Healthcare industry BW

# Autophagy – a stupid idea?

**The phenomenon of autophagy seems to be one of nature's fairly stupid ideas, at least at first sight. On closer inspection, however, the mechanism turns out to be a smart move by the cell to keep itself clean and intact. The term autophagy, or autophagocytosis, comes from the Greek and means something like "to eat oneself". During normal cell operation, waste accumulates that needs to be disposed of in some way as it would otherwise impair crucial cellular processes. But even in times of starvation, cells behave just as the body as a whole does: the system does not become inoperative immediately and die, but draws on its reserves. On the cellular level, this happens by way of autophagy. Dr. Jörn Dengjel and his group of researchers at the Centre for Biological Systems Analysis (ZBSA) at the University of Freiburg have discovered new regulatory mechanisms of cellular recycling.**

Migratory birds do it in order to survive their long journeys, insects do it when they emerge from the larva to take on the adult form: they shrink organs and tissue in order to generate energy or raw material for new organs. On the cellular level, the survival of important cell organelles is guaranteed by the degradation of organelles that are of lesser importance. It is assumed that autophagy most likely developed in order to overcome cellular deficiency states. However, even under normal conditions, autophagy is a helpful process for maintaining the balance between the production of new cells and the degradation of old, no longer needed cell components. Mitochondria, to name but one example, have a lifespan of just ten days before they are degraded. Defective proteins remain limited in number due to constant renewal.

There are three types of autophagy – microautophagy, macroautophagy and chaperone-mediated autophagy. Microautography is the direct engulfment of cytoplasmic material into the lysosomes. Macroautophagy is the eradication of larger cell components such as protein complexes and cell organelles. In chaperone-mediated autophagy, a chaperone captures the proteins to be degraded and accompanies them to the lysosome. The area that all three types of autophagy have in common is that the cellular material is broken down in lysosomes.

## Cellular stress increases autophagy activity

Dr. Jörn Dengjel and his team at the University of Freiburg have been focussing on classical macroautophagy for around four and a half years. Their goal is to obtain a detailed understanding of the molecular mechanisms that can lead to autophagy.

Macroautophagy differs from other autophagic processes by the formation of an autophagosome with a membrane bilayer. A closer look at the processes makes it clear why this is so. "In cells, new

