Karolinska Institutet

DEPARTMENT OF MICROBIOLOGY, TUMOR AND CELL BIOLOGY

Regulation of autophagy and mTOR during Semliki Forest virus infection

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av

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ABSTRACT

Semliki Forest virus (SFV) infection causes dramatic changes to the infected cell. For example, synthesis of most cellular proteins shuts off within 4 hours. The cell launches an antiviral response, forms stress granules and, as we found in the work leading up to this thesis, accumulates autophagosomes. Studies on various host responses to viral infections are relevant for understanding both viral pathogenesis and innate immunity against viruses.

In the past decade autophagy has gained prominence as a protein degradation system, and the autophagy field is only just beginning to understand how this cellular mechanism is modulated during viral infection, and what role it plays either in host cell defence, or in supporting viral replication. To be better equipped for studying autophagy, we developed a flow cytometry-based method for quantifying autophagosomes, in **Paper I**. The method was quicker and less subjective than most pre-existing methods. Then, in **Paper II** we investigated autophagy during SFV infection, and found that autophagosomes accumulated during infection not due to increased synthesis of new autophagosomes, but due to a decreased rate of degradation of autophagosomes. We also found that expression of the SFV glycoproteins was necessary for the accumulation of autophagosomes.

Our work on autophagy led us to investigate the status of mTOR, a regulator of autophagy, during SFV infection. mTOR is normally active under nutrient rich conditions, and inactive under nutrient starvation conditions. In **Paper III**, we showed that SFV infection caused mTOR to remain active during nutrient starvation. Unlike the effect on autophagosome accumulation, this effect on mTOR did not depend on expression of the SFV glycoproteins. Despite the maintenance of mTOR activity in SFV infected cells, inhibition of mTOR activity with rapamycin had no effect on SFV growth rate.

Collectively, the results presented in this thesis provide a novel, practical tool for measuring autophagy, as well as insight on how autophagy and its regulator mTOR are modulated during SFV infection.

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