Quantitative proteomic analysis of regulated intramembrane proteolysis with QARIP web-server

Dmitry N. Ivankov[1], Natalya S. Bogatyreva[2], Peter Hönigschmid[1], Bastian Dislich[3,4], Sebastian Hogl[3,4], Peer-Hendrik Kuhn[3,4], Dmitrij Frishman[1,5,*], Stefan F. Lichtenthaler[3,4,6,*]

[1]*Department of Genome Oriented Bioinformatics, Technische Universität München, Wissenschaftszentrum Weihenstephan, Maximus-von-Imhof Forum 3, 85354 Freising, Germany,*
[2]*Laboratory of Protein Physics, Institute of Protein Research, Russian Academy of Sciences, Institutskaya Str. 4, 142290 Pushchino, Moscow Region, Russia,*
[3]*German Centre for Neurodegenerative Diseases (DZNE), Max Lebsche Platz 30, 81377 Munich, Germany,*
[4]*Neuroproteomics, Klinikum rechts der Isar, Technische Universität München, Max-Lebsche-Platz 30, 81377 Munich, Germany,*
[5]*Helmholtz Center Munich—German Research Center for Environmental Health (GmbH), Institute of Bioinformatics and Systems Biology, Ingolstädter Landstraße 1, D-85764 Neuherberg, Germany*
[6]*Munich Cluster for Systems Neurology (SyNergy), Adolf-Butenandt-Institut, Ludwig-Maximilians-Universität München, Schillerstrasse 44, 80336 Munich, Germany*

Regulated intramembrane proteolysis (RIP) is a critical mechanism for intercellular communication and regulates the function of membrane proteins through sequential proteolysis (1,2). RIP typically starts with ectodomain shedding of membrane proteins by extracellular membrane-bound proteases followed by intramembrane proteolysis of the resulting membrane-tethered fragment. However, for the majority of RIP proteases the corresponding substrates and thus, their functions, remain unknown. Proteome-wide identification of RIP protease substrates is possible by mass spectrometry-based quantitative comparison of RIP substrates or their cleavage products between different biological states. However, this requires quantification of peptides

from only the ectodomain or cytoplasmic domain. Current analysis software does not allow matching peptides to either domain.

Here we describe the QARIP (Quantitative Analysis of Regulated Intramembrane Proteolysis) web-server, available at http://webclu.bio.wzw.tum.de/qarip/, which matches identified peptides to the protein transmembrane topology (3). QARIP allows determination of quantitative ratios separately for the topological domains (cytoplasmic, ectodomain) of a given protein and is thus a powerful tool for quality control, improvement of quantitative ratios and identification of novel substrates in proteomic RIP datasets. To our knowledge, the QARIP web-server is the first tool directly addressing the phenomenon of regulated intramembrane proteolysis.

References

1. Lichtenthaler S.F., Haass C. and Steiner H. (2011) Regulated intramembrane proteolysis--lessons from amyloid precursor protein processing. *Journal of neurochemistry*, **117**, 779–96.
2. Brown M.S., Ye J., Rawson R.B. and Goldstein J.L. (2000) Regulated intramembrane proteolysis: a control mechanism conserved from bacteria to humans. *Cell*, **100**, 391–8.
3. Ivankov D.N., Bogatyreva N.S., Hönigschmid P., Dislich B., Hogl S., Kuhn P.-H., Frishman D., Lichtenthaler S.F. (2013) QARIP: a web server for quantitative proteomic analysis of regulated intramembrane proteolysis. *Nucl. Acids Res.,* doi: 10.1093/nar/gkt436.

Acknowledgements

DFG International Training and Research Group RECESS (Regulation and Evolution of Cellular Systems); Program “Molecular and Cellular Biology” of the Russian Academy of Sciences [01201358029]; DFG within the framework of the Munich Cluster for Systems Neurology [EXC 1010 SyNergy]; the BMBF project KNDD; Carl von Linde Junior Fellowship [TUM-IAS]. Funding for open access charge: DFG, Munich Cluster for Systems Neurology [EXC 1010 SyNergy].