The ubiquitin-proteasome-system

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Thomas Sommer, Dieter H. Wolf, The Ubiquitin-Proteasome-System, *BBA - Molecular Cell Research*. 2014 Jan ; 1843(1): 1 | doi: 10.1016/j.bbamcr.2013.09.009
Elsevier ►

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The discovery of the ubiquitin conjugation pathway and the identification of the 26S proteasome as the machine degrading polyubiquitinated proteins opened a view into a completely new world of cellular regulation. Proteolysis, previously considered as unspecific and thus less important, suddenly evolved into a field of pre-eminent importance. Central cellular processes such as signal transduction, metabolic regulation, cell cycle control, development, apoptosis, protein quality control, or antigen presentation were found to depend on a functional ubiquitin-proteasome-system. Defects in this system lead to severe diseases as for instance inflammation, cancer or neurodegeneration. It is therefore of utmost importance to understand the players of the system, their function and their molecular mechanism in the different cellular processes comprehensively.

When in 2004 the first review issue of Biochimica et Biophysica Acta Molecular Cell Research on the ubiquitin-proteasome machinery appeared, the field had started to blossom.
Ten years later, improved and novel biochemical, cell biological and structural approaches have led to a wealth of new insights into the system. This has led to a significantly deeper understanding of many cellular processes and connected diseases. For example good structural knowledge was only available of the 20S core particle, the proteolytically active cylinder of the proteasome. However, recently the structural and mechanistic features of the 19S regulatory particle and its cooperation with the protease core begin to unravel. In addition, we begin to see that ubiquitin is not a single "word" but the unit of a whole biological 'language'. Key to this complex 'language' is the type of modification of a specific substrate protein. It can vary between mono-ubiquitination, multiple monoubiquitination and modification by ubiquitin chains. Since ubiquitin chains are characterized by the lysine residues in ubiquitin used for the ubiquitin-ubiquitin linkage, a variety of different chains can be used to modify target molecules. Then, the dynamics of building, processing and disassembly of ubiquitin chains is still far from being understood. The number of substrate proteins and accordingly the number of cellular processes these proteins are involved in, is steadily increasing. Additional ubiquitin like proteins (UBL´s) interconnecting with the ubiquitin language diversify and refine this modification even more. Separate UBL activation- and ligation systems operate and in certain cases UBL (SUMO) and ubiquitin modification is

intertwined. Together with this we learn about an increasing number of diseases which are connected with the system. We have to learn about the mistakes in the ubiquitin language as well as in the processing and degradation machineries to be able to understand the molecular basis of the diseases, and hopefully some time from now will be able to find drugs to combat them. The discovery of the proteasome inhibitors bortezomib (Velcade ®) and carfilzomib (Kyprolis ®) for treatment of multiple myeloma is a promising start.

The reviews in this volume will provide insights into our present knowledge of the proteasome, its components, its assembly and its dynamics in the cell. Furthermore, the varying components of the ubiquitin-proteasome system acting in different cellular processes as well as the dynamics of ubiquitin linkage, assembly and disassembly will be highlighted. Finally, diseases linked with defects in the system will be presented.

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Dr. Thomas Sommer, is a Senior Investigator at the Max-Delbrück-Center for Molecular Medicine (MDC), Berlin, and a Professor for cellular Biochemistry at the Humbold-University zu Berlin, Germany. He received his Doctoral degree from the Free University of Berlin, where he studied Biology. He performed the experimental part of his doctoral Thesis at the Max-Planck-Institute for Molecular Genetics, Berlin, where he studied transcriptional regulation in Neurospora crassa. Following a postdoctoral position at the Friedrich-Miescher-Institute of the Max-Planck-Society, Tübingen, he took an appointment at the MDC: First as a member of the junior faculty, then he became a Senior PI. From 2004 on he is the vice scientific Director of this Helmholtz Center. At the MDC he made significant contributions to the role of the ubiquitin protesaome pathway in proteolysis in and at the Endoplasmic Reticulum. The focus of his current research is directed at understanding the interplay of ubiquitin ligases and molecular chaperones in protein quality control pathways.

Dr. Dieter H. Wolf is Professor emeritus and former Director of the Institute of Biochemistry of the University of Stuttgart. At present he is leading a research group on the ubiquitin-proteasome system at the same institute. He received his PhD in Biochemistry in 1972 from the University of Freiburg. In 1973 he joined the laboratory of Dr. Gerald R. Fink as a postdoctoral fellow, at the time at Cornell University in Ithaca, New York. After his return to Germany he worked as junior group leader in the Biochemisty Institute of the University of Freiburg. In 1980 he was promoted to Assistant Professor and in 1985 to Associate Professor. In 1989 he took the chair of Biochemistry at the University of Stuttgart and became Director of the same Institute. Since 2011 he is Professor emeritus and leader of a research group which focuses on the function of the ubiquitin-proteasome system in metabolic regulation and protein quality control using the eukaryotic model organism yeast. Major achievemnts of his lab are the elucidation of the function of vacuolar proteolysis, the discovery of the yeast proteasome and the function of the machine in ubiquitin linked proteolysis *in vivo* as well as the discovery of cytoplasmic retro-translocation and ubiquitin-proteasome mediated degradation of misfolded lumenal protein of the endoplasmic reticulum (ERAD). He is member of the European Molecular Biology Organization (EMBO) and corresponding member of the Heidelberg Academy of Sciences.