VNIVERSITAT DE VALÈNCIA

Course Guide
43104 Molecular basis of development and liver function

COURSE DATA

Data Subject	
Code	43104
Name	Molecular basis of development and liver function
Cycle	Master's degree
ECTS Credits	4.5
Academic year	2021 - 2022

Study (s)

Degree	Center	Acad. year	Period
2142 - M.U. en Aproximaciones Moleculares CC Salud 12-V.2	Faculty of Biological Sciences	1	First term

Subject-matter

Degree	Subject-matter	Character
2142 - M.U. en Aproximaciones Moleculares CC Salud 12-V.2	3 - Biotransformation, metabolism of drugs and xenobiotics	Obligatory

Coordination

Name	Department
JOVER ATIENZA, RAMIRO	30 - Biochemistry and Molecular Biology
O'CONNOR BLASCO, JOSE ENRIQUE	30 - Biochemistry and Molecular Biology

SUMMARY

The liver is a highly differentiated organ that plays a key role in our body as it is the principal center of metabolism and homeostasis. The liver receives, processes and stores compounds absorbed from the gastrointestinal tract and releases metabolites from these compounds according to body needs. It has an essential role in the metabolism of carbohydrates, lipids, amino acids and bile acids; synthesizes most plasma proteins and cooperates with the immune system through the hepatic acute phase response. It is also the center of metabolism and biotransformation of drugs and xenobiotics, and the site where many hormones are broken. All these processes are tailored to the needs of the body and are highly regulated.

Because of its key role, the study of liver development and function, and the factors involved in its regulation, has become a very active area of basic research. Moreover, as liver disease have a high prevalence in our society, the research in hepatology has also become a very active area in biomedicine. The objective of this course is to make students know and understand the basic concepts, methods and techniques related to the molecular basis of liver development, regulation of liver functions and hepatic

phenotype, as well as for their related diseases.

PREVIOUS KNOWLEDGE

Relationship to other subjects of the same degree

There are no specified enrollment restrictions with other subjects of the curriculum.

Other requirements

None

OUTCOMES

2142 - M.U. en Aproximaciones Moleculares CC Salud 12-V.2

- Students should apply acquired knowledge to solve problems in unfamiliar contexts within their field of study, including multidisciplinary scenarios.
- Students should be able to integrate knowledge and address the complexity of making informed judgments based on incomplete or limited information, including reflections on the social and ethical responsibilities associated with the application of their knowledge and judgments.
- Students should communicate conclusions and underlying knowledge clearly and unambiguously to both specialized and non-specialized audiences.
- Students should demonstrate self-directed learning skills for continued academic growth.
- Students should possess and understand foundational knowledge that enables original thinking and research in the field.
- Conocer en profundidad y comprender la organización a nivel molecular de células, sistemas y procesos de relevancia en las Ciencias de la Salud.
- Conocer en profundidad y comprender las bases moleculares de la enfermedad.
- Conocer en profundidad y comprender las metodologías de investigación básica aplicables a las Ciencias de la Salud.
- Tener capacidad de analizar y sintetizar un problema.
- Tener capacidad de comunicación oral y escrita en una segunda lengua científica.
- Tener capacidad de localizar información.
- Tener capacidad de desarrollar un trabajo interdisciplinar.
- Conocer y comprender los conceptos básicos sobre las bases moleculares del desarrollo embrionario del hígado y del control del fenotipo hepático, así como las implicaciones clínicas derivadas de las alteraciones de estos procesos.

- Conocer, comprender y manejar en la práctica métodos y técnicas de biología molecular aplicados al estudio de la regulación del desarrollo y de la función hepática.
- Aprender a identificar, manejar y presentar adecuadamente en informes y exposiciones públicas, conocimientos existentes sobre aspectos básicos y clínicos de del desarrollo embrionario del hígado, el control génico de su fenotipo y la regulación del metabolismo hepático.
- Aprendizaje, manejo y presentación de informes y trabajos en exposición publica de las aplicaciones biomédicas de los conceptos farmacogenéticos en las distintas terapias actuales, usando como vehículo la lengua inglesa.

