Establishing a System for Viral Delivered Gene Therapy as a Treatment for CPVT

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Catecholaminergic polymorphic ventricular tachycardia (CPVT), a lethal human arrhythmia provoked by exercise or emotional stress. Beta-adrenergic blockers are the therapy of choice for human CPVT but they only achieve complete arrhythmia control in less than 50% of cases. Therefore alternative therapy is obligated. Gene therapy has become atractive treatement for genetic disorders.

We established a new delivery system in CASQ2 knock-out mice. AAV2 recombinant plasmids were generated by cloning the gene of interest into pAAV-IRES-hrGFP vector. The expression plasmid was co-transfected into the AAV-293 cells with pHelper (carrying adenovirus-derived genes) and pAAV-RC (carrying AAV-2 replication and capsid genes), which together supplied all the transacting factors required for AAV replication and packaging in the AAV-293 cells. Viral particles were purified from crude cell lysates and first examined for infectivity and transgene expression in neonatal rat cardiomyocytes by GFP fluorescence. Based on the success of the viral infection technique, we succeeded to inject the vector to a murine model of recessively-inherited CPVT. Viral particles were concentrated and injected into the left ventricle of 16-week-old mice. GFP expression in various tissues was observed using cryo sections. Cardiac muscle and lung tissues were infected with AAV and GFP and were seen in the sections 4 weeks after injection ($p=0.05$). Other tissues that were examined for infection did not show any GFP expression (liver and spleen). Control mice had no GFP expression in any of the tissues ($n=4$). This method has proven as a good delivery method for viral particles to the heart muscle and is being used now for different vectors that can attenuate the sevirity of the arrhythmia.