal cells, they are excised and replaced.

DNA Mutation

As mentioned, most mistakes are caught and corrected; however, if they are not, they may result in a mutation. A mutation is defined as a permanent change in the DNA sequence. Changes in the DNA sequence can have effects on the protein products, which can be either beneficial or detrimental.

Evolution, the genetic change in a population over time, is heavily dependent on mutation. Mutations in the DNA lead to variations among individuals which can lead to new or different traits within a population. These new or different traits can be beneficial to individuals within the population and can provide advantages, for example increased reproductive success, when compared to others in the population. Without genetic changes to the DNA, evolution would not occur.

Mutations can also be detrimental. Changes in the DNA sequence can lead to the inability to properly synthesize proteins. Changes in the DNA sequence can lead to changes in the amino acid sequence of a protein. If the amino acid sequence of a protein changes, the protein usually does not function properly.

Types of mutations

There are two kinds of mutation i.e. gene mutation and chromosome mutation

Chromosome mutation is already discussed under errors in meiosis

GENE MUTATION /POINT MUTATION

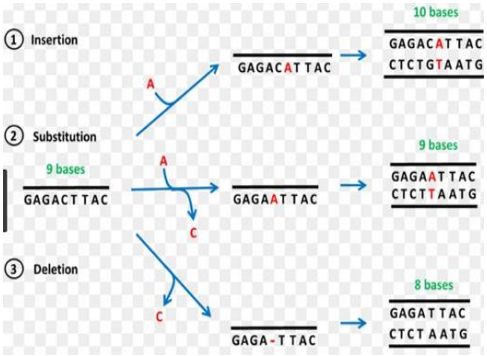
This is the change in structure of DNA which occurs on a single locus on a chromosome. There are different forms of gene mutations and they are:

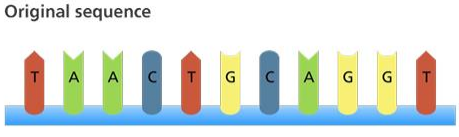
Duplication: A portion of a nucleotide chain becomes repeated

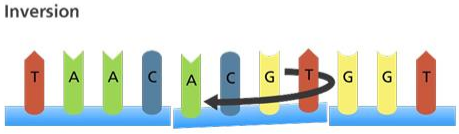
Deletion: A portion of a nucleotide chain is lost from the sequence.

Inversion: A nucleotide sequence becomes separated from the chain and rejoins its original position only when it is inverted.

Substitution: One of the nucleotides is replaced by another which has a different sequence







NOTE:

Mutations can be caused by several different factors. As discussed, errors by DNA polymerase during replication can cause mutations. Mutations can also occur because the DNA is damaged in some way. Such mutations are classified as being induced or spontaneous. Induced mutations are those that result from exposure to chemicals, UV rays, x-rays, or some other environmental agent. Spontaneous mutations occur without any exposure to any environmental agent; they are a result of natural reactions taking place within the body.

Mutations in repair genes have been known to cause cancer. Many mutated repair genes have been implicated in certain forms of pancreatic cancer, colon cancer, and colorectal cancer. Mutations can affect either somatic cells or germline cells.

Mutations can affect either somatic cells or germline cells. Recall that human somatic cells contain 46 chromosomes and these cells do not lead to the formation of gametes. Most cells that make up the human body are somatic cells. If mutations accumulate in a somatic cell, they may lead to problems such as the uncontrolled cell division observed in cancer. Somatic cell mutations can be extremely dangerous to the individual organism, but are not passed on to their offspring, therefore they are not heritable.

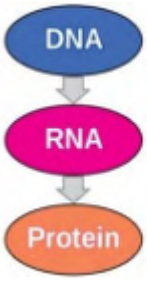
Germline cells, also called gametes, have half the number of chromosomes compared to a somatic cell. If a mutation takes place in germline cells, the mutation will be passed on to the next generation, and therefore is considered a heritable mutation. Hemophilia, a condition that effects an individual's ability to form blood clotting proteins, is an example of a germline mutation.

TRANSLATION

In both prokaryotes and eukaryotes, DNA contains the information necessary for the cell to build proteins. Most structural components of the cell are made up, at least in part, by proteins. Virtually all the functions that a cell carries out are completed with the help of proteins. In order to make proteins, the DNA is "read" or **transcribed** into an mRNA molecule. The mRNA then leaves the nucleus and provides the information necessary to synthesize the protein through a process called **translation.**

The Central Dogma: DNA Encodes RNA; RNA Encodes Protein

The flow of genetic information in cells from DNA to RNA to protein is described by the central dogma.
The central dogma states that genes specify the sequences of RNAs, which in turn specify the sequences of proteins. Recall, that a gene is a functional segment of DNA that provides the genetic information necessary to build a protein.



The copying of DNA to mRNA is relatively straightforward. During transcription, mRNA is synthesized with the help of many enzymes. RNA nucleotides complementary base pair with DNA nucleotides forming the RNA transcript. The translation to protein is more complex and will be discussed in the next section. Before taking a closer look at the process of transcription, let's first review the three types of RNA introduced earlier on: mRNA, tRNA, and rRNA.

Types of RNA

As mentioned, ribonucleic acid, or RNA, is mainly involved in the process of protein synthesis. RNA is usually single-stranded and is comprised of nucleotides that are linked by phosphodiester bonds. A nucleotide in the RNA chain contains the sugar ribose, one of the four nitrogenous bases (adenine, uracil, guanine, and cytosine), and a phosphate group. There are three major types of RNA: messenger RNA (mRNA), ribosomal RNA (rRNA), and transfer RNA (tRNA).

Ribosomal RNA (rRNA) (80%)

Ribosomal RNA (rRNA) is a large molecule that is complexed with proteins to form the subunits of ribosomes. It has a sequence of organic bases which is very similar in organisms within the same kingdom. A ribosome is made up of ribosomal RNA (rRNA) and protein. Each ribosome consists of two sub-units.

The rRNA ensures the proper alignment of the mRNA and the ribosomes. The ribosome's rRNA also has an enzymatic activity and catalyzes peptide bond formation between two aligned amino acids.

Messenger RNA

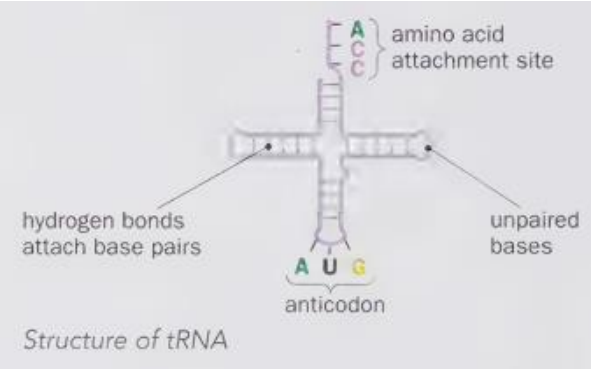
The first type, messenger RNA (mRNA), carries the message encoded in the DNA on how to build proteins. If a cell needs to synthesize a certain protein, the gene for this protein "turns on" and the messenger RNA is transcribed.

