New insights on how pathogens escape the immune system

The bacterium Salmonella enterica causes gastroenteritis in humans and is one of the leading causes of food borne infectious diseases. Thereby, the germ is able to trick the immune system. Researchers from the Cluster of Excellence for Aging Research CECAD led by Nirmal Robinson found a mechanism the pathogen uses. They hope to use the gained knowledge in the fight against cancer and other aging diseases. The results are published in the journal PLoS Pathogens.

Our immune system has various ways to deal with threats from the outside like pathogens. One of the defense mechanisms is a process called autophagy. "You can imagine autophagy as the vacuum cleaner of the cell", states Nirmal Robinson, leading scientist of the study. "It keeps the cell clean by clearing and degrading pathogens or damaged parts of the cell." Thereby toxic accumulation of cellular waste is prevented thus preserves the function of cellular organelles. A decline in autophagy also plays an important role in aging and longevity. If the genes linked to autophagy are deleted in animals like the nematode *C. elegans*, a decrease in lifespan and early onset of aging can be observed.

For his current research the bacterium *Salmonella typhimurium* was used. With 13823 reported cases in Germany in 2015, Salmonella infections belong to the group of common infectious diseases in humans. In healthy patients, symptoms are gone without antibiotic treatment, but in risk groups such as old people or immune-deficient persons, risk of serious illness remains. This pathogen is known to escape the process of autophagy. The goal of the researchers was to understand, how this pathogen identifies these processes and tricks them. They found that these two proteins called Sirtuin1 and AMPK, which sense changes in metabolism were reduced upon infection. Usually, loss of energy within the cell is detected by AMPK and it gets activated resulting in autophagy. Sirtuins are another class of metabolic sensors and their action is dependent on the metabolite NAD+. Together they help in inducing autophagy when there is an energy demand. During infection, energy loss occurs which normally would enhance autophagy. For Robinson´s research immune cells were infected with the pathogen. As expected, energy levels dropped. One would then expect that AMPK gets activated – and so it does, but only for a very short time. Although energy levels are low, the activation is not sustained. Further investigations on the process, revealed the mechanism. Soon after infection, the proteins required to activate autophagy get degraded in lysosomes (a membranous bag containing degrading enzymes). "The pathogen dismantles the machinery by targeting it for degradation and thereby escapes the immune system", says the researcher.

With improved understanding of the process of autophagy, Nirmal Robinson hopes to find ways to use it therapeutically. "We can learn to make use of this pathway." For example cancer cells upregulate autophagy to survive stressful conditions and to increase growth. They would like to manipulate the process to strengthen or to weaken the level of autophagy in the way they need it." He compares his research to an everyday-situation. "Pathogens are like burglars. By following a burglar we can also identify, where we are weak." By understanding host-pathogen interaction we can

understand more of our own self and how we are designed to protect ourselves against dangerous threats.

Original publication:

Ganesan R, Hos NJ, Gutierrez S, Fischer J, Stepek JM, Daglidu E, et al. (2017) *Salmonella* Typhimurium disrupts Sirt1/AMPK checkpoint control of mTOR to impair autophagy. PLoS Pathog 13(2): e1006227. doi:10.1371/journal.ppat.1006227

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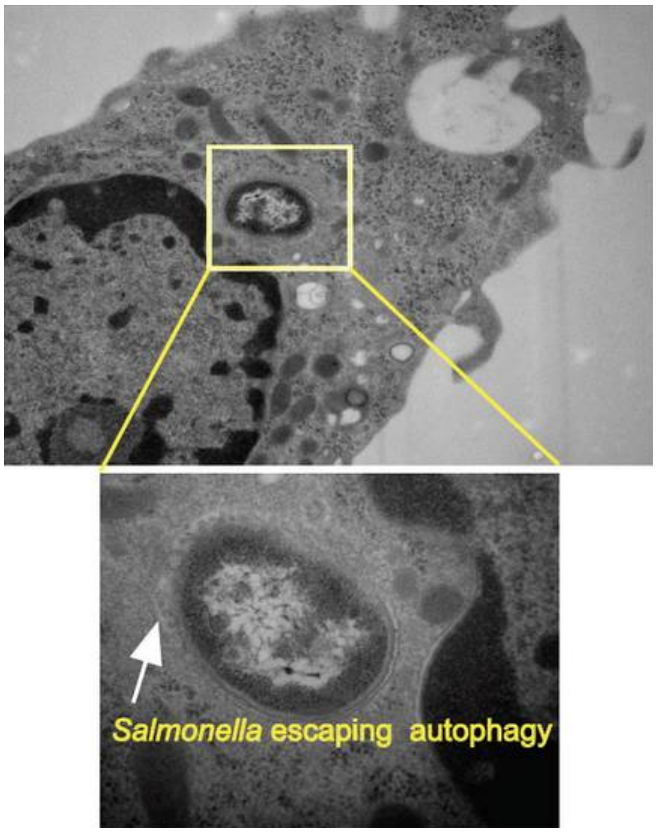

Image caption:
Autophagosomes are found as vesicles (sac) surrounded by double membrane. The white arrow head points to an incomplete double-membrane around *Salmonella* Typhimurium in a macrophage.