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Harald Renz, MD

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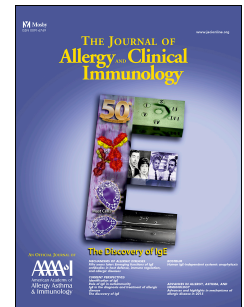
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Revision - Unmarked Version

Editorial

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Autophagy – Nobel Prize 2016 and Allergy and Asthma Research

Harald Renz, MD

Institute of Laboratory Medicine

Philipps University Marburg

Baldinger Straße

35043 Marburg

Phone: +49-(0)6421-5866235

Fax: +49-(0)6421-5865594

Email: harald.renz@uk-gm.de

The 2016 Nobel Prize in Physiology or Medicine was awarded to Yoshinori Ohsumi, Professor at the Tokyo Institute of Technology for “Recycling”. Recycling on the cellular level is termed autophagy and is a fundamental process for degrading and recycling cellular components. It is now well regarded that this process plays an important role not only in physiological cellular homeostasis, but also in a variety of diseases.

The story starts about 60 years ago with the discovery of the lysosome. The lysosomes are specialized organelles containing enzymes that digest proteins, carbohydrates and lipids. For the discovery of this process Christian de Duve, a Belgian scientist, was awarded the Nobel Prize in Physiology or Medicine in 1974. The next important step in this journey was the observation that under certain conditions large cellular components and sometimes whole organelles can be found inside the lysosomes. In order to understand the mechanism how such large cargos get into the lysosome, a new type of vesicle was discovered and named autophagosomes, describing a process of “self-eating”. A few years later, researchers discovered an additional system to degrade proteins, but not as large “fragments”, but one-by-one. This system was termed the proteasome, and Aaron Ciechanover, Avram Herskho and Irwin Rose were awarded the Nobel Prize in Chemistry in 2004 for the discovery of ubiquitin-mediated protein degradation (Table 1).

Ohsumi now discovered many steps and the molecular tools involved in this complex process of recycling¹⁻⁴. He recognized very soon that external cellular stress such as heat, radiation, starvation and infection turn on the cellular recycling machinery in order to promote survival of the cells. Today more than 14000 proteins have been

catalogued, among them about three dozen proteins involved in autophagy and 113 regulators involved in recycling of survival-eminent materials. Ohsumi conducted a series of brilliant experiments in the early 1990s using the bakers' yeast *saccharomyces cerevisiae* to identify the essential genes for this process. Through random mutation he knocked out one after the other of these relevant genes and elucidated the underlying mechanism for autophagy. Through this process he discovered 15 genes, originally termed ATG 1-15, and today renamed ATG Genes.

Today a disturbed process of autophagy has been linked to many diseases including Parkinson's Disease, Type-II diabetes, Alzheimers' Disease, certain cancers and many infections. Furthermore, this process also regulates our own appetite. This process starts in certain neurons in the hypothalamus where under starvation mediators are produced under the control of autophagy. These mediators then trigger our appetite.

Recent data indicate that autophagy plays also an important role in the inflammatory pathways in allergy and asthma. In this Journal Radonjic-Hoesli and co-workers⁸ investigate a mechanism which leads to the release of cytotoxic granules from eosinophils. Cytolysis is one of these mechanisms which lead to the release of intra-granules, so termed clusters of the eosinophil granules. The investigators employed *state-of-the-art* technologies including time-lab fluorescence microscopy, electron microscopy, and immuno-histochemistry to prove that cytoplasmic membrane disintegration and the release of intra-granule depends on a signaling pathway including receptor-interacting protein kinase-3 (RIPK3) and mixed lineage kinase-like protein (MLKL). Importantly, if they activate autophagy in eosinophils, this counter-regulates eosinophil cytolysis. Therefore, the authors not only demonstrate in a very

elegant fashion a new pathway for eosinophil cytolysis, they were also able to link cytolysis with counter-regulating autophagy, open new pathways for at least experimental intervention.