Transfer RNA (tRNA) (15%)

Transfer RNA (tRNA) is a relatively small molecule which is made up of around 70-90 nucleotides. It is manufactured by DNA and makes up 10 – 15% of the total RNA in a cell. Although there are a number of types of tRNA, they are very similar, each having a single stranded chain folded into a clover-leaf shape, with one end of the chain extending beyond the other. This extended chain always has the organic base sequence of cytosine-cytosine-adenine, this is the part of the tRNA molecule to which an amino acid can easily attach. There are at least 20 types of tRNA, each able to carry a different amino acid.

At the opposite end of the tRNA molecule is a sequence of three other organic bases, known as the anticodon. For each amino acid there is a different sequence of organic bases on the anticodon. During protein synthesis, this anticodon pairs with the complementary three organic bases that make up the triplet of bases on mRNA, known as the codon.

The tRNA structure with its end chain for attaching amino acids and its anticodon for pairing with the codon of the mRNA, is structurally suited to its role of lining up amino acids on the mRNA template during protein synthesis.



Structure of tRNA

Note: Hydrogen bonds give tRNA a stable structure. The role of tRNA is to carry amino acids to the ribosomes. To do this it has an amino acid attachment site at one end. Each amino acid has its own specific tRNA molecule. Each of the 20 amino acids has a tRNA molecule specific to it. The tRNA attaches itself to a specific amino acid in the presence of a specific enzyme (aminoacyl-tRNA synthetase) and ATP. This is sometimes' called amino acid activation.

At one end of the tRNA is a base triplet called an anticodon. The anticodon is different for each amino acid: for instance, CGA for alanine, AGU for serine, and UUC for lysine. The anticodon

attaches itself to the compatible mRNA codon. For instance, anticodon CGA will attach itself to codon GCU.

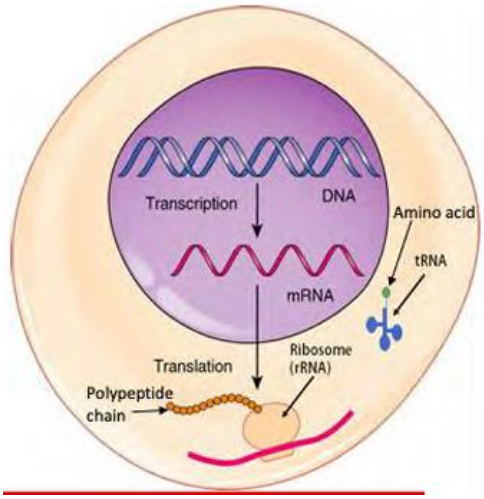


Figure: A eukaryotic cell showing mRNA, rRNA, and tRNA.

Transcription: from DNA to mRNA

Both prokaryotes and eukaryotes perform fundamentally the same process of transcription, with one very important difference. In eukaryotes, transcription occurs in the membrane-bound nucleus. In prokaryotes, transcription occurs in the nucleoid region; recall that prokaryotes lack membrane bound organelles. Once the mRNA is formed in eukaryotic cells it must be transported to the cytoplasm. Because the mRNA of prokaryotes does not need to be transported anywhere, translation can immediately follow.

In both prokaryotes and eukaryotes, transcription occurs in three main stages: initiation, elongation, and termination.

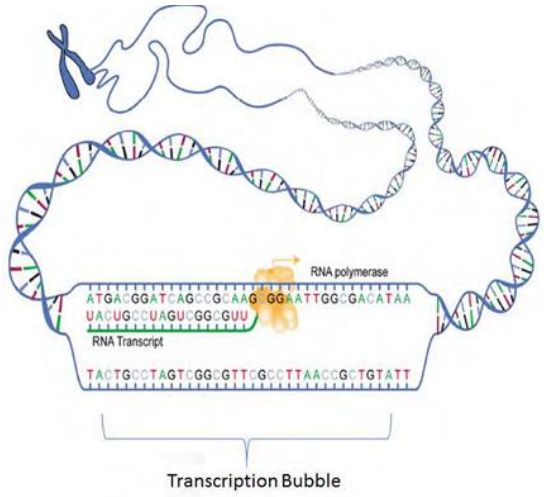


Figure: Transcription: from DNA to mRNA.

Initiation

Transcription requires a small part of the DNA double helix to partially unwind. The DNA must unwind to allow enzymes and additional proteins (transcription factors) to access specific genes which will then be used to make mRNA. The region of the DNA that is unwound is called the transcription bubble (Figure above). Several proteins and enzymes bind to a region at the beginning of the gene called a promoter, a particular sequence of nucleotides that triggers the start of transcription. In most cases, promoters exist upstream, or in front of, the genes they regulate. The specific sequence of a promoter is very important because it determines whether the corresponding gene is transcribed all of the time, some of the time, or hardly at all.

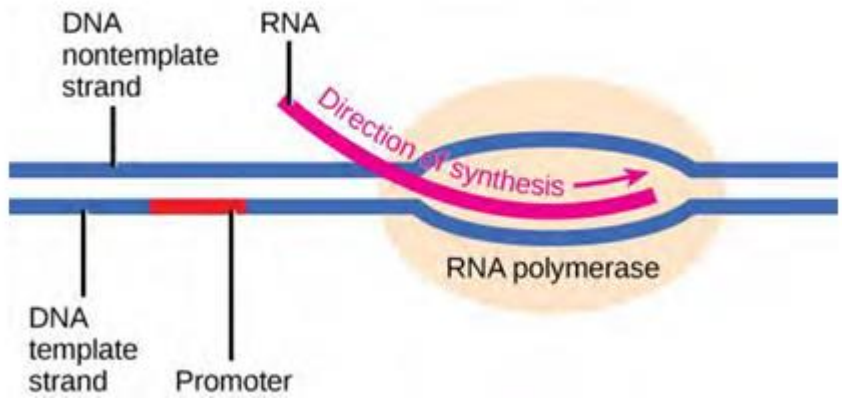


Figure: The initiation of transcription begins when DNA is unwound, forming a transcription bubble. Enzymes and other proteins involved in transcription bind at the promoter.

Elongation

Transcription always proceeds from one of the two DNA strands, which is called the template strand. The mRNA is complementary to the template strand and is almost identical to the other DNA strand, called the non-template strand. The two big exceptions are that RNA nucleotides contain the sugar ribose while DNA nucleotides contain the sugar deoxyribose, and that RNA contains the nitrogenous base uracil (U) instead of the thymine (T) found in DNA. During elongation, an enzyme called RNA polymerase proceeds along the DNA template adding RNA nucleotides by base pairing with the DNA template in a manner similar to DNA replication. As elongation proceeds, the DNA is continuously unwound ahead of the enzyme and then rewound behind it.

