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Autophagic flux without a block differentiates varicella from herpes simplex virus infection

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Abstract

Varicella-zoster virus (VZV) is a herpesvirus that causes a characteristic vesicular exanthem in humans with primary infection (varicella) or reactivation (zoster). We have previously observed that vesicular cells are filled with autophagosomes that are easily detectable by confocal microscopy after immunolabeling for the LC3 protein. Through a 3D imaging software program called Imaris we have quantitated autophagosomes as greater than 100 per cell. Similarly, we have assessed autophagy in VZV-infected monolayers after inoculation by the traditional method with infected cells at a ratio of one infected to 8 uninfected cells. Again, autophagosomes are easily detected, but their count is lower than that observed in human skin cells. As an additional control, we enumerated the autophagosomes in the Severe Combined Immuno-Deficient (SCID) Mouse model of VZV infection. In this model, human skin is inserted under the skin of the mouse and subsequently inoculated with VZV-infected cells. Again, autophagy was abundant in the VZV-infected skin and minimal in the mock-infected skin sample. Subsequently, we investigated autophagy following infection with sonically prepared cell free virus in cultured cells. After cell free virus inoculation, autophagy was detected in a majority of infected cells at all time points, but was less than that seen after an infected-cell inoculum. Finally, we investigated VZV-induced autophagic flux by two different methods (radiolabeling proteins and a dual-colored LC3 plasmid);

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both showed no evidence of a block in autophagy. Overall therefore autophagy within a VZV infected cell was remarkably different from autophagy within an HSV infected cell whose genome contains two modifiers of autophagy ICP34.5 and US11 not present in VZV