"Structuromics": another step toward a holistic view of the cell

Levy, Emmanuel; Vogel, Christine

How to cite

LEVY, Emmanuel, VOGEL, Christine. "Structuromics": another step toward a holistic view of the cell. In: Cell, 2021, vol. 184, n° 2, p. 301–303. doi: 10.1016/j.cell.2020.12.030

This publication URL: https://archive-ouverte.unige.ch/unige:176900
Publication DOI: 10.1016/j.cell.2020.12.030

modulation of a voltage-gated sodium channel. J. Biol. Chem. *293*, 4981–4992.

Nguyen, H.M., Miyazaki, H., Hoshi, N., Smith, B.J., Nukina, N., Goldin, A.L., and Chandy, K.G. (2012). Modulation of voltage-gated K^+ channels by the sodium channel β1 subunit. Proc. Natl. Acad. Sci. USA *109*, 18577–18582.

Paulino, C., Kalienkova, V., Lam, A.K.M., Neldner, Y., and Dutzler, R. (2017). Activation mechanism of the calcium-activated chloride channel TMEM16A revealed by cryo-EM. Nature *552*, 421–425.

Pedemonte, N., and Galietta, L.J.V. (2014). Structure and function of TMEM16 proteins (anoctamins). Physiol. Rev. *94*, 419–459.

Sun, J., and MacKinnon, R. (2020). Structural Basis of Human KCNQ1 Modulation and Gating. Cell *180*, 340–347.e9.

Wang, Y., Eldstrom, J., and Fedida, D. (2020). Gating and Regulation of KCNQ1 and KCNQ1 + KCNE1 Channel Complexes. Front. Physiol. *11*, 504.

Yu, K., Jiang, T., Cui, Y., Tajkhorshid, E., and Hartzell, H.C. (2019). A network of phosphatidylinositol 4,5-bisphosphate binding sites regulates gating of the Ca^{2+}-activated Cl^- channel ANO1 (TMEM16A). Proc. Natl. Acad. Sci. USA *116*, 19952–19962.

"Structuromics": another step toward a holistic view of the cell

Emmanuel D. Levy[1,*] and Christine Vogel[2,*]
[1]Department of Structural Biology, Weizmann Institute of Science, Rehovot, Israel
[2]Department of Biology, New York University, NY, USA
*Correspondence: emmanuel.levy@weizmann.ac.il (E.D.L.), cvogel@nyu.edu (C.V.)
https://doi.org/10.1016/j.cell.2020.12.030

Large-scale mapping of protein structures and their different states is crucial for gaining a mechanistic understanding of proteome function and regulation. In this issue of *Cell*, Cappelletti et al. achieve such a feat and identify hundreds of protein structural changes in response to outside stressors, providing a rich "structuromics" resource characterizing cellular adaptation.

One of the oldest aspects of scientific inquiry, particularly in biology, is observation. This practice also applies to the study of proteins. When examining proteins, we aim to understand their activity, structure, dynamics, interactions, and modifications in response to a stimulus. Extensive characterization of the protein repertoire began with the genomics revolution and has been ongoing through "omics" approaches that quantify protein concentrations, modifications, and interactions in a high-throughput manner. Together, these data provide a comprehensive albeit static picture of proteomes. The next challenge now lies in revealing how changes in these characteristics, in response to stimuli, alter protein function and cellular processes (Figure 1).

Although current omics approaches probe changes in protein abundance to profile cellular responses, it has become increasingly clear that the structural remodeling of proteins is also an important factor. For example, upon exposure to sugar, the yeast glucokinase Glk1 changes structure to assemble into long filaments, which allows the cell to regulate the rate of glucose phosphorylation independently of enzyme concentration (Stoddard et al., 2020).

Several methods exist to determine protein structure at atomic resolution. However, these methods typically cannot operate on a large scale or directly observe proteins within functioning cells. Recent developments have started to bridge these gaps, with structure prediction tackling entire proteomes and experimental approaches aiming to peek at the structure of protein assemblies in their cellular context, e.g. Bäuerlein et al. (2017).

