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Meeting abstract

Heterologous expression of membrane proteins in cardiac myocytes

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The cardiac isoform of the Na^+ channel ($Na_V1.5$) is known to accumulate in the endoplasmic reticulum (ER). This retention presumably reflects quality control in the ER. In order to understand the underlying mechanism, we heterologously expressed the human orthologue of the Na^+ channel ($Na_V1.5$) in neonatal primary rat and murine cardiomyocytes, in a cardiomyoblast cell line (H9c2) and in HEK293 cells (internal control). In HEK293 cells, $Na_V1.5$ readily accumulated at the cell surface and gave rise to functional channels with the expected electrophysiological properties. In contrast, in cardiomyocytes and H9c2 cells, the $Na_V1.5$ accumulated in the ER regardless of the transfection method employed (lipofection, nucleofection). As a positive control, we employed G protein-coupled β_1-adrenergic, A_1 and A_{2A} adenosine receptors. In HEK293 cells, export of the A_{2A} receptor is known to be enhanced by the deubiquinating enzyme USP4. Accordingly, we also co-expressed USP4 and the A_{2A} receptor in the different cardiomyocyte preparations. However, in all instances, the membrane proteins were trapped within intracellular compartments. This was, in particular true for the $Na_V1.5$, which, in many instances, accumulated in circular bodies, which are reminiscent of calnexin-rich organized smooth ER structures. Based on these findings, we conclude that (i) membrane proteins undergo stringent quality control in cardiac myocytes and (ii) ER-export of the $Na_V1.5$ is limited by the availability of additional cardiomyocyte-specific components.

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