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Spotlight

Novel Molecular Insights into the Autophagy-Virus Arms Race

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Abstract

Autophagy can restrict virus replication so efficiently that viruses have evolved means to avoid or oppose the autophagic response. Two recent studies have revealed that the autophagy receptor optineurin restricts HSV-1 replication in neurons and have elucidated how the M2 protein of IAV inhibits the completion of autophagy.

Key words: Autophagy, Viruses, Virophagy, Autophagy receptor, Co-evolution.

Autophagy is a process that results in the degradation of cytosolic compounds via the lysosomal pathway. Autophagy requires several molecular complexes that are involved in three major steps: biogenesis of a cup-shaped membrane named phagophore (initiation); its growth/closure to form a double membraned vesicle called autophagosome, that sequesters substrates (elongation), and the fusion of autophagosomes with endo-lysosomes for cargo degradation (maturation). The selective targeting of cargoes relies on their interaction with selective autophagy receptors (SARs) [1] that also bind to lipidated forms of LC3 proteins for anchoring onto autophagic membranes. Apart from material recycling, autophagy can mediate cell-autonomous defense against viruses by degrading viral factors or particles, a process called viroplasm. In response, viruses have evolved means to interfere with the autophagy flux in order to oppose, evade or manipulate the autophagy response [2]. Two recent studies add to our knowledge on these intricate issues.

Since the SAR Optineurin (OPTN) is instrumental for central nervous system (CNS) homeostasis and because CNS primary infection with the herpes simplex virus-1 (HSV-1) is relatively well controlled, Ames *et al.* [3] examined a possible role for this SAR [4] during HSV-1 infection. The authors found that OPTN deficiency promotes HSV-1 replication level *in vitro*. OPTN-mediated restriction of HSV-1 involved the selective autophagic degradation of two important viral proteins, namely the HSV-1 transactivator VP16 and the HSV-1 envelope glycoprotein B (gB) (**Fig. 1**). This finding represents the first description of OPTN as an antiviral SAR. The results also consolidated the notion that post-translational phosphorylation of OPTN optimizes its cargo targeting function. Studies conducted with OPTN-deficient mice provided additional important information. First, OPTN-deficient mice showed extended neurological lesions and increased mortality upon infection, indicating that OPTN restricts neuro-invasion, encephalitis and neurodegeneration. Importantly, OPTN was also important for the activation of T lymphocytes and their recruitment to the CNS, revealing that OPTN impacts the anti-HSV-1 immune response at the systemic level. Second, OPTN was found to restrict neuron death during infection, notably through the autophagic degradation of RIPK1, a kinase crucial for necroptosis execution [5]. Thus, besides cell autonomous restriction of the virus, OPTN also influences adaptive immunity and regulates neuron survival, indicating that it is instrumental for the coordination of antiviral defense and tissue maintenance during HSV-1 infection.

Martin-Sancho *et al.* identified genes able to restrict the replication of the Influenza A virus (IAV) in macrophage-like cells and integrated their results with available transcriptomic profiles of IAV-infected macrophages [6]. This approach delineated interferon-inducible and constitutive pathways associated with IAV resistance, including autophagy. Because the Matrix 2 ion-channel protein (M2) of IAV was known to modify several cellular pathways, the authors searched for host proteins able to both restrict IAV and interact with M2 and focused on TBC1 Domain family member 5 (TBC1D5), a factor that regulates endosome maturation and lysosomal degradation by controlling the activation of the small GTPase Rab7 [7]. As M2 colocalizes with autophagosomal markers, interferes with autophagosome maturation [8] [9] and re-routes the autophagic vesicles to the cell membrane to assist IAV budding [10], the antiviral role of TBC1D5 was considered in the context of autophagy. Rab7, TBC1D5 and M2 co-localized closely in IAV-infected cells and TBC1D5 deficiency led to lowered Rab7 activation along with diminished autophagosome maturation (**Fig. 1**). Hence, IAV M2 inhibits the Rab7-TBC1D5 interaction to reduce autophagosome-lysosome fusion and reroute M2 and autophagic membranes to cell surface to favor budding. This study extends our knowledge of the control of IAV replication, particularly in the context of immune effectors important for rapid

response to the virus. As TBC1D5 was not a top-ranked factor in the sole genetic screen, the work also indicates that a “multi-omics” integrative approach can allow for the identification of host factors with important function that are not prioritized otherwise. Finally, this strategy uncovered additional cellular pathways associated with antiviral resistance and M2 engagement (such as mitochondrial homeostasis) that remain to be dissected.

Together, the studies by Ames *et al.* and Martin-Sancho *et al.* provide novel molecular insights into the restrictive pressure autophagy can oppose to invading viruses and extend our knowledge of strategies that viruses have evolutionarily adopted to accommodate/manipulate such a pressure. The identification of OPTN as an anti-HSV-1 SAR indicates that its role in antimicrobial autophagy is not restricted to anti-bacterial resistance. It also extends the known repertoire of SARs capable of opposing neurotropic viral infection, in particular, and of mediating selective virophagy in general. Additional studies are needed to detail the conditions of VP16/gB targeting by OPTN, in particular whether VP16/gB are targeted as soluble or complexed proteins and whether cargo ubiquitination is required. With respect to IAV infection, the inhibitory role of M2 on the Rab7-TBC1D5 interaction resolves the long-standing enigma of autophagy subversion by M2. This finding also points to Rab7 targeting as a major evasion strategy for pathogens as some bacteria are already known to target Rab7 for degradation escape. Further work should help to determine whether the inhibition of autophagosome maturation by M2 also reduces the selective autophagic degradation of IAV factors. Answers to these issues will increase our knowledge of both the capacity of autophagy to oppose invading viruses and the detailed functioning of the autophagy machinery.

