Commentary

Neurodegener Dis 2013;11:215–218
DOI: 10.1159/000341594

Received: April 26, 2012
Accepted after revision: July 2, 2012
Published online: August 30, 2012

Meeting Report: 7th Fabisch Symposium for Cancer Research and Molecular Cell Biology – Regulated Intramembrane Proteolysis in Cancer Development and Neurodegenerative Diseases

Daniela Kaden[a] Gerd Multhaup[a, b]

[a]Institut für Chemie und Biochemie, Freie Universität Berlin, Berlin, Germany; [b]Department of Pharmacology and Therapeutics, McGill University, Montreal, Que., Canada

Regulated intramembrane proteolysis (RIP) is a central cellular event which is of crucial importance for normal functioning of the immune and nervous system. If the tightly regulated RIP process is disturbed, it might be associated with diseases, such as leukemia, rheumatoid arthritis, cancer, and Alzheimer's disease. Today, our understanding of the RIP process is only partial and many questions on functional and molecular levels are still open. To discuss these scientific issues, scientists from 5 European countries and Japan met at a symposium for RIP in Potsdam, Germany, on October 5–7, 2011. The two major aims of the meeting were (1) to give all participants the opportunity to present and discuss their current research data on RIP and (2) to build up a network for successful cooperation between different groups working on RIP. The venue selected by the organizers Daniela Kaden and Gerd Multhaup was the Seminaris Seehotel in Potsdam, located at the beautiful lake Templin. It was the 7th meeting in a row funded by the Luzie Fabisch Foundation and a follow-up meeting to the 6th Fabisch Symposium for Cancer Research and Molecular Cell Biology – Enzymes in Physiology and Pathogenesis: Signaling by Secretases in 2009 organized by Lisa M. Munter and Gerd Multhaup. Ferdinand Hucho, honorary chairman of the Luzie Fabisch Foundation, stated: 'Luzie Fabisch donated to the Freie Universität Berlin a sizeable sum of money and dedicated it to "Cancer Research and Cellular Biology". To give the donation maximum impact, the university decided to set it aside for young, not yet settled researchers of the Department of Biology, Chemistry and Pharmacy, who wish to organize a symposium related to their field of research.' During the meeting, young scientists were given plenty of opportunity to discuss these topics with highly recognized researchers in the field, and the size of the meeting with approximately 60 participants, including 15 invited speakers, reflects this. As a new feature, 6 young investigators had the opportunity to present and discuss their data in short talks integrated in the meeting program. Furthermore, young investigators presented and extensively discussed their data in the poster session. The Verum Foundation, which promotes basic research in neurodegenerative diseases, supported the young scientists by awarding the best talks and posters of young investigators (Box 1), which had been selected by an independent jury of national and international speakers and participants of the meeting.

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Dr. rer. nat. Gerhard Multhaup, Professor and Chair
Department of Pharmacology and Therapeutics, McGill University
McIntyre Building, Room 1325, 3655 Promenade Sir-William-Osler
Montreal, QC H3G 1Y6 (Canada)
E-Mail gmulthaup@me.com

Box 1

A jury of eight independent researchers (V. Dötsch, M. Freeman, G. Gouras, O. Andersen, S. Weggen, O.Huber, A.-N. Bondar, and P. Hildebrand) was asked to vote for the best poster and short talks (young investigator talks). Prizes were funded by the Verum Foundation and were awarded for the best posters to:

(1) Nina Bergbold, University of Heidelberg, ZMBH, Germany – The Intramembrane Protease RHBDL4 Facilitates Dislocation in Endoplasmic Reticulum-Associated Degradation.
(2) Arnela Mehmedbasic, Aarhus University, Denmark – SorLA Glycosylation and Binding to APP.
(3) Christian Tackenberg, University of Zürich, Switzerland – Neuro- and Synaptotoxicity of Different Aβ Mutants.

For the best short talks, there were three equal prizes given to:

- Amelie Ebke, LMU and DZNE Munich, Germany – Novel γ-Secretase Modulators Directly Target Presenilin.
- Luise Richter, Free University Berlin, Germany – Small Compounds Interfering with APP Transmembrane Sequence Dimerization as Promising Therapeutic Agents against Alzheimer's Disease.
- Lina Fleig, University of Heidelberg, ZMBH, Germany – The Intramembrane Protease RHBDL4 Facilitates Dislocation in Endoplasmic Reticulum-Associated Degradation.

