Striatin knock out induces a gain of function of Na^+ current in mESC-derived cardiomyocytes.

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Abstract:

Striatin (Strn) is a scaffold protein expressed in cardiomyocytes (CMs), whose altered expression has been found in several cardiac diseases. However, the alteration underlying its pathogenicity have been poorly investigated. Here we studied the role(s) of cardiac Strn in CMs generated from Strn-KO and isogenic WT mouse embryonic stem cell (mESC) lines. Strn-KO cells had a higher beating rate and faster action potential phase 0 than WT, correlated with a larger fast I_{Na} conductance. In HEK cells, downregulation of Strn destabilizes microtubules and increase I_{Na}. Immunofluorescence analysis confirmed a higher Na^+ channel expression and a more dynamic microtubule networking in KO CMs than in WT. Video motion tracking analysis highlighted an altered contraction in Strn-KO CMs, and this was associated with a global increase in intracellular Ca^{2+}.This was likely due to increased late Na^+ current (I_{NaL}) and reduction of Ca^{2+} extrusion through the Na^+/Ca^{2+} exchanger (NCX). Incubation of Strn-KO CMs with the microtubule stabilizer taxol, induced a rescue (downregulation) of I_{Na} conductance toward WT levels. In conclusion, loss of Strn affects cell functionality by a disarrangement of strn-related multi-protein complexes. This leads to the impairment of microtubules dynamics and trafficking of Na^+ channels to the plasma membrane.