
Binder-Innovationspreis für Frauke Melchior

Wissenschaftliche Laufbahn:

1981 - 1987	Diploma in Chemistry, at the Philipps-University, Marburg, Germany, and the University of Bristol, UK (1984-1985).
1987 - 1990	Ph.D in Biochemistry, University of Marburg, Germany; doctoral work on grape wine stilbene synthase in the group of Prof. Dr. H. Kiendl.
1990-1992	Postdoctoral work on the fission yeast protein Rna1p in the group of Dr. Volker Gerke, Max Planck Institute, Goettingen, Germany;
1992-1998	Postdoctoral work on nucleocytoplasmic transport in the group of Dr. Larry Gerace, Scripps Research Institute, La Jolla, USA.
1998-1999	Group leader, Max-Planck Institute for Biochemistry, Martinsried, and Laboratory for Molecular Biology, Gene Center, LMU Munich.
1999-2004	BioFUTURE group leader at the Max-Planck Institute of Biochemistry, Martinsried
Since 2004	Professor of Biochemistry, Georg-August University Goettingen



Fellowships and awards:

1984-1985	Undergraduate Fellowship from the German Academic Exchange Program
1992-1994	Postdoctoral Fellowship from the Deutsche Forschungs-Gemeinschaft
1995-1997	Senior Postdoctoral Fellowship from the American Cancer Society, California Division
1998	BioFuture -Young Investigator award by the German Ministry for Education and Research

Ubiquitin-related modifier SUMO

Research in our group centers around posttranslational modification with small ubiquitin-related proteins of the SUMO family. SUMO proteins are ubiquitously expressed in eukaryotic cells, and are essential for life. They are reversibly coupled to a large number of cellular targets, and thereby modulate protein/protein or protein/DNA interactions, alter intracellular localization, or protect from ubiquitin mediated degradation. Most of the known targets for sumoylation can be associated with a few specific pathways: signal transduction, transcription, chromatin remodelling, DNA repair, mitosis, viral infection, and nucleocytoplasmic trafficking.

As often in science, serendipity played a major role in our discovery of SUMO as a posttranslational modifier. We and others who studied the Ran GTPase activating protein RanGAP1, a protein involved in nucleocytoplasmic transport and mitosis, noticed that RanGAP1 carries a posttranslational modification that gives rise to a 20 kD change in mobility. When following up on this observation, we identified an at that time unknown 10 kD protein as a covalent binding partner for RanGAP1. This protein, dubbed SUMO-1 by us, or GMP1, sentrin, Pic1, Ubl1 or Smt3 by others, is only 18% identical to ubiquitin, but resembles it in three-dimensional structure. As it quickly turned out, SUMO resembles ubiquitin also in the mechanism and nature of its attachment to other proteins. ATP-dependent modification results in isopeptide

bond formation between the Carboxy-terminus of SUMO-1 and the ϵ -amino group of a specific lysine residue in its targets, and SUMO conjugating enzymes resemble their ubiquitin enzyme relatives. However, the molecular consequences of sumoylation are quite distinct to that of ubiquitination, and are specific for any given target. While some proteins including RanGAP1 gain novel binding partners upon modification, others lose their specific interactions when attached to SUMO. In that sense, posttranslational modification with SUMO resembles phosphorylation more than ubiquitination.

Since our initial description of SUMO as a modifier of RanGAP1, more than 100 SUMO targets were identified worldwide. Examples are yeast septins, the tumor suppressor p53, I κ B α , topoisomerases, MAP kinase kinase 1, PCNA and histone deacetylases. While some targets including RanGAP1 are modified constitutively, others require cues such as heat shock, DNA damage, or a specific time in the cell cycle. Consequently, one of the most exciting questions in the field is the mechanism and target specific regulation of SUMOylation. Early studies demonstrated that SUMO attachment can be accomplished by just two enzymes, the E1 activating enzyme Aos1/uba2 and the E2 conjugating enzyme Ubc9. This is due to the unique feature of Ubc9 to efficiently bind to - and modify - certain substrates including RanGAP1. However, most SUMO targets seem to require E3 ligases for effi-

