Poster

Fibroblasts derived from nemaline myopathy patients: a useful cellular model for studying the pathophysiological mechanisms implicated in disease's development and for pharmacological screenings

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ABSTRACT

Motivation: Nemaline myopathy (NM) is one of the most common forms of congenital myopathy and it is identified by the presence of inclusions in muscle fibers called "nemaline bodies" or rods which are considered to be derived from Z lines because they have a similar structure and express similar proteins. Clinical features include hypotonia and muscle weakness, nevertheless, the clinical spectrum varies between lethal neonatal forms and less severe forms of later onset. This pathology is heterogeneous from a genetic point of view, its inheritance can be autosomal-dominant(AD), autosomal-recessive(AR) or sporadic. Although most cases of NM result from mutations in the genes encoding skeletal α-actin (ACTA1) and nebulin (NEB), mutations have been found in more than 10 genes that cause the disease, including genes encoding proteins for sarcomeric thin filament components (NEB, ACTA1, TPM2, TPM3, TNNT1, CFL2, LMOD3), Kelch domain-associated proteins (KBTBD13, KLHL40 and KLHL41) and an unconventional myosin (MYO18B). Unfortunately, there is no curative treatment for NM patients and the pathogenetic mechanisms remains unclear, therefore, studying fibroblasts derived from patients can be useful to understand the pathophysiological alterations of NM and to identify potential therapies.

Methods: We study the pathophysiological alterations in NM using fibroblasts from patients with mutations in ACTA1 and NEB genes which are obtained by performing a skin biopsy. As a screening strategy, fibroblasts are treated with different compounds for a week and after that, they are stained with rhodamine-phalloidin in order to analyze the status of the cytoskeletal actin filaments by fluorescence microscopy techniques using DeltaVision system. Positive compounds are those that improve the formation of actin filaments.

Results: Fibroblasts from NM patients showed incorrect actin filament formation compared to control fibroblasts. Moreover, we identified two compounds that improved the correct formation of actin filaments with an increase in the length of the filaments compared to untreated fibroblasts from patients ($p<0,01$).

Conclusions: Our results suggest that fibroblasts derived from NM patients can be a useful cellular model to study the pathophysiological mechanisms involved in NM and to find new therapies. However, further studies are needed to elucidate the mechanism of action of the two positive compounds identified and to determine their therapeutic applications.

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