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Differential impact of SEC61B on the processing and function of filovirus glycoproteins

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Current antiviral drugs mainly target viral proteins, resulting in resistance development and the need for new antivirals. In particularly, broad-spectrum are urgently needed to combat zoonotic spillover events. Generating host-directed antivirals may constitute a strategy to combat both issues and endoplasmic reticulum (ER) proteins may represent suitable targets. We assessed the potential of the ER translocation channel SEC61 as a therapeutic target. For this, we created cell lines with a knockout (KO) of SEC61B, a subunit of the SEC61 channel, and examined the effects on processing and function of glycoproteins (GPs) of zoonotic viruses. While SEC61B-KO had no impact on processing of the Ebola virus (EBOV) GP, cleavage of Marburg virus (MARV) GP was abrogated. SEC61B-KO in target cells reduced entry of particles pseudotyped with EBOV-GP while SEC61B-KO in cells producing MARV-GP pseudotypes reduced production of infectious particles. To determine whether SEC61B-KO affects viral replication, we used replication-competent, chimeric vesicular stomatitis virus (VSV) expressing EBOV-GP or MARV-GP. Both chimeric viruses but not VSV showed reduced replication in SEC61B-KO cells and an inhibitor of the SEC61 channel, Apratoxin S4, was more active against VSV-EBOV-GP and VSV-MARV-GP as compared to VSV. Although the mechanism of underlying antiviral activity remains to be fully elucidated, our data suggest that targeting the SEC61 channel may represent a viable antiviral strategy.

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Filoviruses, Glycoproteins, ER translocation, CRISPR/Cas9

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Junior Scientist Status

Yes, I am a Junior Scientist.

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