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Abstract

Mapping the Interface between New World Hantaviruses and Their Receptor, PCDH1 †

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Abstract: Hantaviruses are found throughout the world and can cause deadly diseases in humans, specifically, hantavirus cardiopulmonary syndrome (HCPS) in the New World and hemorrhagic fever with renal syndrome (HFRS) in the Old World. Currently, no FDA-approved, specific antiviral drugs or vaccines are available. Recently, we showed that New World hantaviruses utilize protocadherin-1 (PCDH1) for endothelial cell entry and infection by directly engaging its first extracellular cadherin repeat (EC1) domain. The knockout of *PCDH1* also greatly reduced pulmonary infection and was highly protective in a Syrian hamster model of lethal challenge with Andes virus (ANDV). To further understand PCDH1's role in hantavirus entry, we sought to map the binding interface between hantavirus Gn/Gc and PCDH1-EC1. Accordingly, we screened a panel of EC1 proteins, bearing point mutations in solvent-exposed residues, for their capacity to recognize Gn/Gc and block viral entry. EC1 mutations defective in Gn/Gc binding were engineered individually and in combinations into full-length PCDH1, expressed in PCDH1-knockout cells, and evaluated for their capacity to complement viral infection. We identified a surface in the PCDH1-EC1 domain, comprising contiguous residues, which was required for virus PCDH1 recognition and PCDH1-dependent viral entry. However, this region does not overlap with the EC1–EC4 heterodimer interface recently described by Modak and Sotomayor. In addition, through the use of recombinant vesicular stomatitis viruses bearing chimeric hantavirus Gn/Gc glycoproteins, we were able to pinpoint the importance of the N-terminal domain of the Gn subunit for PCDH1-mediated entry. With these taken together, identifying the location of the interface could provide a direction for the development of host-directed antiviral drugs that do not interfere with PCDH1's endogenous function, as well as help to map an antigen target on Gn/Gc for antiviral antibodies.

Keywords: hantavirus; PCDH1; receptor; vesicular stomatitis virus