Indian J Physiol Pharmacol 2005; 49 (1): 121–122

News

Nobel Prize in Chemistry, 2004

The Nobel Prize in Chemistry 2004 has been awarded to **Aaron Ciechanover, Avram Hershko and Irwin Rose** for "the discovery of ubiquitin-mediated protein degradation".

Aaron Ciechanover

Avram Hershko

Irwin Rose

Proteins are the building block of all cells. Most of early work in biochemistry was dedicated to elucidate the process of protein synthesis (five Nobel prizes). Though it was known as early as in 1950's that protein degradation also needed energy, the paradox of energy requirement for a destructive process was resolved only in 1980 (1). Cell-free extracts of reticulocyte as model to study the energy dependent process of degradation was developed by Goldberg in 1977 (2). Aaron, Avram and Irwin while using this model serendipitously discovered that extract could be divided into two components, each inactive on its own. This discovery was made while they were attempting to remove hemoglobin from extract. Next year, they identified the active component (later named ubiquitin). The breakthrough was achieved in 1980 when they demonstrated that ubiquitin binds covalently to various proteins and that this 'kiss of death' was essential step in protein degradation (3). Later numerous enzymes associated with ubiquitin mediated protein degradation were identified.

Physiological relevance of these processes has now been deciphered using immunological methods developed by Avram and co-workers. We now know 30% of newly synthesized protein, unable to pass quality control, are degraded. The protein to be degraded, marked for death by polyubiquitination, are broken in proteasomes. Many processes like cell division, DNA repair, quality control of newly-produced proteins, and important parts of the immune defence are governed by this system. Cervical cancer and cystic fibrosis are two examples of diseases of improper destruction.

These Nobel Laureates in chemistry have explicated the molecular background to a protein regulation system of great importance for all cells. With each passing day newer functions controlled by ubiquitination are being discovered. It has become an interesting area of research for medicines against various diseases. A medicine already being tested clinically is the proteasome inhibitor Velcade (PS341) which is used against multiple myeloma, a cancer disease that affects the body's antigen-producing cells.

REFERENCES

1. Ciechanover A, Heller H, Elias S, Haas AL, Hershko A. ATP-dependent conjugation of reticulocyte proteins with the polypeptide required for protein degradation. *Proc Natl Acad Sci USA* 1980; 77: 1365–1368.

2. Etlinger JD, Goldberg AL. A soluble ATP-dependent proteolytic system responsible for the degradation of abnormal proteins in reticulocytes. *Proc Natl Acad Sci USA* 1977; 74; 54–8.

3. Ciechanover A, Hod Y, Hershko A. A heat-stable polypeptide component of an ATP-dependent proteolytic system from reticulocytes. *Biochem Biophys Res Commun* 1978; 81: 1100–1105.

Web source

The Nobel Foundation. *http://nobelprize. org/chemistry/laureates/2004/index.html*

Nobel Prize in Physiology or Medicine, 2004

The Nobel Prize in Physiology or Medicine 2004 has been awarded to **Richard Axel** and **Linda B Buck** "for their discoveries of odorant receptors and the organization of the olfactory system".

Richard Axel

The sense of smell, olfaction, is the most primitive and primal of all the senses of living organisms. Yet, the olfaction lagged behind other senses as far as our understanding was concerned. The early attempts to identify 'primary smell senses' (as analogous to primary colours in vision) failed as miserably as our attempts to influence human behaviour with commercially available scents.

Linda B Buck

In 1991, with the seminal study of Linda and Richard, then working together, our understanding nose dived into molecular aspects of olfaction (1). The reductionist tools of molecular biology gave insight into the perceptual world of fragrance. Earlier work by others had shown that olfaction was associated with changes in the intracellular concentration of different types of secondary messengers. Using assumptions that odorant receptors will be GTP-coupled and that they will be expressed selectively only in olfactory epithelium Richard and Linda identified a large family of G-protein coupled receptors (ORs) in mice.

This knowledge put forth an astonishing problem of linking ~1,000 OR genes (3% of total genes) in human and our ability to perceive and discriminate ~10,000 closely related odours (2, 3). How did the brain know what the nose smelt? It was shown that each odorant stimulates more than one OR. Peter Mombaerts and Fan Wang in Richard Axel's lab showed that each receptor neuron expresses only one type of OR and that different neurons are distributed randomly in the olfactory epithelium. They also showed that all the neurons that express same receptors converge onto a single locus in olfactory glomeruli and more importantly these points are invariant in all the individuals of a species. Thus, there is a sort of anatomical map of different ORs and different odorants result in stimulation of precise but overlapping maps.

Linda's group has found a separate set of receptors for vomeronasal organ and identification of taste receptors in mammals. Richard Axel's group has been working on mammals and insects to further understand olfactory sensation and functional correlates of anatomical maps.

REFERENCES

1. Buck L, Axel R. A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. *Cell* 1991; 65: 175–187.
2. Axel R. The molecular logic of smell. *Sci Am* 1995; 2730: 154–159.
3. Buck LB. Information coding in the vertebrate olfactory system. *Annu Rev Neurosci* 1996; 19: 517–544.

Web sources

1. Press Release : The 2004 Nobel Prize in Physiology or Medicine 4 October 2004. *http://nobelprize.org/medicine/laureates/2004/press.html*
2. Axel R. Scents and Sensibility : Towards a Molecular Logic of Perception. In Columbia 250 Symposia. Brain and Mind. Columbia University video archive. May 13, 2004. *http://c250.columbia.edu/c250_events/symposia/brain_mind/brain mind_vid_archive.html*
3. Linda B Buck. The Logic of Smell. In Nobel Symposia : Beyond Genes. The Nobel Foundation. Dec & 2004. *http://nobelprize.org/medicine/laureates/2004/buck-symp.html*