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Gene Expressions Of C9ORF72 And Rab7A During Endoplasmic Reticulum (ER) Stress In Familial Amyotrophic Lateral Sclerosis (FALS)

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ABSTRACT

The non-coding hexanucleotide repeat expansions (HRE) in intron 1 of theC9ORF72gene have been identified as the most frequent genetic cause of familial ALS and familial frontotemporal degeneration (FTD).In this report, we studied the effect of C9ORF72 HREduring ER stress in lymphoblastoid cell lines (LCLs) derived from familial ALS and healthy controls and explore the C9ORF72role in the pathogenesis of ALS. In order to investigate the pathogenic effects of this mutation, the gene expression approach was applied through cell culture, quantitative PCR, RNA and protein extractions and Western blotting.Here, we showed that C9ORF72 isoform a and bmRNA expressions were upregulated in the C9-positive lymphoblastoid cell lines in basal condition. We also showed that Rab7a mRNA level was also upregulated in the C9-positive FALS cell lines compared to wild types in basal condition. During ER stress, C9ORF72 isoform a mRNA level was downregulated whereas C9ORF72 isoform b and Rab7a mRNA levels were upregulated. Western blotting analysis of C9ORF72-L protein showed a downregulation trend in the C9-positive cell lines during ER stress. Our study therefore further provides a strong evidence of autophagy involvement in C9ORF72-ALS. Therefore, the study indicated that endoplasmic reticulum (ER) stress might aggravate C9ORF72 HRE effect in FALS lymphoblastoid cell lines particularly in autophagyas an important pathway in C9 ALS/FTD pathogenesis.Our data indicated that the percentage of apoptotic cells was higher in C9-positive cell lines with or without staurosporine treatment when comparing to wild types, therefore suggesting C9 HRE may aggravate cell death in lymphoblastoid cell lines. The upregulation of lymphoblastoid cells apoptosis may be achieved by the activation of pro-apoptotic pathways or inactivation of anti-apoptotic pathways

Keywords: Amyotrophic lateral sclerosis, C9ORF72, Rab7A, autophagy, ER stress, apoptosis.

INTRODUCTION