Ubiquitous Activities of Ubiquitin

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The ubiquitin-proteolytic system is a mechanism by which cells degrade and rid themselves of undesired, malfunctioning, and aberrantly expressed proteins. However, our expanding knowledge of the processes involved in cell development, differentiation, antigen presentation, signal transduction, and a multitude of other cellular activities has given insight into the importance of this system in disease and health. Moreover, our understanding of the ubiquitin-proteasomal pathways has proven this system to be essential for cell survival and has also revealed new targets for therapeutic intervention. It is now apparent that the ubiquitin-proteasome system is more than a cellular waste-shredding barrel. It is rather an integral part of cellular functioning and survival. During yesterday's Ham-Wasserman Lecture, Dr. Aaron Ciechanover, 2004 Nobel Laureate in Chemistry, took us on a journey through the ubiquitin-proteolytic system, from its discovery to current clinical applications.

Initially, it was believed that protein degradation occurred uniformly by lysosomal/vacuolar mechanisms. This "one-shoe-fits-all" hypothesis was subsequently challenged with the discovery of heterogeneity in protein stability and half-life, which could not be attributed solely to lysosomal degradation. Furthermore, the observation of pH-independent, energy-requiring protein-degrading processes further supported the notion that protein turnover can occur independent of lysosomes. The ubiquitin-proteolytic system was initially proposed in the late 1970s with the detection of ubiquitin as a marker for protein degradation. "The language that ubiquitin talks is a very rich language," Dr. Ciechanover said, referring to the extensive capacity of the ubiquitin-proteasome system to regulate a whole host of cellular activities.

In the 1980s, investigations of the mechanisms involved in downstream proteolysis of ubiquitinated substrates led to the discovery of the proteasome, a multi-subunit, cylindrical complex consisting of a 20S core catalytic component and 19S regulatory particles. The proteasome degrades a variety of proteins, including those involved in cell cycle regulation and apoptosis such as cyclins, p53 tumor suppressor, and inhibitor of NF-κB (IκB). It is therefore of no surprise that disturbances in this finely tuned system can lead to various disease states, defined by the resulting defect in the ubiquitin-proteasome system (i.e., either promoting or inhibiting proteolysis) and the physiologic function of the involved protein. Age-related neurodegenerative disorders (e.g., Parkinson's disease and Alzheimer's disease), childhood illnesses (e.g., Angelman syndrome), and various malignancies have been associated with aberrancies in ubiquitin-proteasome pathways.

"We hardly see the tip of the iceberg," stated Dr. Ciechanover, referring to the failure of many novel agents to reach the clinical setting. However, our expanding knowledge of the ubiquitin-proteasome system has paved the way for the application of proteasome inhibitors to the therapy of cancer. Bortezomib (Velcade®) is the first proteasome inhibitor approved by the U.S. Food and Drug Administration in 2003 for the treatment of multiple myeloma. It is believed to exert its antineoplastic effects by increasing the stability of p53 tumor suppressor and blocking the degradation of IκB, therefore shifting the balance toward a pro-apoptotic state. Bortezomib is also currently being investigated for the treatment of lymphoma, leukemia, and even solid tumors. Dr. Ciechanover also pointed out numerous steps and pathways related to the ubiquitin-proteasome system that may be potential drug-targets — "Clearly the future will reside in [targeting] other levels of the ubiquitin system."