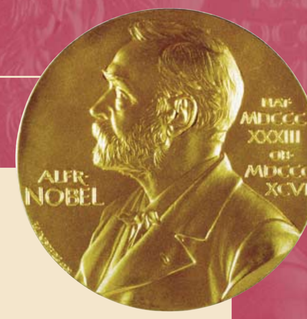
The Royal Swedish Academy of Sciences has decided to award the Nobel Prize in Chemistry for 2004 "for the discovery of ubiquitin-mediated protein degradation" jointly to Aaron Ciechanover, Avram Hershko and Irwin Rose

THE NOBEL PRIZE IN CHEMISTRY 2004



Proteins that are marked for hacking into small pieces

It has long been clear how proteins are built up in the cell. But the opposite, how they are broken down, was long thought to be less exciting to study. This year's Nobel Laureates, Aaron Ciechanover, Avram Hershko and Irwin Rose, went against the stream and, at the beginning of the 1980s, discovered one of the cell's most important control mechanisms, controlled protein degradation.

Ubiquitin

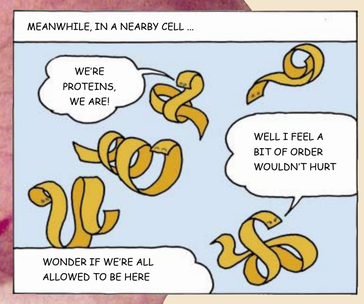
This is what the actual label looks like. It consists of a short polypeptide chain, a small protein that is so common in the cells of different organisms that it was early named ubiquitin, from the Latin *ubique*, 'everywhere'. This protein is not broken down in the proteasome but can be used again and again.

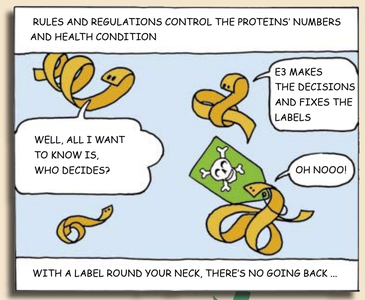
ILLUSTRATION: S. GRIFFITHS-JONES, UNIVERSITY OF NOTTINGHAM

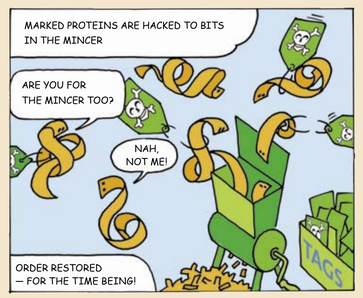
PHOTO: TORSTEN ERIKSSON, THE BERGIUS FOUNDATION

Proteins are life's building-blocks

In the tiniest intestinal bacteria, in roses and toadstools, in mice and men – in all living cells – proteins answer for both form and function. Naturally, research into proteins is therefore of the greatest interest, particularly for chemists wishing to know how things function at molecular level.







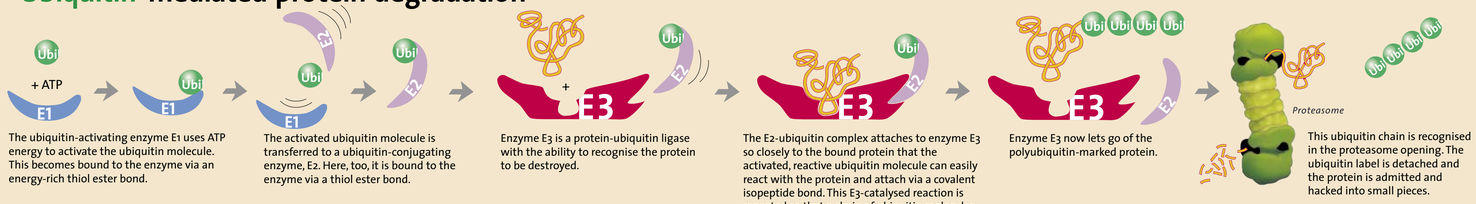
The cell – a teeming mini-workshop

In the cell, proteins are being built up and broken down all the time. For everything to function optimally, the cell also has an integral checkpoint where the composition of various proteins is controlled. Unlike in the spontaneous protein breakdown that food undergoes in our intestines, breaking down proteins inside cells requires energy. This was long a research mystery. Thanks to this year's Nobel Laureates, however, we know that this form of breakdown is an extremely detailed control process in which the protein to be destroyed is marked with a special "label". This happens through a series of chemical reactions, as shown to the right.

What proteins are marked?

Surprisingly many of the proteins created in the cell are faulty from the start. They must be broken down and rebuilt since they can damage the organism. But perhaps the most important reason for a cell to get rid of a protein is that in this way the cell can control a given chemical reaction. By quickly destroying a protein that has a special function, the cell gets the same result as when one turns off a switch. When the proteins have been hacked to pieces, the cell can use their amino acids to synthesize other proteins. When protein degradation does not function correctly, we can become ill.

