Chapter

Introductory Chapter: Introduction to Novel Aspects on Motor Neuron Disease

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1. Introduction

Motor neuron disease (MND) represents a wide and heterogeneous expanding group of diseases affecting the upper or lower motor neurons, mainly represented by amyotrophic lateral sclerosis (ALS), primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), and progressive bulbar palsy. ALS is a disease of motor neuron degeneration in the cerebral hemisphere, brainstem, and spinal cord with a fatal prognosis in most of the cases due to a progressive paralysis of the diaphragm and other respiratory muscles leading to respiratory dysfunction and failure. Another recently recognized hallmark of ALS pathogenesis is vascular pathology apart from central nervous system capillary injury and microvascular impairment outside of the CNS [1].

2. Comments

Our first chapter is about stem cell therapy as a novel and promising modality for the treatment of ALS/MND. Robust safety profiles, low risk to benefit ratio, and ease of access make this approach a strong contender in the race against ALS/MND. Our authors concluded that this procedure is not a curative treatment, but a combinatorial approach integrating stem cell therapy, intensive neurorehabilitation, and current pharmacotherapeutic agents (e.g., Riluzole, Lithium, etc.) may be the best way forward. This chapter was written early last year (2019), but unfortunately, a prolonged editorial process impeded to publish this information at due time. However, we reviewed the medical literature and found that the abovementioned information has been confirmed recently (March 2020) by other authors [2].

In this book, we discussed about the pathogenic contribution of a subtype of aberrant glial phenotype into the progression and output of the neurodegenerative disease ALS and concluded that aberrant astrocytes or more generally aberrant glial cells are among the most important players in CNS damage causing deleterious effects through many potential pathological mechanisms, mostly sustained on their exacerbated proliferation together with their unprecedented neurotoxicity suggest that controlling these populations seems at least equally important than maintenance or restoration of homeostatic astrocyte functions to achieve CNS protection and repair. Another authors also suggest that aberrant glial cells (AbGC) isolated from the spinal cords of adult paralytic SOD1G93A rats exhibit highly proliferative and neurotoxic properties and may contribute to disease progression [4]. Same authors also established that mitochondrial dysfunction and neurotoxicity that can

be reduced by dichloroacetate (DCA), a metabolic modulator that has been used in humans, show beneficial effects on disease outcome in SOD1G93A mice. They also highlight that DCA treatment of AbGC reduced extracellular lactate levels indicating that the main recognized DCA action targets the pyruvate dehydrogenase kinase/pyruvate dehydrogenase complex, and the results confirmed that AbGC metabolic phenotype is related to their toxicity to MNs and indicated that its modulation can reduce glial mediated pathology in the spinal cord [3]. At this point, it is important to emphasize that neuronal cell death is the main pathological feature of chronic neurodegenerative diseases (NDs) like ALS. A common hallmark of several NDs is the accumulation and aggregation of proteins; such proteins are thought to be primarily turned over by autophagy. Therefore, autophagy is considered a critical ND-protective pathway, which opens up potential new therapeutic interventions, and some authors have been considering the roles of autophagy and its contribution to neurodegeneration in neurons and concluded that little is known about the functions and disease contribution of the autophagy machinery in glia cells [4].

The next chapter of this book is related to the structural and functional consequences of the SMA-linked missense mutations of the survival motor neuron protein, where the authors deliver a brief update of the structural and functional consequences of the missense mutations of this SMA protein. There is another before published chapter where the same author investigates how SMA-linked mutations of SMN1 lead to structural/functional deficiency of SMN, and a set of computational analysis of SMN-related structures was conducted, described, and highlighted three residues of SMN (Asp44, Glu134, and Gln136), and the electrostatic basis of how the SMA-linked missense mutations of the three residues cause structural/functional deficiency of SMN and also a possibility of SMN's Lys45 and Asp36 acting as two electrostatically stabilizing clips at the SMN-Gemin2 complex structure interface [5].

Mutations to the gene encoding superoxide dismutase-1 (SOD1) were the first genetic elements discovered that cause motor neuron disease (MND). Around 10 years back, the unique way to test ALS-related gene was SOD1 sequencing. Based on this postulate, we approved to include into this project a novel review about the current understanding of ALS-related genes, summarize the worldwide ALS distribution feature by frequency of occurrence in different regions, and outline the genetic testing consideration, within many advances in the field of ALS genetics. In this chapter, the author highlights the recent advances in ALS gene map, genome-wide association study on ALS, genetic testing, and gene therapy.

Finally, we made a bibliography research about MND and the most recent advances on treatment and reviewed the most relevant papers published on the first trimester of 2019, but as was before-mentioned, this chapter is going to be published more than 1 year later when some of our information is already old-fashioned. Last year, we reviewed on novel information about edaravone, riluzole (already approved by Food and Drug Administration), nusinersen, EH301, 5Fluoroucil, Tryptophan, RNS60, Rasagiline, Tirasemtiv, Aquaporin, Fasudil, and Lunasil. In order to deliver to our reader community, more novel information about MND/ALS is important to highlight other procedure that has been proposed for treatment such as the multifaceted role of kinases in ALS. The comprehensive regulation of kinases, however, a better understanding of the disturbances in the kinome network in ALS, is needed to properly target specific kinases in the clinic. Different kinases have been recently involved in TDP-43 phosphorylation. Among these, protein casein kinase-1 is the first kinase identified to phosphorylate TDP-43 *in vivo*, followed by tau tubulin kinase 1 and cell division cycle kinase 7. Currently, it is recognized that TDP-43 proteinopathy characterized by truncation, ubiquitination, hyperphosphorylation, and/or nuclear depletion in neurons is the prominent

and common pathological feature of sporadic and familiar ALS [6]. Some authors explored the effects of a chronic treatment with the compound IGS-2.7 in the TDP-43 (A315T) transgenic mouse model and found a significant decrease in the levels of phosphorylation of TDP-43 in sporadic ALS lymphoblast, while no differences were observed in control group, and they arrived to the following conclusion: prolonged treatment with IGS-2.7 prevents the phosphorylation of TDP-43 *in vivo* in the cord of TDP-43 transgenic mice, being this effect associated with an attenuation of most of the events that reflect the worsening of the pathological phenotype, then the inhibition of CK-1δ with the benzothiazole derivative IGS-2.7 may modulate TDP-43 toxicity *in vivo* by limiting TDP-43 phosphorylation, which could explain the benefits obtained with this drug candidate in the preservation of spinal motor neurons. Therefore, benzothiazole IGS-2.7 has neuroprotective properties and not only decreases TDP-43 phosphorylation in cells derived from ALS patients but also corrects the subcellular localization of TDP-43, preventing the abnormal cytosolic TDP-43 accumulation in ALS lymphoblasts [6].

For another hand, other authors reported that 185 miRNAs in serum of affected patients and controls confirmed a downregulation of miR-335-5p in ALS patients [7].

Because we are under obligation to deliver the most recent information about MND/ALS therapy to our reader's community, then we would like to comment about clinically used ebselen and related analogues to promote thermal stability of A4V SOD1 when binding to Cys111 only [8]. Ebselen is an organoselenium compound with activity similar to glutathione peroxidase [9]. Several studies have demonstrated the neuroprotective activity of ebselen, possibly via its anti-oxidant properties [10, 11]. The capacity of ebselen to decrease mitochondrial cellular toxicity caused by mutant SOD1 confirmed that this compound plays an important role in alleviating familial ALS [12].

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