HUMANITAS UNIVERSITY

MEDICINE AND SURGERY

Course: The Cell: Functions and Control (CFC)

Year: 1st

Period: 2nd semester

Credits: 9 (Biochemistry 6, Physiology 3)

Objectives

Knowledge. The CFC course offers the student a first comprehensive perspective on the mechanisms that sustain life and the functioning of the human organism, through regulation and control of cellular processes. Major themes and aspects of the course are outlined here.

- The initial focus will be on thermodynamics of life: how cells and organisms gather energy from the environment, and employ it to establish an "internal milieu", respond to stimuli, adapt to, and even anticipate, changes in the external environment and actively behave.
- Paradigmatic examples of the evolutionary journey from small organic compounds to complex macro-biomolecules will be discussed as a way to illustrate the process of function selection in living systems; in this respect the major structure/function relationships of macro-biomolecules will be examined.
- The pathways and mechanisms of the metabolisms of carbohydrates, lipids, proteins, amino-acids, nucleotides and their regulation will be described and reviewed. Cellular respiration, oxidation of energetic substrates and their control will be discussed. Major emphasis will be on the regulatory mechanisms that allow energy to be harvested from food and smartly released to fuel biochemical reactions in the cell.
- Fundamental cellular and molecular processes will be presented and critically discussed in light of their roles in the human body and the modes and mechanisms of their regulation. The students will be provided with critical information on how cells and tissues organize metabolic inter-organ pathways.
- The students will be introduced to the physiological perspective on the cell as a complex system in which numerous processes and programs take place concurrently in a finely controlled way. Ongoining internal programs, anticipation of or response to external signals, or activation of receptors and their signal transduction pathways achieve this by regulating gene expression, biochemical and bioelectrical functions and substrate transport and exchanges.
- The specific properties of excitable cells and the cellular physiology of neurons will be explored to understand how they can sense, elaborate, interpret, code and communicate information, and plastically modify their synaptic connection as a consequence of such activity.
- Key inter- and transdisciplinary aspects will be addressed through seminars, collaborative work and flipped classrooms to train students to re-elaborate information in a broader perspective.

Competences and skills. At completion of the course, the students are expected to:

- understand, describe and explain the major bioenergetic aspects of life, and in particular how cells and organisms harvest energy from the environment, and use it to establish, maintain, adapt and restore homeostasis;
- discuss why and how the structural complexity of macro-biomolecules is required to provide and support biological functions;
- illustrate and critically review the structure/function relationships underlying the activity and regulation of enzymes and haemoglobin;
- understand and discuss the major catabolic and anabolic routes of cell metabolism, and their regulation;
- illustrate how cells and tissues organize the metabolic inter-organ pathways, and how this relates to the functions of the human body;
- understand and explain the mechanisms of control of the cellular functions, by integrating pathways and processes of cellular biochemistry and physiology;
- understand the bases of bioelectricity, the "passive" and "active" electric properties of cells and the interrelations between electrical and biochemical events in the cell;
- understand and argue how excitable cells function, how they can sense, interpret, code and communicate information;
- explain how neurons plastically modify their synaptic connections as a consequence of their own activity and the relation of these cellular processes to learning and memory;
- develop a reasoning attitude that integrates and complement cell biochemistry and physiology, via attendance to joint seminars, collaborative work and flipped classrooms;
- improve communication and presentation skills, through active participation in oral and written assignments, and flipped classrooms;
- appreciate the value of collaboration and peer discussion.

Prerequisites

The students must possess the bases of maths, physics and chemistry that are needed to grasp the conceptual aspects of regulation of the biological processes, and deal with them in quantitative terms: these are the topics faced in the PLM course (Principles of the Living Matter) that must have been attended.

Contents

The CFC course comprises the Biochemistry (6 formative credits) and Cell Physiology (3 formative credits) modules, and is organized on three distinct levels (knowledge transfer, active knowledge mastering, and knowledge activation), as described in the "Teaching methods" section. Contents and level-specific learning goals are detailed below.

INTRODUCTION TO CELL PHYSIOLOGY. ***Life: energy, homoeostasis, control, development*** *(3 lectures)*

Topics: the internal milieu: transport, metabolism, dynamic equilibrium. Membranes. Intra/extracellular components.

