Endogenous petides as markers of abnormal SOD-1 protein in familial and sporadic ALS

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Research Abstract

Abstract: Endogenous peptides as markers of abnormal SOD-1 protein in familial and sporadic ALS Amyotrophic lateral sclerosis is a fatal adult onset motor neuron disease that currently lacks an effective therapeutic intervention as well as an accurate method for diagnosis. The molecular pathology of the disease is also unclear; where familial forms of the disease (fALS) have known mutations in protein encoding genes (e.g. SOD1, FUS, TDP-43) or even a repeat expansion (i.e. c9orf72) that cause disease onset, whereas the majority of cases are sporadic with no identified cause. Recent studies have found non-genetic abnormalities of SOD1 protein in sALS though, implicating a controversial role for this protein in sporadic ALS pathology. Our

preliminary biomarker study using cerebrospinal fluid (CSF) of ALS-SOD1 rat models (G93A and H46R) with our novel mass spectrometry platform identified two related endogenous peptides of SOD1 with post- translational modifications that were a log-fold elevated in two distinct genetic variants. On the other hand, the concentration of intact hSOD1 protein in spinal fluid of G93A and H46R SOD-rats was either similar or less than hSOD1-controls. We next targeted one of these compounds in human CSF of fALS (eight SOD1 patients, all unique genetic variants as well as six controls), sporadic (four patient samples), and c9orf72 (three patients), and confirmed 4.5-10 fold elevation in most of the fALS-SOD1 variants, and a milder but still significant increase in sporadic patients (1.6-fold, $p < 0.05$), with no change observed for the expansion repeat carrying cohort (c9orf72). The endogenous fragment of SOD1 protein may therefore be a direct readout of aberrant/misfolded SOD1 protein, with a unique pattern of modification and/or degradation in the cell. The elevation of this peptide in sALS samples is especially interesting, as its presence may clarify a controversial debate as to whether SOD1 protein is involved the sporadic form of the disease. If so, we feel this may be critical in assessing a potential role for SOD1 targeted antisense oligonucleotide therapy in even a subset of sALS patients, a therapy currently under clinical trial for SOD-fALS. We are proposing to investigate this potential marker in much larger cohorts of both fALS and sALS patients to further identify the specificity of this marker in different ALS cohorts as compared to both healthy control and neurologic-disease control patients. We will also investigate the correlation of this marker to known severities of SOD-fALS forms as well, which appear stratified from our initial investigation, and the potential link between protein misfolding/aggregation and the peptide concentration. In addition, with the remaining material from the above study, we are proposing to use our newly developed platform from which we discovered the current marker, for an exploratory investigation of the sALS cohort, to potentially discover further markers or pathways in common that are perturbed in this poorly described disease state.

Further information available at:

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