LEARNING OUTCOMES

- Have knowledge of the key role of the liver in our body as the metabolic center for excellence and key active site of homeostasis control.

- Have knowledge of embryonic development of the liver and the applications of progenitor cells in biomedicine.

- Identify the key mechanisms of transcriptional regulation in the long-term metabolic control and hepatic dysfunction.

- Identify the different families of transcription factors and their pleiotropic role in metabolism.

DESCRIPTION OF CONTENTS

1. Embryonic development of the liver

In this thematic unit we will explain morphogenetic mechanisms involved in the embryonic development of the liver. Introduce the structure of the liver, the cells that compose it and their embryonic origin.

2. Genes involved in liver development

In this unit we will study the development of the liver through the genes involved in the process. Transcription factors, signaling pathways and important stages.

3. Alternative sources of hepatocytes: progenitor, stem and reprogrammed cells (transdifferentiation)

Possible alternatives to human hepatocytes. Its applications depending on the method of cell production. Main advantages and disadvantage of each.

4. Metabolic liver functions and integration

Review of the functions of the liver and their integration into the overall context of the organism. Key issues and importance of hepatocyte-specific functions (cholesterol, plasma proteins, lipoproteins, bile acids, bilirubin, etc..).

5. Regulation of metabolism and liver functions

Review of general and specific mechanisms of regulation of hepatic metabolism. Examples of characteristic liver regulatory mechanisms in the short and long term.

6. Transcriptional and post-transcriptional regulation of gene expression in eukaryotes

Basic and advanced regulation of gene expression in eukaryotes at the transcriptional and post-transcriptional levels. Basic and advanced aspects of epigenetic regulation.

7. Hepatic transcription factors, nuclear receptors and coactivators

Structural and dynamic characteristics of hepatic transcription factors. Classification. The nuclear receptor superfamily: main characteristics. Liver nuclear receptors and their metabolic connection. Other typical hepatic transcription factors: Examples and importance in metabolism and metabolic diseases.

8. Transcriptional regulation of liver endogenous functions and control of hepatic phenotype: PXR and CAR, the xenobiotic sensor nuclear receptors

From this thematic unit on we will begin the study of a number of regulatory processes, directed by transcription factors, which are key in different liver metabolic contexts:
Nuclear receptors PXR and CAR, and its role in the regulation of xenobiotic metabolism and disposition. Role in drug-drug interactions. PXR and CAR in the control of energy metabolism, and bilirubin disposition.

9. The aromatic hydrocarbon receptor

he aromatic hydrocarbon receptor and its role in the metabolism and bioactivation of xenobiotics. Mechanism of activation and canonical and noncanonical signaling pathways. Implications in carcinogenesis.

10. Lipid metabolism and its regulation. Sterol-regulatory element binding proteins. PPARa and PPARg: the lipid sensor nuclear receptors

Routes of synthesis, storage and lipid oxidation in the liver. Regulation of cholesterol, fatty acid and triglyceride synthesis by SREBP factors. The nuclear receptor PPARa: fatty acid oxidation and transport, lipoprotein synthesis and glucose metabolism. The nuclear receptor PPARg: lipolysis of circulating triglycerides and accumulation in tissues. Ligands of PPARs: therapeutic use and adverse effects.

11. Cholesterol, bile salts and their regulation. Nuclear receptors LXR and FXR

Control of cholesterol homeostasis in the body. LXR: the oxysterol receptor and its functions. FXR: the bile acid receptor and its functions. Nuclear receptors LRH-1 and SHP. Interconnections and control of cholesterol catabolism. Other functions of LXR, FXR and SHP.

12. Other mechanisms of transcriptional control of energy homeostasis: FoxO1, CREB, PGC1a, FOXA1, CEBPs, HNF4A ...

FoxO1 and the control of gluconeogenesis by insulin. The CREB/PGC1a pathway and the control of gluconeogenesis by glucagon. FOXA hepatic transcription factors. C/EBP and HNF4A: control of energy metabolism and consequences of their inactivation or deficiency.

13. Liver regeneration

Molecular processes in the different stages of liver regeneration. Hepatectomy. Cells involved. Regeneration in liver transplantation and hepatotoxicity.

