International Research Journal of Innovations in Engineering and Technology (IRJIET)

ISSN (online): 2581-3048

Volume 8, Issue 8, pp 264-267, August-2024

https://doi.org/10.47001/IRJIET/2024.808030

Analysis of Emerging Therapeutic Approaches for Treating DMD

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***Abstract* - Muscular dystrophy, also known as Duchenne muscular dystrophy (DMD), is a fatal muscle disorder, changes to the DMD gene be the cause of this disease, DMD primarily impacts boys during childhood. For DMD there was no treatment available up until, in recent years, a range of curative approaches to Muscular Dystrophy have been under research; a few among them are development of corticosteroids, viral vector mediated gene therapy, exon skipping, etc. exon-skipping is the one of the optimistic approaches for correcting DMD, this therapy's main aim is to transform an out-of-frame mutation to convert an out-of-frame mutation into an in-frame mutation, to change of a severe DMD phenotype into a mild phenotype by restoration of reduced dystrophin aspect.**

Keywords: Duchenne muscular dystrophy (DMD), Corticosteroids, gene therapy, viral vector mediated gene therapy, out-of-frame mutation, in-frame mutation.

I. INTRODUCTION

DMD is a malignant muscle disorder, be brought about by changes in the DMD gene. Mutation causes structural protein deficiency called dystrophin from the muscles; It results from changes made to the gene for DMD, it is an infrequent, serious, death dealing neuromuscular disorder which affect about 1 in 3500 and 5000 boys born worldwide. [1]

An Avant positional cloning's application to human disorders began in 1986 with the discovery of the DMD/BMD gene by A.P. Monaco et.al. of L. Kunkel's group [1], with its 79 exons, the 2,500 kb long DMD gene constitutes 1% of the X chromosome, after transcription, a 14 kb cDNA is produced.[1]

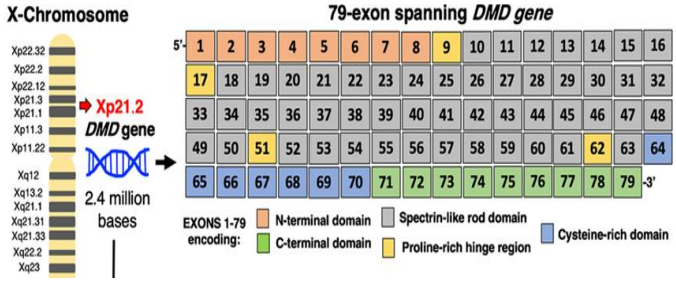

Figure 1: 79 exons covering X-chromosome

In 1987, E.P. Hoffman et al. identified a 427kD protein encoded by the gene for DMD and this protein was named "dystrophin", which is absent from skeletal muscle of most patients with DMD [1], up until recently, there was no effective treatment for DMD. In recent years, a range of therapeutic approaches to muscular dystrophy have been proven. There are two possible categories for these modern therapeutic approaches.[4]

- Methods centred on dystrophin that aim to restore the protein's expression and/or functionality, including protein replacement therapies, gene therapy, and cell therapy.
- Targeting the downstream pathological alterations, such as inflammation, fibrosis, and muscle atrophy, is the goal of the other line of treatment approaches, which seeks to enhance muscular function and quality.

The creation of corticosteroids, vector-mediated gene therapy, multipotent stem-cell therapy, antisense oligonucleotides (AOs) for exon skipping, etc. are a few examples. However, the majority of these techniques are still in the preclinical and clinical phases.

II. LITERATURE SURVEY

Details regarding the subject have been gathered since doctors first documented the disease in the 19th century. Among the colleagues, Sugita, was among the first to publish findings that showed a rise in patients' serum levels of CK associated with progressive muscular dystrophy.

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Sibley and Lehninger's 1949 study was the first to discover biochemical abnormalities in patients with muscular dystrophy. When aldolase levels in the blood of patients with muscular dystrophy were examined, the researchers discovered that the patients had greater blood levels of the enzyme.

In 1958, Sugita examined the serum aldolase levels of patients and established that those who has muscular dystrophy showed increased serum aldolase activity. This discovery was documented in a Japanese publication.

Okinaka initially diagnosed a patient when one has muscular dystrophy, but during grand rounds, the attending physician stated that the patient actually had muscular dystrophy. Okinaka then reevaluated the diagnosis and concluded that it was motor neuronitis, according to the serum aldolase activities measured by Sugita. Okinaka angrily told Sugita that it was not appropriate to diagnose based solely on evidence discovered in the blood. Looking back, Okinaka was right; most likely the patient had polymyositis instead muscular dystrophy.

Nevertheless, Setsuro Ebashi's exceptional professional intuition resulted generated a noteworthy advancement in the knowledge of research on muscular dystrophy after the event.

Rather than using aldolase to predict muscular diseases, researchers began focusing on creatine phosphokinase since it is more specific to skeletal muscle. A group led by Ebashi, including other doctors. Momoi, Toyokura, and Sugita conducted research on creatine phosphokinase (CPK), additionally referred to ascreatine kinase or CK. Therefore, the initial study on serum CK levels in progressive muscular dystrophy was released by Ebashi and colleagues in 1959. In comparing different neuromuscular disorders, researchers discovered that individuals with muscular dystrophy had higher serum CK levels., making it the most dependable laboratory test for identifying the condition. This is still true up to now.

More than 50 years following theoriginal publication, an elevated CK concentration remains auseful marker for the identification of DMD, providing an accurate evaluation of thestate of the skeletal muscles and assisting in the evaluation of the effectiveness of treatment.

