**AL-FARABI KAZAKH NATIONAL UNIVERSITY**

***Faculty of Medicine and Healthcare, Higher School of Medicine***

***Department of Fundamental Medicine***

"Cell and molecular pathobiology"

**Lectures  of the Cell and molecular pathobiology**

**Lecture 1-2**

***Introduction to Cell and molecular biology***

Informational macromolecules: proteins, nucleic acids. DNA as a carrier of genetic information: key experiments. Central dogma of molecular biology. The role of molecular biology in medicine.

***Goal:***

Demonstrate knowledge and understanding in the field of cell biology and molecular biology. Understand the structure of cells and mechanism of molecular biology. Differences in structure, location and functions of DNA and RNA. Сlinical features of molecular disorders, and their molecular forms*.*

***Content:***

Informational properties of macromolecules; the central dogma of molecular biology; the role of molecular biology in medicine.

Diagnosis and management of molecular abnormalities.

Nucleotides, nucleic acids. Structure of nucleotides. Structure and biochemical functions of DNA. Types of RNA, their structural organization and their biological role. Differences in structure, location and functions of DNA and RNA.

The cell is the basic morphological, functional and reproductive unit of all organisms. It is an autonomous and dynamic system which is characterized by basic life manifestations (metabolism, growth, irritability, reproduction and development). Science which deals with the study of cells is called cytology.

Improvement of light microscopy and introduction of electron microscopy helped to a more accurate understanding of the structure of cells. According to the organization of nucleus and other structures, we distinguished prokaryotic and eukaryotic cells. All cells are composed of nucleus, cytoplasm and cytoplasmic membrane.

The transfer of genetic information by the process of replication, transcription and translation is in biology termed as the central dogma. The biosynthesis of proteins represents the process of the transfer of genetic information between three types of macromolecules: DNA, RNA and proteins. The direction of this transfer was postulated by Francis Crick in 1959.

In 1970 Temin and Baltimore proved the existence of the transfer of genetic information from an RNA virus to the DNA of a host cell; with the help of the reverse transcriptase enzyme (it synthesizes DNA according to the RNA matrix). This altered the central dogma of molecules.

There are two pentose sugars, ribose and deoxyribose, and five nucleotide bases, adenine (A), guanine (G), cytosine (C), thymine (T), and uracil (U). Deoxyribonucleic acid (DNA) is a chain of nucleotides in which each nucleotide consists of a deoxyribose sugar bound to a phosphate and one of the four bases A, G, C, or T. Ribonucleic acid (RNA) is also a chain of nucleotides in which each nucleotide consists of a ribose sugar and a phosphate bound to one of the four bases A, G, C, or U.

Organ transplantion (heart, liver, lung, or kidney) and Cell transplantation (example: diabetes, transplantation of hematopoietic stem cells) like medical treatment has become possible since the structure and properties of cells and tissue were elucidated.

***Questions for control:***

1. explain structure and difference of macromolecules
2. explain structure, location and functions of DNA and RNA
3. explain the central dogma of molecular biology
4. identify clinical features of cellular and molecular abnormalities and explain their clinical variability.
5. compare different diagnostic strategies for diagnosing molecular disorders and discuss related methods and legal issues.

***Recommended References:***

1. Human Genetics, Ricki Lewis. 2018

2. Medical Genetics at a Glance, Dorian J.Pritchard, Bruce R.Korf. 2013

3. Basic pathology, Robbins, 2017

4. Alberts et al.

5. http://csls-text3.c.u-tokyo.ac.jp/inactive/10\_03.html

**Lecture 3-4**

***DNA replication and repair***

***Goal:***

Demonstrate the understanding of the mechanism of DNA replication and repair. Hypothetical mechanisms of DNA replication. Replication enzymology. Molecular underpinnings of DNA synthesis. Sources of DNA damage in cells. DNA repair enzymology.

***Content:***

As units of life, cells have fundamental and shared properties/functions of dividing and proliferating to produce offspring. During cell proliferation, the DNA molecule in the parent cell is accurately replicated, dividing into two identical molecules, with each molecule being accurately segregated to the two daughter cells.

Genetic information plays the role of heredity in which genetic information is transmitted from the parent to progeny. And Replication of genetic information occurs prior to cell division. In this lesson, we examine that mechanism.

