Structural basis of erythromycin binding to hERG K+ channels

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A wide range of structurally unrelated drugs can bind to *human ether-a-go-go related gene* (hERG) potassium channels and thereby increase the risk of acquired long QT syndrome and sudden cardiac arrest. Thus during pre-clinical drug development, industry spends billions of dollars screening for hERG binding and engaging in labour-intensive medicinal chemistry approaches to reduce affinity for hERG channel whilst maintaining affinity for the intended target of the lead compounds. Despite of many biophysical and computational investigations into hERG drug binding the primary question of 'how and why so many structurally unrelated drugs bind to hERG channels' remains uncertain. hERG channels can exist in closed (non-conducting), open (conducting), and inactivated (non-conducting) states (1). Previous studies have shown that most high affinity drugs preferentially bind to the inactivated state (2). Whilst prior structural studies have investigated drug binding to WT hERG channels no studies have specifically looked at the structural basis of state dependence of drug binding to hERG. To start to address this question, we expressed N588E hERG channels (enhances occupancy of the inactivated state) in HEK293 GnTI$^-$ cells and purified at 3 mM K^+, to further enhance inactivation, in the presence of 30 μM erythromycin. CryoEM data were acquired using an FEI Titan Krios (3). A preliminary structure, determined using RELION-5.0.0 software, will be presented.

Reference

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