CMLS, Cell. Mol. Life Sci. 61 (2004) 1545
1420-682X/04/131545-01
DOI 10.1007/s00018-004-4128-6

CMLS Cellular and Molecular Life Sciences

The ubiquitin-proteasome system: past, present and future

W. Hilt and D. H. Wolf*

Institut für Biochemie, Universität Stuttgart, Pfaffenwaldring 55, 70569 Stuttgart (Germany), Fax: +49 711 685 4392, e-mail: dieter.wolf@po.uni-stuttgart.de

Regulation of cell functions via proteolysis of members of its proteome was neglected for a long time. This was mainly due to 'economic thinking': it was hard for scientists to imagine that the cell would ever destroy its proteins, which it had synthesized at the expense of a huge amount of energy. When the lysosome was discovered, this organelle was mainly considered as the gut of the cell, required for digestion of protein waste. The discovery of ubiquitin and thereafter the proteasome finally revolutionized the thinking of the scientific community completely. It became apparent that the ubiquitin proteasome system, as it is known today, is a regulatory system, vital to all eukaryotic cells. Ironically, this proteolytic device also requires a lot of the cell's energy to function. Not only does synthesis of the members of the proteolytic machinery require energy, but the proteolysis process itself does, too. It starts with tagging the proteins with ubiquitin for destruction and ends with the energy requirement of the proteasome to unfold and digest the protein targets. Why would evolution create such an expensive regulatory mechanism when it has a much 'cheaper' option: the reversible mechanism of protein-phosphorylation-dephosphorylation? One answer rests in the equilibrium of the active and inactivated proteins. Phosphorylation-dephosphorylation will always be incomplete, leaving either active or inactive molecules behind. Degradation of a protein is complete. No degraded protein will regain activity. The equilibrium of the reaction will be completely on the product side, the peptides and amino acids. For many regulatory pathways this is crucial. No active protein may remain. Otherwise severe cell damage will occur.

It is gradually emerging that tagging proteins with ubiquitin is a finely tuned mechanism. Proteins can be tagged with one ubiquitin moiety or several moieties in a chain. The buildup of a chain at internal lysine residues of ubiquitin is highly selective. Only chain assembly via K29 or K48 leads to proteasomal degradation of a protein. Other assemblies result in different functions. Thus, the protein surface created by different ubiquitin linkages is decisive in the fate of a protein. We know now that ultimately all basic cellular functions rely on the action of the ubiquitin-proteasome system, for instance transcriptional regulation, cell metabolism, the cell cycle, apoptosis, protein quality control, and in plants even the daily circadian clock determining flowering time over the year. At the moment we have uncovered only the tip of the iceberg of this immensely important proteolytic system in cellular control. In the future, a large variety of new substrates of the ubiquitin-proteasome machinery will appear; their mechanism of degradation and the players involved in these processes will have to be characterized. The role of such substrates in cellular regulation will then be revealed in detail. Interestingly, the proteasome not only degrades its substrates, it can process defined targets and, to our astonishment, even splice proteins. The mechanisms underlying these different degradation processes will have to be defined in more detail. Moreover, pre-proteasomal processes such as substrate tagging, liberation and acquisition await further examination. The spatial linkage of the proteasome to other cellular machines and the role of such an interaction in correct timing or the high effectiveness of proteolysis has to be clarified. Furthermore, investigation of the purpose of the proteasome's physical interaction with nonsubstrate proteins will shed light on new functions and regulatory mechanisms; in yeast more than a hundred potential interactors are already known. We will have to 'dig' more and deeper to really understand the multiple regulatory functions of the ubqiuitin-proteasome system.

* Corresponding author.