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Mannosidase Alpha Class 1B Member 1 Targets F Severe Acute Respiratory Syndrome Coronavirus 2 Spike Protein and Ebola Virus Glycoprotein to Endoplasmic Reticulum-To-Lysosome-Associated Degradation by Micro-Endoplasmic Reticulum-Phagy

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Abstract : Viruses hijack host machineries to propagate and spread, which disrupts cellular homeostasis and activates various counteractive mechanisms. Infection of enveloped viruses is dependent on their fusion proteins, which bind to viral receptors to allow virus entry into cells. Fusion proteins are glycoproteins and expressed in the endoplasmic reticulum (ER) by hijacking the secretory pathway. Previously, we reported that Zaire ebolavirus (EBOV)-glycoprotein (GP) expression induces ER stress, and EBOV-GP is targeted by the calnexin cycle to macro-ER-phagy for degradation. We now report that expression of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2/SARS2)-spike (S) protein also causes ER stress, and its expression is strongly downregulated by mannosidase alpha class 1B member 1 (MAN1B1), a class I α-mannosidase from the ER. MAN1B1 co-localizes with SARS2-S in the ER, and its downregulation of SARS2-S is blocked by inhibitors targeting lysosomes and autophagy, but not proteasomes, indicating SARS2-S degradation by autolysosomes. Notably, the SARS2-S degradation does not require the core autophagy machinery including ATG3, ATG5, ATG7, and phosphatidylinositol 3-kinase catalytic subunit type 3 (PI3KC3)/vacuolar protein sorting 34 (VPS34), and instead, it requires Beclin 1 (BECN1), a core component in the PI3KC3 complex. In addition, MAN1B1 does not trigger SARS2-S polyubiquitination, and consistently, the SARS2-S degradation does not require the autophagy receptor sequestosome 1 (SQSTM1)/p62. MAN1B1 also downregulates EBOV-GP similarly, but this degradation does not require BECN1. Collectively, we conclude that MAN1B1 downregulates viral fusions by micro-ER-phagy, and importantly, we have identified BECN1-dependent and BECN1-independent mechanisms for micro-ER-phagy.

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