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BIOMEDICAL ENGINEERING AND PROTEOMICS

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Abstract: The term "proteomics" was created in 1997, by analogy of genomics, genome studies. "Proteom" refers to a mixture of proteins and genome and was created by Marcom Wilkins in 1994. Proteomics is the large-scale study of proteins, particularly their structures and functions. Proteins are vital parts of living organisms, as they are the main components of the physiological metabolic pathways of cells. After genomics and transcriptomics, proteomics is the “next step” in the study of biological systems. It is more complicated than genomics because an organism's genome is approximated by the constant, whereas the proteome differs from cell to cell and from time to time. Distinct genes are expressed in different cell types, which means that even the basic set of proteins that are produced in a cell needs to be identified.

1 Defining proteomics goals

Protein study, determination of its amount, primary structure, higher structures, their functions and changes under different conditions is not a new task of biological sciences. At the turn of the 20th and 21st centuries, however, two new moments began to be more prominent in this endeavor. Despite the significant contribution of molecular genetics to many issues, we still can not give a satisfactory response, including the answer to the question of how and how many genes a function performs. If one gene only corresponds to one final product, then one would have no more than 25,000 proteins. Since proteins are the centerpiece in understanding cellular functions as well as disease processes, without knowing the relationship between genes and proteins, it is not possible to make effective use of the knowledge of the genomic era. In 1994, the role of proteomics was defined as the identification and characterization of all proteins expressed in the organism, but it soon became apparent that its role was also to determine the amount, function, localization and post-translational modification of these proteins present in the cell at a given moment. The truth has not been as well defined because it has not evaluated the effect of envirobiomechanical, metabolic, pharmacological, genetic and pathological conditions on the proteome. We can summarize that the goal of proteomics is to get a global and integrated view of biology by studying the complete cell protein network rather than by studying individual proteins. The second goal is not only to identify proteins, but also to understand their function and structure and to create a 3D map of the cells (to determine the localization of the individual proteins). Another significant milestone for the above-mentioned goals has also been the unprecedented methodological possibilities of separation and analysis of proteins using a robust technique that is able to provide the desired proteomic data much faster, more reliably and more accurately.

Today, we are aware that the path from genomics to proteomics would not have been possible without the application of improved bioengineering techniques using mass spectrometry principles. There is probably no other current technique that would overcome the mass spectrometer in a variety of applications in basic and applied research as well as in diagnostics [1].

2 Why is not the number of proteins consistent with the number of genes?

Thanks to molecular genetics and its methods we know the composition of the genome (nucleotide sequence) of many microorganisms, model higher organisms as well as genome of its own kind. However, the nucleotide structure of the gene is only a chemical information template. And although this information for knowledge and practice is extremely valuable, it does not give a satisfactory answer to the question of what is in fact the functional radius of this information. We know that the genome consists of only about 25,000 genes and not 100,000 than originally assumed. On the other hand, there are estimates that the total number of protein variants, including post-translational ones, can be as high as 300,000 in humans. How could more proteins be produced from a given number of genes? Current known solutions to this paradox are at the RNA level as well as at the level of the synthesized proteins.

One answer is that each gene can encode more proteins in a process called alternate splicing. Alternative splicing means that one gene can produce different mRNA products, and thus different proteins. Another answer is that one protein can be chemically modified after it is

synthesized so as to obtain another function. The third answer is that proteins interact with each other in complex ways that could change their function. Thus, one gene can produce several, functionally different proteins in many different ways.

The known mechanisms of the formation of functionally different protein variants by post-translational processing include acetylation, phosphorylation, adenylation, adenosyl ribosylation, glycosylation and the like. Other changes may be caused by cleavage of a part of the chain or modification of the amino acid residues [1]. Some primary transcripts (for mRNA) undergo alternate splicing, which will allow the formation of two or more types of mRNA. Polyadenylation may also affect the final mRNA structure. These processes are illustrated in Figure 1.