- *Acquire the notions of energy intake and use by living systems, steady state, turnover, "dynamic equilibrium", homeostasis, adaptation, anticipatory responses, feed-back and feed-forward control*
- *Study the composition of intra- and extracellular fluids and the mechanisms of ion and substrate transfer across cell membranes.*

INTRODUCTION TO BIOCHEMISTRY. ***How chemical reactions take place in the cell*** *(1 workshop + 4 lectures)*
Topics: Structure/function of biomolecules. Enzymes and cofactors. Mechanisms and control of the enzymes' activity. Thermodynamics of metabolism. Principles of the metabolic control.

- *Understand basic structure/function relationships of complex biological macromolecules (e.g., enzymes), and how they mediate biological functions and control*
- *Define, classify, and describe the general properties of enzymes*
- *Explain the role of cofactors, mechanisms and regulation in enzyme-mediated catalysis*
- *Illustrate the fundamentals of enzyme kinetics (Michaelis-Menten theory)*
- *Present and discuss hemoglobin as a model of allosterism*
- *Explain how energy flows through and across metabolic pathways and their control*

BIOCHEMISTRY. ***Catabolic and anabolic pathways of carbohydrate metabolism*** *(6 lectures + 1 flipped classroom)*
Topics: Carbohydrate digestion. Glycolysis. Catabolism of fructose, galactose and mannose. Homolactic fermentation. The pentose phosphate pathway. Glycogen phosphorylase. Properties and functions of glycogen synthase. Gluconeogenesis.

- *Understand how polysaccharides and disaccharides are digested and adsorbed in the gut*
- *Describe the reactions and the regulation of glycolysis*
- *Explain how hexoses other than glucose enter glycolysis*
- *Illustrate the anaerobic fate of pyruvate (homolactic fermentation)*
- *Describe reactions and roles of the pentose phosphate pathway*
- *Explain how glucose is mobilized from glycogen, describe the chemical reactions involved*
- *Illustrate how the opposing processes of glycogen breakdown and synthesis are regulated*
- *Define the non-carbohydrate precursors in gluconeogenesis and the reactions involved*
- *Illustrate the reciprocal control of glycolysis and gluconeogenesis*

BIOCHEMISTRY. *Mitochondrial ATP synthesis* *(4 lectures)*

Topics: Acetyl-CoA as a metabolic "hub". Reactions and regulation of the citric acid cycle. Oxidation-reduction reactions in the mitochondrial redox centers. Oxidative phosphorylation.

- *Illustrate the central role of acetyl CoA in metabolism*
- *Discuss structure, catalytic mechanism and regulation of pyruvate dehydrogenase*
- *Illustrate the shuttle systems for electrons across the inner mitochondrial membrane*
- *Describe reactions and control of the citric acid cycle and itscross-talks to other metabolic pathways: cataplerotic and anaplerotic reactions*
- *Describe organization and function of the electron transport chain in the mitochondrion*
- *Illustrate how the proton gradient across the inner mitochondrial membrane links electron transport to ATP synthesis: discuss structure/function of ATP synthase*
- *Describe eat generation in brown adipose through electron transport and ATP uncoupling*
- *Discuss formation of radical oxygen species (ROS) during oxidative phosphorylation and the major defensive mechanisms against ROS.*

BIOCHEMISTRY. Lipid metabolism *(5 lectures + 1 flipped classroom)*
Topics: Metabolism of fatty acids and eicosanoids. Biosynthesis of triacyglycerols and membrane phospholipids. Cholesterol and bile acids metabolism.

- *Explain how lipids are digested, absorbed, and transported*
- *Describe reactions and energy yield of fatty acid β-oxidation*
- *Discuss how the cell catabolizes unsaturated and odd-chain fatty acids*
- *Describe the synthesis of ketone bodies and their metabolism in peripheral tissues*
- *Illustrate the transfer of acetyl-CoA into the cytosol for fatty acid synthesis*
- *Illustrate the reactions of fatty acid biosynthesis and β-oxidation and their control*
- *Describe the mechanisms of fatty acid chain elongation and desaturation*
- *Illustrate the biosynthesis of triacylglycerols and major membrane phospholipids*
- *Discuss cholesterol synthesis and its use as a precursor of steroid hormones and bile acids*

BIOCHEMISTRY. Nitrogen homeostasis and iron metabolism *(4 lectures)*

Topics: Nitrogen homeostasis. Digestion and absorption of proteins. Urea cycle. Synthesis and breakdown of amino acids. δ-aminolevulinic acid, porphobilinogen, uroporphyrinogen III synthase. Bilirubin and its conjugation with glucuronic acid. Ferrochelatase. Iron absorption and transport.