14. Liver fibrosis

Liver Fibrosis: definition, causes and consequences. Molecular determinants. Cells involved. Experimental models. New therapeutic strategies.

15. Nonalcoholic fatty liver and steatohepatitis

Liver disease by fat accumulation (non-alcoholic fatty liver disease): definition, causes and consequences. Prevalence and grades. Metabolic origin and basis of iatrogenic fatty liver by drugs. Molecular determinants. Transcriptional mechanisms involved: canonical and noncanonical pathways.

WORKLOAD

ACTIVITY	Hours	% To be attended
Theory classes	20,00	100
Seminars	10,00	100
Graduation project		100
Laboratory practices	5,00	100
Development of group work	37,50	0
Study and independent work	30,00	0
TOTAL	**102,50**	

TEACHING METHODOLOGY

Teaching of this matter will be carried out by the following methodological approaches: teacher lectures, seminars and practical sessions; seminars by the students and tutoring assistance.
During lectures an overview of the topic will be presented, with special emphasis on the key concepts. The teacher will indicate the most appropriate resources for a more in depth study of the subject, so that students can complete their education.
The subject is devised to be developed in both classroom attendance and homework.

EVALUATION

Assessment of student learning will be made by the following criteria:

1. A theoretical examination with multiple-choice questions to be held in the classroom. This test will be worth 50% of the grade and will be made after finishing classes in the semester in which the course is taught.

2. In addition the student will prepare a seminar on a topic chosen in relation to the explained theoretical concepts that will be worth 40% of the grade.

3. The teacher will also assess the interest in the subject, expressed as participation in organized discussions, the answers to teacher asked questions during the sessions, tutoring assistance and/or any other activity carried out by the student in relation to the subject. These concepts can account for up to 10% of the final grade.

The final grade for the course will be the sum of the grades in evaluation of the theoretical credits and additional activities as mentioned above.

REFERENCES

Basic

- The liver: biology and pathology. Editor: Irwin M. Arias; James L. Boyer; etc. Lippincott Williams & Wilkins, 2001.
- Desvergne B, Michalik L, Wahli W. Transcriptional regulation of metabolism. Physiol Rev. 2006; 86(2):465-514
- Pinzani M, Dooley JS, Lok ASF, Garcia-Tsao G. Sherlock's Diseases of the Liver and Biliary System. Wiley-Blackwell; 2018.
- Friedman L, Martin P. Handbook of Liver Disease. 4th ed. Elsevier Health Sciences; 2018

- Schiff ER, Maddrey WC, Reddy KR. Schiff's Diseases of the Liver. 12th ed. Newark: John Wiley & Sons, Incorporated; 2017
- Sanyal AJ, Terrault NA, Lindor KD, Boyer TD. Zakim and Boyer's Hepatology: A Textbook of Liver Disease. Seventh;7; ed. US: Elsevier; 2016.

Additional

- Manipulating the mouse embryo: a laboratory manual. Editor: Andras Nagy. Cold Spring Harbor (NY) : Cold Spring Harbor Laboratoty Press, 2003.
- Schrem H, Klempnauer J, Borlak J. Liver-enriched transcription factors in liver function and development. Part I: the hepatocyte nuclear factor network and liver-specific gene expression. Pharmacol Rev. 2002; 54(1):129-58.
- Schrem H, Klempnauer J, Borlak J. Liver-enriched transcription factors in liver function and development. Part II: the C/EBPs and D site-binding protein in cell cycle control, carcinogenesis, circadian gene regulation, liver regeneration, apoptosis, and liver-specific gene regulation. Pharmacol Rev. 2004; 56(2):291-330.

ADDENDUM COVID-19

This addendum will only be activated if the health situation requires so and with the prior agreement of the Governing Council

In the event that the health situation so requires:

A) Face-to-face teaching will be replaced by online teaching, through synchronous or asynchronous presentations by teachers of the teaching materials, using the tools made available to teachers and students in the Virtual Classroom.

B) The tutorials will be carried out exclusively telematically.

C) The final evaluation of the subject will be done through an online test.