Autophagy has been also previously linked to the pathogenesis of asthma. Although, little work has been carried out in this regard so far, there are convincing data available linking autophagy in airway epithelium, and autophagy might be essential for bronchial epithelial mucus secretion, as has been shown in an allergic asthma model. Interestingly, autophagy, rather than ER-stress, contributed to IL-13 induced eotaxin-3 peptide secretion also from human airway epithelial cells⁵⁻⁷. A link between the epithelial-mesenchymal transition (EMT) unit and autophagy has been also previously shown in other models of allergic asthma^{9,10}. A further link of autophagy and asthma has been established for human rhinovirus, respiratory syncytial virus, corona virus, adeno virus and influenza A virus through the role of autophagy in the defence against respiratory viruses, which represent a major exacerbation-factor of asthma. In this regard, autophagy impairs replication of viruses, and autophagy is enhanced in asthmatic airways^{11,12}. Finally, a single nucleotide polymorphism (SNP) has been discovered in the ATG5 gene which is one of the genes regulating autophagy. This polymorphism was associated with asthma and low FEV1 levels¹³. ATG5 transcripts are enhanced in acute asthma exacerbation in nasal epithelial cells. This could further strengthen the functional link between autophagy and asthma (exacerbation).

In summary, to study autophagy opens a new field in allergy and asthma research. Autophagy is a key process involved in immune responses, inflammation and anti-viral immunity. Further studies are warranted in order to establish firmly this link and

also, more importantly, explore the possibilities of therapeutic intervention in this regard. We are looking forward to reading more papers about autophagy, allergy and inflammation in this *journal*.

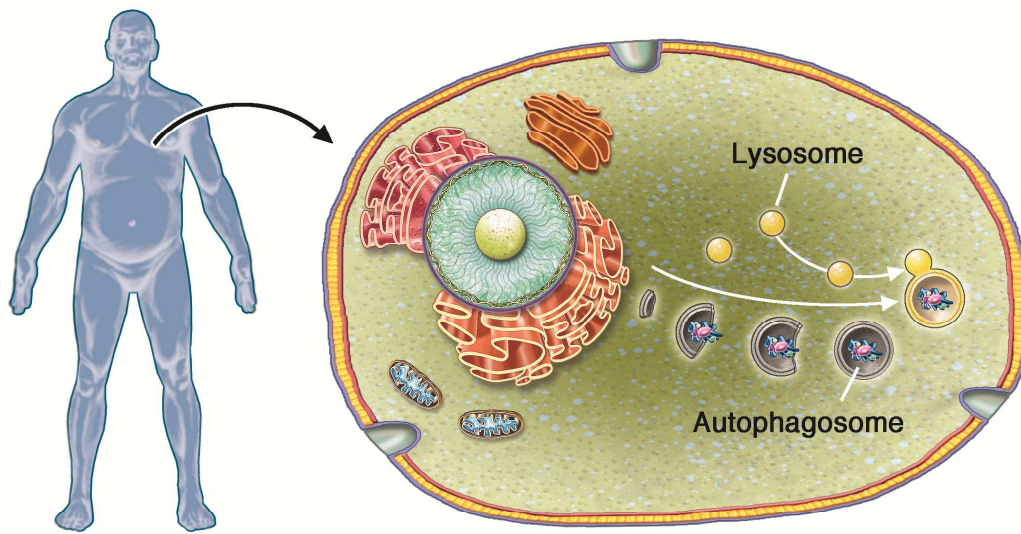
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Table 1: Key discoveries on the journey to the autophagosome

1955	lysosomes	de Duve
1966	function of lysosome ("autophagy")	de Duve
1968	autophagosome	Arstila, Trump
1979	proteasome	Harshko, Chiecanova, Rose
1980	ubiquitin	Wilkinson, Urban, Haas
1992	autophagosome as machinery of autophagy	Ohsumi
1993	the first autophagy gene ATG1	Ohsumi

Figure 1: Autophagy and its role in disease

A**B**