Production of functional antibody targeting Ca^{2+}permeable channel TRPV2 ameliorating dilated cardiomyopathy in animal models

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Abnormal Ca^{2+} handling is essential in the pathophysiology of dilated cardiomyopathy (DCM). One of Ca^{2+} permeable channels, transient receptor potential cation channel, subfamily V, member 2 (TRPV2) has been suggested as a principal candidate for Ca^{2+} entry pathways and a potential therapeutic target for DCM. In this study, we produced selective antibodies recognizing TRPV2 from the outside of cell. One of antibodies inhibited the Ca^{2+} influx via TRPV2 in cultured cells and caused TRPV2 to disappear from the plasma membrane via cellular internalization. The antibody epitope existed in the turret of pore-forming outer gate of TRPV2. We tested the therapeutic efficacy of the antibody in DCM developed in the δ-sarcoglycan-deficient hamsters (J2N-k). Intraperitoneal administration of the antibody (0.5 mg/kg) for 2 weeks (once a week) prevented the progression of cardiac dysfunction as evaluated by echocardiography and improved the abnormal Ca^{2+} handling. Further, the antibody was also effective in preventing heart failure of the murine 4C30 model with end-stage DCM. Interestingly, endogenous TRPV2 accumulated in the cardiac muscle sarcolemma disappeared upon antibody administration. Thus, the produced antibody is capable of ameliorating DCM through enhanced cellular internalization, and may be a promising treatment for patients with DCM.