hERG assays and pro-arrhythmic effects

Structurally hERG channels are formed from four identical α-subunits, each with six α-helical transmembrane domains (Sanguinetti and Tristani-Firouzi, 2006; Vandenberg et al., 2012). The *in vitro* hERG assay uses stable human embryonic kidney (HEK) cell lines, Chinese hamster ovary (CHO) cells) or *Xenopus* oocytes expressing these α-subunits. However, it has been suggested that screening for hERG inhibition alone could be misleading as cloned ion channels do not provide the native conditions and structural architecture of the hERG channel *in vivo* (Davie et al., 2004). In fact, it is unknown if the human rapid potassium delayed rectifier current (I_{Kr}) channels contain ancillary subunits *in vivo* (Hoffmann and Warner, 2006). By contrast, *in vivo* interactions between hERG and α-subunit of slow potassium delayed rectifier current (I_{Ks}) channels have been reported (Ehrlich et al., 2004). Such an interaction should therefore be considered when evaluating and interpreting *in vitro* hERG assay data (Brown, 2004; Valentin et al., 2004; Hoffmann and Warner, 2006).

Voltage clamping is one of the most common techniques to measure the hERG activation and deactivation. By applying voltage clamping to cells transfected with the hERG ion channel, an increasing outward current is observed upon membrane depolarization (channel activation), whereas a decreasing outward hERG current the hERG tail current) is recorded during repolarization (channel deactivation). The amplitude of the hERG tail currents in the absence and presence of drugs can be compared to determine the extent of hERG current block. In fact, concentration-response curves are normally constructed to assess IC_{50} values (that is, the concentration of drug required to block 50% of hERG current), which are often used as readout from these experiments.

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