NOVEL MINI/MICRO-DYSTROPHIN GENES RESTORE NNOS TO THE SARCOLEMMA AND IMPROVE THE THERAPEUTIC OUTCOME FOR DUCHENNE MUSCULAR DYSTROPHY

Duchenne muscular dystrophy (DMD) is a muscle disease caused by mutations of the dystrophin gene. Gene replacement therapy represents a very promising approach to cure this disease. The dystrophin gene is one of the largest genes in the genome and it exceeds the carrying capacity of adeno-associated viral vector (AAV) and lentiviral vector, the most powerful gene delivery vehicles for muscle. The truncated mini/micro-dystrophin genes have been developed to overcome this hurdle. Despite improvement of muscle function and the dystrophic phenotype by these mini/micro-dystrophin genes, none of them can restore sarcolemmal neuronal nitric oxide synthase (nNOS). Sarcolemmal nNOS plays a crucial role in maintaining blood perfusion during muscle contraction. In DMD patients, sarcolemmal nNOS is lost. Consequently, it leads to functional ischemia and muscle damage. To improve the therapeutic efficacy of the truncated dystrophin genes, one has to develop the new synthetic dystrophin genes with the ability to restore sarcolemmal nNOS.

The motif for nNOS sarcolemmal localization was identified and incorporated into new mini/micro-dystrophin genes. The effect of sarcolemmal nNOS restoration on the muscle functions, blood perfusion in contracting muscle and exercise performance was evaluated.

Dystrophin spectrin-like repeats 16 and 17 (R16/17) are required for sarcolemmal nNOS localization. The synthetic mini/micro-dystrophin genes carrying R16/17 significantly improved muscle function, blood perfusion and exercise capacity. Our newly developed R16/17 mini/micro-dystrophin genes provide functions close to that of the full-length dystrophin gene. They represent excellent candidate genes for DMD gene therapy.

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