HUMANITAS UNIVERSITY

MEDICINE AND SURGERY

Course: The Cell: Functions and Control (CFC)

Year: 1st (first)

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. The course aims at leading the students to:

- understand – by studying the thermodynamics of life – how cells and organisms gather energy from the environment and employ it to establish an "internal milieu", to respond to stimuli, to adapt and anticipate changes in the external environment, to actively behave;
- examining paradigmatic examples of the evolution from small organic compounds to complex macro-biomolecules and thus learn how function selection works in living systems;
- understand – by examining the main structure/function relationships of macro-biomolecules – how the dynamic and regulated assembly into hierarchical structures makes it possible to perform biological functions (this will help them to grasp the general aspects of enzymology, and gas transport by haemoglobin);
- learn the pathways and mechanisms of the metabolism of carbohydrates, lipids, proteins, amino-acids, nucleotides, and how they are regulated;
- learn how cellular respiration and oxidation of energetic substrates works, and through what regulatory mechanisms energy is harvested from food, converted into suitable "currency" for utilization in the human body, and smartly released to fuel biochemical reactions in the cell;
- understand the modes and mechanisms of the regulation of cellular and molecular processes, their roles in the human body and how they generate metabolic inter-organ pathways;
- acquire a systematic view of the cell as a complex system, in which housekeeping and complex programs take place concurrently (through the regulation of gene expression, biochemical and bioelectrical functions, substrate transports and exchanges) in a way finely controlled by the interaction of ongoing internal programs, responses to (or anticipation of) external signals, activation of receptors and activation of their signal transduction pathways;
- understand the specific properties of excitable cells and the cellular physiology of neurons: how these cells can sense, elaborate, interpret, code and communicate information, and plastically modify their synaptic connection as a consequence of such activity;
- integrate and re-elaborate information in a broader perspective, by discussing key inter-and trans-disciplinary aspects through seminars, collaborative work and flipped classrooms.

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

- understand and explain the major bioenergetic aspects of life: how cells and organisms harvest energy from the environment and use it to establish, maintain, adapt and restore homeostasis;
- know how the structural complexity of macro-biomolecules supports biological functions;
- critically review the structure/function relationships that underlie the activity and regulation of enzymes and haemoglobin;
- describe the major catabolic and anabolic routes of cell metabolism, and their regulation;
- explain how cells and tissues organize the metabolic inter-organ pathways to sustain the functions of the human body;
- understand and explain the mechanisms that control cellular functions, by integrating pathways and processes of cellular biochemistry and physiology;
- discuss the bases of bioelectricity, the "passive" and "active" electric properties of cells and the interrelations between electrical and biochemical events in the cells;
- 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;
- exhibit a reasoning attitude that integrates and complements cell biochemistry and physiology, having attended joint seminars, collaborative work and flipped classrooms;
- effectively communicate and present data, thanks to 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 is comprised of two modules: Biochemistry (6 credits) and Cell Physiology (3 credits). It is organized on three levels (knowledge transfer, active knowledge mastering, and knowledge activation), as described in the "Teaching methods" section. Contents and learning goals are detailed below.

INTRODUCTION TO CELL PHYSIOLOGY. ***Life: energy, homoeostasis, control, development***

Knowledge transfer goals

- *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*
- *Learn the composition of intra- and extracellular fluids and the mechanisms of ion and substrate transfer across cell membranes.*

Active knowledge mastering goals

- *Describe a physiological process in terms of rates and steady state values of its parameters*
- *How can transport mechanisms be classified in a rational manner?*
- *What determines the concentration of a substance in a biological compartment?*
- *How can distinct membranes in a cell maintain different compositions?*

Knowledge activation goals

- *Explain the relations between the internal and external environmentand their relevance to cellular homoeostasis; the general paradigm of life, persist through change; how cells perform their tasks; the interactions between the cell and the extracellular environment*

INTRODUCTION TO BIOCHEMISTRY. ***How chemical reactions take place in the cell***

Knowledge transfer goals

- *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 and the role of cofactors*
- *Illustrate the fundamentals of enzyme kinetics (Michaelis-Menten theory)*
- *A non-enzymatic protein to understand enzymes: hemoglobin as a model of allosterism*
- *Explain energy flow through and across metabolic pathways ("high-energy" and "electron carrier" compounds as energetic "currencies" of the cell) and how these are controlled*