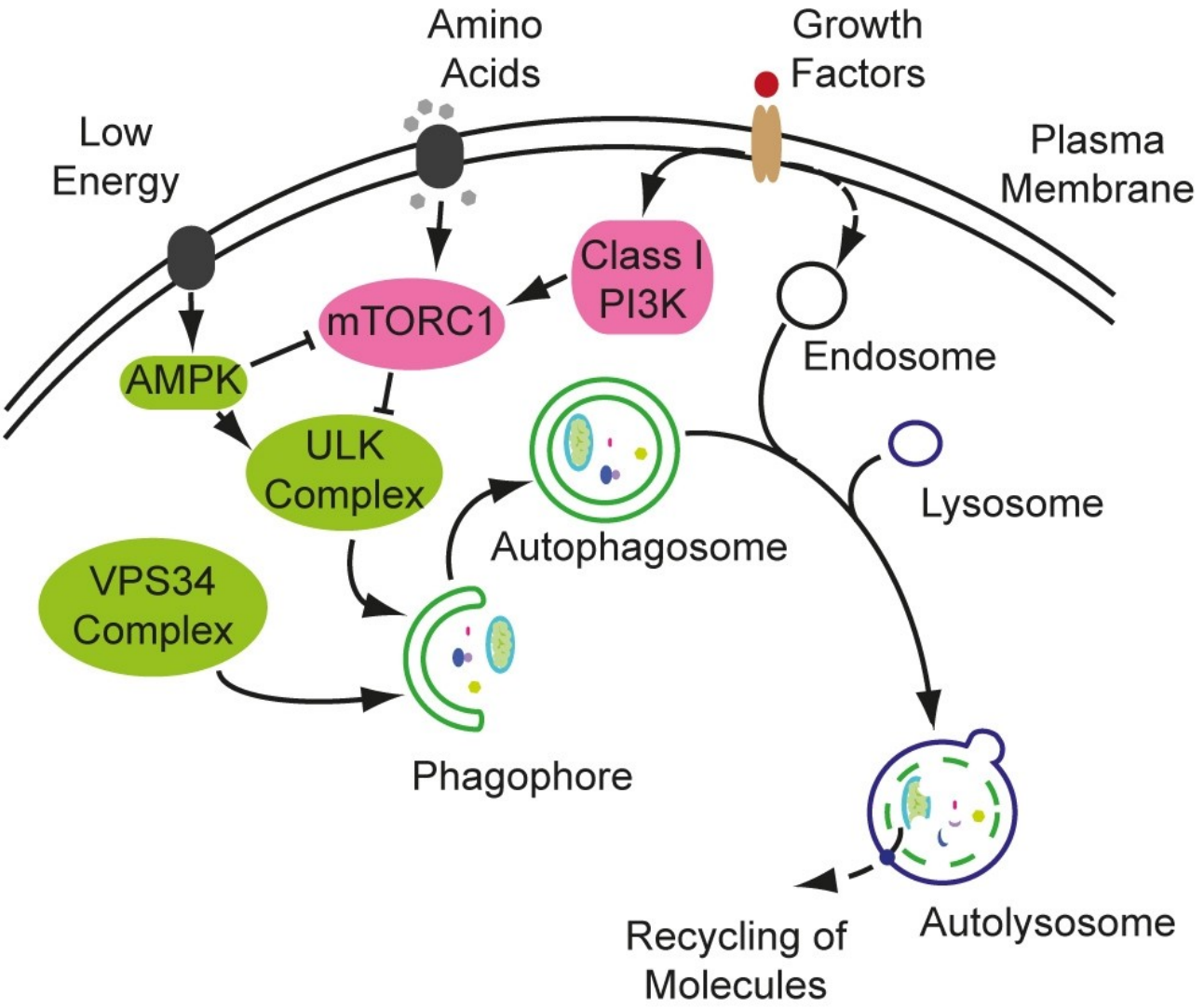

Jörn Dengjel's team is focussed on autophagy (Dr. Jörn Dengjel, back row 4th from the left)


membranes can only be formed by vesicles, which are enclosed by a lipid bilayer," said Dengjel. "The flattening of these vesicles automatically leads to a membrane made of two layers." As it gets bigger, the membrane bends like a sickle and encloses the garbage. But where do the components for making the membrane larger come from? "There is no agreement between scientists on where the lipids required for the lipid bilayer come from," said the biochemist, going on to add, "they seem to come from everywhere, from mitochondrial vesicles, from those of the endoplasmic reticulum and the plasma membrane."

Dengjel also knows what triggers autophagy. "Any type of cellular stress leads to the increased formation of autophagosomes," said Dengjel referring to stress factors such as nutrient deficiency or UV irradiation. Dengjel and his colleagues make use of this knowledge by exposing certain mammalian cell cultures to hunger stress. The researchers reduce the amount of amino acids, glucose or growth factors in order to explore the outcome of certain stress factors. "Every type of stress triggers a specific form of autophagy," said Dengjel. The composition of the autophagosomes alters considerably depending on the type of stress to which the cells are exposed. Cells that are deprived of amino acids break down larger numbers of ribosomes as they do not have the building blocks required for making proteins.

## Many things relate to ULK

Quantitative mass spectrometry is the major tool used by Dengjel's 11-member team that specifically focusses on the spatio-temporal protein dynamics during autophagy. They are focussing on the proteome as a whole, which enables them to find out whether proteins occur more frequently in certain tissues, cells or even organelles than in others. This allows conclusions to be drawn on the




Signals that induce autophagosome formation: mTORC1 inhibits (purple) the formation of autophagosomes, active AMPK, ULK and VPS34 induce (green) the formation of autophagosomes.
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proteins that might be promising candidates for the molecular regulation of autophagy.

It is known that autophagy is preceded by a complex cascade of reactions involving proteins that can be varied in relation to the stress to which a cell is exposed. One of these proteins is AMBRA1, which has several phosphorylation sites. AMBRA1 is one of the causes of hunger-induced autophagy. The lack of growth factors leads to the removal of a specific phosphate group from AMBRA1, resulting in its activation and in the induction of autophagy.

mTOR (mammalian target of rapamycin) not only plays a key role in cell growth, but also in cellular self-digestion, i.e. autophagy. If the mTOR kinase is active, the cell grows and thrives and autophagy is suppressed. In contrast, cellular stress leads to the downregulation of mTOR1 activity, which in turn triggers autophagy. mTOR kinase is a master regulator and as such key in many essential molecular processes, and therefore unsuitable as a drug target.

The kinase ULK seems to be better suited for such purposes as it is crucial for the development of autophagosomes. "At present, a lot of research revolves around ULK," said Dengjel, commenting on the researchers' finding. "We are hoping to find that this specific kinase is a major regulator of autophagic processes." A decrease in intracellular energy results in the activation of AMP-K, which is an ubiquituous sensor of cellular energy. High levels of AMP therefore mean low levels of ATP, i.e. energy. AMP-K then activates (phosphorylates) the ULK protein kinase. This results in the initiation of

autophagy, which provides ATP and other macromolecules as energy sources to enable cell survival.

## How can autophagy be triggered or inhibited?

Autophagy plays a key role in every organism. This becomes particularly obvious when the process of autophagy is either too slow, too quick or faulty. The cells age more rapidly or are unable to fulfil their functions. Dengjel and his team are specifically focussed on the molecular mechanisms of autophagy: "We hope that deregulated autophagy processes will provide us with information about the pathology of certain diseases."

The team works closely with scientists from the Department of Dermatology at the Freiburg University Medical Centre with the goal of finding therapeutic targets for the treatment of hereditary skin diseases such as epidermolysis bullosa (EB). Moreover, it is assumed that the pathology of Alzheimer's and Parkinson's is, amongst other things, due to inefficient autophagy, which leads to slow but unpreventable changes in the brain. The plaques of Alzheimer's patients have been shown to contain neurons with large numbers of immature autophagosomes. Irradiation and chemotherapy have also been shown to trigger autophagy, which in turn might enable the cells to survive this stress and repair themselves.

Research also suggests that dietary restriction without malnutrition has a lifespan-prolonging effect. This form of stress triggers autophagy; the constant disposal process is kept at a high level, resulting in the clearing of unwanted, defective proteins.

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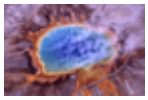

Stress and molecular defence mechanisms


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