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**Pro-Autophagic Signal Induction by Bacterial Pore Forming Toxins**

M Husmann* et al

*Institute of Medical Microbiology and Hygiene, University Medical Centre, Johannes Gutenberg-University, Mainz, Germany*

Nucleated target cells of bacterial pore forming toxins (PFT) mount responses which allow them to survive moderate membrane damage. Autophagy has recently been implicated in the defense against PFT, but how this process is triggered is not known, and the significance of the phenomenon is not understood.

Using fluorescence microscopy, electron microscopy, and biochemical techniques we studied signaling pathways contributing to the autophagic response of human epithelial cells (HaCaT) to PFT from three structural families.

Two major pro-autophagic pathways were found to be uniformly activated. The first one is triggered *via* AMP-activated protein kinase (AMPK). AMPK is a major energy-sensor which induces autophagy by inhibiting target of rapamycin complex 1 (TORC1) in response to a drop of the cellular ATP/AMP-ratio, as is also observed in response to membrane perforation. The second pathway is activated by the conserved eIF2$\alpha$-kinase GCN2, which causes global translational arrest and promotes autophagy in response to starvation. The latter could be accounted for by impaired amino acid transport into target cells. Notably, PKR, an eIF2$\alpha$-kinase which has been implicated in autophagy-induction during viral infection, was also activated upon membrane perforation, and evidence was obtained that phosphorylation of eIF2$\alpha$ is required for the accumulation of autophagosomes in $\alpha$-toxin-treated cells. Inhibition of autophagy disrupted the ability of cells to recover from sublethal attack by *S. aureus* $\alpha$-toxin.

We propose that PFT induce pro-autophagic signals through membrane perforation dependent nutrient- and energy depletion, and that an important function of autophagy in this context is to maintain metabolic homoeostasis.

Keywords: autophagy, pore forming toxins, transient membrane damage, starvation