- *Understand the concept of nitrogen balance*
- *Describe the major mechanisms of intracellular protein degradation*
- *Illustrate amino acid transamination and oxidative deamination of glutamate*
- *Describe the reactions of urea cycle and its connection with the citric acid cycle*
- *Discuss the catabolic fates of the carbon skeleton of amino acids*
- *Illustrate the major reactions involved in the synthesis of nonessential amino acids*
- *Describe reactions and control of heme synthesis*
- *Illustrate the general features of heme degradation*
- *Discuss how iron is adsorbed, transported and stored in the body*

BIOCHEMISTRY. Nucleotide synthesis and degradation *(2 lectures)*

Topics: De novo and salvage pathways of nucleotide synthesis. Ribonucleotide reductase. Synthesis of dTTP. Nucleotide catabolism.

- *Illustrate the general scheme of the de novo and salvage pathways of purine and pyrimidine biosynthesis*
- *Discuss the coordinated regulation of purine and pyrimidine synthesis*
- *Describe the reaction mechanism and control of ribonucleotide reductase*
- *Illustrate the strategy to convert dUMP to dTMP*
- *Describe the catabolic reactions of nucleotides*

BIOCHEMISTRY. Biochemistry of synapses *(2 lectures)*
Topics: paths and control of neurotransmitter biosynthesis and metabolism. Synaptic scaffolding proteins.

- *describe the biosynthetic pathways of small nitrogen-containing neurotransmitters from common amino acid or membrane lipid precursors;*
- *discuss the mechanisms that control synthesis and availability of neurotransmitters, with major regard to catecholamines, serotonin, histamine, glutamate, GABA, and acetylcholine;*
- *illustrate the proteolytic processing of model pro-neuropeptides to active peptides;*
- *discuss the post-synaptic density (PSD), a post-synaptic membrane microdomain harboring receptors, adhesive systems, ion channels, signaling enzymes, and scaffold proteins;*
- *understand the major differences between PSDs of excitatory and inhibitory synapses in terms of composition and 3D organization;*
- *describe structure/function of the PSD95-dependent molecular network in the excitatory PSD and the role of PSD95 in tuning neurotransmission.*

BIOCHEMISTRY. An integrated view of fuel metabolism *(2 lectures + 1 seminar + 1 flipped classroom)*

Topics: Organ specialization. Insulin, glucagon and catecholamines. Regulation of energy metabolism, appetite and body weight. Alterations of the metabolic homeostasis. Metabolomics as a branch of systems biology.

Knowledge transfer goals:

- *Discuss the metabolic requirements of major organs*
- *Describe the counteracting effects of insulin and glucagon/catecholamines on metabolisms*
- *Illustrate the effects of AMP-dependent protein kinase (AMPK) on cell metabolisms*
- *Understand regulation of fuel use and appetite by hormones produced in adipose tissue, hypothalamus, stomach, and intestine*
- *Discuss the metabolic adaptation during starvation*
- *Describe the major types of metabolomic analyses (from targeted to holistic approaches)*
- *Illustrate the key properties of common preparative and analytical tools of metabolomics*
- *Discuss applications of metabolomics in the discovery of cancer biomarkers and unexpected metabolic links.*

CELL PHYSIOLOGY. Control: regulation and change – Ion channels, receptors, signal transduction – Endocrine and neural controls *(3 lectures + 4 hr group work)*

- *Study the structure and function of ion channels, how they are regulated and how they affect the cell*
- *Study the distinct classes of receptors and their transduction mechanisms*
- *Investigate the concepts of affinity, set-point, capacity, rate and velocity; reason about how these parameters intervene in regulating a cellular process*
- *Study how calcium ions are handled by the cell and try to explain what may be the usefulness / purpose of calcium-induced calcium release*