The scientific part was opened by a session on the structure and functions of Alzheimer-related proteins. Volker Dötsch, from the Goethe University Frankfurt, Germany, is a leading researcher in the expression of membrane proteins in cell-free systems. Efficient and combinatorial labeling of specific amino acids enables him to determine highly resolved NMR structures. In more detail, he presented data on the structure of the C-terminal domain of presenilin (PS) which is part of the catalytic center of the γ-secretase complex. Moving on from NMR to X-ray crystallography, Manuel Than from the Leibniz Institute for Age Research in Jena, Germany, discussed the structural data of the E1 and E2 domains of the amyloid precursor protein (APP). Interestingly, they found that copper and zinc binding to the E2 domain leads to a conformational switch in the protein. As the final speaker of the opening session, Jochen Walter from the University of Bonn, Germany, discussed the cross talk of membrane lipids and Alzheimer-related proteins. He reported about glycosphingolipids which are glycosylated derivatives of ceramides highly expressed in neurons. Glycosphingolipids affect the secretion of APP and stabilize the APP C-terminal fragment by inhibiting its degradation by a blockage of the autophagy.

The pioneer in rhomboid research, Matthew Freeman from the MRC Laboratory of Molecular Biology in Cambridge, UK, convinced the audience with the concept of inactive rhomboid proteases, the so-called iRhoms, which may function in the regulation of other active proteases. He stated that pseudoproteases are common and dead enzymes are good templates for specific regulators. Karina Reiss from the University of Kiel, Germany, a leading scientist in the field of the ADAM (a disintegrin and metalloproteinase) proteases and inflammation found that ADAM10 and ADAM17 are important regulators of interendothelial cell-cell adhesion mediated by vascular endothelial cadherin and might thereby affect arteriosclerosis. Furthermore and in line with Jochen Walter, she demonstrated that the membrane lipid composition is important for ADAM regulation and determines the substrate cleavage. Unsaturated fatty acids result in more fluidity of the membrane and more efficient cleavage. Ana-Nicoleta Bondar from the Department of Physics of the Free University of Berlin, Germany, supported the experimental data on RIP proteases by molecular dynamics simulations of the rhomboid protease GlpG. Consistent with the data presented by Jochen Walter and Karina Reiss, she nicely illustrated the conformational dynamics of the substrate-docking site, which is largely affected by the presence of specific lipids and the substrate. Shedding of the extracellular substrate domain to generate short C- or N-terminal fragments is a prerequisite for most RIP proteases. Using the example of SPPL (signal peptide peptidase-like proteases) cleavage of the foamy virus envelope protein (HFVenv), Regina Fluhrer from the Ludwig Maximilians University (LMU) and German Center for Neurodegenerative Diseases (DZNE) in Munich, Germany, nicely demonstrated in a young investigator talk that SPPL3 is able to cleave the full-length substrate HFVenv and is therefore independent of a preceding shedding event. Jörg B. Schulz from the RWTH Aachen, Germany, presented data on the lifeguard protein Faim2 (Fas inhibitory molecule). An ischemia model in mice revealed functions of Faim2 in the protection of DD95L/FasL-mediated toxicity. The session was closed by an excellent young investigator talk of Lina Fleig from the group of Marius Lemberg at the University in Heidelberg, Germany. She presented data showing that the intramembrane protease RHBDL4 is upregulated by endoplasmic reticulum (ER) unfolded protein response and participates in the ER-associated degradation of mem-

brane proteins. Inactive RHBDL4 leads to ER stress and unfolded protein response induction, suggesting that this protease plays an important role in the surveillance of ER protein folding.

The afternoon session focused on RIP, gene regulation and the trafficking and toxicity of the amyloid-β (Aβ) peptides. Uwe Konietzko from the Psychiatric University Hospital Zürich, Switzerland, reported on the roles of the APP protein family in nuclear signaling. He found that APP and the amyloid precursor-like protein 2 (APLP2) have a higher turnover than APLP1 and that the intracellular domain of APLP1 is not involved in nuclear signaling like the other two family members. In a young investigator talk, Christian Barucker from the Free University Berlin, Germany, described the role of the neurotoxic Aβ42 peptide in nuclear signaling and gene regulation. Several publications suggest that the APP intracellular domain has gene regulatory functions; however, the Aβ42-mediated gene regulation is novel and unique, as other nontoxic Aβ peptides (Aβ38, Aβ40, or Aβ42 G33A) translocate to the nucleus, but do not affect gene regulation. In line with a proposed intracellular Aβ function or dysfunction, Gunnar Gouras from the Lund University in Sweden discussed novel data on the intraneuronal accumulation of Aβ, which occurs a long time before extracellular amyloid plaques appear.

