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Johns Hopkins University Provost's Undergraduate Research Award Project Summary

Amyotrophic lateral sclerosis (ALS) induced changes in basigin expression patterns

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Abstract

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by a progressive loss of motor function due to premature spinal and cortical motor neuron degeneration and death. Mutations in the superoxide dismutase 1 (SOD1) gene cause approximately 20% of inherited cases of ALS. Overexpression of a mutant form of SOD1 (G93A) in mice appears to produce disease progression through an unknown gain of toxicity. To further elucidate mechanisms of neurodegeneration in ALS, we examined expression patterns of the transmembrane glycoprotein, basigin (CD147, Emmprin) in end-stage of the SOD1 G93A mouse model. Basigin, a member of the immunoglobulin superfamily, has various physiological roles including trafficking of monocarboxylate transporters (MCTs) to the plasma membrane, induction of matrix metalloproteinases (MMPs), and leukocyte activation. We focused on interactions of basigin with MCTs and implications for energy-metabolism in the disease state. The astrocyte-neuron lactate shuttle hypothesis states that lactate release from glucose metabolism in glia fuels neuronal metabolism, particularly in states of oxidative stress. Previous studies have shown that inhibition or down-regulation of MCTs leads to impaired lactate transport and neuronal degeneration, likely due to a lack of energy resources. Basigin is essential for localization of MCT1 and MCT4 to the plasma membrane, and inhibition of basigin has been shown to prevent lactate release by astrocytes. Additionally, basigin has been implicated in several other neurological diseases, including roles in leukocyte transmigration in multiple sclerosis and regulation of the γ -secretase complex in Alzheimer's disease. Interactions with MCT isoforms and implication in related diseases make basigin a viable candidate for study in ALS. We show that basigin co-localizes with MCT1 at the plasma membrane and is well-expressed in myelin-rich areas. We also show that basigin mRNA levels are reduced in brain and spinal cord in SOD1 end-stage disease. Basigin protein levels show differential expression, but not uniform down-regulation. These preliminary results indicate that basigin is likely involved in ALS-related neurodegeneration. Further investigation of the role of basigin in disease and normal states may provide insights regarding pathological changes in ALS.

Figure 1: Basigin co-localizes with MCT1 at the plasma membrane. Immunostaining of white matter tracts in ventral brain (A) and corpus callosum (B), SOD1 end-stage. MCT1 and basigin display a high degree of co-localization in the myelin sheath. Antibodies used: rabbit anti-MCT1 (1:50, Santa Cruz Biotechnology) and goat anti-Basigin (1:50, Santa Cruz Biotechnology)

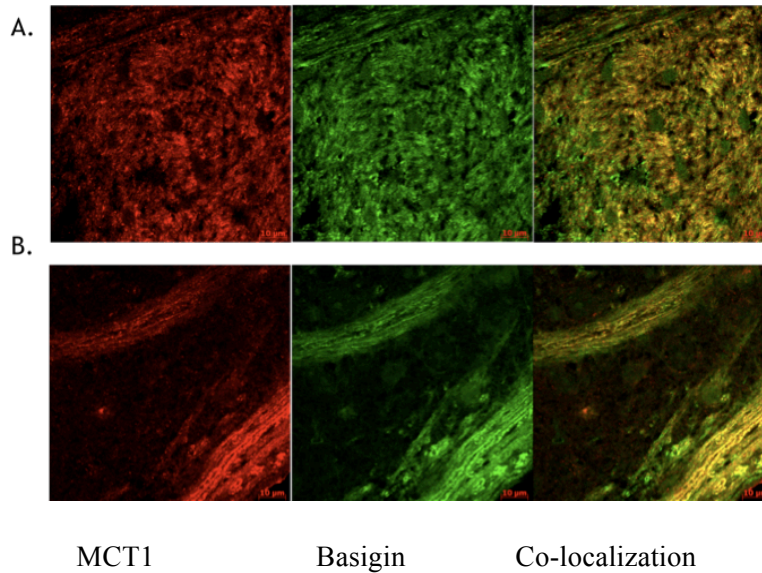


Figure 2: Basigin protein is differentially expressed in SOD1 end-stage and wild type. Western blots of brain tissue from SOD1 G93A end-stage and wild type (WT) mice. Antibody used: goat anti-Basigin (1:1000, Santa Cruz Biotechnology). Equal protein amounts of SOD1 and WT samples were loaded. A. Basigin appears to be slightly over-expressed in SOD1 white matter as compared to wild type. There appears to be no change in basigin expression in gray matter. B. Basigin shows highly reduced expression in SOD1 spinal cord gray matter and unchanged expression in SOD1 spinal cord white matter. C. Basigin shows highly reduced expression in SOD1 sciatic nerve and slightly reduced expression in SOD1 hamstring muscle.