Active knowledge mastering goals

- *How can the structure of a biological macromolecule mediate a biological function*
- *Which are the major mechanisms of enzymatic catalysis and how are they controlled?*
- *Why do some molecules act as enzymatic inhibitors? Which mechanisms do they exploit?*
- *What is allosterism, and how does it apply to oxygen transport by haemoglobin?*
- *How are "high-energy" compounds synthesized and utilized to fuel endoergonic reactions?*
- *How do matter and energy flow through metabolic networks? How are these regulated?*

Knowledge activation goals

- *To be able to discuss fundamental structure/function relationships of biological macro-molecules and their regulation, illustrate major mechanisms of enzymatic catalisys and its inhibition, explain how allosterism controls biological functions, and discuss how energy and matter flow through and across metabolic pathways.*

BIOCHEMISTRY. ***Catabolic and anabolic pathways of carbohydrate metabolism***

Knowledge transfer goals

- *Understand how polysaccharides and disaccharides are digested and adsorbed in the gut*
- *Describe reactions and regulation of glycolysis, and how hexoses other than glucose enter it*

- *Illustrate the anaerobic fate of pyruvate (homolactic fermentation)*
- *Describe reactions and roles of the pentose phosphate pathway*
- *Explain how glucose is mobilized from glycogen*
- *Illustrate how glycogen breakdown and synthesis are opposedly regulated*
- *Define non-carbohydrate precursors of glucose in gluconeogenesis (Cori and alanine cycles)*
- *Describe the reactions of gluconeogenesis*
- *Illustrate the reciprocal control of glycolysis and gluconeogenesis by allosteric effectors and phosphorylation/dephosphorylation*

Active knowledge mastering goals

- *How are polysaccharides and sugars absorbed and transported in the intestine?*
- *How is glucose (and other hexoses) oxidized in glycolysis? What are the fates of pyruvate?*
- *What are the metabolic precursors of glucose in gluconeogenesis? How and when does it take over glycolysis?*
- *How is glucose mobilized from glycogen? How is glycogen synthesized from glucose?*
- *How and why is the pentose phosphate pathway connected to other metabolic pathways?*
- *How is the carbohydrate metabolism controlled? What are the roles of hormones, nerve impulses, and second messengers?*

Knowledge activation goals

- *To be able to present and discuss mechanisms and processes of carbohydrate digestion, absorption and transport, illustrate reactions and metabolic intermediates of glycolysis, gluconeogenesis, glycogenolysis, glycogenogenesis and pentose phosphate pathway, explain how the carbohydrate metabolism in the cell is controlled, with major regard to the action of hormones and their signalling mechanisms.*

BIOCHEMISTRY. *Mitochondrial ATP synthesis*

Knowledge transfer goals

- *Illustrate the central role of acetyl CoA in metabolism*
- *Discuss structure, catalytic mechanism and regulation of pyruvate dehydrogenase*
- *Describe reactions and control of the citric acid cycle and its cross-talks to other metabolic pathways: cataplerotic and anaplerotic reactions*
- *Describe ultrastructure of the mitochondrion and illustrate the shuttle systems of electron transfer across the inner mitochondrial membrane*
- *Discuss organization and function of the electron transport chain components and the role of the proton gradient across the inner mitochondrial membrane*
- *Discuss structure/function of ATP synthase and describe electron transport /ATP uncoupling*
- *Discuss formation of radical oxygen species (ROS) during oxidative phosphorylation*

Active knowledge mastering goals

- *What is the physiological significance of pyruvate oxidative decarboxylation to acetyl-CoA?*
- *What are the structure/function relations of pyruvate dehydrogenase? How is it regulated?*
- *How is carbon oxidized in citric acid cycle? Why is this cycle central in cell metabolism?*
- *How do electrons generate the proton gradient across the inner mitochondrial membrane?*
- *How is this gradient utilized to synthesize ATP?*

Knowledge activation goals

- *To be able to present and discuss catalytic and regulatory mechanisms of pyruvate dehydrogenase, explain how citric acid cycle oxidizes carbon and generates intermediates that crosstalk to other metabolisms, illustrate ultrastucture and function of the electron transport chain, and describe how ATP is synthesized via oxidative phosphorylation.*

BIOCHEMISTRY. Lipid metabolism

Knowledge transfer goals

- *Study 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 how the tricarboxylate transport system transfers acetyl-CoA into the cytosol for fatty acid synthesis*
- *Illustrate fatty acid biosynthesis and β-oxidation reactions and their reciprocal 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*