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Figure 1. Autophagy is mobilized for the selective lysosomal degradation of HSV-1 proteins and inhibited at its maturation phase by the M2 IAV protein to promote IAV viral cycle.

The hierarchized steps of the autophagy flux include the formation of the phagophore, its elongation/closure to form the autophagosome that sequesters autophagy cargoes and the fusion of the autophagosome with endo/lysosomes for cargo degradation in an autolysosome. The link between specific cargoes and the developing phagophore is ensured by selective autophagy receptors, such as OPTN, that bind to both the targeted cargo and lipidated ATG8 proteins (LC3s or GABARAPs) onto the phagophore. In cells infected with the DNA virus HSV-1, such as neurons, OPTN binds to both the viral transactivator VP16 and envelope glycoprotein B and selectively direct them to the autophagy machinery for lysosomal degradation, leading to lowered HSV-1 replication. The fusion of autophagosomes with endolysosomes (maturation) involves multiples factors. Under condition of infection with the RNA virus IAV, the viral M2 protein interferes with autophagosome maturation by directly disrupting one of the important interactions that drive maturation: the interaction of Rab7 with the GTPase activating protein TBC1D5. This interference involves the interaction of the cytoplasmic domain of M2 with TBC1D5. As a result, vesicle trafficking is altered and fractions of the autophagosome pool get rerouted toward cell surface where M2 promotes budding of viral particles. Note that for simplification, several steps of the intracellular HSV-1 and IAV cycles are not represented, including viral assembly.

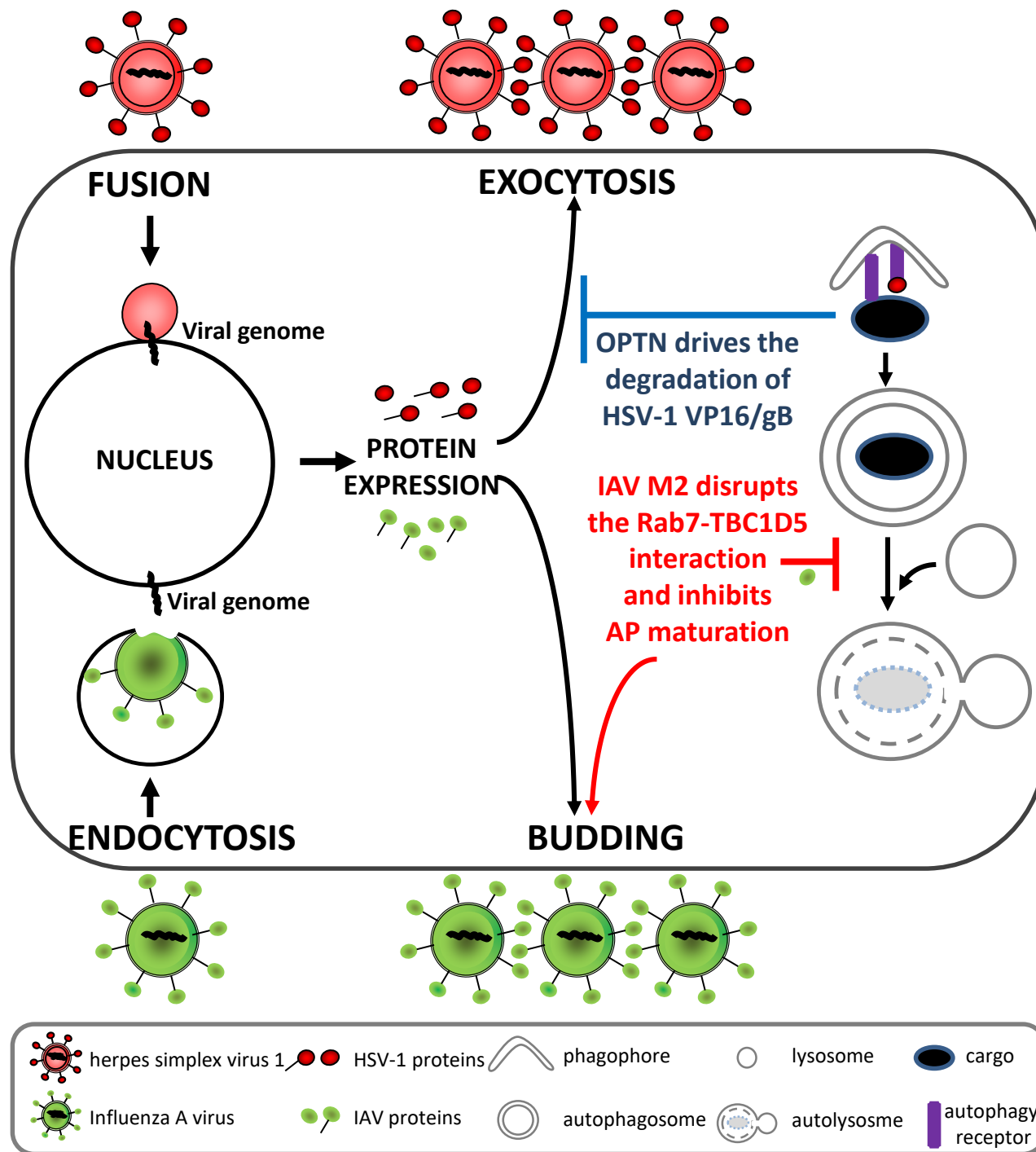


Figure 1.