Filling in the gaps on the protein map

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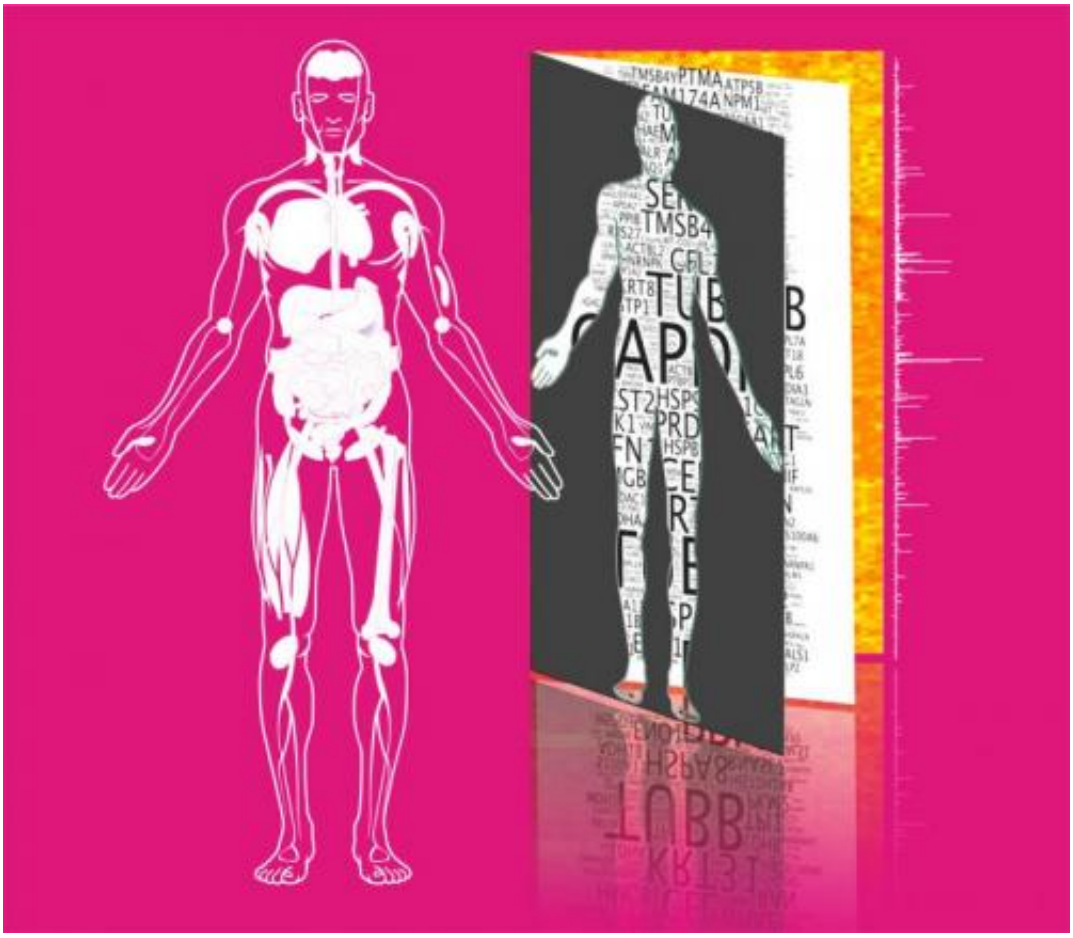

Using a technique termed mass-spectrometry-based proteomics, TUM researchers generated a first comprehensive draft map of the all proteins in the human body and made their results available via proteomicsdb.org. Credit: H. Hahne/TUM, BioJS

Substantial progress has been made in decoding the human proteome.

Under the leadership of the Technische Universität München researchers have now mapped more than 18,000 human proteins—92 percent of the entire proteome. Their work has also delivered fascinating insights into the interplay of DNA, RNA and proteins as the main molecular players of life. The team is presenting its findings in the latest edition of *Nature*.

By cataloging over 18,000 proteins, researchers from TUM have produced an almost complete inventory of the human proteome. This information is now freely available in the ProteomicsDB database, which is a joint development of TUM and software company SAP. The database includes information for example on the types, distribution, and abundance of proteins in various cells and tissues as well as in body fluids.

The investigations show that, on the one hand, around 10,000 proteins are concerned with housekeeping processes in many different places. On the other hand, it was also found that the protein profile of every organ is unique and essential for its function. Two high-performance technologies were instrumental for the success of the project – mass spectrometry and in-memory computing.

From blueprint to protein: RNA determines copy numbers

How does a protein arise from a gene? The answer is that it takes several steps for the DNA blueprint to be transcribed into an RNA copy. These messenger RNA (mRNA) molecules then act as a template for the production of a protein. In their study, the researchers demonstrated that each mRNA determines the number of protein copies to be produced by the cell.

This "copying key" is specific to each protein. "It appears that every

mRNA molecule knows the unit amount for its protein – so it knows whether to produce 10, 100 or 1,000 copies," explains Prof. Bernhard Küster of the TUM Chair of Proteomics and Bioanalytics. "Since we now know this ratio for a large number of proteins, we can infer protein abundance from mRNA abundance in just about every tissue – and vice versa."

New genes – old genes

Using a technique termed mass-spectrometry-based proteomics, TUM researchers generated a first comprehensive draft map of the all proteins in the human body and made their results available via proteomicsdb.org. Credit: Frank Weisbrodt/Cellzome

The researchers were very surprised to discover hundreds of protein fragments that are encoded by DNA outside of currently known genes. These new proteins potentially possess novel biological properties and functions, but the relevance of which is not yet understood.

In contrast, the scientists have so far been unable to locate around 2,000 proteins which ought to exist according to the gene map. Some of these proteins may only exist during embryonic development. However, it also seems that many known genes have become non-functional. This particularly affects olfactory receptors– an indication that modern humans no longer rely on a sophisticated sense of smell to survive.

"We might be watching evolution in action here," declares Küster. "The human organism deactivates superfluous genes – and tests new gene prototypes at the same time." That being the case, it might never be possible to determine exactly how many proteins there are in the human body.

Protein profiles predict drug sensitivity

Earlier studies have shown that specific protein patterns can predict the efficacy of a given drug. In this latest research, the scientists examined 24 cancer drugs whose effectiveness against 35 cancer cell lines were found to correlate strongly with their protein profiles.

According to Küster, "This edges us a little bit closer to the individualized treatment of patients. If we knew the protein profile of a tumor in detail, we might be able to administer drugs in a more targeted way. The new insights also allow medical researchers to investigate combinations of drugs and, thereby, tailoring treatments even more closely to a patient's individual needs."

More information: Mathias Wilhelm, Judith Schlegl, Hannes Hahne,

Amin Moghaddas Gholami, Marcus Lieberenz, Mikhail M. Savitski, Emanuel Ziegler, Lars Butzmann, Siegfried Gessulat, Harald Marx, Toby Mathieson, Simone Lemeer, Karsten Schnatbaum, Ulf Reimer, Holger Wenschuh, Martin Mollenhauer, Julia Slotta-Huspenina, Joos-Hendrik Boese, Marcus Bantscheff, Anja Gerstmair, Franz Faerber & Bernhard Küster, Mass-spectrometry-based draft of the human proteome; *Nature*, DOI: 10.1038/nature13319