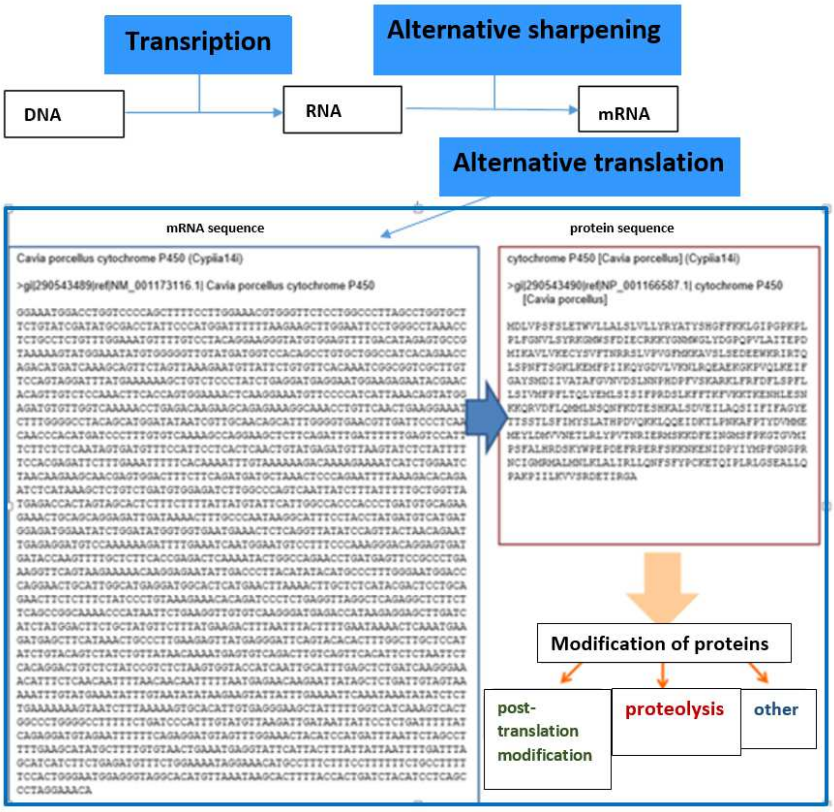

Figure 1 The emergence of different proteins.

3 Proteins

Proteins are polymer chains composed of monomers called amino acids. Proteins are an essential part of every biological system and participate in every process in the cell. Together with nucleic acids, lipids and sugars, they form a group of biopolymers that condition the existence of living systems.

Functions and importance of proteins: Enzyme proteins - biocatalysts of many chemical reactions in biological systems, transport proteins - transfer of necessary substances to preserve life inside the biological organism (myoglobin, hemoglobin, serum albumin). Protective proteins - Protective function (immunoglobulins), regulatory proteins - hormones - control and regulation molecules (insulin, somatotropin, growth hormones), structural proteins (collagen, elastin) and receptor proteins - serving as external signal receptors.

We distinguish four protein structures (Figure 2): primary structure - amino acid sequence in the polypeptide chain, secondary structure - local 3-D "folding" of the polypeptide chain - the most commonly occurring structures: α-helix, - a loop, a tertiary structure - the total 3-D structure of the polypeptide, comprising a spatial arrangement of the side chains and the geometry of the arrangement between the distant portions of the polypeptide chain and the quaternary structure - the mutual arrangement of several polypeptides in the protein [2-4].

