Nobel Prize in Physiology or Medicine 2016[1]

Shekhar C Mande and Jyoti Rao

The Nobel Prize in Physiology or Medicine 2016 was awarded to Yoshinori Ohsumi of the Tokyo Institute of Technology, Japan, *for his discoveries of mechanisms for autophagy* [1].

Autophagy is a commonly used word in biology. It derives from the Greek words – 'auto' meaning 'oneself', and 'phagy' meaning 'eating', and was coined by the Belgian scientist Christian de Duve. The 1974 Nobel laureate for Physiology or Medicine, de Duve, had discovered cellular compartments, named 'lysosomes', in which most of the worn out biological material of the cell is degraded. Explained beautifully by Daniel Klionsky in an insightful video on 'Science and Art Collaboration' at the University of Michigan: "Autophagy is the process in which our cells break down parts of themselves. As with many things, parts of cells wear out, and how the cells get rid of these things – that are no longer functional – is the process of autophagy". However, digestion of their own components by cells remained enigmatic for a long time. Why would a cell compel degradation of its own constituents? Moreover, what are the underlying molecular mechanisms of autophagy? These questions were addressed in a series of experiments carried out since the early 1990s by Yoshinori Ohsumi. These experiments have led to the current understanding of autophagy and its immense physiological relevance. The press release of the Nobel committee [2] states, "Ohsumi's discoveries led to a new paradigm in our understanding of how the cell recycles its content. His discoveries opened the path to understanding the fundamental importance of autophagy in many physiological processes, such as in the adaptation to starvation or response to infection. Mutations in autophagy genes can cause disease, and the autophagic process is involved in several conditions including cancer and neurological disease." Thus, autophagy is now believed to play an important role in many diverse cellular processes

Dr. Shekhar Mande, Director of the National Centre for Cell Science, is a structural computational biologist, with an interest in studying *Mycobacterium tuberculosis*.

Jyoti Rao, a scientist at NCCS, Pune, is a microbiologist with an interest in ecology and sociobiology, and exploring the interface of science and art.

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Figure 1. Yoshinori Ohsumi, Tokyo Institute of Technology, Tokyo, Japan.

such as ageing, development, response to infections, neurodegeneration, etc.

Lysosomes are subcellular compartments, which serve as the workhorse for the degradation of biological material. Cells have evolved clever molecular strategies for carrying the materials destined for degradation to the lysosomes, and then enzymatically degrading them. A remarkable step in the process of autophagy is the formation of a new double membrane-bound subcellular compartment called the 'autophagosome'. Autophagosomes concomitantly sequesters the material to be degraded while it is being formed, and eventually fuses with lysosomes, allowing enzymes in the lysosomes to degrade the material. Ohsumi designed an elegant experimental strategy using baker's yeast to test what the outcome would be if these enzymes are inactivated. Baker's yeast was a convenient model for use because the cells are large enough to be observed with a light microscope. It was known that autophagy can be induced under nutrient starvation. Therefore, Ohsumi subjected strains of yeast that were deficient in proteases[2] to nutrient starvation, and observed them under a microscope. He found that within a few hours, vesicles (autophagic bodies) accumulated within the lysosomes [3]. This was the first instance of a step in the process of autophagy being observed, which was made possible by the fact that these yeast cells were deficient in proteases. If proteolytic enzymes had been present, the cellular material would have been degraded instantly, and the phenomenon could not have been spotted. It is no wonder therefore, that no one had been able to detect this phenomenon earlier. Ohsumi acknowledges that his love for microscopes led him to make the fundamental observation [4]. Thus, the combination of a clever experimental strategy, use of yeast as the model, and visual examination under a microscope, laid the foundation for discovering the mechanisms of autophagy.

[2] Enzymes that degrade proteins.

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The discovery of autophagy in yeast soon led to a search for the genes involved in this process. Ohsumi was once again at the forefront of identifying these genes. He conducted a genetic screen in yeast and analyzed mutants which were defective in au-

tophagy [5]. This was much before the importance of autophagy in physiology and disease was recognized. As of today, around 15 genes are known to be involved in autophagosome initiation and maturation, which comprise a cascade of events involved in autophagy. This cascade includes formation of a double layered membrane structure (autophagosome) under appropriate conditions, which encloses and isolates the cellular components to be degraded, fusion of this vesicle with lysosomes, release into or activation of lysosomal degradation enzymes in the vesicle, and finally, degradation of biological macromolecules into their respective building blocks such as nucleotides, amino acids, etc. The degraded components are then recycled by the cells, thereby promoting cell survival. The genes which participate in all these processes, which were identified through the genetic screens performed by Ohsumi and other groups, are now collectively termed as the *'ATG* genes' [6].

