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ROLE OF AUTOPHAGY AND HISTORY OF ITS DISCOVERY

АННОТАЦИЯ. Данная статья посвящена процессу аутофагии и механизмам, лежащим в основе данного процесса. В статье представлена информация об истории открытия феномена и исследованиях, открывших новый путь в понимании фундаментальной значимости аутофагии во многих физиологических процессах, таких как адаптация к голоданию или ответная реакция на инфекцию. Основная цель статьи заключается в ознакомлении читателя с новыми, неизвестными до недавнего времени, функциями аутофагосом в клетках живых организмов и механизмом образования самих органелл - аутофагосом.

КЛЮЧЕВЫЕ СЛОВА: Аутофагия, аутофагосомы, лизосомы, Кристиан де Дюв, Есинори Осуми, переваривание, органелла, гены, хлебопекарные дрожжи, везикулы, ферменты, голодание.

ABSTRACT. This article is devoted to the process of autophagy and mechanisms underlying it. The article presents information on the history of phenomenon's discovery and researches that have opened a new path in understanding of autophagy's fundamental importance in many physiological aspects, such as adaptation to starvation and infection response. The main purpose of the article is to get acquainted with new, recently discovered autophagosome's functions in cells of living organisms, as well as to understand the mechanism underlying autophagosome formation.

KEY WORDS: Autophagy, autophagosomes, lysosomes, Christian de Duve, Yoshinori Ohsumi, degradation, organelle, genes, bakery yeast, vesicles, enzymes, starvation.

Relevance of the topic

The concept was already known in 1960's when scientists first discovered large cargo inside of lysosomes. However, there was no particular knowledge of mechanisms that took place in the process of large protein complexes' and damaged organelles' digestion. Due to further investigations that were made by Yoshinori Ohsumi we now know those mechanisms. Researches today are well aware of the consequences of autophagy disruption. The emerged knowledge is now used in medicine.

Degradation – a central function in all living cells

In 1950's Christian de Duve discovered a new organelle, containing different enzymes that digest carbohydrates, proteins and lipids. The scientist called this organelle "lysosome". The main role of a lysosome in a cell include degradation of different cellular components. Although the digestion workstation was already spotted it was still unclear how large cargos, such as whole organelles or even parts of cellular membrane could be transferred into lysosomes. The answer was simple, cells had to have a specialized transporting organelle that was able to deliver such cargos to the lysosomes. After few years of research due to biochemical and microscopic analysis a new organelle was found. It was called "autophagosome". The main principle is simple: when an autophagosome forms, it engulfs that part of the cellular that has to be digested, after that it combines with the lysosome and cargos there are being degraded into smaller parts. It is very important that at the end of this process a cell gets new material for its renewal as well as a lot of nutrients. (*Figure 1*).

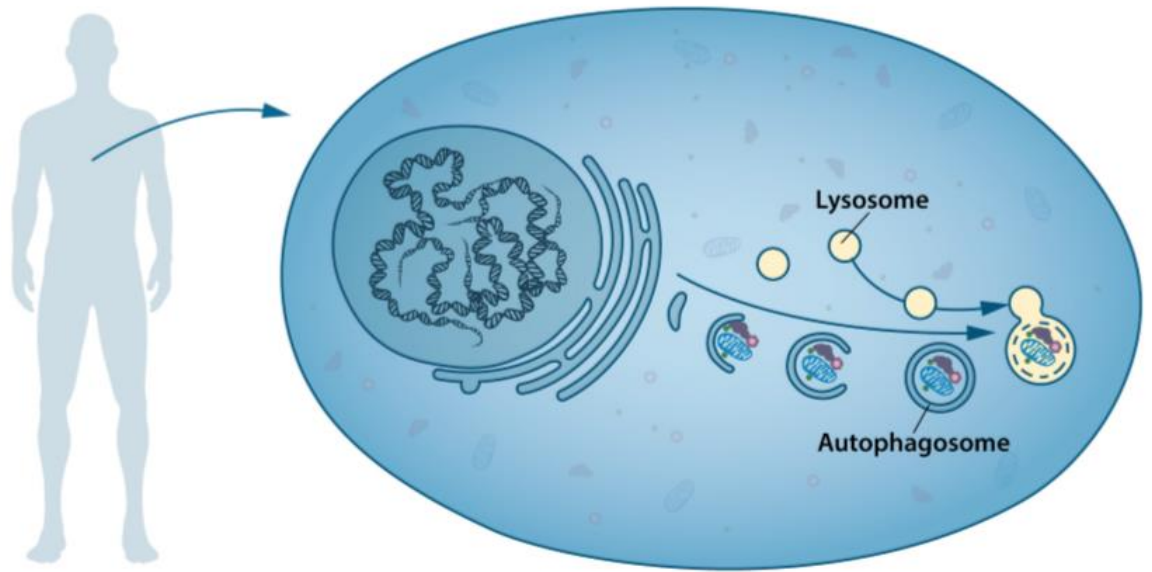


Figure 1: The autophagosome formation

A groundbreaking experiment

In 1988 Yoshinori Ohsumi started his research in a field of protein degradation. In his experiments he used bakery yeast's vacuoles, organelles that correspond to the lysosomes in our cells. Due to the sizes of bakery yeast's vacuoles, the scientist wasn't certain whether autophagy even existed there. To check his assumptions Ohsumi cultured yeast that lacked vacuolar degradation enzymes and made cells starve in order to stimulate autophagy. His strategy worked in a few hours; the scientist got yeast vacuoles filled with autophagosomes. It was now clear that autophagy existed in yeast cells. However, the most important outcome of his experiment was that now he had an opportunity to find specific genes which were responsible for autophagy (Figure 2).

