Mapping proteins in space and time within cells

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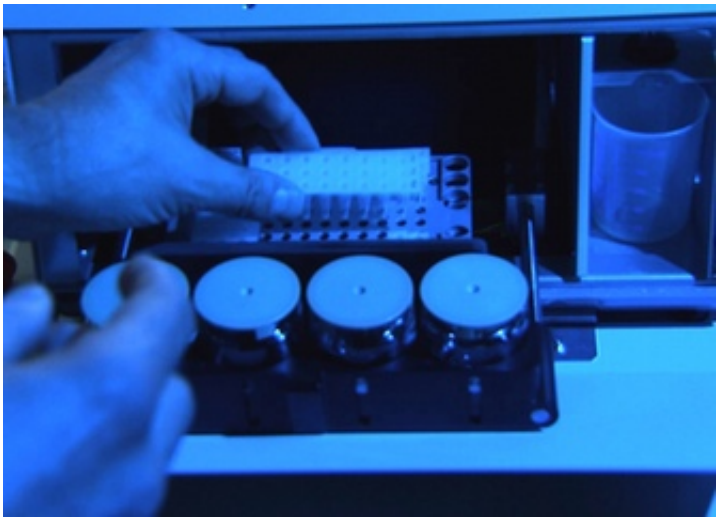

How many types of proteins are there in a cell? How many of each type are there and where are they at any given time? New methods may shed light on these fundamental biological questions.

The human genome and those of several other organisms have been mapped. But it is proteins that perform the majority of biological functions within every organism. Yet knowing the diversity of protein types inside cells, how many of each type there are and where they are at any given time, remains a major scientific challenge. Now, the EU-funded project PROSPECTS, completed in 2013, may have provided

further insights into these fundamental questions by using novel technologies.

"No one really knows how a living organism functions in its entirety", says project partner Ruedi Aebersold, professor at the Institute for Molecular Systems Biology at the ETH Zürich, in Switzerland. Knowing where and when proteins are located will help scientists better understand cellular processes and disease mechanisms.

According to Aebersold about 14,000 to 15,000 different types of human protein have been mapped. "The vast majority of proteins that are expressed in a particular cell can be identified and to some extent quantified. The project has made significant contribution and progress in this area," he says. But people should not carry over their thinking from genomics to proteomics. "It makes sense to map the genome sequence. It is stable and quite similar among cells and cell types. But this is different with proteins. The proteome constantly changes as a reflection of the cells' function and state," Aebersold tells youris.com.

Another issue is that each gene locus, that is a particular DNA sequence on a chromosome, can produce several to hundreds of protein variants through so-called post-translational modifications. "If you are concerned with the proteome you need to characterise these variations," Aebersold says. The project scientists therefore applied advanced methodologies, such as mass spectrometry, electron microscopy and cell imaging to capture the location of proteins in time and space. And the project data is available through various databases.

However, it is only the beginning of a long path towards proteins' understanding. "It certainly remains a challenge to figure out what is actually the diversity of the proteome in a cell," Aebersold says. "It is interesting to map the proteome, but it will be an abstract database. The value of the map is to facilitate identifying the acute state of the

proteome," he tells youris.com. Aebersold explains that comparing the proteome of cells in different states, such as in a healthy cell and in a cancer cell could help identify new therapeutic targets.

But there are concerns regarding how useful the project might be. Due to rapid technological advances, data obtained five years ago may be "no longer of interest because they cannot be reproduced", says Helmut Meyer, head of the Medical Proteome Center at the Ruhr-Universität Bochum, in Germany. While he considers the consortium's work as "scientifically excellent" he doubts whether the mere collection of protein data will be useful for medical purposes. "If it comes to clinical applications, you have to know exactly what you are looking for," comments Meyer. He stresses that the high biological variability of proteins is even enhanced in a diseased state. "Instead of mapping all proteins, researchers should specifically look for markers based on carefully conducted pathological analyses," he tells youris.com.

However, another expert applauds the project's work. "The project consortium has done a tremendous effort," comments Kathryn Lilley, director of the Cambridge Centre for Proteomics at the University of Cambridge, UK. "It has advanced the field on various fronts" she tells youris.com. She particularly appreciates the methodological advancements and the project's contribution to the mapping of the human proteome as pushed forward by the Human Protein Organisation (HUPO). She also compares it with a related project. The Human Protein Atlas, run by Swedish project partners, offers "a hypothesis testing scenario," she points out. This database contains a library of antibodies that can be used to target specific proteins for specific research questions. The proteome database directed by the project's coordinator Matthias Mann of the Max Planck Institute of Biochemistry in Martinsried, in Germany, greatly facilitates "hypotheses generating studies" she adds.

According to Lilley, the project has advanced the spatial mapping of proteins and the development of software tools to study time-dependent changes in protein dynamics. However, "these focussed on only a few biological systems. There is still much to do to fully interpret the spatial organisation of the cell, but this is a tricky thing to do," she tells youris.com. She does see potential medical benefit down the road. This kind of data collecting research "paves the way for applications to a great many clinical studies, " she notes and concludes: "If you are interested in comparing proteins between healthy and sick tissue, you have to start somewhere."

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