GENE THERAPY MEDITED BY EXON-SKIPPING IN DUCHEINNE MUSCULAR DYSTROPHY

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ABSTRACT
Duchenne Muscular Dystrophy (DMD) is a neuromuscular degenerative disease linked to X chromosome caused by a mutation in the dystrophin gene. DMD affects 1/3500 males and causes premature death, before their 30s, due generally to cardiovascular dysfunctions. Patients have a early onset of the disease, between 2 and 5 years old, and at the age of 15 most of them have to use a wheelchair: There are three main treatments for the disease but only drugs are being used nowadays. Last investigations in the field propose cell therapy and gene therapy as alternatives.

INTRODUCTION

What is the cause of DMD?
Mutation in the dystrophin (2.5 millions of bp with 79 exons) cause the truncation of the protein dystrophin which is mostly expressed in the muscular tissue and in the brain.
Dystrophin links the cell-communication and the extracellular matrix maintaining the stability during the contraction. When it is interrupted, in patients, there are problems during contraction.
Patients have necrosis of the esqueletical muscles fibers and invasion of inflammatory cells. There is a degeneration of muscle which is substituted by fibroadipose tissue.

EXON-SKIPPING

The exon-skipping therapy consists on the introduction of anti-sense oligonucleotides (AOs) at local or systemic level to generate a shorter but functional dystrophin product. The AOs are short sequences (20-25bps) complementary to a pre-mRNA region near the acceptor or donor sites of splicing or between exons. As a result the splicing machinery is altered and the final mRNA, which is shorter, generates a truncated protein. This truncation doesn’t include the internal region of the protein and the N terminal and C terminal regions, the most important ones, remain functional.

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OBJECTIVES
The aim of the present review is to explain what are the causes of the disease and their consequences, specially in a molecular level. We focus the attention on the last era of one of the most important treatments which is currently being tested: exon-skipping of the altered exons of the dystrophin gene.

EXON-SKIPPING

Animal models

Types of AOs

There are two main types of chemicals used in clinical trials as AOs: 2’-O-Methyl phosphorothioate antisense oligonucleotides (2’-O-MPS AO) and phosphorodiamidate morpholino oligomers (PMO). PMO has a stronger pairing to target RNA than RNA or DNA.

CONCLUSION
The gene therapy of Duchenne Muscular Dystrophy has always had two main difficulties: the length of the gene and to target all the affected tissues by systemic administration. The exon-skipping seems to solve this two problems. On the one hand, the function of the protein is restored without needing to introduce the complete gene in a vector. On the other hand, some preclinical trials have restored dystrophin levels significantly in all the affected muscles. For these reasons, the therapy proposed in the present review supposes an encouraging approach to an effective treatment of the disease. However, there is still needed a more accurate technique with the final goal of offering to the patient a personal therapy in order to improve his life quality.

REFERENCES