MS08-02 | Structural Basis of Adamantane Resistance in the Influenza A M2 Proton Channel

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The M2 protein is a homotetrameric proton channel found in the influenza A virus. It is the target of the anti-influenza drugs amantadine and rimantadine. However, in the past decade, viral resistance has emerged in the majority of currently circulating strains of influenza. The most prevalent drug-resistant M2 mutants are S31N and V27A. Here we report X-ray crystal structures of both of these mutants. A newly solved 2.1 Å structure of the S31N mutant contains two conformations of the channel ($Inward_{open}$ and $Inward_{closed}$) in the asymmetric unit of a novel crystal form, allowing us to observe the $Inward_{closed}$ conformation of the S31N mutant for the first time. In the $Inward_{open}$ conformation, Asn31 faces the center of the channel pore and sterically occludes the binding site of the adamantane drugs. In the $Inward_{closed}$ conformation, Asn31 faces away from the channel pore and instead forms hydrogen bond interactions with backbone carbonyls. We have also characterized the V27A mutant bound to a spiroadamantane inhibitor in a 2.5 Å structure. The mutation of Val to Ala removes hydrophobic contacts that previously stabilized binding of the adamantane drugs; the spiroadamantane inhibitor is observed to bind to this larger pocket. This work provides a structural explanation for adamantane resistance in the M2 channel that will be useful for the design of new compounds targeting these drug-resistant mutants.