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Good Science Shows the Way

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the degeneration of pyramidal neurons in the motor cortex and motor neurons in the brain stem and spinal cord. There is not cure for ALS and the patients typically die of respiratory failure between 1 and 5 years after diagnostic. The causes of ALS are unknown. Most of the cases are sporadic and 10% of the cases are hereditary (familial ALS) [1]. In 1993, mutations in the gene of the antioxidant enzyme superoxide dismutase were linked to 2–3% of the cases of familial ALS [2]. These reports lead to the oxidative stress hypothesis in ALS, which was first thought to be produced by a loss-of-function. Soon after, it becomes clear that the mutations were responsible for a gain-of-function. The mutant SOD gain of toxic function hypothesis was based in the fact that some mutant enzymes had the same activity than wild type SOD, mice deficient for SOD do not develop motor neuron disease and mice transgenic for mutant, but not to wild type SOD develop an ALS-like disease [3]. At the same time markers of oxidative damage were reported in human ALS patients and transgenic mice models of ALS. Although, the oxidative hypothesis to explain the mutant SOD gain-in-function does not have general acceptance [4], the fact that oxidation occurs in ALS patients and animal models of the disease is incontrovertible [5]. However, whether oxidative damage plays a central role in the induction of motor neuron death, or is a co-phenomenon without pathological implications, remains unknown. This unknown has lead to skepticism in many ALS investigators, which consider oxidative stress no more than a secondary phenomenon of little or no importance in the pathogenesis of the disease [4]. The main problem in the research of oxidant-induced damage has been identifying relevant targets of oxidative damage. In 1995, two papers were publishing that brought the strength of powerful analytical methods to oxidative stress in ALS [6,7]. One identified carbonyl formation [6] and the other tyrosine nitration [7] in pre-symptomatic animal models of ALS using two-dimension gel electrophoresis and mass spectrometry analysis. More importantly was the identification of specific target proteins with possible implications in the pathology of the disease. Remarkably, the oxidized proteins identified by Poon et al are present in aggregates in human patients and animal models of ALS [6]. One of the oxidized proteins identified was SOD1 itself. Oxidation of SOD changes its biochemical properties and the metal binding properties. In addition, the paper this report takes a more conservative approach on previously extreme positions. In this publication, the Butterfield group discusses how protein aggregation could be caused by oxidative stress, linking two apparently irreconcilable positions, more because of the attitude of the researches than the nature of the results [6]. It is possible that many investigators dismiss these papers as more of those oxidative stress papers; but the fact the Poon's report is one of the higher download papers from Free Radical Biology and Medicine indicates it has also awaken the curiosity of many other investigators. It seems that making an interpretation that explains much of the available results attract new interest in continue these important investigations. In this era in which new ideas and hypotheses are embraced as the last "true," while at the same time old ideas and hypotheses are forget, even

those supported by experimental evidence. In which it becomes very difficult to publish anything against the new “dogma,” or that is not “fashionable” anymore and only a few recognizable journals keep reviewing and publishing these “old and out of fashion papers.” Scientist that test the hypothesis using sound and accepted and many times state of the art approaches are always refreshing. When in addition, these papers further advance the knowledge in one field based on evidence and a fair interpretation of the results supported by previous knowledge is always something worthy to read. We are still do not know whether oxidative stress or any of the identified oxidized proteins play a role in ALS. We do not know either whether protein aggregation plays a role in the pathogenesis of ALS. There is not irrefutable evidence linking protein oxidation and aggregation in motor neuron degeneration. Would it not be great to know?

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