Lecture 12. Regulomics and metabolomics.

Learning outcomes:
1. Give the definition to the terms “metabolites”, “metabolism”, “regulome”, “regulomics”, “metabolome”, “metabolomics”.
2. Explain the mechanisms of enzyme activity regulation, give the specific examples.
3. Briefly describe the metabolism of all organic and non-organic substances in human organism (metabolism of proteins, carbohydrates, lypids, minerals, salts and water) and its regulation (hormonal, neural and biochemical).
4. Characterize the methods of research the metabolism.
5. Explain how metabolic disturbances connected with different human diseases, give the specific examples.

Metabolomics is the scientific study of chemical processes involving **metabolites**, the **small molecule substrates**, **intermediates** and **products of cell metabolism**. Specifically, metabolomics is the "**systematic study of the unique chemical fingerprints that specific cellular processes leave behind**", the study of their small-molecule metabolite profiles. The **metabolome** represents the **complete set of metabolites** in a biological cell, tissue, organ or organism, which are the end products of cellular processes. Messenger RNA (mRNA), gene expression data and proteomic analyses reveal the set of gene products being produced in the cell, data that represents one aspect of cellular function. Conversely, metabolic profiling can give an instantaneous snapshot of the physiology of that cell, and thus, metabolomics provides a direct "functional readout of the physiological state" of an organism. One of the challenges of systems biology and functional genomics is to integrate genomics, transcriptomic, proteomic, and metabolomic information to provide a better understanding of cellular biology.
Metabolism (/məˈtæbəlɪzəm/, from Greek: μεταβολή metabolē, "change") is **the set of life-sustaining chemical reactions in organisms**. The **three main purposes of metabolism** are: the **conversion of food to energy** to run cellular processes; the **conversion of food/fuel to building blocks for proteins, lipids, nucleic acids, and some carbohydrates; and the elimination of metabolic wastes**. These enzyme-catalyzed reactions allow organisms to grow and reproduce, maintain their structures, and respond to their environments. The word metabolism can also refer to the sum of all chemical reactions that occur in living organisms, including digestion and the transport of substances into and between different cells, in which case the above described set of reactions within the cells is called intermediary metabolism or intermediate metabolism. In various diseases, such as type II diabetes, metabolic syndrome, and cancer, normal metabolism is disrupted.
Metabolic reactions may be categorized as **catabolic** – the breaking down of compounds (for example, the breaking down of glucose to pyruvate by cellular respiration); or **anabolic** – the building up (synthesis) of compounds (such as proteins, carbohydrates, lipids, and nucleic acids). Usually, catabolism releases energy, and anabolism consumes energy.
The chemical reactions of metabolism are organized into metabolic pathways, in which one chemical is transformed through a series of steps into another chemical, each step being facilitated by a specific enzyme. **Enzymes** are crucial to metabolism because they allow organisms to drive desirable reactions that require energy that will not occur by themselves, by coupling them to spontaneous reactions that release energy. Enzymes act as catalysts – they allow a reaction to proceed more rapidly – and they also allow the regulation of the rate of a metabolic reaction, for example in response to changes in the cell's environment or to signals from other cells.
Regulome refers to the **whole set of regulatory components** in a cell. Those components can be **regulatory elements, genes, mRNAs, proteins, and metabolites**. The description includes the interplay of regulatory effects between these components, and their dependence on variables such as subcellular localization, tissue, developmental stage, and pathological state. So

regulomics studies the **transcription factors** and other molecules involved in the **regulation of gene expression.**

Enzymes can be either **activated** or **inhibited** by other molecules. For example, the end product(s) of a metabolic pathway are often inhibitors for one of the first enzymes of the pathway (usually the first irreversible step, called committed step), thus regulating the amount of end product made by the pathways. Such a regulatory mechanism is called a negative feedback mechanism, because the amount of the end product produced is regulated by its own concentration. Negative feedback mechanism can effectively adjust the rate of synthesis of intermediate metabolites according to the demands of the cells. This helps with effective allocations of materials and energy economy, and it prevents the excess manufacture of end products. Like other homeostatic devices, the control of enzymatic action helps to maintain a stable internal environment in living organisms. **Factors affecting enzyme activity: pH, temperature, substrate concentration, allosteric regulation and inhibition.**