Ubiquitin-mediated protein degradation



The ubiquitin-activating enzyme E1 uses ATP energy to activate the ubiquitin molecule. This becomes bound to the enzyme via an energy-rich thiol ester bond.

The activated ubiquitin molecule is transferred to a ubiquitin-conjugating enzyme, E2. Here, too, it is bound to the enzyme via a thiol ester bond.

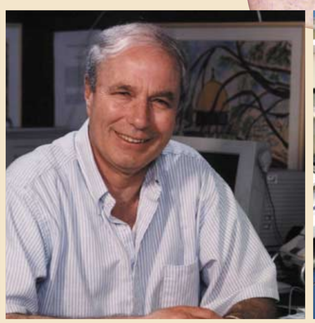
Enzyme E3 is a protein-ubiquitin ligase with the ability to recognise the protein to be destroyed.

The E2-ubiquitin complex attaches to enzyme E3 so closely to the bound protein that the activated, reactive ubiquitin molecule can easily react with the protein and attach via a covalent isopeptide bond. This E3-catalysed reaction is repeated so that a chain of ubiquitin molecules is attached to the protein to be destroyed.

Enzyme E3 now lets go of the polyubiquitin-marked protein.

This ubiquitin chain is recognised in the proteasome opening. The ubiquitin label is detached and the protein is admitted and hacked into small pieces.

Irwin Rose
College of Medicine, University of California, Irvine, USA.



Avram Hershko
Rappaport Institute, Technion – Israel Institute of Technology, Haifa, Israel.

Aaron Ciechanover
Rappaport Institute, Technion – Israel Institute of Technology, Haifa, Israel.

The discovery was made at the beginning of the 1980s at the Fox Chase Cancer Center in Philadelphia, USA, jointly by the three scientists.

Prevents self-pollination

Did you know that roses are bisexual? Most plants are like this – they're *hermaphrodites*. With such an arrangement, one wonders what prevents plants from fertilising themselves. In fact, ubiquitin-mediated protein breakdown is involved: the plant recognises and rejects its own pollen! The exact mechanism is not yet fully clear, but enzyme E3 has been found and when a proteasome inhibitor has been added, the rejection has been noticeably impaired.

PHOTO: IBL/SPL

The most common reason for miscarriage is an error when the mother's and the father's chromosomes are to be separated in the formation of sex cells. Ubiquitin-marking plays an important role here. The picture shows a calf embryo.

How are sex cells formed?

The formation of sex cells, *meiosis*, like normal cell separation, *mitosis*, has many points of contact with the subject of this year's Nobel Prize. A certain E3 enzyme is responsible, among other things, for separating the chromosomes.

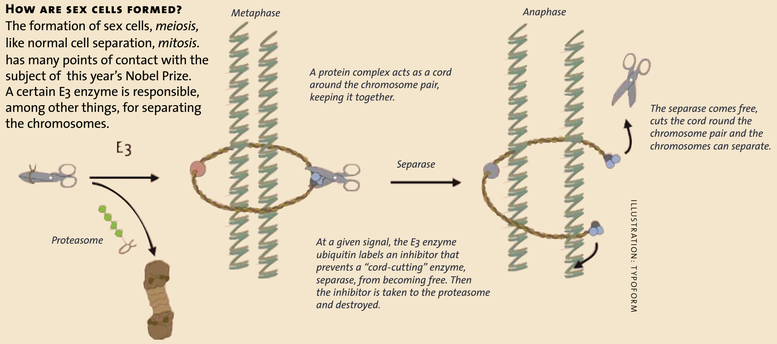


ILLUSTRATION: TYPOFORM

Further reading!

- **Information on the Nobel Prize in Chemistry 2004:** *www.nobelprize.org*
- **Scientific American** nr 1/2001
- **The Road to the Proteasome,** *http://embojournal.npgjournals.com/cgi/content/full/17/24/7151*
- **About Ubiquitin,** *www.free-definition.com/Ubiquitin.html*
- **The Ubiquitin System**, *http://homepages.bw.edu/~mbumbuli/cell/ublec/*
- Ciechanover et al. Proc. Natl. Acad. Sci. USA, 77, *1365-1368*, 1980
- Hershko et al. Proc. Natl. Acad. Sci. USA, 77, *1783-1786, 1980.*

www.kva.se

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P.O. Box 50005, SE-104 05 Stockholm, Sweden
Tel. +46 8-673 95 00, fax +46 8-15 56 70, e-mail: info@kva.se, www.kva.se. Posters may be obtained free of charge, and may be ordered by telephone, fax or email.

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