SFB 1078

Protonation Dynamics in Protein Function

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14:00 Uhr

FMP, Robert-Rössle-Str. 10, 13125 Berlin

Seminarraum B1.16

Colloquium

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Hydrogen bonding geometry and drug binding kinetics in the Influenza A M2 proton channel

The arrangement of histidine side chains in influenza A M2 tetramer determines their pKa values, which define pH-controlled proton conduction critical to the virus lifecycle. Both water-associated and hydrogen-bonded imidazole−imidazolium histidine quaternary structures have been proposed, based on crystal structures and NMR chemical shifts, respectively. We show, using the conduction domain construct of M2 in lipid bilayers, that the imidazole rings are hydrogen bonded at a pH of 7.8 in the neutral charge state. We also detect a bound water molecule at a chemical shift of 11 ppm, located near the histidine residue. Combining NMR and density functional theory calculations, we show that the bound water forms a hydrogen bond to the delta1 nitrogen of histidine 37. The histidine hydrogen-bonding interaction is not detected in the drug-bound sample, indicating reforming of the histidine geometry in the channel. We track the dynamics of drug binding via NMR, which reveals a particularly high energy barrier, suggesting a kinetic constraint on development of new proton conduction inhibitors.

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