Roland Brandt and the young investigator Lidia Bakota from the University of Osnabrück, Germany, discussed the relationship of tau and Aβ toxicity in ex vivo and in vitro models. They found that Aβ fragments (3–42) induce a specific retention of tau in axons and dendrites. However, at moderate Aβ concentrations the presence of tau does not promote degeneration. Moreover, moderate concentrations of Aβ physiologically modulate synaptic connectivity in vivo.

As special guest from Tokyo, Japan, Taisuke Tomita gave a detailed overview about novel inspiring findings on the modulation of β- and γ-secretase activity. On the one hand, he found that sphingosin-1-phosphate (S1P) specifically binds to the β-site APP-cleaving enzyme 1 (BACE1) and increases its proteolytic activity, suggesting that cellular S1P directly modulates BACE1 activity and provides therefore a novel potential therapeutic target for Alzheimer's disease. On the other hand, he showed by photolabeling experiments that the γ-secretase modulator 1 (GSM1) directly targets the transmembrane domain 1 of PS1, thereby affecting the structure of the initial substrate binding and the catalytic sites of the γ-secretase.

Gerd Multhaup continued the session with the description of a novel putative role of BACE1 in copper transport. Copper stabilizes BACE1 dimers via a cysteine residue in the transmembrane sequence (TMS) and influences secretion of soluble APPβ. Another function of BACE1 was demonstrated in a young investigator talk by Manuel Gersbacher from the group of Dora Kovacs at the Massachusetts General Hospital, USA. He reported that BACE1 activity controls voltage-gated sodium channel levels (Nav1.1) under physiological conditions. Nav1.1 protein and mRNA levels are regulated by successive β- and γ-secretase cleavage of the voltage-gated sodium channel β2 subunit (Navβ2). Thus, one needs to keep in mind that BACE1 inhibition as a therapeutic target for Alzheimer's disease may affect Nav1.1 metabolism and alter neuronal membrane excitability. To map novel physiological BACE1 substrates, Stefan Lichtenthaler from the LMU and DZNE in Munich, Germany, developed the method of secretome protein enrichment with click sugars. By using this method he is able to specifically label glycosylated soluble proteins whereas enrichment of serum proteins is reduced by a factor of 100. By using specific inhibitors, he could also quantify the rate of BACE1 cleavage over other sheddases such as the α-secretases, e.g. ADAM proteases. The session was closed by Lisa M. Munter from the Free University Berlin, Germany, with the finding that mutations around the β-secretase cleavage site may also affect the γ-secretase cleavage. In turn, certain mutations around the γ-secretase cleavage site in the TMS enhanced or decreased shedding by BACE1 to produce sAPPβ.

The final session dealt with the controversial issue of γ-secretase modulators (GSMs). The central question which arises is whether GSMs bind to the APP-TMS and Aβ or to the PS1 NTF. But first, Johan Lundkvist from AstraZenecka, Sweden, presented data on a novel method to quanify tri- and tetrapeptides generated by sequential γ-secretase cleavages. However, he also reported about alternative cleavages and less frequently generated tripeptides. He introduced novel nonacidic GSMs which differentially affect the generation of shorter Aβ species. In addition to the binding of GSM1 to the transmembrane domain 1 of PS1 as described by T. Tomita, Luise Richter a young investigator from the group of Gerd Multhaup at the Free University in Berlin, Germany, reported specific binding of GSM1 to the Aβ sequence, decreasing the dimerization of the APP TMS. Her data indicate that one possible mode of GSM action is to vary, e.g. stabilize or destabilize, the dimerization strength of the APP TMS. The data were supported by structural models envisaged by Peter Hildebrand from the Charité Berlin, Germany. He presented a model of GSM1 binding to the APP mono-

mer via π-electron interactions with main-chain atoms and van der Waals packing with side chains by means of flexible docking. The session and the meeting were closed by a young investigator talk of Amelie Ebke from the group of Harald Steiner at LMU and DZNE Munich, Germany. By using a photoaffinity-labeling approach she demonstrated that novel nonacidic bridged aromatic GSMs, developed by F. Hoffmann-La Roche Ltd., specifically target the PS N-terminal fragments. Further, she identified shared and overlapping binding sites with nonacidic and acidic GSMs, respectively.

The question of whether GSMs bind to APP or PS is still controversial, but the data presented at the meeting do not preclude one or the other possibility. Rather, a dual mode of action of the acidic GSMs is to be assumed, e.g. binding of GSMs to both proteins, the substrate APP and the catalytical component PS.

In summary, the meeting introduced a lot of novel concepts and ideas and facilitated extensive discussions of the speakers and participants. The organizers are not only grateful to the Luzie Fabisch Foundation but also to the Verum Foundation (Box 1), the GRK1123, Neurocure and the SFB740 for financial support (for more information, see http://tinyurl.com/3m45o3h).