One such experimental approach is called limited proteolysis coupled to mass spectrometry, or LiP-MS (Feng et al., 2014). LiP-MS does not deliver a direct, atom-level picture of a protein structure but rather provides information on the structural changes that peptide segments within a protein undergo. Strikingly, LiP-MS can monitor thousands of proteins in complex mixtures such as cell lysates with just a few days of experimentation. It has, therefore, taken structure inference to the omics level, creating what we might call "structuromics" (Figure 1A) (Doerr, 2014).

The overall idea behind LiP-MS is straightforward: the residues in a protein structure that are shielded (e.g., by post-translational modifications, interactions with specific molecules, or with other parts of the structure) are less accessible to digestion by proteases than are other residues. This effect can be measured through timed proteolytic digest, whose resultant peptides are a reflection of their accessibility in the structure. The peptide products are then identified through mass spectrometry, allowing for efficient, quantitative, and reproducible profiling (Feng et al., 2014).

In this issue of *Cell*, Cappelletti et al. (2020) add a crucial expansion to the method. First, the authors demonstrate that LiP-MS can successfully identify structural changes occurring in the

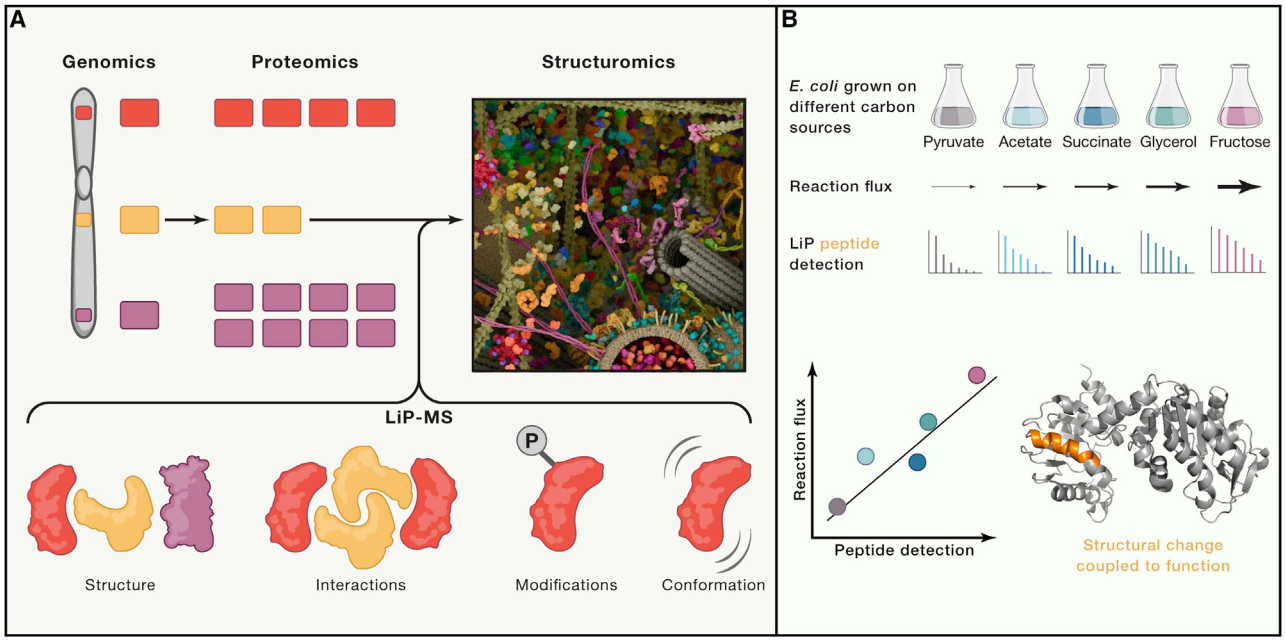

Figure 1. Toward a structural view of proteomes

(A) Genomics has advanced our holistic understanding of living systems by providing us with knowledge about the protein identities. Subsequently, proteomics revealed the relative protein abundances. This information can now be augmented with LiP-MS data, which captures information on the change in structure, interactions, post-translational modifications, and conformations of proteins. Ultimately, further advancing such methods is critical for gaining a detailed, structural view of cells and their processes.