CELL PHYSIOLOGY. Electricity and Cellular bioelectricity *(3 lectures)*

- *Study the basic notions related to electric current, resistors, and capacitors*
- *Study the rules of ion partition: chemical, electric and electrochemical potential – Nernst equation*
- *Study the concept of "membrane potential": Goldman's equation and graded potentials*
- *Study the sequence of events during the action potential*

CELL PHYSIOLOGY. Intercellular communication *(5 lectures + 4 hr group work)*

- *Study the structure and functioning of electric synapses and chemical synapses*
- *Study the neuromuscular junction (NMJ) as a paradigmatic system: quantal release, synaptic facilitation, potentiation and depression*
- *Study the synaptic vesicle cycle and the dynamics of SNARE/SM complex assembly and disassembly*
- *Study the classification of neurotransmitter receptors, their transduction path, distribution and cellular roles*
- *Study the principles of spatial and temporal integration and the properties of the spike encoder*
- *Review the work by Kandel on Aplysia, define "synaptic plasticity" and study the mechanisms that sustain it*

INTERDISCIPLINARY ACTIVITIES

Signalling *(1 flipped classroom)*

The active role of signalling mechanisms in the transduction of receptor activation and in the regulation of biochemical and biophysical functions of the cells.

Electrochemistry *(1 flipped classroom)*

Electrochemistry and its relations with ion partition, electron transport and reactive oxygen species. The intersection between biophysical/bioelectrical phenomena and the metabolic processes

Teaching Methods

The course will be implemented based on a teaching schedule that combines and integrates:

- lectures;
- indication of readings;
- personal and group assignments – quizzes, research assignments, open questions, self-evaluation;
- interactive and multidisciplinary re-elaborations;
- flipped classrooms;
- formative revision tests, question time.

The course is organized on three distinct levels:

1. knowledge transfer – lectures (face-to-face but also available in streaming or recorded) will remain accessible to students online; students will also be addressed to textbook chapters, scientific articles and other studying material: through all this the students are expected to acquire the notions needed to master the topics at hand. These activities are programmed in the daily schedule, but can be performed by the students at the times most convenient for them, if they are forced to stay in other Countries, as long as the pandemic lasts;
2. active knowledge mastering – self-assessment tests, small-group (either physical or digital) assignments and suggested readings will help the students process and master the acquired notions;
3. knowledge activation – interactive lectures, joint interdisciplinary seminars, question and answer sessions, discussions of group assignments and flipped classrooms will help the student to fully understand, assimilate and frame the acquired notions in an organized general perspective, and to clearly and linearly explain the complex issues of the functioning of living systems.

Knowledge activation sessions will be held on Campus in the afternoon (Italian time), whenever possible, to make online synchronous attendance easier from most Countries in the world.

Verification of learning

Learning by the students will be monitored during the course through assignments and interactive formative sessions and will be eventually assessed through the final examination.
This consists in a written test comprised of 30 items:

- 28 among multiple choice questions (with one or more right answers), matching, ordering and other similar quizes (20 Biochemistry, 8 Cell Physiology);
- plus 2 open questions (1 for Biochemistry and 1 for Cell Physiology); insight, conceptual organization, clarity, appropriateness of terms, essentiality (no redundancy) will be graded in the answers to these questions

The various items will be differently weighted depending on the complexity (this will be written in the exam text) so that the total sum will amount to 33. A score >30 achieves the laude.
Time allotted: 90 minutes.

Texts

- Principles of Biochemistry. International student version - Voet, Voet and Pratt - Publisher: Wiley (4th edition) or Voet's Principles of Biochemistry. Global Edition - Voet, Voet and Pratt - Publisher: Wiley (5th edition)
- Lehninger Principles of Biochemistry -Albert Lehninger, David L Nelson and Michael M Cox - Publisher: W. H. Freeman (7th edition)
- Biochemistry –Berg JM, Tymoczko JL and Stryer L -Publisher: Palgrave MacMillan (7th edition)
- Guyton and Hall – Textbook of Medical Physiology, 13th ed. Elsevier, 2016.
- W.F. Boron, E.L. Boulpaep – Medical Physiology, 3rd ed. Elsevier, 2017.
- E.R. Kandel, J.H. Schwartz et al. – Principles of neural science. McGraw Hill 2013.