Active knowledge mastering goals

- *How are lipids digested, absorbed and transported?*
- *How are fatty acids "primed" and transported into the mitochondrion for □-oxidation?*
- *How is acetyl-CoA used for ketogenesis, or moved to the cytosol for fatty acid synthesis?*
- *How are lipolysis and lipogenesis mutually controlled? What do insulin and glucagon do?*
- *How is acetyl-CoA utilized to synthesize cholesterol? How is this pathway controlled?*
- *What is the pharmacological mechanism of statins?*

Knowledge activation goals

- *To be able to present and discuss digestion, absorption and transport of lipids, illustrate pathways and reactions of lipolysis and lipogenesis, explain how these processes are mutually controlled, describe ketogenesis and its physiological significance, describe cholesterol biosynthesis and its regulation, as a way to explain pharmacology of the statins.*

BIOCHEMISTRY. Nitrogen homeostasis and iron metabolism

Knowledge transfer goals

- *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 and general features of heme degradation*
- *Discuss how iron is adsorbed, transported and stored in the body*

Active knowledge mastering goals

- *What are the mechanisms of protein turnoves in the cell? What are the fates of nitrogen?*
- *How are amino acids catabolized? How are nonessential amino acids synthesized?*
- *How is heme broken down and synthesized?*
- *How is iron digested, absorbed and transported?*

Knowledge activation goals

- *To be able to critically discuss the major mechanisms of intracellular protein degradation, illustrate the metabolic flux of nitrogen and its excretion via the urea cycle, explain how and when amino acids feed glucogenic and/or ketogenic pathways, discuss heme metabolism and its dysregulation, present and explain iron hoemostasis.*

BIOCHEMISTRY. Nucleotide synthesis and degradation

Knowledge transfer goals

- *Delineate 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*

Active knowledge mastering goals

- *What are the major control points in the biosynthetic pathways of purine and pyrimidine nucleotides ?*
- *What are the catalytic mechanisms of ribonucleotide reductase and thymidylate synthase? Why are they pharmacologically relevant?*
- *How are nucleotides catabolized?*

Knowledge activation goals

- *To be able to present the pathways of synthesis and catabolism of nucleotides, with major regard to the reactions catalized by ribonucleotide reductase and thymidylate synthase.*

BIOCHEMISTRY. Biochemistry of synapses

Knowledge transfer goals

- describe the biosynthetic pathways of small nitrogen-containing neurotransmitters;
- discuss the mechanisms that control synthesis and availability of neurotransmitters;
- illustrate the proteolytical processing of model pro-neuropeptides to active peptides;
- discuss the post-synaptic density (PSD) as a protein-rich microdomain;
- understand the major differences between PSDs of excitatory and inhibitory synapses;
- describe structure/function of the PSD95-dependent molecular network in the excitatory PSD and the role of PSD95 in tuning neurotransmission.

Active knowledge mastering goals

- *How are neurotransmitters synthesized and catabolized? What are the major control points in these pathways?*
- *What are the primary ultrastructural themes of the post-synaptic densities of excitatory and inhibitory synapses? How do they support inter- and intra-cellular communications?*

Knowledge activation goals

- *To be able to describe and critically discuss synthesis and catabolism of neurotransmitters and ttheir control; illustrate ultrastructure and function of the post-synaptic densities*

BIOCHEMISTRY. An integrated view of fuel metabolism

Knowledge transfer goals:

- *Discuss the metabolic requirements of major organs*
- *Describe the opposed effects of insulin and glucagon/catecholamines on organ metabolism*
- *Illustrate the effects of AMP-dependent protein kinase on organ metabolism*
- *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, the key properties of preparative and analytical tools of metabolomics*

Active knowledge mastering goals

- *How does the human body adapt to starvation and stress?*
- *How do insulin, glucagon and epinephrine convey their biochemical messages?*
- *What is the role of the brain-gut axis in the hormonal control of appetite/satiety?*
- *How is metabolomics applied to the discovery of cancer biomarkers and unexpected metabolic links?*

Knowledge activation goals

- *To be able to explain how the human body metabolically adapts to starvation and stress, to describe the roles of insulin, glucagon and epinephrine, to critically present metabolic homeostasis and its dysregulations, to discuss novel applications of metabolomics.*

CELL PHYSIOLOGY. Control: regulation and change – Ion channels, receptors, signal transduction – Endocrine and neural controls

Knowledge transfer goals

- *Study the structure and function of ion channels, their regulation and role in the cell*
- *Study the distinct classes of receptors and their transduction mechanisms*

