Guest Editorial

Highlight: GTP- and ATP-dependent membrane processes

DOI 10.1515/hsz-2017-0132

This Highlight Issue of *Biological Chemistry* publishes a wide selection of the results obtained within the research groups of the collaborative research centre Sonderforschungsbereich (SFB) 642 of the German Research Council (DFG). The SFB 642 contributed to a detailed understanding of GTP- and ATP-dependent signal transduction and transport processes at biological membranes at different scales. Single recombinant proteins up to complex protein-interaction networks in living cells have been studied. The complex, dynamic interplay between the proteins at membranes have been elucidated here with highest possible spatiotemporal resolution. The orchestration of expertise within the SFB 642 provided the unique opportunity to start with a detailed understanding of molecular reaction mechanisms and interactions of proteins *in vitro* in order to arrive at a thorough comprehension of how these processes are being integrated into the entire activity of the living cell. Determination of the three-dimensional structure of recombinant proteins *in vitro* is always a milestone in protein sciences, but the ultimate goal is the detailed understanding of the dynamic interplay of the proteins *in vivo*. As such a broad approach is a prerequisite to elucidate a biological issue of this complexity, a large consortium like the SFB was needed to succeed over different scales. Besides X-ray structure analysis and nuclear magnetic resonance (NMR)-spectroscopy also label-free time-resolved Fourier-Transform-Infra-Red (FTIR)-spectroscopy in combination with biomolecular simulations were the key experimental approaches by the SFB 642 to provide not only 'snapshots' but complete 'movies' of protein mechanisms and interactions. Chemical biology provides probes for fluorescence studies and drug candidates for a targeted therapy. Most of the projects were arranged around small GTPases of the Ras superfamily and their effectors. During the founding period PIs of the SFB 642 solved the structural models of 427 proteins deposited in the PDB data base, mostly of small G-proteins and their interaction partners. Furthermore, the projects contributed to a deeper understanding of the membrane insertion of small G-proteins, anchoring and extraction, especially by PDEδ. In addition Gα of heterotrimeric G-proteins which share the same G-domain motive with the Ras superfamily were studied. The results on GTPases are reported in Gerwert et al. (2017), Martín-Gago et al. (2017), Erwin et al. (2017), Goody et al. (2017), Koturenkiene et al. (2017), Schöpel et al. (2017), Potheraveedu et al. (2017), Vetter (2017), Ziehe et al. (2017) and Ulc et al. (2017), starting with molecular reaction mechanisms and interactions of small GTPases, their membrane lipidation and finally their role in the living cell as schematically illustrated in Figure 1.

Besides GTPases the structures and functions of membrane-bound ATPases, especially peroxisomal proteins, were also studied in great detail. These results are described in Schwerter et al. (2017), Bittner et al. (2017) and Reidick et al. (2017). The GTP- and ATP-dependent membrane processes were bridged by a central Project Z addressing proteome analysis, see the contribution by Lindemann et al. (2017). Mutations of the involved proteins can cause serious diseases. Thus, the issues addressed by SFB 642 provide a deeper understanding of these processes and contribute to precision medicine.

The principal investigators (Teilprojektleiter) of SFB 642 were recruited from the Ruhr-University Bochum, the Technical University Dortmund and the Max Planck Institute of Molecular Physiology in Dortmund. When it was established in 2004 SFB 642 was one of the first third-party financed consortiums within the later founded University Alliance Ruhr (UA Ruhr). In its 12-year funding period the consortium delivered 639 publications, 153 with impact factors above 9, and 174 common publications of which at least two PIs from different research groups of the SFB contributed. The generous €26.6 million funding of the DFG allowed us to promote a number of qualified young scientists. One hundred and nineteen graduate students performed their thesis within the SFB in an integrated research training group. Six younger PIs (Nachwuchsgruppenleiter) without permanent positions obtained tenure and became tenured Professors during the funding period at other universities.

SFB 642 has brought about structural changes at the Ruhr-University Bochum by being a precondition for the

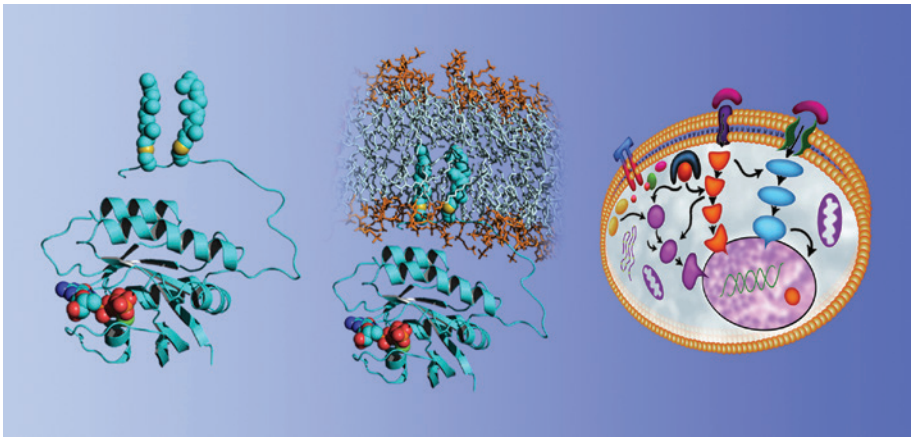

Figure 1: Schematic illustration of the Ras protein at different scales.
The isolated protein (left) and anchored membrane (middle) are both shown in atomic detail, (right) the schematic representation of the protein network by which Ras switches external signals to the nucleus in the living cell.