Replication: process by which DNA is copied with very high fidelity. Transcription: process by which the DNA genetic code is read and transferred to messenger RNA (mRNA). This is an intermediate step in protein expression. Translation: The process by which the genetic code is converted to a protein, the end product of gene expression. The biosynthesis of proteins represents the process of the transfer of genetic information between three types of macromolecules: DNA, RNA and proteins.

Enzymes involved in DNA Replication. – DNA Helicase – DNA Polymerase – DNA clamp – Single-Strand Binding (SSB) Proteins – Topoisomerase / DNA Gyrase – DNA Ligase – Primase.

Sometimes during replication or just spontaneously DNA will encounter errors that need to be repaired and there are two different ways that DNA can be repaired one of them is during replication, and the way that is repaired is the DNA polymerase 3 which is the main DNA polymerase. During replication there is an ongoing proofreading process that's something you should be very aware of the exonuclease is attached to the DNA polymerase group and so it proof reads and it corrects errors that occur during the replication process however if mutations show up later and there are various sources of this then there are a few different approaches that you can use that allows you to remove the damage and replace those with the correct bases.

***Questions for control:***

1. describe the DNA replication;
2. explain the role of main enzymes implicated in the replication process;
3. explain proofreading mechanisms and error correction during DNA replication.
4. discuss clinical features of mutation diseases and explain their clinical variability.
5. explain genetic mutations as the cause of disorders.
6. explain the importance of DNA repair; explain the mechanisms of repair.

***Recommended References:***

1. Cooper GM. The Cell: A Molecular Approach. (<https://www.ncbi.nlm.nih.gov/books/NBK9940/>) <http://csls-text3.c.u-tokyo.ac.jp/inactive/07_00.html>
2. Human Genetics, Ricki Lewis. 2018
3. Alberts et al.
4. http://csls-text3.c.u-tokyo.ac.jp/inactive/10\_03.html

**Lecture 5-6**

***Transcription of genetic information. Post-transcriptional RNA modifications.***

***Goal:***

Gene structure: promoter, exons, introns, terminator. Transcription enzymology. The mechanism of gene transcription: initiation, elongation, termination.

Post-transcriptional maturation of mRNA: 3' polyadenylation, 5' capping, exon excision.

***Content:***

We have five important components of gene: exons, introns, transcription start site, and promoters, enhancers.

During DNA synthesis, the entire sequences (DNA) of the parent DNA strand are accurately replicated from end to end and passed from the parent cell to the daughter cell. On the other hand, RNA transcription does not proceed end to end similar to DNA synthesis, only the gene segment is transcribed. During transcription, RNA polymerase unwinds a short section of the DNA double helix near the start of the gene (the transcription start site). This unwound section is known as the transcription bubble. The RNA polymerase, and with it the transcription bubble, travels along the noncoding strand in the opposite, 3' to 5', direction, as well as polymerizing a newly synthesized strand in 5' to 3' or downstream direction. The DNA double helix is rewound by RNA polymerase at the rear of the transcription bubble. Like how two adjacent zippers work, when pulled together, they unzip and rezip as they proceed in a particular direction. Various factors can cause double-stranded DNA to break; thus, reorder genes or cause cell death. Precursor messenger RNA has to undergo several important types of modifications, several important types of post transcriptional processes within the nucleus of cell.

* 7-Methylguanosine cap at 5’end
* Addition of poly A tail at 3’end
* Splicing

***Questions for control:***

1. define the terms: transcription, promoter, enhancer, terminator;
2. describe phases of transcription, explain the processes happening at each phase and their importance;
3. explain e the cap structure, its synthesis and functions;
4. describe the mechanism of splicing and its importance;
5. explain the effect of splicing on gene expression.
6. work with genetic databases (Ensembl & etc).

***Recommended References:***

1. Human Genetics, Ricki Lewis. 2018

2. Medical Genetics at a Glance, Dorian J.Pritchard, Bruce R.Korf. 2013

3. Alberts et al.

4. http://csls-text3.c.u-tokyo.ac.jp/inactive/10\_03.html

**Lecture 7-8**

***Translation of genetic information. Post-translational protein modifications and folding.***

***Goal:***

Ribosome structure: rRNA and ribosomal proteins. Genetic code: properties and key experiments. tRNAs, aminoacyl-tRNA synthetases. The mechanism of translation: initiation, elongation, termination.