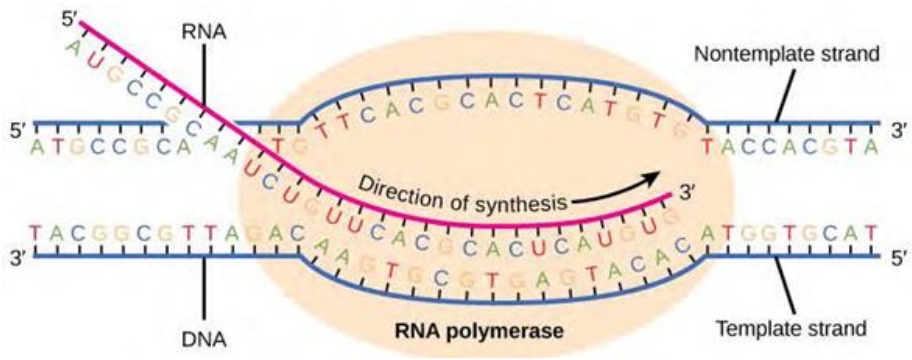


Figure 3 During elongation, RNA polymerase tracks along the DNA template, synthesizes mRNA in the 5' to 3' direction, and unwinds then rewinds the DNA as it is read.

Termination

When the polymerase has reached the end of the gene, the RNA polymerase needs to be instructed to dissociate, or separate, from the DNA template strand (receives termination signal). Once the RNA polymerase dissociates, the newly made mRNA transcript is released. Depending on the gene being transcribed, there are two kinds of termination signals, but both involve repeated nucleotide sequences in the DNA template. These repeated sequences cause the RNA polymerase to stall, separate from the DNA template, and free the newly synthesized mRNA.

At the end of termination, the process of transcription is complete. In a prokaryotic cell, by the time termination occurs, the mRNA is already being used to synthesize numerous copies of the encoded protein. This is possible because prokaryotic cells do not have their DNA enclosed in membrane bound nuclei. As soon as the mRNA is partially synthesized, ribosomes attach and begin generating the protein. Because of their nucleus, this is not possible for eukaryotic cells. Once the mRNA has been synthesized and undergoes modifications it must first be moved out of the nucleus and into the cytoplasm before translation can begin. This prevents simultaneous transcription and translation in eukaryotic cells.

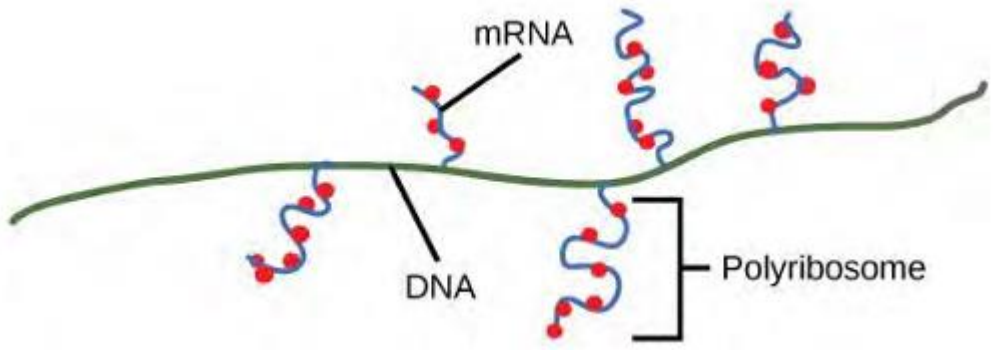


Figure: Multiple polymerases can transcribe a single bacterial gene while numerous ribosomes concurrently translate the mRNA transcripts into polypeptides.

Eukaryotic RNA Processing

The newly transcribed eukaryotic mRNAs are referred to as primary transcripts. These primary transcripts must undergo several processing steps before they can be transferred from the nucleus to the cytoplasm and then translated into a protein. The additional steps involved in eukaryotic mRNA maturation create a molecule that is much more stable than a prokaryotic mRNA. For example, eukaryotic mRNAs last for several hours, whereas the typical prokaryotic mRNA lasts no more than five seconds.

The mRNA transcript is first coated in RNA-stabilizing proteins to prevent it from degrading while it is processed and exported out of the nucleus. This occurs while the mRNA transcript is still being synthesized and involves adding a special nucleotide "cap" to the 5' end of the growing transcript. In addition to preventing degradation, factors involved in protein synthesis recognize the cap to help initiate translation by ribosomes.

Once elongation is complete, an enzyme then adds a string of approximately 200 adenine nucleotides to the 3' end, called the poly-A tail. This modification further protects the mRNA transcript from degradation and signals that the mRNA transcript is ready to be exported to the cytoplasm.

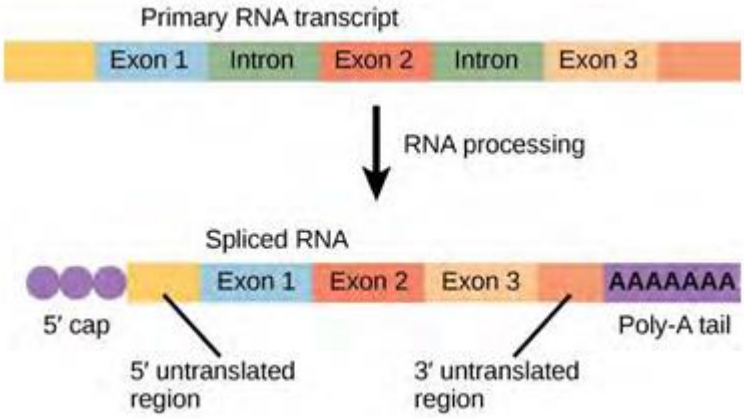


Figure: Eukaryotic mRNA contains introns that must be spliced out. A 5' cap and 3' tail are also added.

Eukaryotic DNA, and thus complementary mRNA, contains long non-coding regions that do not code for amino acids. Their function is still not well understood, but the process called splicing removes these non-coding regions, called introns, from the mRNA transcript. The non-coding regions are called introns because they are intervening sequences. The coding regions are called exons; ex on signifies that they are expressed.

A spliceosome, a structure composed of various proteins and other molecules, attaches to the mRNA transcript and "splices" or cuts out the non-coding, introns. The remaining exons are pasted together to form the mature mRNA which will then be transported to the cytoplasm.

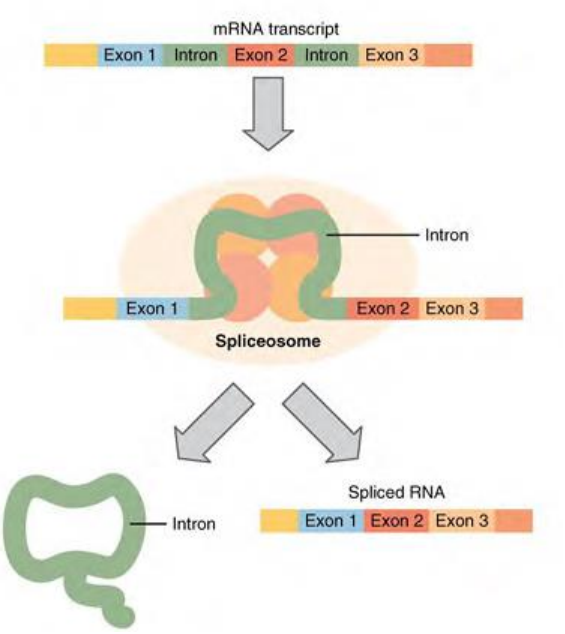


Figure 4 Splicing DNA in the nucleus, a structure called a spliceosome cuts out introns (noncoding regions) within a pre mRNA transcript and reconnects the exons.

