Investigating a2-chimaerin-dependent motor neuron protection in ALS

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Investigating a2-chimaerin-dependent motor neuron protection in ALS

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5

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Motor neurone diseases

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motor neuron degeneration, Amyotrophic Lateral Sclerosis, Motor Neurons, Onset of illness, Neuromuscular Junction

Research Abstract

? DESCRIPTION (provided by applicant): Amyotrophic lateral sclerosis (ALS) is a relentless motor neuron disease that rapidly leads to paralysis and death. The highly sporadic nature and

confounding array of aberrant cellular processes involved in disease pathogenesis are major barriers that prevent targeting causal mechanisms. Currently, there are no effective options to slow disease onset or progression, even for patients with identified genetic lesions, highlighting the critical need for therapies that target fundamental disease mechanisms. Axonal retraction and denervation of neuromuscular junctions (NMJs) are early pathological events that precede motor neuron death. Emerging evidence suggests that alterations in axon guidance receptor expression or function play a key role in pathophysiological axon retraction and NMJ dismantling. Significantly, reduced expression of EphA4, a prominent repulsive axon guidance receptor, has been shown to protect motor neurons from degeneration, delay disease onset and extend lifespan in human ALS patients. Antagonizing EphA4 is one approach to prevent motor neuron degeneration, but the receptors indispensible role in diverse cellular and physiological processes are major impediments to developing specific and tolerable drugs. An alternate strategy to circumvent these obstacles is to inhibit downstream effector proteins that mediate EphA4-dependent motor neuron degeneration, however, these molecules are currently unknown. We have identified that inhibition of ?2-chimaerin, an essential EphA4 effector protein and potent regulator of actin cytoskeletal dynamics, protects motor neurons from degeneration, delays disease onset and progression, and extends lifespan in ALS animal models. Significant benefit is observed in both heterozygous and homozygous knockout mice, revealing that ?2-chimaerin is a strong candidate for potential therapeutic targeting in ALS. We hypothesize these beneficial effects are due to blocking EphA4-dependent destabilization of the actin cytoskeleton which normally causes axonal retraction and NMJ denervation. The goal of this proposal is to determine the precise cellular and molecular mechanisms underlying motor neuron protection through ?2-chimaerin inhibition. First, we will determine if neuromuscular innervation, function and regeneration are enhanced in ?2-chimaerin mutant mice. Second, we will delineate the role that EphA4 interactions and Rac1-dependent cytoskeletal changes have in ?2-chimaerin-dependent neuroprotection. Third, we will use conditional ?2-chimaerin mice to determine if neuroprotection occurs though cell- autonomous mechanisms in motor neurons, or is due to non-cell autonomous function in non-neuronal cells. Our results will provide critical insight into the mechanisms of motor neuron degeneration and will facilitate new strategies to slow ALS disease onset and progression.

Lay Summary

PUBLIC HEALTH RELEVANCE: Amyotrophic lateral sclerosis (ALS) is a devastating disease that causes paralysis and death due to motor neuron degeneration. Due to the heterogeneous genetic and cellular origins of ALS, modifying treatment strategies that interfere with core pathological mechanisms are likely to have the widest beneficial effect. We have identified a target modifier gene whose inhibition confers resistance against motor neuron degeneration, delays disease onset, and extends lifespan in ALS animal models. Our proposal addresses a critical and unmet need in ALS combination therapy development and will provide key insight into the underlying cellular and molecular mechanisms of motor neuron degeneration.

Further information available at:

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