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Mutational analysis of the M2 ion channel proteins of avian and bat influenza A viruses

Content

The matrix protein 2 (M2) is a multifunctional protein, which plays a crucial role in influenza A virus entry and egress. In this study, we investigated the role of M2 protein in the context of a glycoprotein (G)-deficient vesicular stomatitis virus (VSVΔG) encoding the three envelope proteins hemagglutinin (HA), neuraminidase (NA) and M2 of A/chicken/Rostock/8/34 (H7N1), a highly pathogenic avian influenza A virus. We found that M2 ion channel activity was essentially required to obtain an infectious chimeric virus, most likely because this preserves the native conformation of HA in the acidic milieu of the secretory pathway. VSVΔG(HA,NA,M2) virus was sensitive to amantadine, a well-known inhibitor of the ion channel protein. The mutation S31N in the pore-forming transmembrane domain rendered the virus resistant to amantadine, but also affected virus fitness. Analysis of a series of C-terminally truncated M2 proteins revealed that certain regions of the cytoplasmic domain are important for ion channel activity, while mutation of key amino acid residues in the amphipathic helix (F47A, F48A), in the cholesterol binding motif (Y52A, Y57A), and the acylation site (C50S) did not significantly affect M2 activity. The highly diverse M2 proteins of the recently discovered bat influenza viruses H17N10 and H18N11 were unable to rescue infectious VSVΔG(HA-NA-M2), suggesting that they do not have ion channel activity. However, a single amino acid change (N31S) was sufficient to recover infectious virus. In conclusion, VSVΔG(HA,NA,M2) proved to be a powerful vector system to functionally characterize the ion channel proteins of various influenza A viruses.

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Viral Replication

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