

MARCH8 Targets Cytoplasmic Lysine Residues of Various Viral Envelope Glycoproteins.

Abstract

The host transmembrane protein MARCH8 is a RING finger E3 ubiquitin ligase that downregulates various host transmembrane proteins, such as MHC-II. We have recently reported that MARCH8 expression in virus-producing cells impairs viral infectivity by reducing virion incorporation of not only HIV-1 envelope glycoprotein but also vesicular stomatitis virus G-glycoprotein through two different pathways. However, the MARCH8 inhibition spectrum remains largely unknown. Here, we show the antiviral spectrum of MARCH8 using viruses pseudotyped with a variety of viral envelope glycoproteins. Infection experiments revealed that viral envelope glycoproteins derived from the rhabdovirus, arenavirus, coronavirus, and togavirus (alphavirus) families were sensitive to MARCH8-mediated inhibition. Lysine mutations at the cytoplasmic tails of rabies virus-G, lymphocytic choriomeningitis virus glycoproteins, SARS-CoV and SARS-CoV-2 spike proteins, and Chikungunya virus and Ross River virus E2 proteins conferred resistance to MARCH8. Immunofluorescence showed impaired downregulation of the mutants of these viral envelope glycoproteins by MARCH8, followed by lysosomal degradation, suggesting that MARCH8-mediated ubiquitination leads to intracellular degradation of these envelopes. Indeed, rabies virus-G and Chikungunya virus E2 proteins proved to be clearly ubiquitinated. We conclude that MARCH8 has inhibitory activity on a variety of viral envelope glycoproteins whose cytoplasmic lysine residues are targeted by this antiviral factor. **IMPORTANCE** A member of the MARCH E3 ubiquitin ligase family, MARCH8, downregulates many different kinds of host transmembrane proteins, resulting in the regulation of cellular homeostasis. On the other hands, MARCH8 acts as an antiviral factor when it binds to and downregulates HIV-1 envelope glycoprotein and vesicular stomatitis virus G-glycoprotein that are viral transmembrane proteins. This study reveals that, as in the case of cellular membrane proteins, MARCH8 shows broad-spectrum inhibition against various viral envelope glycoproteins by recognizing their cytoplasmic lysine residues, resulting in lysosomal degradation.