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The molecular mechanisms of autophagy have now been demonstrated to be conserved in many species – from yeast to humans. In the past 15–20 years, there has been a growing appreciation for the role of autophagy in diverse cellular processes, but more important has been the recognition of the correlation between dysfunctional autophagy and many different disease conditions. For example, loss of autophagy in the central nervous system was found to cause increased neurodegeneration in mice [7, 8]. The Beclin 1 protein, encoded by a mammalian autophagy gene, has been shown to inhibit tumorigenesis, thereby acting as a tumour suppressor in different cancers [9]. Similarly, decreased expression of many autophagy proteins is related to the progression of tumours in humans. Thus, the increasing awareness about the link between autophagy and disease conditions has opened up avenues for understanding disease processes better and designing possible intervention strategies.

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Thanks to the work of Ohsumi and others, the progress made over the last 20 years in understanding autophagy has revealed that autophagy is an important physiological process, which plays diverse roles. It is required for recycling cellular components, and

also provides a quality control mechanism by eliminating damaged biological macromolecules. In starving cells, autophagy provides fuel for cellular processes. During invasion by foreign organisms, autophagy acts to eliminate the pathogen from the host. Autophagy also regulates cell growth, development and differentiation, and thereby provides effective control to prevent unregulated growth, such as that observed in cancer. All the correlations of autophagy and cellular processes can be traced to the initial discovery of Ohsumi in 1992.

Ohsumi remains steadfastly active in the field, passionately attempting to further decipher the details of the mechanisms of various steps of autophagy. On the website of the Tokyo Institute of Technology, he has the following advice to offer to young researchers [10]:

"So my message to all of you, who want to pursue a career in science, is to do what no one else is doing, and do what you find truly interesting. Research isn't easy. However, if you're really drawn to a subject and you're interested in it, you'll certainly overcome all the obstacles, even if, say, your work isn't appreciated for a time. You only live once. Others aren't interested in trivia. In the end, you have to want to taste the pleasures of success after all is said and done."

Suggested Reading

[1] http:// www.nobelprize.org/nobel_prizes/medicine/laureates/2016/

[2] http://www.nobelprize.org/nobel_prizes/medicine/laureates/2016/press.html

[3] http://www.titech.ac.jp/english/ research/stories/ohsumi.html

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[6] D J Klionsky, et al., *Dev. Cell*, Vol.5, pp.539–545, 2003.

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[9] X H Liang, et al., *Nature*, Vol.402, pp.672–676, 1999.

[10] http://www.titech.ac.jp/english/ research/stories/ohsumi.html

Address for Correspondence
Shekhar C Mande
Jyoti Rao*
National Centre for Cell Science
Ganeshkhind
Pune 411 007, India.
Email:shekhar@nccs.res.in
*jyoti@nccs.res.in

Box 1. Glossary

Amino acid: Organic acid which contains at least one amino group ($-NH_2$) and one carboxyl group (COOH) in each molecule. Amino acids are the building blocks (monomer units) of proteins, which are chains (polymers) of amino acids linked through peptide bonds. Consequently, degradation of protein molecules during autophagy, which is effected through breaking these peptide bonds, results in amino acids.

Autophagosome: An intracellular membrane-enclosed bubble-like compartment (vesicle) that is formed when a double membrane surrounds and isolates a portion of the cell's cytoplasm containing components targeted to be degraded. It could be considered as the functional unit of the process of autophagy, since it transports cell debris to the cell's lysosome to be broken down.

Autophagy: Self-digestion of dysfunctional or unnecessary cellular components through the action of membrane-enclosed compartments of the cells called lysosomes, which contain digestive enzymes. This process can serve several functions, and is often a defensive or self-preservation mechanism.

Baker's yeast: A species of yeast, *Saccharomyces cerevisiae*, which is commonly used in baking as a leavening agent, due to its ability to appropriately ferment the sugars present in dough into carbon dioxide.

Genetic screen: A laboratory procedure used to artificially create mutations in genes, *i.e*., introduce changes in the DNA, and identify organisms with these mutations (mutants). Introduction of a mutation usually leads to a change in the functioning of the gene, and consequently, difference(s) in the physical properties (phenotype) that are determined by this gene, thus helping in identifying the genes involved in certain cellular processes and the function of unknown genes.

Lysosome: A membrane-enclosed bag-like structure/organelle in the cell, which contains digestive enzymes, *i.e*., proteins that selectively catalyze the degradation of specific molecules.

Neurodegeneration: Death or loss of function (degeneration) of cells of the nervous system, such as the neurons in the brain and spinal cord.

Nucleotide: Basic building block of nucleic acids (RNA and DNA), which are long chains (polymers) of nucleotides. Degradation of nucleic acids results in this chain being broken into its constituent nucleotides, each of which consists of a sugar molecule (deoxyribose in DNA / ribose in RNA) linked to a phosphate group and a nitrogen-containing base (adenine / cytosine / guanine / thymine / uracil).

Tumorigenesis: The process of development of a tumor, *i.e*., a mass of tissue resulting from abnormal growth. Tumors can be benign (non-cancerous) or malignant (cancerous).

Vesicle: A membrane-enclosed sac-like structure.