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Bioinformatics analysis identifies deregulated genes of induced pluripotent stem cell derived motor neurons from sporadic Amyotrophic Lateral Sclerosis patients

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Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease characterized by death of motor neurons. The generation of specific human-induced pluripotent stem cells (hiPSC) that can be differentiated into motor neurons, associated with a large gene profiling and bioinformatics analyses, are the most promising approaches to provide a better understanding of the mechanisms underlying motor neuron degeneration. The aim of this study was to use bioinformatics and computational analyses to investigate the deregulated genes in hiPSC derived motor neurons from sporadic ALS patients. Microarray analysis was performed by using RNA of differentiated motor neurons from sporadic ALS and non-ALS subjects. Differentially expressed genes were identified by specific software. Gene Ontology (GO) analyses of differentially expressed mRNAs were conducted using the NCBI's online DAVID bioinformatics interface. High stringency parameters were selected to improve confidence in those values designated as enriched. Computational analyses were performed to evaluate the network representation of differentially expressed genes. The String software was used to predict protein interactions. Interaction confidence score was based on the measure of interaction confidence between two nodes, i.e. the likelihood that an interaction may occur, calculated automatically by the database. Connection score was measured by the number of connections per node based in the protein interaction network representing the actions of one protein over the other. The DAVID analysis focused on the Cellular Component Ontology (CCO) of differentially expressed genes and has pointed to 23 enriched GO terms under high stringency conditions. The CCO indicated four GO terms related to mitochondrion in hiPSC derived motor neurons. Cellular component terms related to mitochondrion gene list were, then, organized and submitted to STRING. This analysis generated 105 nodes and 232 edges based on the confidence score. In conclusion, large gene profiling of differentiated motor neurons from sporadic ALS patients indicates the mitochondrial dysfunction as a key factor in this cell-autonomous neurodegeneration process. FUNDING: This work was supported by FAPESP and CNPq, Brazil.

Biography

The authors, which have equal contribution to the work, belong to the Neuroregeneration Center of the Department of Neurology of the University of Sao Paulo Medical School, Brazil. The Center was stablished in 2006 and it is composed by students, post doctoral, post doctorates, biologists, molecular biologists, bioinformatics, physiotherapists, speech therapists, psychologists, physicians and clinicians interested to perform translational neurology and clinical neurology research in the field of neurodegenerative disorders. The group is headed by Professor Gerson Chadi, MD. PHD, Full Professor of the Department. The Group has put a great effort on the mechanisms of neuronal degeneration of Amyotrophic Lateral Sclerosis (ALS) by developing Translational Neurology Projects (bench to bed), being responsible for various clinical and laboratory studies. The Group members have published important papers in the most prestigious journals in the field.

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