Poster

Understanding underlying mechanisms in Nemaline Myopathy: the role of cardiolipin

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ABSTRACT

Motivation: Nemaline myopathy (NM) is one of the most common forms of congenital myopathies, a group of heterogeneous genetic muscle disorders. The main characteristic of NM is the presence of inclusion bodies in muscle fibers, the so-called 'nemaline body' or rods. These rod-like inclusions are mostly composed of actin, alpha-actin, and other Z-band filaments. Actin Alpha 1 (ACTA1) and Nebulin (NEB) gene mutations are the main cause of NM. A recent study, employing dermal fibroblasts from individuals with NM mutations demonstrated that incorrect actin filament polymerization is associated with mitochondrial dysfunction; In addition, L-carnitine and linoleic acid, two mitochondrial-boosting compounds, enhanced actin filament polymerization and restore mitochondrial bioenergetics. However, the underlying molecular mechanisms of these compounds are unknown. This study aims to bridge this gap by analyzing the effect of these compounds on cardiolipin (CL) concentrations, due to its significant role in the structure and the functioning of the mitochondria. Cardiolipin is a tetra-acylated diphosphatidylglycerol lipid that is predominantly localized in the inner mitochondrial membrane (IMM).

Methods: Four NM patients participated in this research, two patients with ACTA1 mutations and, two patients with NEB mutations. Variations in the expression of proteina involved in cardiolipin synthesis were analyzed by Western Blotting: cardiolipin synthase 1 (CLS1), which synthesized immature CL on the stromal side of the IMM and phospholipid-lysophospholipid transacylase Tafazzin (TAZ), which is involved in the remodeling phase to produce mature CL. Also, the concentration of cardiolipin in fibroblast was analyzed by fluorometric assay. Fibroblasts from two patients carrying one of these mutations were treated with L-carnitine and linoleic acid for a week.

Results: Mutant fibroblasts derived from NM patients presented lower expression levels of TAZ protein. In addition, CL concentration was decreased in patients' fibroblasts compared to untreated fibroblasts and controls.

Conclusions: Due to the mitochondrial dysfunction in mutant fibroblasts, cardiolipin is not maturing properly. Therefore, CL levels are decreased. The increased cardiolipin concentration by L-carnitine and linoleic acid treatment suggests that this may be one of the mechanisms of action by which these compounds improve mitochondrial function and actin polymerization.

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