Basic Science - Cardiac Diseases

When multiple caveolins make the difference: Cav1 partly compensates Cav3 alterations and rescues ion channels expression

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Caveolae are small-membrane invagination that contribute both to buffering excessive contraction-dependent membrane strain and to initiation of membrane repair. Moreover, they constitute micro-domains where receptors and ion channels are clustered, favouring their functional interaction. Caveolin-3 (Cav3) is the key structural component of muscular caveolae. Mutations in Cav3 gene are associated with alterations of the skeletal muscle architecture leading to some rare forms of hereditary skeletal myopathies and/or cardiomyopathies called caveolinopathies. Notably, skeletal muscle dysfunctions usually precede cardiac dysfunctions, even though the mutated Cav3 is expressed in both cell types.

An important difference between skeletal fibers and cardiomyocytes is that in the latter, caveolin-1 (Cav1) participates with Cav3 to form caveolae; skeletal myotubes instead do not express Cav1.The delay or lack of onset of cardiac alterations in caveolinopathies may depend on a preserved micro-domains organization in the heart compared to skeletal muscle, due to Cav1 expression. We decided to focus on a specific mutation T78K found in heterozygous in a patient with Ripple muscle disease and hyperCKemia. We have characterized human cardiomyocytes (CM) differentiated from induced pluripotent stem cells (iPSC) derived from this patient and one healthy control. In particular, we have investigated which caveolin isoforms are expressed at day 30 of differentiation, finding both Cav1 and Cav3, with a significant decrease of Cav3 isoform in T78K-CM. Their different expressions significantly increase T78K membrane resistance (3.27 ± 0.6 GΩ versus 1.64 ± 0.4 GΩ in the CTRL-CM), and consequently membrane excitability. The T78K_CM showed an increase spontaneous beating rate compared to CTRL (1,75± 0,08 Hz and 0,89 ± 0,4 Hz, respectively).

Previous laboratory analysis conducted in caveolin-free MEF cells, co-transfected with WT and T78K Cav3 mutation, revealed that the T78K mutant is dominant, inducing the retention of WT Cav3 in the perinuclear areas and causes significant reduction in current density of three ion channels (HCN4, Kv1.5 and Kir2.1) known to interact with caveolins. The dominant decreased in cav3 expression is in line with previous data in skeletal muscle biopsy, however, electrophysiological data would be likely incompatible with life. For this reason, we decided to compare the impact of this mutation in CHO cells that exhibit high levels of Cav1, and in cav-1 expressing MEF line. In these systems, the membrane localization of Cav3 T78K is rescued both in heterozygous and homozygous conditions. In line with caveolin membrane expression, HCN4, Kv1.5 and Kir2.1 density is also rescued to normal levels. These results constitute the first evidence of a possible role of Cav1 in compensating membrane disorganization and disfunction due to Cav3 mutations in the heart, making this organ less susceptible to caveolinopathies.