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Translational neurology in amyotrophic lateral sclerosis: Focus on studies of schwann cells-related to the disease mechanisms

Gerson Chadi

University of Sao Paulo, Brazil

Abstract

Amyotrophic Lateral Sclerosis (ALS) is the most common motor neuron disease, affecting 0.3–2.5 cases/year/100,000 persons, characterized by adult-onset degeneration of the upper and lower motor neurons, and fatal in 2–3 years. Five percent of the cases are familiar form mainly linked to a SOD1 gene mutation. Studies on mechanisms of the disease and target drug have been performed mainly in the transgenic animal model (TG) carrying the mutant human SOD1 gene, expecting the molecular mechanisms giving rise to the disease might eventually translate into new treatment options. However, clinical translation of the proposed therapies has been failed. Recent studies have described astrocyte toxicity to motoneurons (MN) in ALS, via a mechanism involving secretion of uncharacterized factors that opened up the possibility for the involvement of other glial cell type in the physiopathology of the disease, for instance the Schwann cells (SC). In fact, astrocyte and SC execute similar functions centrally and peripherally, respectively, in physiological and pathological situations. Rather animal cells might beneficiate SOD1-model studies, restrictions are raised in the context of sporadic forms of ALS. Thus, employment of human cells from patients would be more efficient regarding translation. Here we used human SC from biopsies (Ethic Committee # 0187/11) of extensor hallucis brevis nerve from sporadic form of ALS patients (n=5) in the initial phase of the disease without showing neurological signs on that limb, and surgical fragment of the nerves obtained during reparation of lesioned brachial plexuses of control patients (n=3). SC cultures were performed according to a method developed in our laboratory, resulting in a highly purified human SC culture (96.5%). Co-cultures were performed by plating a highly purified mouse spinal cord MN cultures (81% imunolabeled ChAT positive cells) derived from P1 neonates above the monolayer of SCs. Neuronal death was quantified by Fluoro Jade C at the culture day five. The RNA of ALS patient nerves and controls was extracted and the microarray analysis of the whole human genome was performed, and analyzed by means GeneSpring GX software (Agilent) and DAVID Bioinformatics Resource. SC from ALS patients triggered a massive death of MN from wild-type (10-fold) and TG (7-fold) mice compared to SC of control patients. Gene expression profiling in the nerve of ALS patients have placed to discover pathways of disease pathogenesis in the SC/MN, favoring potential therapeutic target and biomarker development. Supported by FAPESP and CNPq.

Biography

Gerson Chadi. MD., has completed his Ph.D at the age of 30 years from University of Sao Paulo and postdoctoral studies from Institute Karolinska and University of Toronto. He is a Full Professor, since 1997, of the Experimental Neurology, Department of Neurology, University of São Paulo Medical School, responsible for Translational Neurology Program in his Department. He has published more than 68 papers in reputed journals.