Some of the segments that are removed from mRNA during splicing are not always non-coding. When different coding regions of mRNA are alternatively spliced out, different variations of the protein will result, with differences in structure and function. This process results in a much larger variety of possible proteins and protein functions from a given genome. Humans, for example, have just over 20,000 genes, yet the human body produces over 80,000 different proteins.

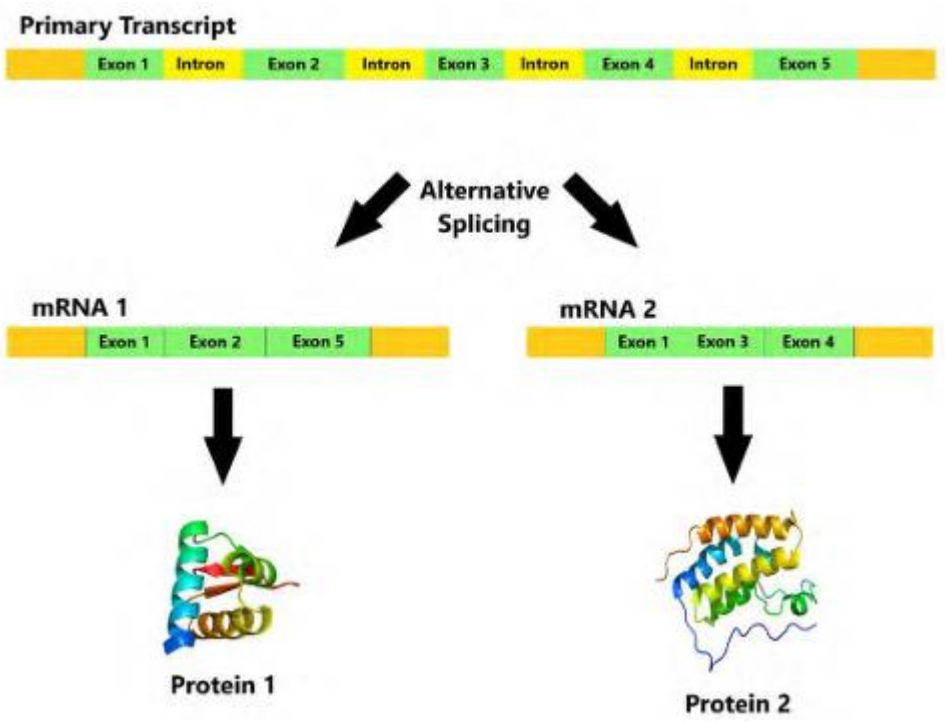


Figure: Alternative splicing of an mRNA primary transcript produces two different mRNA sequences, each of which results in a different protein.

TRANSLATION

Proteins perform a wide variety of functions in a cell and are necessary to maintain homeostasis. Protein synthesis is one of a cell's most energy-consuming metabolic processes. The process of translation, or protein synthesis, involves "decoding" a mRNA molecule with the purpose of forming a polypeptide chain. Amino acids are linked together through covalent bonds to form polypeptide chains that range in lengths from approximately 50 amino acids to more than 1,000.

The Protein Synthesis Machinery

In addition to the mature mRNA, many other molecules contribute to the process of translation. Translation requires not only mRNA, but also ribosomes, tRNAs, and various other enzymes. Although each of these components is necessary, their composition may vary across species. For instance, ribosomes may consist of different ribosomal RNAs (rRNA) and enzymes depending on the organism. Prokaryotic and eukaryotic cells have distinctly different ribosomes that vary in size. Although living cells may have slight differences, the general structures and functions of the protein synthesis machinery are comparable.

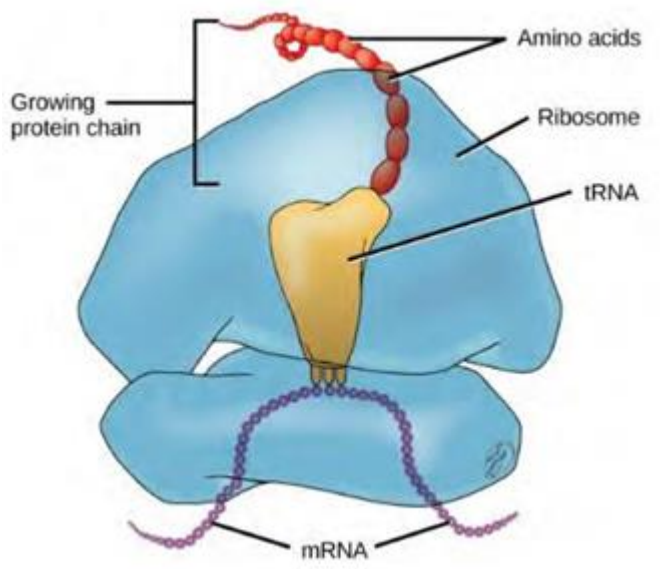


Figure: The protein synthesis machinery includes the large and small subunits of the ribosome, mRNA, and tRNA.

Ribosomes

A ribosome is a complex macromolecule composed of structural and catalytic rRNAs. Ribosomes also consist of many distinct proteins, some of which have enzymatic properties. In eukaryotes, the nucleolus, a region found in the nucleus, is completely specialized for the synthesis and assembly of rRNAs.

Ribosomes are located in the cytoplasm in both prokaryotic and eukaryotic cells. In eukaryotes, ribosomes are also found attached to the rough endoplasmic reticulum. Ribosomes are made up of a large and small subunit that come together for translation. The small subunit is responsible for binding directly to the mRNA, whereas the large subunit sequentially binds transfer RNAs). Transfer RNA (tRNA) is a type of RNA molecule that brings amino acids to the growing polypeptide chain. Each mRNA is simultaneously translated by many ribosomes, all synthesizing the polypeptide chain in the same direction. Once the polypeptide chain is synthesized it must fold into its three-dimensional shape before it is functional. Once folded, the polypeptide chain is considered a protein.