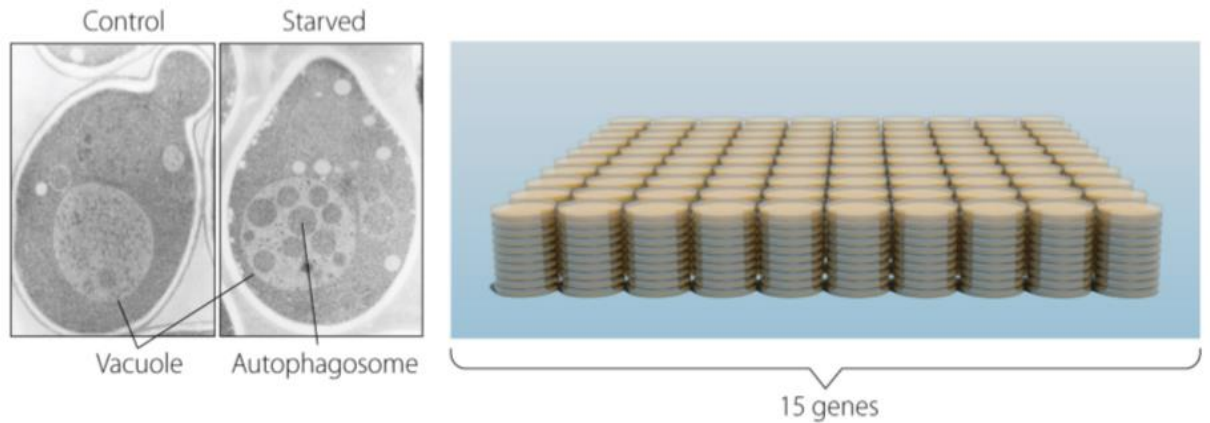


Figure 2: Mutated yeast cells. Control and starved cells side by side

Autophagy genes are discovered

Now Ohsumi had everything to identify autophagy genes. He exposed his mutated yeast strains to a chemical that had to damage genes randomly and then made cells starve to initiate autophagy. It was a success, within one year of his research Ohsumi managed to identify first autophagy genes. Further research showed which proteins were encoded by those genes, those proteins were functionally characterized. It is now known that the process of autophagy is controlled by a cascade of proteins and their complexes, each of which has its own role regulating different autophagy stages (Figure 3).

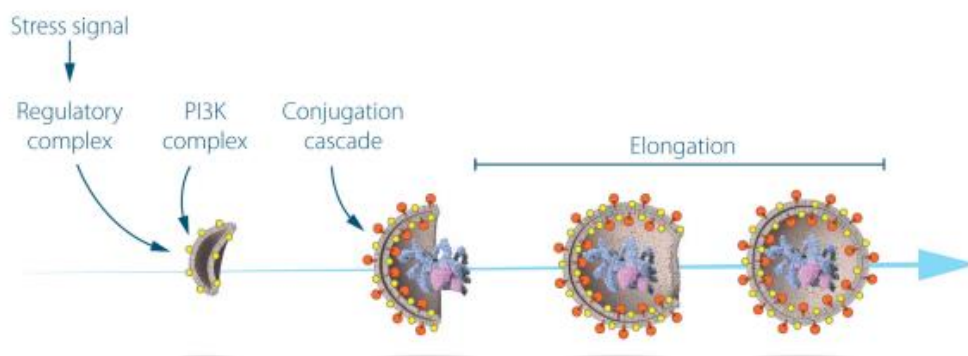


Figure 3: mechanism by which proteins and protein complexes promote distinct stages of autophagosome formation

Autophagy – an essential mechanism in our cells

Due to further investigations it became clear that a corresponding mechanism also exists in other organisms including humans.

Autophagy is in charge of different physiological functions where cellular components need to be recycled and degraded. It can also provide great amounts of energy and building blocks for cellular renewal. Autophagy is a great fast response mechanism that helps an organism to cope with different types of stress, such as starvation or infection. Due to its high efficiency this process doesn't only provide cell with goods, but it also does the clean-up. It reduces the level of cell's waste content, every piece of damaged or worn-out components that spoil cell's functioning are purged by autophagosomes. This process is also involved in cell's quality control system, that doesn't let damaged proteins and organelles contribute negative consequences of aging. Autophagosomes have an ability to eliminate invading viruses or bacteria and that is vitally important function for organisms. Damaged autophagy genes may lead to the development of diseases that occur in the elderly, such as Parkinson's disease or type 2 diabetes etc. Incorrect autophagy mechanism function may also lead to cancer. Today scientists work on aiming autophagy against various types of diseases. Autophagy knowledge is now used by many nutritionists who suggest day or two starvation in order to cleanse the body.

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