cient modification *in vivo*. Their existence has been unclear until 2001 / 2002, when several groups reported that PIAS proteins (Protein inhibitors of activated STAT) function as E3 ligases. At the same time, we discovered that the nuclear pore complex protein RanBP2 functions as a SUMO1 E3 ligase for selected targets *in vitro*. Our findings place SUMOylation at the cytoplasmic filaments of the NPC and suggest that, at least for some targets, modification and nuclear import are linked events. The catalytic domain of RanBP2 is unique in that it does not resemble RING- or HECT-type enzymes and that it exerts its catalytic effect by altering Ubc9's properties rather than by mediating target interactions. Yet another unrelated E3 ligase that was described most recently is the polycomb protein Pc2 - its mode of function remains to be revealed. If one considers the large number of SUMO targets and the divergence of known SUMO E3 ligases, it seems likely that many additional enzymes or cofactors are out there to be discovered. Current projects in our group aim to understand mechanism, regulation and function of SUMOylation. We study enzymes in the pathway, characterize several novel target proteins, and investigate non-covalent SUMO interactors. Other projects focus on the connection between SUMOylation and nucleocytoplasmic transport, the function and regulation of the SUMO target RanGAP1 in nuclear import and mitosis, and crosstalk between SUMO- and ubiquitin-conjugation.

Ausgewählte Publikationen:

- Mahajan, R., Delphin, C., Guan, T., Gerace, L. and Melchior, F. (1997). A small ubiquitin related polypeptide involved in targeting RanGAP1 to nuclear pore complex protein RanBP2. *Cell* 88, 97-107.
- Mahajan, R., Gerace, L. and Melchior, F. (1998). The C-terminal domain of RanGAP1 contains the acceptor site for SUMO1 modification and is sufficient for targeting to the nuclear envelope. *J. Cell Biol.* 140, 259-270.
- Bayer, P., Andreas Arndt, A., Metzger, S., Mahajan, R., Melchior, F., Jaenicke, R., and Becker, J. (1998). Structure determination of the small ubiquitin-related modifier SUMO-1. *J. Mol. Biol.* 280, 275-286.
- Melchior, F. (2000). SUMO-1 - Non-Classical Ubiquitin. *Annu. Rev. Cell Dev. Biol.*, 16, 591-626.
- Sachdev, S., Bruhn, L., Sieber, H., Pichler, A., Melchior, F. and Grosschedl, R. (2001). PIASy represses LEF1 activity by stimulating SUMO conjugation and targeting of LEF1 to nuclear bodies. *Genes Dev.*, 15, 3088-103.
- Pichler, A., Gast, A., Seeler, J.S., Dejean, A. and Melchior, F. (2002) The nucleoporin RanBP2 is a SUMO1 E3 Ligase. *Cell* 108, 109-120
- Melchior, F., Schergaut, M., and Pichler, A. (2003) SUMO: ligases, isopeptidases and nuclear pores. *Trends Biochem Sci.* 28, 612-618.
- Swaminathan, S., Kiendl, F., Körner, R., Lupetti, R., Hengst, L. and Melchior, F. (2004) RanGAP1*SUMO-1 is phosphorylated at the onset of mitosis and remains associated with RanBP2 upon NPC disassembly. *J. Cell Biol.* 164, 965-971.
- Pichler, A., Knipscher, P., Saitoh, H., Sixma, T., and Melchior, F. (2004) SUMO E3 ligase RanBP2 is neither Hect- nor Ring-type. *Nat. Struct. & Mol. Biol.* 11, 984 - 991
- Pichler, A., Knipscher, P., Oberhofer, E., van Dijk, W.J., Körner, R., Olsen, J.V., Jentsch, S., Melchior, F., and Sixma, T.K. (2005) SUMO modification of the ubiquitin conjugating enzyme E2-25K. *Nat. Struct. & Mol. Biol.* 12, 264-269.

Ehrenmitgliedschaft

Anlässlich des 30-jährigen Jubiläums der DGZ wurde Prof. Dr. Werner W. Franke vom Präsidenten Prof. Manfred Schliwa mit der Ehrenmitgliedschaft „überrascht“ und seine Verdienste für die Entwicklung der Zellbiologie und der DGZ geehrt. Werner W. Franke war im Jahre 1975 Gründungsmitglied und diente der Gesellschaft von 1975 bis 1977 als Geschäftsführer, danach mehrere Jahre als Beirat und schließlich von 1999 bis 2001 als Präsident.