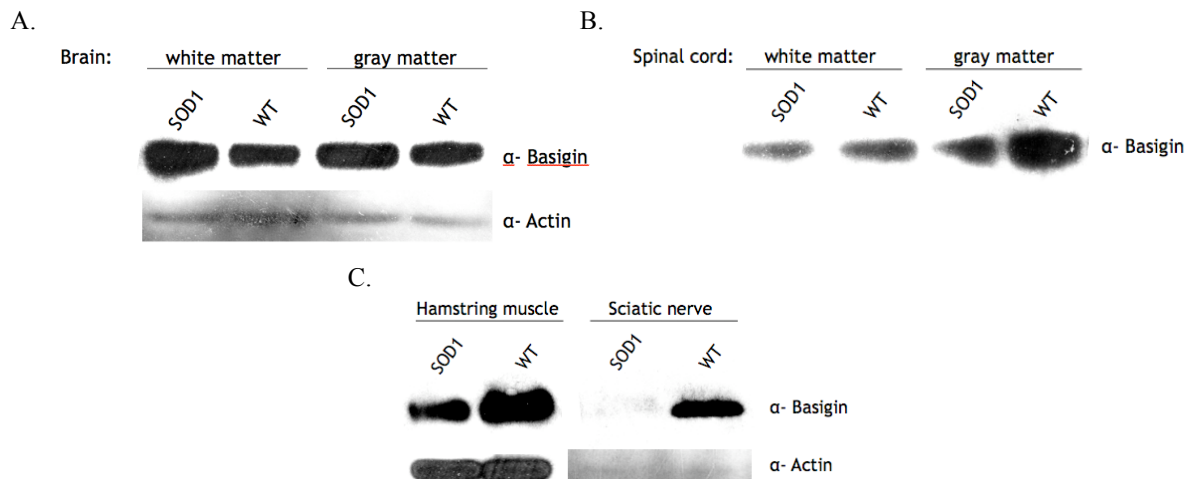
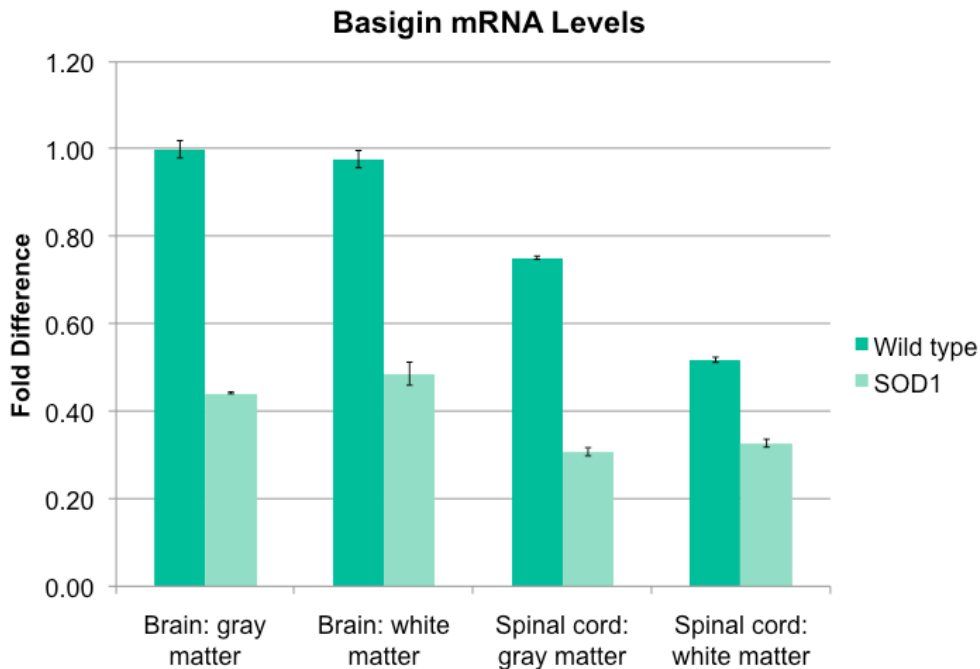


Figure 3: Basigin mRNA levels are reduced in SOD1 end-stage. Quantitative reverse transcription PCR was performed with probes for Basigin and 18S rRNA as a control (Probes from Applied BioSystems, Inc.). As compared to wild-type littermate samples, basigin expression is greatly reduced in SOD1 end-stage. Data is averaged from two experiments.



Conclusions and Future Directions

- MCT1 co-localizes with basigin at the plasma membrane, particularly in myelin-rich areas
- Basigin protein expression is highly reduced in SOD1 end-stage spinal cord gray matter and sciatic nerve
- Basigin mRNA levels are uniformly reduced in SOD1 end-stage brain and spinal cord
- Differences in mRNA and protein expression patterns could be due to altered disease state post-translational processing, normal mRNA degradation mechanisms or changes in translational frequency
- Additional assays (Western blot and qRT-PCR) will be used to corroborate preliminary findings and fully determine changes in expression patterns
 - o Studies with TDP-43 ALS mouse model will be conducted in addition to SOD1 studies
- We aim to monitor basigin expression through disease progression in SOD1 mice
- We are developing lentiviral constructs for basigin overexpression and silencing in a C6 glioma cell line for further studies

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