(B) After growing *E. coli* on different carbon sources, the authors found a number of LiP peptides whose detection intensity scaled with the reaction flux of the respective enzyme. One such peptide in phosphoglycerate kinase is highlighted in orange in the protein's structure (PDB: 1ZMR). Credits: The image illustrating structuromics is an excerpt from *Cellular Landscape* by Evan Ingersoll & Gaël McGill, Ph.D. (Digizyme Inc. & Harvard Medical School).

proteomes of two species, baker's yeast (*Saccharomyces cerevisiae)* and the bacterium *Escherichia coli,* after they were exposed to a stress or change in nutrients. The authors go on to show that these changes are indeed biologically relevant through extensive mapping onto known data on post-translational modifications, enzymatic activity, aggregation, or interactions with other molecules. Doing so, the authors interpret the observed structural rearrangements through mechanisms of protein function regulation, including changes in enzymatic activity, metabolite binding, phosphorylation, aggregation, and protein-protein interactions.

In one such analysis, the authors grew *E. coli* on different carbon sources and through LiP-MS identified hundreds of proteins exhibiting a structural change. They identified structural changes in several enzymes of the central carbon metabolism and localized these changes close to the enzymes' active sites. Relating some of these changes to enzymatic function, the authors identified peptides whose intensity, i.e., abundance, across conditions changed in proportion to the flux in metabolic activity they belonged to (Figure 1B), testifying to the ability of LiP-MS to link structural changes to protein function. Importantly, the observed structural changes were independent of changes in protein abundance. For example, 10%–20% of the detected proteome in *S. cerevisiae* exhibited structural changes within minutes of a heat shock or osmotic stress, but only about 1% of them changed in abundance. This difference highlights that environmental cues can drive significant changes in protein structure and assembly before percolating to the transcription and translation. Even when *E. coli* were given more time to adapt to a range of carbon sources, 15%–25% of the proteins detected in their proteome underwent a change in structure, whereas only 3%–13% changed in abundance. This demonstrates that structural changes in proteomes serve to re-adjust protein function and cellular processes.

So, can LiP-MS really do everything at once? Yes it can, but its most exciting feature is also one of the work's limitations: although the method can detect structural changes originating from any mechanism, it cannot report on the type of mechanism, i.e., whether it was due to phosphorylation, protein aggregation, enzymatic activity, and so on. This information needs to be gained from orthogonal data. Furthermore, although certainly a crucial step toward structuromics analyses, at present, LiP-MS can only partially cover proteomes, due to the inherent limitation of mass spectrometry.

The new work by Cappelletti et al. (2020) represents an important milestone toward the rise of structuromics (Figure 1). Only a few other such approaches exist. One example is thermal proteome profiling (TPP) (Savitski et al., 2014), which assesses a different aspect of protein structure, i.e., a protein's thermal melting

point. As with LiP-MS, TPP allows for the rapid quantitation of thousands of proteins, in this case, with respect to their folding stability upon an increase in temperature. The change in melting point can reveal the binding of a small molecule or protein, but in contrast to LiP-MS, TPP does not inform on the location of the structural change.

Even more excitingly, the new work also illustrates how investigators are beginning to integrate several omics approaches to gain new insights from complementary data. Other such examples include the combination of LiP-MS with TPP and MS (Leuenberger et al., 2017) or the integration of proteomics with transcriptomics and translatomics data (Jovanovic et al., 2015) (Rendleman et al., 2018). This new form of exploration creates another field, that of "integromics" (Vitrinel et al., 2019), which represents another step toward understanding how molecules and their arrangements create the next level up in biological organization, that of the entire cell.

REFERENCES

Bäuerlein, F.J.B., Saha, I., Mishra, A., Kalemanov, M., Martínez-Sánchez, A., Klein, R., Dudanova, I., Hipp, M.S., Hartl, F.U., Baumeister, W., and Fernández-Busnadiego, R. (2017). In Situ Architecture and Cellular Interactions of PolyQ Inclusions. Cell *171*, 179–187.e10.