The typical workflow of metabolomics: samples are collected from tissue, plasma, urine, saliva, cells, etc. Next, metabolites extracted often with the addition of internal standards and **derivatization.[46]** During sample analysis, metabolites are quantified **(liquid chromatography or gas chromatography coupled with MS and/or NMR spectroscopy).** The raw output data can be used for metabolite feature extraction and further processed before statistical analysis (such as **PCA).** Many **bioinformatic tools and software** are available to identify associations with disease states and outcomes, determine significant correlations, and characterize metabolic signatures with existing biological knowledge. The **Human Metabolome Database (HMDB)** is perhaps the most extensive public metabolomic spectral database to date. The HMDB stores more than 40,000 different metabolite entries. They catalogued approximately 2500 metabolites, 1200 drugs and 3500 food components that can be found in the human body, as reported in the literature. This information, available at the Human Metabolome Database (**www.hmdb.ca**) and based on analysis of information available in the current scientific literature, is far from complete. In contrast, much more is known about the metabolomes of other organisms. For example, over 50,000 metabolites have been characterized from the plant kingdom, and many thousands of metabolites have been identified and/or characterized from single plants.

The questions for self - control:

1. What is the meaning of terms “metabolites”, “metabolism”, “regulome”, “regulomics”, “metabolome”, “metabolomics”?
2. Mechanisms of enzyme activity regulation.
3. Metabolism of all organic and non-organic substances in human organism and its regulation (hormonal, neural and biochemical).
4. Methods of metabolic research.
5. Human metabolic diseases.

Recommended readings:

1. Daviss B (April 2005). "Growing pains for metabolomics". The Scientist. 19 (8): 25–28.
2. Jordan KW, Nordenstam J, Lauwers GY, Rothenberger DA, Alavi K, Garwood M, Cheng LL (March 2009). "Metabolomic characterization of human rectal adenocarcinoma with intact tissue magnetic resonance spectroscopy". Diseases of the Colon and Rectum. 52 (3): 520–5. doi:10.1007/DCR.0b013e31819c9a2c. PMC 2720561. PMID 19333056.
3. Villate, Aitor; Nicolas, Markel San; Gallastegi, Mara; Aulas, Pierre-Antoine; Olivares, Maitane; Usobiaga, Aresatz; Etxebarria, Nestor; Aizpurua-Olaizola, Oier (2020-12-09). "Review: Metabolomics as a prediction tool for plants performance under environmental stress". Plant Science: 110789. doi:10.1016/j.plantsci.2020.110789. ISSN 0168-9452.

4. Hollywood K, Brison DR, Goodacre R (September 2006). "Metabolomics: current technologies and future trends". Proteomics. 6 (17): 4716–23. doi:10.1002/pmic.200600106. PMID 16888765. S2CID 14631544.
5. Smith, Reuben L; Soeters, Maarten R; Wüst, Rob C I; Houtkooper, Riekelt H (24 April 2018). "Metabolic flexibility as an adaptation to energy resources and requirements in health and disease". Endocrine Reviews. 39 (4): 489–517. doi:10.1210/er.2017-00211. ISSN 0163-769X. PMC 6093334. PMID 29697773.
6. Suzuki H (2015). "Chapter 8: Control of Enzyme Activity". How Enzymes Work: From Structure to Function. Boca Raton, FL: CRC Press. pp. 141–69. ISBN 978-981-4463-92-8.
7. Dettmer K, Aronov PA, Hammock BD (2007). "Mass spectrometry-based metabolomics". Mass Spectrometry Reviews. 26 (1): 51–78. Bibcode:2007MSRv...26...51D. doi:10.1002/mas.20108. PMC 1904337. PMID 16921475.
8. Rasmiena AA, Ng TW, Meikle PJ (March 2013). "Metabolomics and ischaemic heart disease". Clinical Science. 124 (5): 289–306. doi:10.1042/CS20120268. PMID 23157406.
9. HMDB 3.0 – the human metabolome database in 2013.
10. Pearson H (March 2007). "Meet the human metabolome". Nature. 446 (7131): 8. Bibcode:2007Natur.446....8P. doi:10.1038/446008a. PMID 17330009. S2CID 2235062.
11. De Luca V, St Pierre B (April 2000). "The cell and developmental biology of alkaloid biosynthesis". Trends in Plant Science. 5 (4): 168–73. doi:10.1016/S1360-1385(00)01575-2. PMID 10740298.
12. Griffin JL, Shockcor JP (July 2004). "Metabolic profiles of cancer cells". Nature Reviews. Cancer. 4 (7): 551–61. doi:10.1038/nrc1390. PMID 15229480. S2CID 527894.