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LC3 punctae in IAV-infected cells do not represent double membrane autophagosomes but endosomes

Content

Influenza A virus (IAV) infection causes accumulation of the autophagy protein LC3 at intracellular membranes and the plasma membrane. M2 directly interacts with LC3 and enhances its accumulation. However, the proton channel activity of the viral M2 protein is critical for LC3 lipidation. Thus it resembles LC3 lipidation in response to compounds that raise the pH of vesicles. Many pathogens encode ion channels, and some of these have been shown to affect LC3 lipidation. We propose that this phenomenon represents a novel cellular pathway detecting a 'danger' signal of abnormal pH – i.e. 'erroneous neutrality' - of intracellular vesicles.

It has been proposed that M2 prevents fusion of autophagosomes to lysosomes during IAV infection. We provide evidence that IAV-induced LC3-positive intracellular vesicles are not double-membrane autophagosomes, but endosomal single-membrane vesicles. The formation of these endosomes appears to be induced by the virus and – due to the deacidifying action of the viral M2 protein – these vesicles are targeted by a novel LC3-lipidation pathway.

We have recently shown that recruitment of the lipidation complex ATG5-ATG12/ATG16L1 in IAV-induced LC3-lipidation critically depends on the C-terminal WD40 domain of ATG16L1. This domain is dispensable for macroautophagy, but also required for lipidation complex recruitment in LC3-assisted phagocytosis and iononophore-induced LC3 lipidation. Additionally, essential macroautophagy factors such as the ULK-1 complex and phosphoinositol-3-phosphate, are dispensable for LC3-lipidation during IAV infection.

In summary, IAV-induced LC3-lipidation is clearly different to canonical autophagy in that it targets single membrane vesicles and relies on a distinct ATG16L1 recruitment pathway. To identify genes involved in this novel cellular pathway, we performed a whole genome CRISPR knock out screen. This screen confirmed that this pathway uses the canonical lipidation machinery but none of the upstream factors of canonical autophagy. Work on novel genes involved in this pathway will be presented.

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Innate Immunity

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