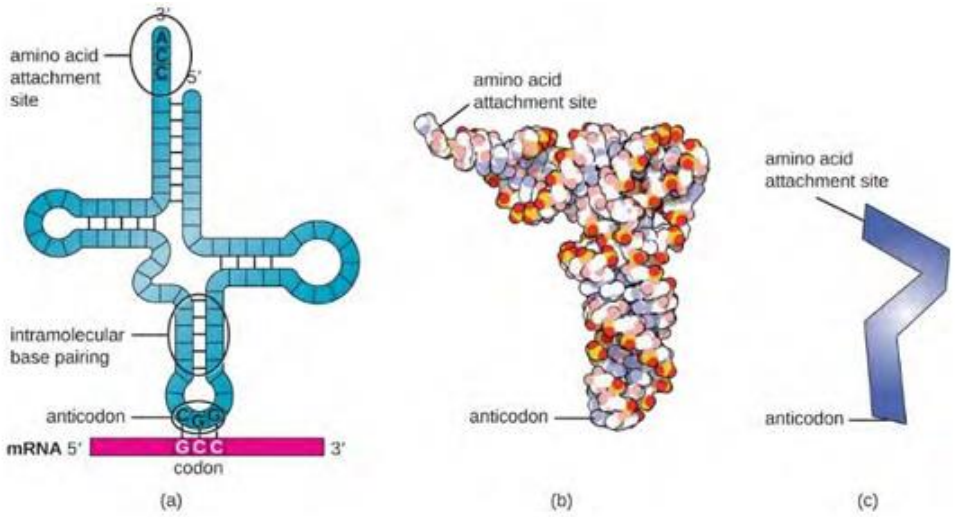


Figure: (a) After folding caused by intramolecular base pairing, a tRNA molecule has one end that contains the anticodon, which interacts with the mRNA codon, and the CCA amino acid binding end. (b) A space-filling model is helpful for visualizing the three-dimensional shape of tRNA. (c) Simplified models are useful when drawing complex processes such as protein synthesis.

Depending on the species, 40 to 60 types of tRNA exist in the cytoplasm. tRNA carrying a specific amino acid binds to sequences on the mRNA template and adds the corresponding amino acid to the polypeptide chain. Therefore, tRNAs are the molecules that actually "translate" the language of RNA into the language of proteins,

How is it that tRNA translates the mRNA nucleotide sequence into protein?

To answer this question, we must first understand the **genetic code,** the relationship between the nucleotide sequence and the different amino acids that make up a protein.

GENETIC CODE

It is the sequence/triplet of bases in DNA which codes for a specific amino acid in the polypeptide chain OR is the set of rules by which information encoded in genetic material is translated into proteins by living cells.

In trying to discover how DNA bases coded for amino acids, scientists suggested that there must be a minimum of three bases that coded for each amino acid. Their reasoning was as follows:

• Only 20 different amino acids regularly occur in proteins.

• Each amino acid must have its own code of bases on the DNA.

• Only four different bases (adenine, guanine, cytosine and thymine) are present in DNA.

• Jf each base coded for a different amino acid, only four different amino acids could be coded for.

• Using a pair of bases, 16 (4^2) different codes are possible, which is still inadequate.

• Three bases produce 64 (4^3) different codes, more than enough to satisfy the requirements of 20 amino acids.

As the code has three bases for each amino acid, each one is called a triplet. As there are 64 possible triplets and only 20 amino acids, it follows that some amino acids are coded for by more than one triplet.

Features of the genetic code

Further experiments have revealed the following features of the genetic code.

• A few amino acids are coded for by only a single triplet.

• The remaining amino acids are coded for by between two and six triplets each.

• The code is known as a 'degenerate code' because most amino acids are coded for by more than one triplet.

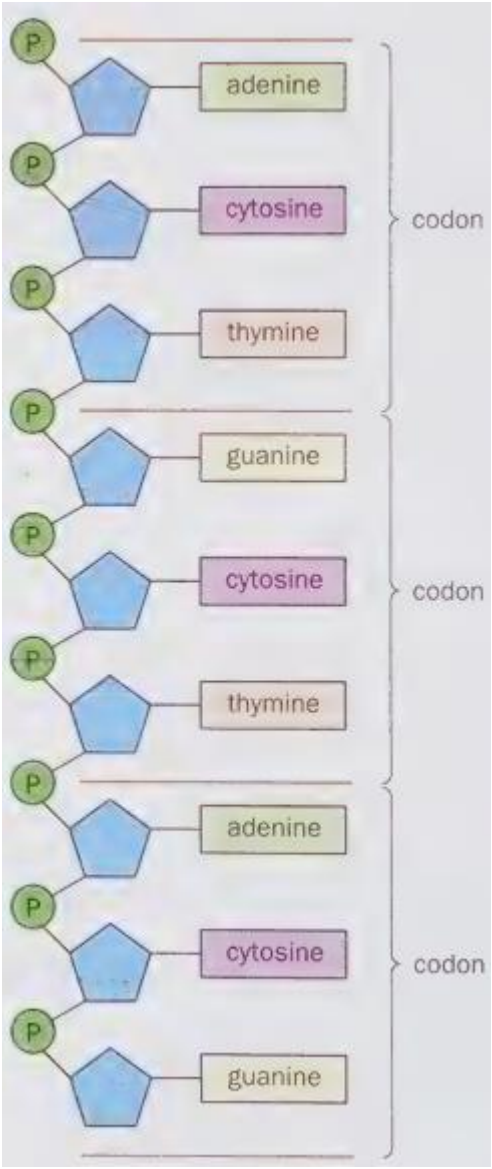
• A triplet is always read in one particular direction along the DNA strand.

• The start of a DNA sequence that codes for a polypeptide is always the same triplet. This codes for the amino acid methionine. Jf this first methionine molecule does not form part of the final polypeptide, it is later removed.

• Three triplets do not code for any amino acid. These are called 'stop codes' and mark the end of a polypeptide chain. They act in much the same way as a full stop at the end of a sentence.

• The code is non-overlapping, in other words each base in the sequence is read only once. Thus six bases numbered 123456 are read as triplets 123 and 456, rather than as triplets 123, 234, 345, 456.

• The code is universal. with a few minor exceptions each triplet codes for the same amino acid in all organisms. This is indirect evidence for evolution.



Interpreting the genetic code

The genetic code table below shows amino acids that each codon (set of three nucleotides in mRNA) is translated into during protein synthesis. Amino acid is indicated by three letters of its name, for

Table of messenger RNA codons and the amino acids for which they code

First base	Second base								Third base
	G		A		C		U		
G	GGG	glycine	GAG	glutamic acid	GCG	alanine	GUG	valine	G
	GGA	glycine	GAA	glutamic acid	GCA	alanine	GUA	valine	A
	GGC	glycine	GAC	aspartic acid	GCC	alanine	GUC	valine	C
	GGU	glycine	GAU	aspartic acid	GCU	alanine	GUU	valine	U
A	AGG	arginine	AAG	lysine	ACG	threonine	AUG	methionine	G
	AGA	arginine	AAA	lysine	ACA	threonine	AUA	isoleucine	A
	AGC	serine	AAC	asparagine	ACC	threonine	AUC	isoleucine	C
	AGU	serine	AAU	asparagine	ACU	threonine	AUU	isoleucine	U
C	CGG	arginine	CAG	glutamine	CCG	proline	CUG	leucine	G
	CGA	arginine	CAA	glutamine	CCA	proline	CUA	leucine	A
	CGC	arginine	CAC	histidine	CCC	proline	CUC	leucine	C
	CGU	arginine	CAU	histdine	CCU	proline	CUU	leucine	U
U	UGG	tryptophan	UAG	stop	UCG	serine	UUG	leucine	G
	UGA	stop	UAA	stop	UCA	serine	UUA	leucine	A
	UGC	cysteine	UAC	tyrosine	UCC	serine	UUC	phenylalanine	C
	UGU	cysteine	UAU	tyrosine	UCU	serine	UUU	phenylalanine	U

Advantage of universality of genetic code to humans

- Genetic material can be transferred between species and humans
- One species could use a useful gene from another species.
- Bacteria and yeast can be genetically engineered to make useful products.