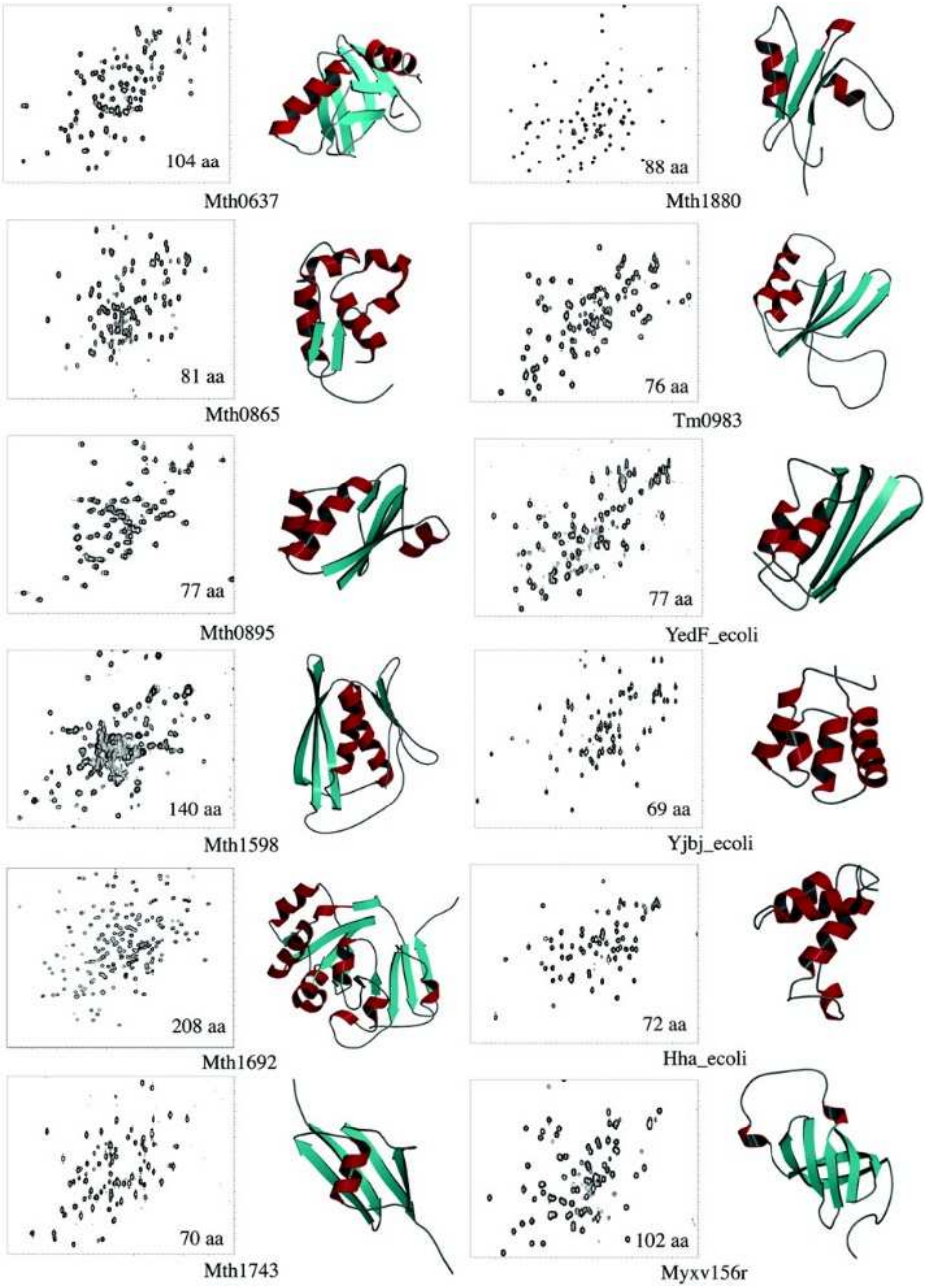

Figure 2 Protein structures [2,3]

3.1 Protein folding

Protein folding is a physical process in which the polypeptide chain is packed into a characteristic 3D structure for a given protein (Figure 3). The mechanism of the folding protein has not yet been explicitly explained, and this remains one of the most attractive unresolved problems in science. The 3D structure of proteins is determined by the amino acid sequence in the polypeptide chain under the physicochemical conditions (temperature, pH, ionic strength, solvent type).

It is generally accepted that the minimization of hydrophobic amino acid contacts with water molecules is the "driving force" of the packaging process, but the contribution of other interactions must also be taken into account (in particular, the formation of hydrogen bonds between the amino acid residues together as well as the binding of these molecules with the solvent molecules). The process of in-vivo protein packaging often takes place during the synthesis of the polypeptide chain on ribosomes. The N-terminus of this chain is already bundled while the C-terminus of the polypeptide is still synthesized. In this process, chaperones play a very important role. Chaperones are molecules (of protein origin) that allow proper packaging of proteins in vivo and prevent the formation of protein aggregates. The rate of protein aggregation depends on the size of the protein and the outer

packing conditions. Small single-domain proteins are able to acquire their native 3D structure in a few milliseconds. Packing large multisubunit proteins takes place over several intermediates and can take several dozen minutes or even hours. The number of possible different conformations of the polypeptide chain is very large (e.g., for a polypeptide consisting of 300 amino acids this number is 10 143). So, if the process of protein collision was randomized through all the possible conformational states, it would take this process for a long time (time longer than the age of the universe), but the proteins are getting too quickly - the Levinthal paradox. It is clear that the folding protein can not be accomplished by randomly searching for the "correct" conformational state of the protein. Incorrectly packed proteins are responsible for several inflammatory diseases: Creutzfeldt-Jacobs disease, bovine spongiform encephalopathy, amyloid plaque formation and spleen (Alzheimer's disease). All of these diseases are caused by the formation of aggregates of improperly packed proteins. In the case of Alzheimer's disease, it is the formation of amyloid plaques from the amyloid B protein (the proteolytic product of the amyloid precursor protein). At high concentrations, these proteins change their tertiary structure, resulting in their aggregation. The amyloid plaques thus formed are deposited around the neurons [4].

