Preface

Amyotrophic lateral sclerosis (ALS) is an adult-onset progressive neurodegenerative disease that affects motor neurons in the brain and the spinal cord in 1.2–1.8 per 100,000 individuals. Patients suffer from muscle weakness and paralysis, and usually die from respiratory insufficiency within 3–5 years after diagnosis. Since it was first described by the French neurologist Jean-Martin Charcot in 1869, intensive research efforts have been made to decipher the mechanisms underlying disease pathogenesis. It is now more than a decade since the discovery linking point mutations in the gene encoding the free radical scavenging enzyme Cu/Zn-superoxide dismutase (SOD1) to a small subset of patients with autosomal dominantly inherited ALS. Because both familial and sporadic forms of the disease display identical clinical outcomes, the use of transgenic mouse models that overexpress several of these SOD1 mutations has represented an important breakthrough in the search for the cause of ALS neurodegeneration. Multiple distinct etiologies have been shown to be involved in ALS including glutamate excitotoxicity, oxidative stress, mitochondrial dysfunction, altered neurofilament expression, disrupted axonal transport, neurotrophin deficiency, inflammation, autoimmunity, metal toxicity and viral infection. Unfortunately, evidence of a causative role for any of these mechanisms is not yet conclusive, and the nature of the characteristic selective loss of motor neurons still remains largely unknown. Indeed, whether motor neurons in ALS die from a complex interaction between multiple factors or because of the manifestation of a unique, yet unidentified genetic-biochemical abnormality is a matter of controversy.

In the spring of 2005, a small group of outstanding scientists joined together in a unique place at the South

Atlantic seashore of Uruguay to debate on new directions for ALS research. Stimulated by three engaged researchers, Luis Barbeito, Joseph S. Beckman and Jean Philippe Loeffler, this meeting provided a general overview of ALS. Discussions addressed the status of several crucial lines of investigation towards the comprehension of disease pathogenesis, including the impact of the structure and aggregation of mutant SOD1 on motor neuron death, the implication of specific toxicity signaling pathways, the analysis of clinical and epidemiological aspects of the disease, and the situation of ongoing and future strategies of therapeutical intervention. The present issue brings together some of the most relevant contributions of the meeting. At the end, two major conclusions emerged. First, the notion that ALS is not exclusively a disease of motor neurons but rather that the loss of these cells is the consequence of earlier events. Certainly, motor neurons may not be the only site where mutant SOD1, or other effectors, act primarily to trigger disease. Growing evidence does support that other cells in the environment of motor neurons, such as astrocytes, oligodendrocytes, Schwann cells, muscle fibers and microglial cells, may play a determining role in the activation of the pathological process. Therefore, the clinical signs of ALS (i.e., motor impairment) will not reflect the loss of motor neurons but rather the global dismantlement of the motor unit. In this scenario, the implication of each cellular/anatomical level in the pathological process must be considered. In particular, the neuromuscular junction is a very specialized structure where motor control can be altered by subtle regulatory pathways. Whether early events of ALS operate at that level is a major issue in current research.

The second point highlighted at the meeting was the technical limitation of ALS research. Although the mutant SOD1 mouse models were regarded from the beginning as a major advance in the field, many physiopathological mechanisms observed in these animals cannot be directly transposed to the human disease. More importantly, whenever scientists or physicians think about applying findings from the laboratory to the clinic, the results are disappointing if not grossly misleading. Indeed, many, if not all compounds showing promising therapeutics to delay disease progression in the mouse models of the disease are ineffective when tested in patients. The considerable biological heterogeneity underlying the disease process of ALS may account for such a defeat. Also, the lack of specific biomarkers is highly detrimental for

both early diagnosis and for patients with borderline clinical features, which makes difficult the early application of an appropriate treatment and the selection of disease relevant population groups for clinical trials. Finally, mutant SOD1 mice may not be adequate enough to predict the efficiency of new therapies. Many scientists agree that it is necessary to discover new disease-linked genes that will provide not only important information in understanding the mechanisms of motor neuron death but also new targets for therapy. Hopefully, many studies are currently being performed to take up this challenge!

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