Disadvantages of universality of genetic code

- Viruses cause diseases.
- Viruses can invade cells and take over their genetic apparatus e.g. HIV.

The Mechanism of Protein Synthesis

The process begins with the activation of the amino acids that will make up the polypeptide.

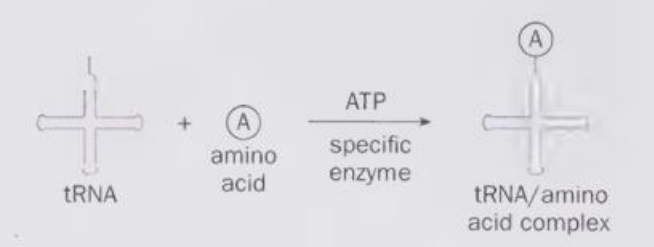
Amino acid activation.

The amino acids present in cells must be activated before they can be assembled into a polypeptide. This occurs in two steps:

Activation: an amino acid reacts with ATP. This reaction is catalysed by aminoacyl-tRNA synthetase, to form a high energy intermediate called aminoacyl-AMP(or an activated amino acid), which remains bound to the enzyme.

This activated intermediate then reacts with its specific, correct tRNA molecule. The amino acid is transferred to the 3' end of the tRNA (specifically to the adenosine nucleotide at the end) to form a final complex called aminoacyl-tRNA

The amino acid first forms an intermediate with ATP(aminoacyl-AMP). The intermediate is then attached to the 3' end of its correct transfer RNA to form an amino acid-tRNA complex called amino-acyl tRNA. The reaction is controlled by the enzyme, amino acyl tRNA synthetase. Much of the energy provided by ATP is conserved for peptide bond formation.



Just as with mRNA synthesis, protein synthesis can be divided into three phases: initiation, elongation, and termination. The process of translation is similar in prokaryotes and eukaryotes. Here we will explore how translation occurs in E. coli, a representative prokaryote.

Protein synthesis begins with the formation of an initiation complex. In E. coli, this complex involves the small ribosome subunit, the mRNA, three initiation proteins, and a tRNA carrying the amino acid methionine. The tRNA has a region called the anticodon. The anticodon complements and interacts with the AUG start codon on the mRNA and delivers the first amino acid, methionine. Once the anticodon of tRNA base pairs with the AUG codon of the mRNA, the large ribosomal subunit binds to the complex. This step completes the initiation of translation.

Protein synthesis begins with the formation of an initiation complex. In E. coli, this complex involves the small ribosome subunit, the mRNA, three initiation proteins, and a tRNA carrying the amino acid methionine.

First of all mRNA arrives from the nucleus with the genetic code. The small subunit of the ribosome becomes attached to one end of the mRNA molecule (5' end). The starting point on the mRNA is normally the triplet of bases (codon), AUG (AUG is often known as **the START codon**).

The amino-acyl tRNA molecule, carrying the amino acid methionine and with the anticodon sequence of UAC moves and attaches itself small ribosomal subunit and pairs with AUG sequence on the mRNA by complementary base pairing. Polypeptides initially have methionine as the first amino acid; however, if this methionine molecule does not make up part of the finished polypeptide, it is removed at the end of the synthesis.

Once the anticodon of tRNA base pairs with the AUG codon of the mRNA, the large ribosomal subunit binds to the complex. This step completes the initiation of translation.

The next step, elongation, takes place as the ribosome moves along the mRNA. Again, the basics of elongation are the same in both prokaryotes and eukaryotes, so we will review elongation from the perspective of E. coli. The large ribosomal subunit consists of three compartments: the A site (aminoacyl site), the P site (peptidyl site), and the E site (Exit site). The A site is responsible for binding incoming charged tRNAs. A charged tRNA is one that is attached to its specific amino acids. The P site binds charged tRNAs carrying the amino acids that are connected by peptide bonds. These amino acids are part of the growing polypeptide chain but have not yet dissociated from their corresponding tRNA

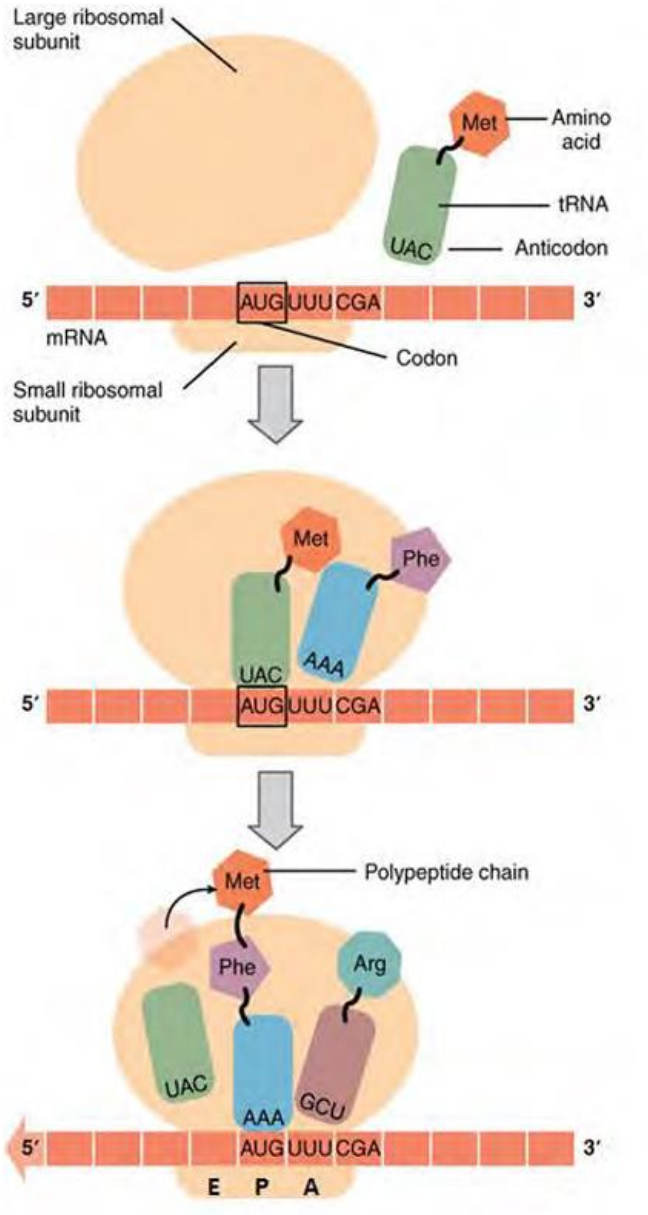


Figure: Translation begins when a tRNA anticodon recognizes a codon on the mRNA. The large ribosomal subunit joins the small subunit, and a second tRNA is recruited. As the mRNA moves relative to the ribosome, the polypeptide chain is formed.

