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The p17 nonstructural protein of avian reovirus triggers autophagy enhancing virus replication via activation of phosphatase and tensin deleted on chromosome 10 (PTEN) and AMP-activated protein kinase (AMPK), as well as dsRNA-dependent protein kinase (PKR)/ eIF2 signaling pathways

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Autophagy has been shown to facilitate replication or production of avian reovirus (ARV); nevertheless, how ARV induces autophagy remains largely unknown. Here, we demonstrate that the nonstructural protein p17 of ARV functions as an activator of autophagy. ARV-infected or p17-transfected cells present a fast and strong induction of autophagy, resulting in an increased level of autophagic proteins Beclin 1 and LC3-II. Although autophagy was suppressed by 3-methyladenine or shRNAs targeting autophagic proteins (Beclin 1, ATG7, and LC3) as well as by overexpression of Bcl-2, viral transcription, C protein synthesis, and virus yield were all significantly reduced, suggesting autophagosomes in supporting ARV replication. Furthermore, we revealed that p17 positively regulates phosphatase and tensin deleted on chromosome 10 (PTEN), AMP-activated protein kinase (AMPK), and dsRNA dependent protein kinase RNA (PKR)/eIF2 signaling pathways, accompanied by down-regulation of Akt and mammalian target of rapamycin complex 1, thereby triggering autophagy. By using p53, PTEN, PKR, AMPK, and p17 short hairpin RNA (shRNA), activation of signaling pathways and LC3-II levels was significantly suppressed, suggesting that p17 triggers autophagy through activation of p53/PTEN, AMPK, and PKR signaling pathways. Furthermore, co-localization of LC3 with viral proteins, p62 with LAMP2 and LC3 with Rab7 was observed under a fluorescence microscope. Disruption of autophagosome-lysosome fusion by shRNAs targeting LAMP2 or Rab7a resulted in inhibition of viral protein synthesis suggesting that formation of autolysosome benefits virus replication. Taken together, the results suggest that ARV induces formation of autolysosome but does not induce complete autophagic flux.

Biography

Pei-I Chi is currently enrolled in a Ph.D. program at National Chung Hsing University, Taiwan. She has published research papers at the journal of biological chemistry and journal of Virology within three years of her master and Ph.D. program.

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