Protein post-translational modifications. Protein folding: chaperones.

***Content:***

Rough ER is called rough because it has ribosomes attached to its surface. The double membranes of smooth and rough ER form sacs called cisternae. Protein molecules are synthesized and collected in the cisternal space/lumen. When enough proteins have been synthesized, they collect and are pinched off in vesicles. Ribosomes are the machinery of the cell that are responsible for translating and synthesizing our polypeptides/proteins. And the way that they synthesize proteins is by using the genetic code to translate the sequence of nucleotides into the sequence of amino acids. Translation proceeds in three phases:

Initiation: The ribosome assembles around the target mRNA. The first tRNA is attached at the start codon.

Elongation: The tRNA transfers an amino acid to the tRNA corresponding to the next codon. The ribosome then moves (translocates) to the next mRNA codon to continue the process, creating an amino acid chain.

Termination: When a stop codon is reached, the ribosome releases the polypeptide.

Once they’re actually synthesized in the ribosome are not complete before they actually arrive at the target location and before they are activated they have to undergo many different types of processes, many different types of modifications and together all these modifications are known as post translational modifications of polypeptide chains.

***Questions for control:***

1. explain the mechanism of translation and its phases;
2. define the genetic code, tRNA, mRNA, codon, anticodon;
3. explain the mechanism of post-translational protein modifications and folding;
4. explain a functional of chaperones in protein folding;
5. discuss examples of human disorders linked with protein misfolding.
6. work with genetic databases (Ensembl & etc).

***Recommended References:***

1. Human Genetics, Ricki Lewis. 2018

2. Medical Genetics at a Glance, Dorian J.Pritchard, Bruce R.Korf. 2013

3. Alberts et al.

4. http://csls-text3.c.u-tokyo.ac.jp/inactive/10\_03.html

**Lecture 9-10**

***Regulation of gene expression in human***

***Goal:***

Demonstrate the understanding of gene structure in humans. Regulation of transcription: transcription factors. Regulation of translation: translation factors. Intracellular signal transduction pathways.

***Content:***

Each cell expresses, or turns on, only a fraction of its genes. The rest of the genes are repressed, or turned off. The process of turning genes on and off is known as gene regulation.

Gene regulation is an important part of normal development. Genes are turned on and off in different patterns during development to make a brain cell look and act different from a liver cell or a muscle cell, for example. Gene regulation also allows cells to react quickly to changes in their environments. Although we know that the regulation of genes is critical for life, this complex process is not yet fully understood.

Gene regulation can occur at any point during gene expression, but most commonly occurs at the level of transcription (when the information in a gene’s DNA is transferred to mRNA). Signals from the environment or from other cells activate proteins called transcription factors. These proteins bind to regulatory regions of a gene and increase or decrease the level of transcription. By controlling the level of transcription, this process can determine the amount of protein product that is made by a gene at any given time.

All cells in one organism contain the same DNA, share the same genotype but phenotypes differ. Because cells have different structure & function from each other. For example, a muscle cell, a skin cell, and a nerve cell, could be distinguished by their gene expression profiles.

A signaling molecule (ligand) from one cell bind to a receptor on another cell, in the intracellular receptors, which bind their ligand inside of the cell and directly activate genes, so, the chains of molecules that relay signals inside a cell are known as intracellular signal transduction pathways. At the general characteristics of intracellular signal transduction pathways, as well as some relay mechanisms commonly used in these pathways.

As an example, consider

* the epidermal growth factor (EGF) pathway that acts through a series of kinases to produce a cellular response.
* Raf, MEK, and the ERKs are three-tiered kinase signaling pathways called a mitogen-activated protein kinase (MAPK) cascade. (A mitogen is a signal that causes cells to undergo mitosis, or divide.) Because they play a central role in promoting cell division, the genes encoding the growth factor receptor, Raf, and c-Myc are all proto-oncogenes, meaning that overactive forms of these proteins are associated with cancer.
* the Wnt signaling pathways are a group of signal transduction pathways which begin with proteins that pass signals into a cell through cell surface receptors.