Peptide bonds are special covalent bonds that exist between the amino group of one amino acid and the carboxyl group of a second amino acid which are close together catalyzed by **peptidyl transferase**. The E site releases uncharged tRNAs so they can be recharged with free amino acids.

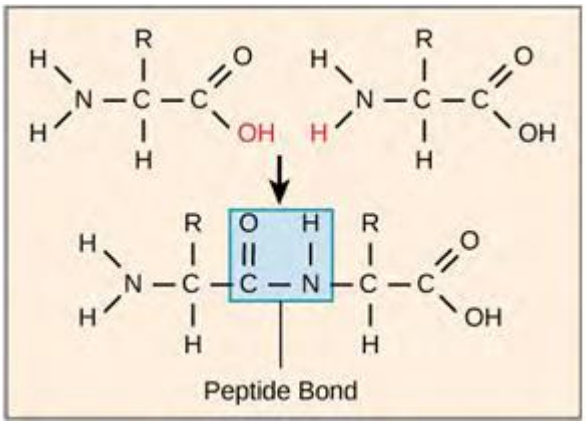
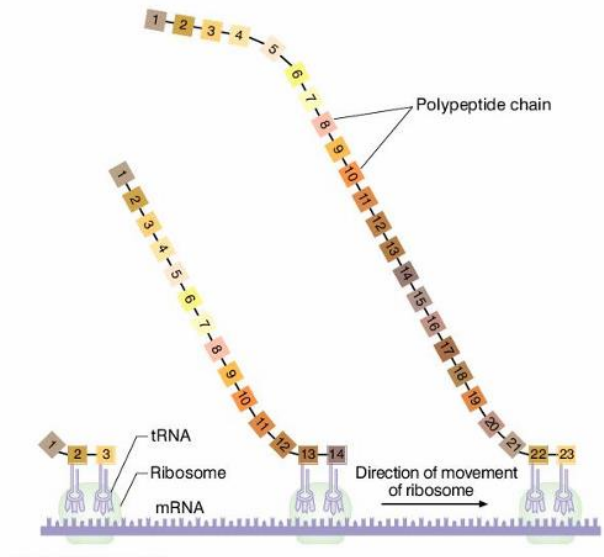


Figure: A peptide bond links the carboxyl end of one amino acid with the amino end of another, producing one water molecule during the process. This is a dehydration synthesis reaction.

The ribosome shifts one codon at a time, catalyzing each process that occurs in the three sites. With each step, a charged tRNA enters the complex, the polypeptide chain becomes one amino acid longer, and an uncharged tRNA departs. The energy for each bond between amino acids is derived from GTP, a molecule similar to ATP.

Termination of translation occurs when a stop codon (UAA, UAG, or UGA) is encountered. When a stop codon enters the ribosome's A site the growing polypeptide is released, and the ribosome subunits dissociate and leave the mRNA. After many ribosomes have completed translation, the mRNA is degraded so the nucleotides can be reused in another transcription reaction.

Note: Both the ribosome and the mRNA can be used again. Each mRNA can code for the production of many molecules of a particular polypeptide before stopping. Usually, a number of ribosomes can be found on a single mRNA (up to 50 ribosomes can pass immediately behind the first), each reading off the coded information at the same time (so that many identical polypeptides can be made at the same time). Such structures are known as polyribosomes or polysomes.



Polypeptide formation

Assembling a protein

Sometimes a single polypeptide chain is a functional protein. Often, a number of polypeptides are linked together to give a functional protein (quaternary structure). What happens to the polypeptide next depends upon the protein being made, but usually involves the following:

• The polypeptide is coiled or folded, producing its secondary structure.

• The secondary structure is folded, producing the tertiary structure.

• Different polypeptide chains, along with any non-protein groups, are linked to form the quaternary structure.

How genes are regulated

All organisms and cells control and regulate the transcription and translation of their DNA into protein. The process of turning on a gene to produce mRNA and then protein is called **gene expression**. All living cells control when and how its genes are expressed. For gene expression to occur, there must be mechanisms that control the following processes (1) when to turn on a gene to make mRNA and then protein (2) how much or what quantity of protein needs to be made, and (3) the ability to stop making that protein once it is no longer needed by the cell.

By regulating gene expression, cells can conserve energy and space. If an organism was to express every single gene at all times, it would require a significant amount of energy. It is much more energy efficient to only turn on the genes when they are required. In addition, only expressing a subset of genes in each cell saves space because DNA must be unwound from its tightly coiled structure to be transcribe and translated. Cells would have to be enormous if every gene were expressed in every cell all the time.

The control of gene expression is extremely complex and will only be covered briefly. To understand how gene expression is regulated, we must first understand how a gene codes for a functional protein in a cell. The process occurs in both prokaryotic and eukaryotic cells, just in slightly different manners.

Prokaryotic Gene Expression

Because prokaryotic organisms lack a cell nucleus, the processes of transcription and translation occur almost simultaneously. When the protein is no longer needed, transcription stops. This is primarily controlled by regulating transcription. Prokaryotic cells use a few methods to control gene expression at the transcriptional level.

One gene control example, **the lac operon**, was discovered using *E. coli* in the 1950s and 1960s by French researchers. The lac operon is a stretch of DNA that codes for proteins involved in absorption and metabolism of lactose, including the enzyme lactase. One promotor controls transcription of operon sequences. The lac operon is controlled using levels of lactose, a disaccharide, in E. coli's environment. When lactose is not present, transcription of the lac operon genes decreases, and the lactase translation slows. A repressor protein binds to the DNA preventing RNA polymerase from binding to the promoter. Thus, mRNA is not made and

lactase translation is low. When lactose is present, the genes are transcribed at a higher rate and more lactase is translated. The repressor protein is removed, and RNA polymerase can bind to the promotor, allowing the organism to make more lactase to metabolize the lactose

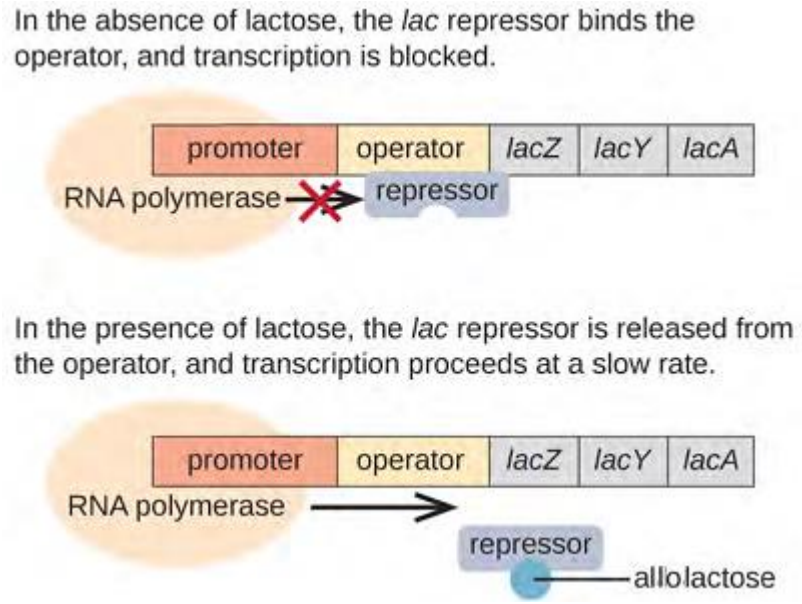


Figure: The three structural genes that are needed to degrade lactose in E. coli are located next to each other in the lac operon. RNA polymerase can bind to the promoter if a repressor is not present.