Cappelletti, V., Hauser, T., Piazza, I., Pepelnjak, M., Malinovska, L., Fuhrer, T., Li, Y., Dörig, C., Boersema, P., Gillet, L., et al. (2021). Dynamic 3D proteomes reveal protein functional alterations at high resolution in situ. Cell *184*, this issue, 545–559.

Doerr, A. (2014). Proteomics: Probing the protein structure-ome. Nat. Methods *11*, 1088–1089.

Feng, Y., De Franceschi, G., Kahraman, A., Soste, M., Melnik, A., Boersema, P.J., de Laureto, P.P., Nikolaev, Y., Oliveira, A.P., and Picotti, P. (2014). Global analysis of protein structural changes in complex proteomes. Nat. Biotechnol. *32*, 1036–1044.

Jovanovic, M., Rooney, M.S., Mertins, P., Przybylski, D., Chevrier, N., Satija, R., Rodriguez, E.H., Fields, A.P., Schwartz, S., Raychowdhury, R., et al. (2015). Immunogenetics. Dynamic profiling of the protein life cycle in response to pathogens. Science *347*, 1259038. Published online Feb 12, 2015.

Leuenberger, P., Ganscha, S., Kahraman, A., Cappelletti, V., Boersema, P.J., von Mering, C., Claassen, M., and Picotti, P. (2017). Cell-wide analysis of protein thermal unfolding reveals determinants of thermostability. Science *355*, 355.

Rendleman, J., Cheng, Z., Maity, S., Kastelic, N., Munschauer, M., Allgoewer, K., Teo, G., Zhang, Y.B.M., Lei, A., Parker, B., et al. (2018). New insights into the cellular temporal response to proteostatic stress. eLife *7*, e39054.

Savitski, M.M., Reinhard, F.B., Franken, H., Werner, T., Savitski, M.F., Eberhard, D., Martinez Molina, D., Jafari, R., Dovega, R.B., Klaeger, S., et al. (2014). Tracking cancer drugs in living cells by thermal profiling of the proteome. Science *346*, 1255784. Published online Oct 2, 2014.

Stoddard, P.R., Lynch, E.M., Farrell, D.P., Dosey, A.M., DiMaio, F., Williams, T.A., Kollman, J.M., Murray, A.W., and Garner, E.C. (2020). Polymerization in the actin ATPase clan regulates hexokinase activity in yeast. Science *367*, 1039–1042.

Vitrinel, B., Koh, H.W.L., Mujgan Kar, F., Maity, S., Rendleman, J., Choi, H., and Vogel, C. (2019). Exploiting Interdata Relationships in Next-generation Proteomics Analysis. Mol. Cell Proteomics *18*, S5–S14.

Fishing for the genetic basis of migratory behavior

Olivia S. Harringmeyer,[1] Maya L. Woolfolk,[1] and Hopi E. Hoekstra[1,*]
[1]Department of Organismic & Evolutionary Biology, Department of Molecular & Cellular Biology, Museum of Comparative Zoology, Howard Hughes Medical Institute, Harvard University, Cambridge, MA 02138, USA
*Correspondence: hoekstra@oeb.harvard.edu
https://doi.org/10.1016/j.cell.2020.12.037

For many species, migrating at just the right time is essential for both survival and reproduction. A new study in salmon localizes a small genomic region associated with migration timing, which in turn affects other physiological traits, suggesting that a seemingly complex suite of migration traits is linked by one "simple" phenotype.

Migration, the seasonal movement of animals from one habitat or region to another, occurs in nearly all major animal groups—from the iconic humpback whale that breeds in the tropics and then heads 9,000 km north to its feeding ground to the monarch butterfly whose migration is longer than its lifespan, so no one butterfly makes the entire trip. There exists striking variation in migration patterns even within species, which can be accompanied by changes in physiology, morphology, and/or other behaviors, often demarcating distinct migration "ecotypes." The tight link between migration pattern and other phenotypes is best exemplified by the approximately 100 species of diadromous fish that migrate between saltwater and freshwater. Chinook salmon, for example, exhibit multiple migratory ecotypes that repeatedly co-occur in rivers across the northwestern United States: early (winter and spring) migrators have higher fat contents, earlier spawning times, and smaller body sizes than late (fall and late fall) migrators. A