

Title: Lipid-mediated conformational equilibrium of gap junction intercellular channels

## Abstract

Connexin family proteins assemble into hexameric hemichannels in the cell membrane. The hemichannels dock together between two adjacent membranes to form gap junction intercellular channels (GJCs). The cryo-electron microscopy structures of Cx36 and Cx43 GJCs reveal dynamic equilibrium states of various channel conformations in phospholipid nanodiscs. Individual protomers undergo dramatic conformational changes in N-terminal helix (NTH) and the first transmembrane helix (TM1) creating lateral openings to the membrane and central pores of different diameters. Amphipathic NTHs interact with TM helices to form a hydrophilic pore and thus open the channel. However, the dissociation of pore-lining NTHs from TM helices is strongly induced by cholesterol derivatives resulting in a closed channel with pore-occluding lipids. This study suggests a potential gating model of GJC mediated by lipids and NTHs.