Eukaryotic Gene Expression

Eukaryotic cells, in contrast, have organelles and are therefore more complex. Recall that in eukaryotic cells, the DNA is contained inside the cell's nucleus where it is transcribed into mRNA. The newly synthesized mRNA is then transported out of the nucleus into the cytoplasm, where ribosomes translate the mRNA into protein. The processes of transcription and translation are physically separated by the nuclear membrane; transcription occurs only within the nucleus, and translation occurs only outside the nucleus in the cytoplasm. The regulation of gene expression can occur before or during both transcription and translation.

Recall, that DNA in the nucleus is condensed by wrapping around histone proteins. When several histone proteins are wrapped together it forms bead like structures called a nucleosome. Nucleosomes can control how accessible the DNA is to transcription proteins, a type of regulation referred to as **epigenetic control**. For example, if a gene is to be transcribed, the histone proteins and DNA in the chromosomal region encoding that gene are modified in a way that opens the promoter region to allow RNA polymerase and other transcription proteins to bind and initiate transcription. If a gene is to remain turned off, or silenced, the histone proteins and DNA have different modifications that signal a closed chromosomal configuration. In this closed configuration, the RNA polymerase and transcription factors do not have access to the DNA and transcription cannot occur.

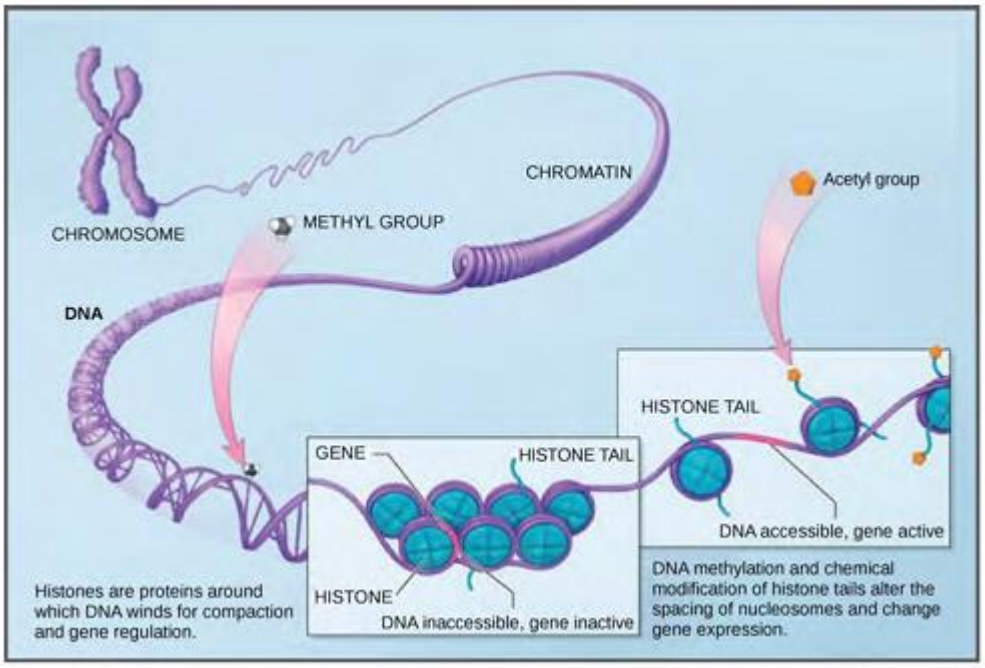


Figure 5 Histone proteins and DNA nucleotides can be modified chemically. Modifications affect nucleosome spacing and gene expression.

Gene expression can also be controlled when the mRNA is transcribed (transcriptional regulation) or when the mRNA is processed and exported to the cytoplasm after it is transcribed (post-transcriptional regulation). Recall that mRNA transcripts undergo alternative RNA splicing. Alternative RNA splicing is a mechanism that allows different protein products to be produced from one gene when different combinations of introns, and sometimes exons, are removed from the transcript. Alternative splicing can be haphazard, but more often it is controlled and acts as a mechanism of post-transcriptional gene regulation. The frequency of different splicing alternatives is controlled by the cell as a way to control the production of different proteins.

Gene expression can also be controlled as the mRNA is translated into protein (translational regulation) or after the protein has been made (post-translational regulation). Like transcription, translation is controlled by proteins that bind and initiate the process. For example, an initiation protein must bind to the small sub-unit of the ribosome to allow translation. If that protein is phosphorylated, translation will be blocked, and the protein cannot be made. This is an example of translational gene regulation. Chemical modifications such as phosphorylation can occur in response to external stimuli such as stress, the lack of nutrients, heat, or ultraviolet light exposure.

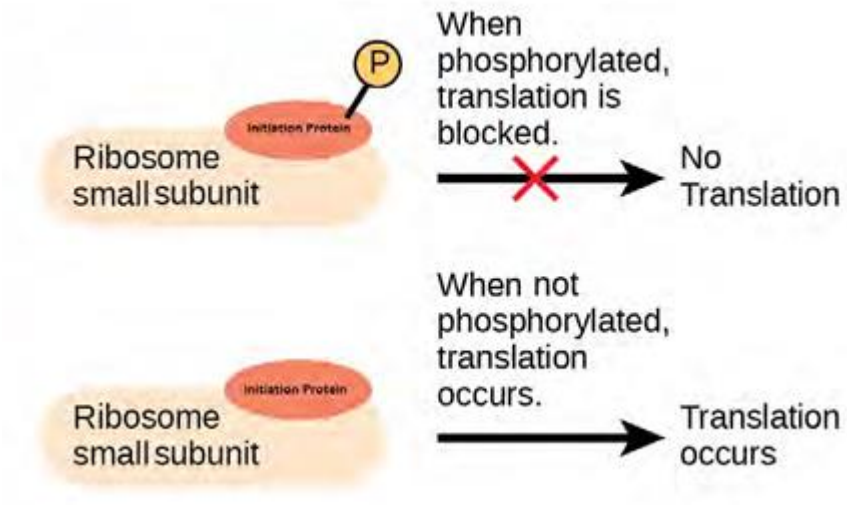


Figure: Gene expression can be controlled by chemical modifications of proteins needed to initiate translation.

THE END