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Celebrating the death of proteins

The 2004 Nobel Prize in chemistry has been awarded to three biochemists. As stated in an announcement from the Royal Swedish Academy of Sciences on 6 November 2004, Aaron Ciechanover, Avram Hershko (both at the Israel Institute of Technology) and Irwin Rose (University of California at Irvine) were recognized for "the discovery of ubiquitin-mediated protein degradation."

Ciechanover and Hershko were interested in understanding why protein degradation inside the cell requires ATP, when many of the well-known secreted proteases, such as trypsin or chymotrypsin, could readily chop up polypeptide chains without an external energy source. In the late 1970s, the three researchers performed a series of classical biochemical experiments that included the fractionation of cell lysates and the reconstitution of activities required for the ATP-dependent protein degradation process. The small protein they identified—later found to be present in many different cell types and in many organisms, and therefore given the name 'ubiquitin'—was covalently attached to proteins, including itself, thus forming an oligomeric ubiquitin chain.

Once again using classical biochemical approaches, the three researchers demonstrated that the covalent modification of proteins by ubiquitin is an unexpectedly complex process involving three enzymes acting in a stepwise manner. Their findings in the early 1980s established the most important aspects of the mechanism of ubiquitination that we know today. The first enzyme, E1, or the ubiquitin-activating enzyme, utilizes ATP to activate ubiqutin by attaching an adenylyl group to its C-terminal carboxylate; the ubiquitin moiety is then transferred to a cysteine residue on E1, forming a high-energy thioester bond and releasing the adenylyl group. In the next step of the reaction, ubiquitin is transferred to an active site cysteine in the second enzyme, E2, called the ubiquitin-conjugating enzyme. E3, or the ubiquitin-ligating enzyme, catalyzes the final step of the reaction, the formation of the stable isopeptide bond between a lysine residue on the substrate and the C-terminal carboxylate group of ubiquitin.

The results of Ciechanover, Hershko and Rose paved the way for further research to understand how ubiquitin functions in protein degradation. Based on the work of many research groups, we now know that the oligomeric ubiquitin chain attached to a protein marks it for destruction by the proteasome, a multicomponent proteolytic machine that processively chops a protein into short peptide segments of about seven to nine residues. The ubiquitin moieties are cleaved from the attached protein before destruction and recycled by the cell.

In addition, we know that ubiquitin-mediated proteolysis not only is used to remove aberrant proteins from the cell, such as those rejected by the quality control system, but also is a crucial component in the regulation of many cellular processes, including cell cycle progression, transcription, DNA repair, inflammation and immune responses, just to name a few. In this regard, it is essential that protein substrates be ubiquitinated in a highly specific and regulated manner. This specificity is achieved by having in the cell a single ATP-consuming E1 that transfers ubiquitin to several E2s, which then cooperate with many E3s that specifically recognize their substrates. In this context, the complexity of the three-tier ubiquitination process makes sense.

The utility of ubiquitination does not end with protein degradation. For example, the attachment of ubiquitin to many receptors on the cell surface regulates their transport through the endocytic pathway. Ubiquitination also seems to be involved in the budding of viral particles from the cell surface. Finally, it has long been known that histone proteins are ubiquitinated, and recent research has begun to reveal that such modifications have a role in both transcription activation and gene silencing. Ubiquitination is thus an integral part of the 'histone code.'

Several proteins are closely related to ubiquitin, and their functional mechanisms involve conjugation of these proteins to their targets. These include bacterial proteins ThiS and MoaD, which are components of the thiamin and molybdenum cofactor biosynthesis pathways, respectively, as well as eukaryotic proteins such as NEDD8, SUMO and some of the autophagins, which seem to be involved in ubiquitination, nuclear transport/transcription repression and autophagy, respectively. Despite the diverse origins and functions of these proteins, they have conjugation systems similar to that for ubiquitin. Thus, the biochemical pathway developed for ubiquitin has been adapted for different biological processes.

The importance of the proteasome in regulating various cellular processes also makes it an attractive therapeutic target, especially as a potential cancer treatment. In fact, proteasome inhibitors are a new class of drugs currently in development, and one of these drugs, bortezomib, has recently been approved in the United States to treat multiple myeloma. Other potential areas for proteasome inhibitors as treatment include anti-angiogenesis and diseases related to the immune system, such as chronic inflammatory conditions, multiple sclerosis and rheumatoid arthritis. In recognition of the broad implications of the regulated protein degradation mediated by the ubiquitin system, Ciechanover and Hershko were also the co-recipients of the Albert Lasker Award for basic medical research in 2000 (shared with Alexander Varshavsky).

Looking back, it is interesting to see how a relatively simple set of biochemical experiments almost three decades ago led to the emergence of an important field that impacts many different areas of biology. The 2004 Nobel Prize in chemistry is a timely recognition of this contribution. ■