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Viral Gene Therapy in Skeletal Muscle: A Work in Progress

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The potential usefulness of viral gene replacement therapy in human disease has been an exciting and extensively-studied topic in the field of skeletal muscle disease for the past 20 years. Unfortunately, while the strategy of replacing or supplementing copies of mutant gene is a straightforward concept, a number of complicating factors have been identified as gene therapy trials have progressed toward clinical studies. While some of these issues, including the immunological response to viral vectors, are issues that are encountered with all forms of gene therapy, the use of gene therapy in skeletal muscle also poses additional challenges for which treatment strategies need to be optimized. Despite these challenges, there has been substantial progress in recent years toward optimizing viral gene therapy for skeletal muscle disease in animal models, with an eye toward optimizing the safety and efficacy of viral gene therapy in humans.

Skeletal muscle disorders represent considerable opportunities for investigators developing viral gene therapy strategies, due to the numerous monogenetic diseases of skeletal muscle, the clear and quantifiable clinical phenotypes, and the easy accessibility of muscle tissue. In the field of skeletal muscle disease, gene therapy has most extensively been studied for the dystrophinopathies, which are due to mutations in the dystrophin gene and cause Duchenne and Becker muscular dystrophies in humans. Dystrophin is a 427 kDa protein that allows the construction of a dystrophin-glycoprotein complex that prevents membrane damage during contraction by connecting the cytoskeleton to the extracellular matrix. Mutations in the dystrophin gene predispose the myofiber membrane to contraction-induced membrane damage, resulting in inflammation, and myonecrosis, and progressive loss of functional muscle tissue. Several murine and canine models of dystrophinopathy have been used to study these diseases and evaluate potential therapies, including several viral gene therapy approaches [1-4]. The most widely used murine model of dystrophinopathy is the mdx mouse, which produces no dystrophin but has a less severe clinical course than seen in human patients. Viral gene therapy studies using mdx mice have demonstrated that delivery of full-length or truncated dystrophin through adenoviral, Adeno-Associated Viral (AAV), and retroviral vectors can produce an improvement of the disease phenotype and partial restoration of dystrophin expression [4]. Of these vectors, various serotypes of AAV have become the preferred vectors for viral gene therapy to skeletal muscle, due to the relatively low (but not absent) degree of inflammatory response produced and the development of AAV's that transduce efficiently into skeletal muscle tissue[1-4]. While AAV vectors have a limited cloning capacity of less than 5kb, there has been considerable success in using truncated dystrophin inserts that preserve the most essential components of the dystrophin protein. Based on the improvements in muscle function and pathology seen using these "minidystrophin" and "microdystrophin" approaches, a number of novel strategies to deliver these transcripts or proteins are currently under investigation.

While these murine gene therapy studies for dystrophinopathy demonstrated the substantial promise of this therapeutic approach, studies using dogs, primates, and humans have uncovered additional technical problems when translating viral gene therapy protocols to larger animals. A substantial financial and technical limitation to the translation of these studies involves the production of sufficient amounts of virus to perform these evaluations, especially for studies attempting to distribute the virus to all muscle tissues. While the viral dose required for dosing would be smaller for infants, the effects of virus administration to an immature immune system are currently unclear. Fortunately, several techniques for local limb infusion have been developed, which allow the pursuit of "proof of concept" work in large animal models without requiring extremely large amounts of virus [5]. Another potential hurdle is that adenoviral and AAV vectors that had been well-tolerated in mice produced robust immunological responses in the dog, which limited therapeutic efficacy and long-term transgene expression [6]. Fortunately, as these immune responses have become more completely understood, immunosuppressive strategies have been developed to improve the degree and duration of viral transgene expression [7]. Thus, while translation from murine models of dystrophinopathy to canine and human dystrophinopathy has encountered a number of technical complications, substantial progress has recently been made toward overcoming these obstacles.

Viral gene therapy approaches have also been investigated for other disorders of skeletal muscle, including lysosomal storage disorders and congenital myopathies, and these studies have benefitted immensely from the pioneering work that was performed using dystrophinopathy models. A murine model of Pompe disease displayed considerable improvement in disease pathology and the function of skeletal and cardiac muscle following AAV-mediated gene-replacement for acid alpha glycosidase [8]. In the field of congenital myopathy, local AAV-mediated gene replacement for myotubularin produced dramatic improvements in disease pathology and skeletal muscle function [9], and evaluations of systemically-delivered AAV's are currently in progress.

While the replacement of the mutant gene is the most straightforward approach to addressing monogenetic skeletal muscle diseases, several viral gene therapy studies have been performed in an attempt to modulate disease severity through more indirect methods. In dystrophinopathy, therapeutic benefits have been observed following gene supplementation to increase utrophin expression, which can partially replace the function of dystrophin in dystrophin-deficient animals [10]. In contrast, AAV gene therapy has also been used to silence NF-kappaB in mdx mice and ameliorate disease pathology due to a decrease in NF-kappaB-mediated inflammation [11]. Additionally, viral gene therapy has also been used to inhibit myostatin, which is a negative regulator of muscle mass. Inhibition of myostatin signaling

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has shown therapeutic benefits in animal models of dystrophinopathy and myotubular myopathy, and offers considerable therapeutic promise for a number of sarcopenic muscle disorders [12]. Although these indirect gene therapeutic strategies do not specifically address the genes responsible for these disorders, they illustrate the potential to modulate symptomatic severity for a range of disease processes once the optimal protocols for viral gene therapy in muscle are defined.

Overall, despite the unexpected challenges that the field of skeletal muscle biology has faced over the past 20 years, the potential of gene therapy remains as bright as it ever was. The technical challenges of viral gene therapy have also enhanced the development of a number of ingenious and innovative therapeutic strategies in recent years, including exon skipping, stem cell therapies, and enzyme replacement therapies, and clinical trials are being pursued with a greater variety of agents and for a greater variety of muscle diseases than ever before. It is an exciting time to be an investigator in the field of skeletal muscle disease, and it is increasingly apparent that only a few technical leaps separate us from the treatments that we have been pursuing for decades.

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