***Questions for control:***

1. explain the gene regulation in gene expression
2. explain the roles of transcription factors and transcription activators in transcription regulation;
3. explain significance of DNA-binding domains and transcription activation domains;
4. explain mechanism of three commonly used pathways
5. work with genetic databases (Ensembl & etc).

***Recommended References:***

1. Human Genetics, Ricki Lewis. 2018

2. Medical Genetics at a Glance, Dorian J.Pritchard, Bruce R.Korf. 2013

3. Alberts et al.

4. http://csls-text3.c.u-tokyo.ac.jp/inactive/10\_03.html

**Lecture 11**

***Epigenetics***

***Goal:***

Demonstrate the understanding of significance of epigenetic regulation of gene expression. Mechanisms of epigenetic regulation: DNA methylation.

***Content:***

The epigenome is involved in producing multiple cell types from one genome. In the human body, about 200 broad categories of specialized cells are known, including cells of organs such as the liver, cells of blood vessels of the entire body, and neurons of nerves. These cells are formed by differentiation from one zygote, but once they have differentiated, they stabilize and exhibit mutually identical characteristics. For example, a transplanted kidney will function as a kidney, and a transplanted liver will function as a liver. Analysis of each kind of cell reveals differences in their DNA methylation. In other words, cells that have different epigenomes become different cells.

Human development begins when the DNA of the father's sperm and mother's egg are inherited in a zygote. Shortly after fertilization, most of the DNA methylation are reset by removal of methyl groups. In undifferentiated cells with the ability to differentiate into various kinds of cells, the epigenome changes as the cell differentiates. Once the genome is modified, it will be replicated and inherited even when the cell divides as it is. Consequently, the number of genes with repressed expression will increase. Methylated DNA is also increased by various kinds of environmental stimulations. Methylation modifications are replicated, and if such modifications accumulate in the DNA over many years, the amount of non-functional DNA with repressed expression will increase. This type of increase may be accompanied by aging of the cells. On the other hand, when the sperm and egg unite as described above, the methylation in the zygote is reset, and thus, a baby is born with healthy cells.

For example, during the differentiation of bone marrow stem cells into the several different types of blood cells, a hematopoietic stem cell divides into two daughter cells, one of which continues to have the properties of a hematopoietic stem cell, including the potential to differentiate into all the different types of blood cells.

The daughter cell becomes either a lymphoid progenitor cell or a myeloid progenitor cell. The various types of blood cells all derive from a single type of multipotent, self-renewing hematopoietic stem cell (HSC). Lymphoid progenitor cells generate daughter cells that differentiate into lymphocytes, which perform many of the functions involved in immune responses to pathogens. Myeloid progenitor cells divide into daughter cells that are committed to differentiating into red blood cells, different kinds of phagocytic white blood cells, or the cells that generate platelets involved in blood clotting.

Lymphoid and myeloid progenitor cells both have the same DNA sequence as the zygote (generated by fertilization of an egg cell by a sperm cell) from which they developed, but they have restricted developmental potential because of epigenetic differences between them. In this specific case, Epigenetic regulates which gene will be turned on or turned off to differentiate to the different types of blood cells by using specific proteins.

***Questions for control:***

1. explain the importance of epigenetic regulation and its role in heritability of cellular traits;
2. explain the role of DNA methylation in regulation of gene expression;
3. describe the mechanisms and major players of above mentioned processes in diseases.
4. discuss the importance of determining the epigenetic processes in human diseases.

***Recommended References:***

1. Human Genetics, Ricki Lewis. 2018

2. Medical Genetics at a Glance, Dorian J.Pritchard, Bruce R.Korf. 2013

3. Basic pathology, Robbins, 2017

4. Alberts et al.

5. http://csls-text3.c.u-tokyo.ac.jp/inactive/10\_03.html

**Lecture 12-13**

**Modern techniques in medicine**

***Goal:***

The understanding of DNA technology, genome sequencing: Sanger method, Next Generation sequencing, Immunohistochemistry, FISH. Genomic data as a gateway to personalized medicine: SNPs, Human Genome Project. Databases: Ensembl, NCBI, Cosmic, etc.

