

Muscle-mediated gene therapy

SUMMARY

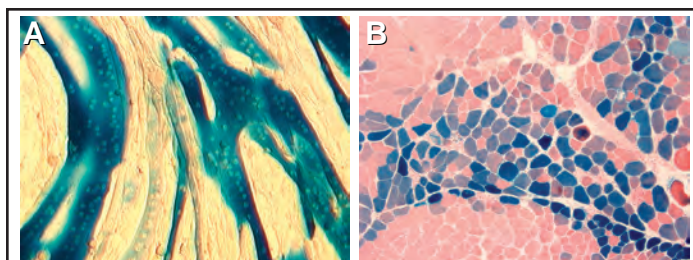
Gene therapy opens therapeutic hopes for many hereditary and acquired diseases. Typically, it involves the incorporation of a functional gene or gene product into target cells of affected individuals turning them into therapeutic agent factories. In the present technology, novel vectors/vehicles were developed for the delivery and expression of genes of interest in muscle cells. Their small size and exceptional expression efficiency among muscle-specific constructs makes them very attractive candidate for human gene therapy.

APPLICATIONS

- Treatment of muscles injuries and muscular disorders like muscular dystrophy.
- Treatment of circulatory system disorders, metabolic disorders and neurological disorders.
- Treatment of cancer.

CONCEPT

The success of gene therapy depends on the efficient transfer of genes to target cells, the stable and high level expression of the gene of interest by these cells, and limited side effects. Among the candidate targets are muscle cells which can be used to produce locally acting or circulating therapeutic proteins. This technology provides novel muscle cell-specific vectors. These vectors contain two or more copies of the upstream enhancer (USE) of the human slow-twitch skeletal muscle isoform of troponin I (TnIs) gene and/or a truncated form of the same enhancer (Δ USE). The different enhancers are fused to the minimal promoter of the TnIs gene.



Strong expression of β -galactosidase (blue stain) regulated by a promoter containing multimerized sequences of the muscle-specific USE enhancer (USEx3)

A) Cultures of muscle cells after transfection of plasmid

B) Section of mouse muscle after electrotransfer of plasmid

These control elements can then be operably linked to a nucleotide sequence of interest. The 100-bp deletion at the 5' end of Δ USE confers expression in both the slow and the fast-twitch muscle fibers. The small size of these constructs (less than 600-bp) and one of the highest expression among muscle specific constructs to date makes them amenable for gene therapy.

FEATURES AND BENEFITS

Numerous therapeutic opportunities

In addition to treating muscle wasting, such gene therapy strategy may prove efficacious in preventing or treating an array of other diseases such as cancer, heart failure, and kidney disease by using the muscle as a factory for producing the desired protein. Further, muscle-mediated gene therapy could be used in the treatment of, especially (but not limited to), monogenic disorders for which there are currently little or no cure.

The muscle: an advantageous target tissue

Muscle tissue offers several advantages for the delivery of therapeutic genes and the production of gene therapy products. Muscle cells are abundant (skeletal muscle makes up approximately 10% of the total human body mass) and readily accessible. They are also highly vascularized making them efficient for systemic delivery of therapeutic proteins through blood circulation. In addition, myofibers are long-lived cells, providing a stable environment for long-term expression of genes of interest. Moreover, specific post-translational modifications such as gamma carboxylation essential to the production of functional coagulation factors in the liver can also occur in muscle cells.

Versatile and adaptable tool

With a size of less than 600 bp, these vectors are sufficiently small to drive muscle-specific expression of large therapeutic genes carried by viral vectors such as recombinant AAV. Furthermore, the constructs are amenable to further improvement of the level and stability of gene expression *in vivo* by using introns

Potential for lessened side effects

As the expression is restricted to skeletal muscle, the possibility of an adverse immune response may be lower. There is reduced toxicity that is associated with widespread protein expression in other tissues when non-specific viral derived constructs are used.

PROTECTION STATUS

Constructs for enhancement of gene expression (NRC no. 11887-1).

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