III. DISCUSSION

The objective of our work is analysing existing literature and therapies available for Duchenne muscular dystrophy treatment, to understand, compare the performance and efficiency of the various methodologies, therefore offering the most effective therapy for those with DMD.

Corticosteroid Therapy

Recent publications authored by prominent experts have outlined these extensive recommendations for the diagnosis and holistic therapy for DMD, which encompass the utilization of corticosteroids. Throughout history, corticosteroids have been beneficial for male DMD patients by helping to maintain muscle strength and function, extending the period of being able to walk independently, and slowing the development of scoliosis and cardiomyopathy. Prolonged therapy following the inability to ambulate independently has been demonstrated to have positive effects. Based on existing literature and clinical practice, current clinical guidelines strongly advise the inclusion of corticosteroid treatment for all DMD patients, beginning at the early ambulatory phase.

Drawback of Corticosteroid Therapy

Recurring negative consequences linked to steroids include decreased height, weight gain, development of cataracts, and increased risk of bone fractures. Specifically, around 33% of male individuals with a diagnosis of DMDmay experience vertebral compression fractures due to of prolonged corticosteroid treatment, advancing muscle deterioration, hindered absorption of vitamin D and calcium, and limited mobility.

Vector-mediated gene therapy

There are currently significant advancement in understanding the molecular causes of various kinds of muscular dystrophies over the last ten years. Consequently, there have been instances where viral vector technology has helped to considerably halt the advancement of MD in mice models. Nevertheless, It's critical to understand the significant shortcomings of current vector systems that require attention before effectively treating humans using these methods. In this presentation, we will discuss several viral-based treatment approaches with the goal of addressing the muscle-wasting issues linked to muscular dystrophy.

Myoblast Transplantation

The first type of almost-gene therapy suggested for testing in small animal models of DMD muscle disease was myoblast transplantation, which helped to validate the hypotheses about the missing gene. An option is to use healthy myoblasts to target and repair damaged muscle fibers caused by the disease through grafting.

Drawback of Myoblast Transplantation

This therapy was only restricted to a small surrounding of injected area.

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Exon-skipping therapy

Without a doubt, exon skipping is among the hopeful methods for fixing DMD. After dystrophin was discovered in 1987, researchers have been assessing different ways to treat DMD, and currently exon skipping, considered among the most hopeful methods, is being tested in clinical trials. Because of the unique mutations present in each individual with DMD, exon skipping therapy needs to accurately assess the modifications to the genome and cDNA, and confirm splicing patterns in each patient's muscle.

At this stage, an exon skipping approach involves recent, individualized approach to therapy. As clinicians and researchers engaged in the study muscular dystrophies for over 50 years, we are happy to see the recent advancements in the field, aiming that those who have DMD will benefit them.[2]

Benefits of Exon-skipping therapy

Exon skipping is the predominant form of alternative splicing in mammals, playing a significant role in enhancing protein diversity in this class of animals. Exon-skipping leads to the removal of a specific exon from the alternatively spliced mRNA. In this setting, the middle exon within a sequence of three exons might be present in the final mRNA in certain situations or specific tissues, while It might be absent in the final mRNA in other cases. Many techniques have been devised to identify instances of exon skipping, including AS profile, DiffSplice, and DS Gseq.

It's important to note that the techniques listed above have been demonstrated to be effective in identifying new patterns and understanding the reasoning behind alternative splicing. In pursuit of this objective, the research group has created an innovative computational tool known as the graph-based exon-skipping scanner (GESS). One remarkable benefit of the GESS method lies in its ability to identify new exon-skipping events directly from raw RNA-seq data without relying on pre-existing gene annotation information.[2]

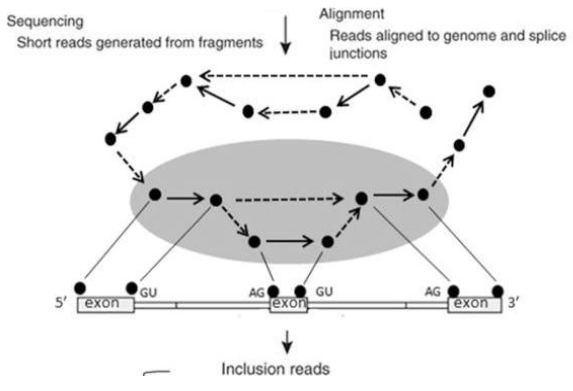

Figure 2: Graph-based exon-skipping scanner

IV. CONCLUSION

Among a range of underdeveloped therapies available to treat DMD, but Exon skipping is the only mutation-targeted therapy that is available today. "Exon-skipping therapy is a promising treatment strategy for DMD, which is caused by loss-of-function mutations in the DMD gene encoding dystrophin, leading to progressive cardiomyopathy".

Exon skipping is a relatively new, individualized treatment approach. Clinicians and researchers studying muscular dystrophies are pleased with recent advancements in the field and hope that patients with DMD will benefit from this new therapy in the future.

Author here suggests the important developments in above few strategies, particularly those possessing a great deal of clinical translation potential and/or those who have entered the clinical phase. Pre-clinical and clinical trials examine the rationale behind and efficacy of each drug. In addition, a meta-analysis of gene expression patterns in people who suffer from DMD has been carried out to look at the underlying molecular mechanisms of the disease.

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Citation of this Article:

Venugopal C. S., Dr. Asha K. R., & Dr. Prakash B. R. (2024). Analysis of Emerging Therapeutic Approaches for Treating DMD. *International Research Journal of Innovations in Engineering and Technology - IRJIET*, 8(8), 264-267. Article DOI https://doi.org/10.47001/IRJIET/2024.808030

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