PAD2 Dysregulation and Abnormal Protein Citrullination in ALS Disease Models

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Abstract

Amyotrophic lateral sclerosis (ALS) is a deadly neurodegenerative disease characterized by loss of motor neurons, paralysis and eventual death. The mechanism of ALS is still incompletely understood, and the disease is to date without an effective remedy. Protein arginine deiminase 2 (PAD2) converts pepdyll-Arginine into pepdyll-Citrulline, a post-translational modification referred to as citrullination. Aberrant expression of PAD2 and protein citrullination are increased in several neurodegenerative conditions. Whether this increase is involved in ALS is unknown. In this study, we investigated PAD2 and protein citrullination in two genetic mouse models of ALS expressing human mutant SOD1G93A and PFN1C71G, and in human ALS spinal cord. We show that PAD2 gene expressions and protein citrullination are increased along ALS progression. These changes occur in areas with the most severe motor neuron degeneration including the spinal cord, and brainstem.

We show that the increase in PAD2 and citrullinated proteins occur specifically in astrocytes, while decreasing in neurons. Citrullinated proteins also form non-astrocyte aggregate patterns; and are dominantly expressed in insoluble protein fractions. Furthermore, the ALS mouse spinal cord shows altered citrullinome. Finally, knocking out PAD2 prevented protein citrullination in SOD1G93A mice, quicker disease onset, while slowing disease progression. These results demonstrate that aberration of PAD2 protein citrullination are key characteristics of active astroglialitis, and possibly drive some type of protein aggregation in the pathogenesis of ALS. Because protein citrullination alters protein functions, our results suggest that PAD2 and protein citrullination play a role in astroglialitis and astrocytic toxicity in ALS and other neurodegenerative conditions.

PAD2 is increase in SOD1G93A and PFN1C71G ALS mouse models

Protein citrullination increase in astrocytes in SOD1G93A and PFN1C71G ALS mouse models

Proteomics demonstrate alteration of protein citrullination in SOD1G93A ALS mouse model

PANTHER classification of citrullinated proteins in SOD1G93A ALS mouse model

Summary

Our results show that PAD2 expression and protein citrullination increase as the disease progresses in two different genetic mouse models of ALS expressing mutant SOD1 and PFN1; and in ALS patients. This increase particularly occurs in the astrocytes, while decreasing in neurons. The alteration of PAD2 and protein citrullination seen in these mouse models coincides with areas showing motor neuron degeneration in ALS. The ALS mice spinal cord citrullinome shows a significant alteration in a wide range of protein classes and functional pathways. In addition, citrullinated proteins form non-astrocyte aggregate patterns; and are dominantly expressed in insoluble protein fractions, suggesting citrullination may possibly drive protein insolubility. Finally, PAD2 knockout prevented protein citrullination in ALS mice, quicker disease onset, while slowing disease progression. These results suggest that dysregulation of PAD2 and protein citrullination contribute in the pathogenesis of ALS.