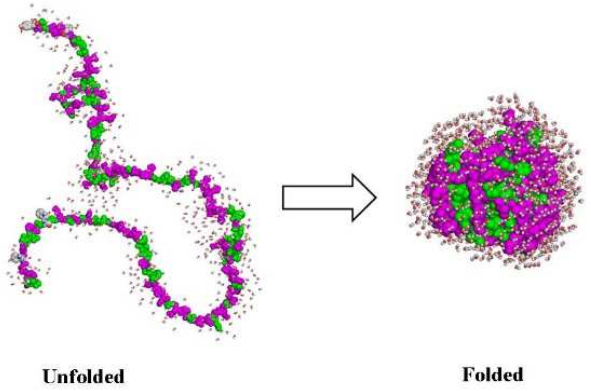

Figure 3 Protein folding [5]

4 Scheme of current proteomics

Figure 4 shows a graphical representation of proteomics and its other disciplines.

Structural proteomics - its goal should be to determine the structure, the amount of proteins including the proportion of post-translationally modified molecules, the mutual protein interactions, as well as the relationship of protein variants to the structure of the gene. It may also lead to the creation of protein maps for different cell types with different physiological and pathological conditions.

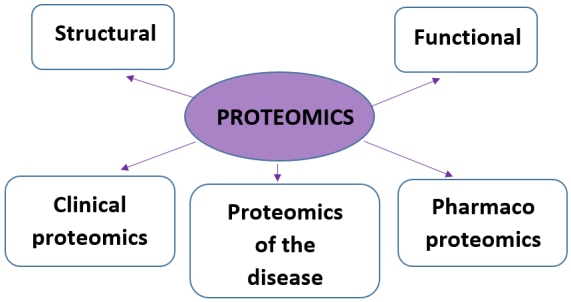

Figure 4 Current proteomics

Functional Proteomics - The amount of individual proteins is affected by transcription factors. These are factors that enter the nucleus and bind to specific DNA segments (enhancers, promoters). These factors can interact directly or indirectly with the transcription apparatus. Furthermore, there is the influence of epigenetic factors (imprints caused by different gene-methylation methylation). Functional state of proteins can be explained by post-translational modifications of proteins, especially phosphorylation, glycosylation. Functional proteomics will help to elucidate enzyme catalysis, transport functions, immunity, nerve impulse transmission, growth regulation, and cell differentiation. It could also help explain the processes of aging and the different predisposition to disease.

Proteomics of the disease - has the potential to capture pathology at an early stage, to determine more precisely the etiopathogenesis and individual variability of molecular phenomena. It will play an important role in elucidating the mechanisms of cancer, neurodegenerative, psychological (Alzheimer's, Parkinson's disease, schizophrenia), inflammatory and metabolic diseases. The fastest development can be observed in oncoproteomics. Survival, Growth, Invasiveness of Tumor Cells - At the root of the genetic defect, there must also be alteration of functional proteins. The proteomic approach will provide important information about altered cellular signaling paths.

Clinical Proteomics - The goal is to discover, find proteins that will be of medical significance. These are proteins that can be used as diagnostic markers because their expression under specific physiological and pathological conditions will be significantly increased (inflammatory, infectious, cancerous). Comparing the sensitivity and specificity parameters of most of the onome markers with proteomic markers favor the use of proteomic markers.

Pharmacoproteomics - Knowing specific proteomic changes in various diseases can influence the decision to select appropriate therapy. At the same time, therapy efficacy and toxicity could be monitored at the level of protein spectrum changes and their functional status [1].

Conclusions

Nowadays proteomics is not applied in the Slovak Republic either in medical-oriented research or in clinical practice. Our aim is to provide information on the current possibilities of proteomics, but also to point out weaknesses in the development of this department in the SR. The advancement of the company in strategic sectors such as proteomics is a strong support for both medical and biomedical engineering applications [1].

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