PURE consortium (Protein Research Unit RUHR within Europe) founded in 2010. In addition to the PIs from SFB 642 clinicians are also integrated into PURE to ensure that the results and techniques developed in protein research in basic science at SFB 642 are translated into clinical applications. In 2014 PURE successfully acquired third-party funding from the German Science Council (Wissenschaftsrat) for a new research building called ProDi (molecular *Pro*tein-*Di*agnostics). ProDi will host 153 basic science researchers and clinical researchers under one roof from 2018 on. The mission is the development of innovative methods, especially label-free vibrational imaging in combination with proteomics, which will monitor protein alterations as biomarkers for an early, precise and predictive diagnosis of oncological and neurodegenerative diseases.

The SFB has set milestones at the Ruhr-University Bochum and the UA Ruhr in the last 12 years. We are very grateful to the DFG for their funding and especially their reviewers for their fruitful advice over the past 12 years. SFB 642 is an illustrative example how the DFG can catalyze excellent science within universities using the SFB program and thereby induce long lasting structural changes within universities to improve their international visibility. SFB 642 also advises the DFG in its support of the SFB program as it is an excellent initiative and thereby supports outstanding research within the universities going forward.

We are grateful to the editorial staff of *Biological Chemistry*, in particular to the Managing Editor Torsten Krüger, who supported the publication of this Highlight Issue.

Funding: Deutsche Forschungsgemeinschaft, (Grant/Award Number: 'SFB 642').

References

Bittner, L.-M., Arends, J., and Narberhaus, F. (2017). When, how and why? Regulated proteolysis by the essential FtsH protease in *Escherichia coli*. Biol. Chem. *398*, 625–635.

Erwin, N., Patra, S., Dwivedi, M., Weise, K., and Winter, R. (2017). Influence of isoform-specific Ras lipidation motifs on protein partitioning and dynamics in model membrane systems of various complexity. Biol. Chem. *398*, 547–563.

Gerwert, K., Mann, D., and Kötting, C. (2017). Common mechanisms of catalysis in small and heterotrimeric GTPases and their respective GAPs. Biol. Chem. *398*, 523–533.

Goody, R.S., Müller, M.P., and Wu, Y.-W. (2017). Mechanisms of action of Rab proteins, key regulators of intracellular vesicular transport. Biol. Chem. *398*, 565–575.

Koturenkiene, A., Makbul, C., Herrmann, C., and Constantinescu-Aruxandei, D. (2017). Kinetic characterization of apoptotic Ras signalling through Nore1-MST1 complex formation. Biol. Chem. *398*, 701–707.

Lindemann, C., Thomanek, N., Hundt, F., Lerari, T., Meyer, H.E., Wolters, D., and Marcus, K. (2017). Strategies in relative and absolute quantitative mass spectrometry based proteomics. Biol. Chem. *398*, 687–699.

Martín-Gago, P., Fansa, E.K., Wittinghofer, A., and Waldmann, H. (2017). Structure-based development of PDEδ inhibitors. Biol. Chem. *398*, 535–545.

Potheraveedu, V.N., Schöpel, M., Stoll, R., and Heumann, R. (2017). Rheb in neuronal degeneration, regeneration, and connectivity. Biol. Chem. *398*, 589–606.

Reidick, C., Boutouja, F., and Platta, H.W. (2017). The class III phosphatidylinositol 3-kinase Vps34 in *Saccharomyces cerevisiae*. Biol. Chem. *398*, 677–685.

Schöpel, M., Potheraveedu, V.N., Al-Harthy, T., Abdel-Jalil, R., Heumann, R., and Stoll, R. (2017), The small GTPases Ras and Rheb studied by multidimensional NMR spectroscopy: structure and function. Biol. Chem. *398*, 577–588.

Schwerter, D.P., Grimm, I., Platta, H.W., and Erdmann, R. (2017). ATP-driven processes of peroxisomal matrix protein import. Biol. Chem. *398*, 607–624.

Ulc, A., Gottschling, C., Schäfer, I., Wegrzyn, D., van Leeuwen, S., Luft, V., Reinhard, J., and Faissner, A. (2017). Involvement of the guanine nucleotide exchange factor Vav3 in central nervous system development and plasticity. Biol. Chem. *398*, 663–675.

Vetter, I.R. (2017). Interface analysis of small GTP binding protein complexes suggests preferred membrane orientations. Biol. Chem. *398*, 637–651.

Ziehe, D., Dünschede, B., and Schünemann, D. (2017). From bacteria to chloroplasts: evolution of the chloroplast SRP system. Biol. Chem. *398*, 653–661.

Klaus Gerwert
Spokesman of SFB 642
Department of Biophysics
Ruhr-University Bochum
Universitätsstrasse 150, D-44801 Bochum, Germany
e-mail: gerwert@bph.rub.de, www.bph.rub.de