***Content:***

In the second half of the 1980s, the unfamiliar term "human genome" began to appear in the general media. The first stage of the human genome project was to determine all base sequences of DNA constituting the human genome. At the end of the 1980s, the United States started the human genome project as a national agenda. With this as a starter, Japan, Europe, Canada and others participated in this project, and the decoding of the human genome proceeded as a publicly acknowledged, international joint project. In 2003, the international joint team of the project announced completion of the decoding of the human genome.

The decoding of the human genome confirmed that the entire base sequence of DNA constituting the human genome is about 3 billion and the number of genes is about 25,000–less than our expectations.

* Polymerase chain reaction (PCR).
* Sanger DNA sequencing
* NGS and other methods of genome sequencing
* Immunohistochemistry

Access to biological information.

***Questions for control:***

1. discuss the perspectives of genomic technologies in medicine.
2. explain the PCR, Sanger sequence, NGS, Immunohistochemistry and other methods of genome sequencing;
3. work with genetic databases, Human Genome Project and the application of genomic data in personalized medicine; describe Ensembl, NCBI, Cosmic, etc. and other bioinformatic databases.

***Recommended References:***

1. Human Genetics, Ricki Lewis. 2018

2. Medical Genetics at a Glance, Dorian J.Pritchard, Bruce R.Korf. 2013

3. Basic pathology, Robbins, 2017

4. Alberts et al.

5. http://csls-text3.c.u-tokyo.ac.jp/inactive/10\_03.html

**Lecture 14-15**

***Cancer Genetics and Genomics***

***Goal:***

Demonstrate the understanding of cancer genetics and genomics, hereditary cancer syndromes and familial occurrence of cancer.

***Content:***

Cancer Genetics and Genomics. Cancer genes.

Hereditary cancer syndromes.

Familial occurrence of cancer. Sporadic cancer and genetic bases.

Genetic technology in cancer prevention, diagnosis and therapy.

Breast ca[ncer](https://en.wikipedia.org/wiki/Breast_cancer): causes and genetic mechanisms (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Cancer. Growth and division of normal cells are regulated by control mechanisms. These control mechanisms result in fixed life span for cells and for the organisms. One such control mechanism is contact inhibition. As a result of multiplication, the cells become crowded and come in contact with one another. This surface contact checks movement and division of cells. Therefore, the genes which control these processes are turned off. Vertebrate cells grown in a culture adhere to the bottom as they need support, divide, and keep in contact with one another and spread as a monolayer. Cell to cell contact inhibits their growth. Cancer is a disease of cells wherein the control mechanism that normally restricts cell proliferation does not operate. In other words, in the case of cancer cells, the mechanism of contact inhibition does not function. The cells continue to divide, forming a tissue mass called tumour.The cancer cells may invade other tissues and cause tumours in them also. Cancer is caused, not only by viruses, but also by other mutagens such as radiation and chemicals. All these factors are called carcinogens.They alter (activate) the protooncogenes.Altered proto oncogenes are called oncogenes.Alteration may in­volve breaking into fragments, amplification or shifting to a new chromosomal location. Intact genes control normal growth and development of cells. Alteration in genes leads to the formation of abnormal proteins, change in gene environment, suspension of the mechanism that controls cell division, which causes uncontrolled cell division and growth, and this is cancer.

***Questions for control:***

1. clinical features of [breast cancer](https://en.wikipedia.org/wiki/Breast_cancer) and explain its lifetime prevalence, genetic variability and summarize data on hereditary cancer syndromes and syndromes with familial cancer.
2. genetic mechanisms of oncogenesis on [breast cancer and](https://en.wikipedia.org/wiki/Breast_cancer) summarize their role in clinical variability of hereditary cancer syndromes and syndromes with familial cancer.
3. management strategies of [breast cancer](https://en.wikipedia.org/wiki/Breast_cancer) prevention, treatment
4. discuss the impact of diagnosis of cancer.
5. work with genetic databases ( Ensembl, NCBI, Cosmic, & etc).

***Recommended References:***

1. Human Genetics, Ricki Lewis. 2018

2. Medical Genetics at a Glance, Dorian J.Pritchard, Bruce R.Korf. 2013

3. Basic pathology, Robbins, 2017

4. Alberts et al.

5. http://csls-text3.c.u-tokyo.ac.jp/inactive/10\_03.html