Active knowledge mastering goals

- *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*
- *Look for definitions of "genome", "transcriptome", "proteome": are these necessary and/or sufficient to define the differentiation, specialization and functional state of a cell?*

Knowledge Activation goals

- *To be able to explain how an ion channel can be selective for one or more ion species, in which modes it can be activated and regulated, how it can interfere with cellular processes*
- *To be able to explain how external signals can regulate intracellular functions, how they can cross-talk, how such regulations can operate on different time scales, be reversible or not*
- *Grasp how Ca^{2+} can simultaneously and differentially regulate many cellular processes*
- *To be able to explain how the capability of processing information evolved in nerve cells*

CELL PHYSIOLOGY. Electricity and Cellular bioelectricity

Knowledge transfer goals

- *Recapitulate the basic notions related to electric current, resistors, and capacitors*
- *Understand 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*

Active knowledge mastering goals

- *Elaborate the expected membrane potential changes in different extracellular solutions*
- *Try and predict the electrical behaviour of a cell membrane in response to current injection*
- *Reason on the factors that influence action potential conduction velocity*

Knowledge Activation goals

- *To be able to explain how ion movements determine the membrane potential, what is the role of the Na/K-ATPase, what is the meaning of Nernst equation and how Goldman equation predicts graded potentials*
- *To understand the static and dynamic behaviour of membrane capacitance and be able to explain its contribution to the electric behaviour of the neuron*

CELL PHYSIOLOGY. Intercellular communication

Learning goals

- *Study the structure and functioning of electric synapses and chemical synapses*
- *Study the neuromuscular junction (NMJ) as a paradigmatic system: quantal release, miniaturised and evoked EPPs; the differences between the NMJ and central synapses; synaptic facilitation, potentiation and depression*
- *Study the synaptic vesicle cycle and the dynamics of SNARE complex assembly / disassembly*
- *Study the classification of neurotransmitter receptors, their transduction paths, their distributions and their cellular roles*
- *Study the principles of spatial and temporal integration and how the spike encoder works*
- *Review the work by Kandel on Aplysia, define 'synaptic plasticity' and study its mechanisms*

Active knowledge mastering goals

- *Predict what will be the postsynaptic response to the activation of different receptor-channels at various values of membrane potential*

Knowledge Activation goals

- *To gain a comprehensive understanding of the mechanisms that sustain and regulate synchronous and asynchronous quantal release of neurotransmitter*
- *To be able to explain the "linear" and "nonlinear" aspects of neuronal integration and the mechanisms of short, medium and long-term plasticity and of associative learning*
- *To understand mechanisms and advantages of frequency coding and synaptic gain modulation*
- *To gain an integrated perspective on the interconnection between bioelectric and biochemical processes*

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 – quizes, 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 – Face-to-face Lectures; 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.
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 & 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.

Assessment

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

Biochemistry

- 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)

Physiology

All the topics faced in this course are fully treated in:

- Molecular Biology of the Cell, 4th edition - Bruce Alberts, Rebecca Heald, Alexander Johnson, David Morgan, Martin Raff, Keith Roberts, Peter Walter – W.W. Norton & Company – UK, 2022.

Further textbooks for a deeper physiological perspective:

- 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.

Appendix

Class attendance

Class attendance is mandatory. Students who have attended <75% of the classes will be warned and reported to the Student Office. They make up for lost time, by presenting an elaborate and/or passing an oral interview or a written test, prior to the first exam session.
Severe cases will be dealt with by the College of Teachers according to University Policy.

Exams and recommendations for studying

The exams will focus on the topics presented in class, but might require the students to apply what they learned to different contexts. Therefore, the students should face the textbook asking themselves questions such as "Why so?", "Is this relevant to other situations?"...
Possibly, the material of the class should be read in advance, to be able to reason and participate during the class, rather than write what is being said. Also, instead of reading and reading again the books and notes, students should discuss and try to explain to each other in their own words.
The students must carry out the exams in accordance with the principles of loyalty and integrity that are stated in the Student Code of Conduct of Humanitas University (https://www.hunimed.eu/content/uploads/2021/05/Students_Code_of_conduct.pdf). Academic dishonesty, with major regard to cheating on registration of attendance, will be immediately reported to the Student Office and dealt with by the College of Teachers.

Policy on Copyright and Intellectual Property

The materials provided in class are for the sole purpose of assisting the CFC students to learn and study. No material from this course may be redistributed without the written consent of the teachers. No material from this course may be uploaded or stored in off-campus websites or at any student organization repository.