Pathogenic role of the novel mitochondrial apoptotic protein PSAP in ALS

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Principal Investigators

XU, XUEMIN

Institution

UNIVERSITY OF TENNESSEE KNOXVILLE

Contact information of lead PI
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Research Abstract

Accumulating evidence suggests that apoptosis is one of the mechanisms responsible for motor-neuron degeneration in amyotrophic lateral sclerosis (ALS). Specifically, a recent study showed that neuronal deletion of both Bax and Bak in SOD1G93A mice (ALS model) not only halted neuronal loss, but also prevented axonal degeneration and NMJ denervation, and extended survival. Thus, these results suggest that the deletion of both Bax and Bak might conferred a

stronger resistance to apoptotic stimuli than deletion of Bax alone, given that a redundant apoptotic pathway can be activated in cells. Thus, these results once again point to the mitochondrial apoptotic pathway as a major contributor to the pathogenesis of ALS and indicate that further investigations, possibly targeting “other relevant pathways” regulating mitochondrial apoptosis, are needed to clarify this issue. In this regard, our recent study revealed a very interesting finding that knockout of the novel mitochondrial proapoptotic protein PSAP (presenilin-associated protein) in SOD1G93A mice greatly improved motor function, increased lifespan, and protected NMJ from denervation in these mice. Specifically, PSAP was shown to induce apoptosis in a Bax- and Bak-independent manner, strongly suggesting that the PSAP pathway is one of the most sought after “other relevant pathways” that contribute to neurodegeneration in ALS. Thus, our novel findings may open a new avenue for studying the pathogenesis of ALS. We also found that PSAP functions downstream of death receptor DR6, which is implicated in ALS recently, and that knockdown of PSAP protected axons from degeneration caused by NGF withdrawal. These novel findings led to our hypothesis that DR6-PSAP represents a novel pathway mediating the pathogenic effect of SOD1G93A in ALS. This innovative hypothesis will be tested by the following two objectives: Aim 1: Determine the role of PSAP in mediating the pathogenic effects of SOD1G93A using a novel PSAP-knockout mouse model. 1-a, Determine the effect of PSAP knockout on ALS onset and survival of SOD1G93A mice. 1-b, Determine the effect of PSAP knockout on motor neuron survival and protection of neuromuscular junction integrity in SOD1G93A mice. Aim 2: Determine the mechanism by which PSAP mediates the pathogenic effect of SOD1G93A in ALS using a cultured cell system. 2-a, Determine a novel DR6-PSAP pathway that mediates the neurotoxicity of SOD1G93A in ALS. 2-b, Determine the role of PSAP in DR6 signaling and PTP opening. Significance: The novel finding that knockout of the apoptotic mitochondrial protein PSAP greatly improved motor function and inreased lifespan in ALS SOD1G93A mice provides a new avenue for studying the mechanism underlying ALS pathogenesis. Specifically, the finding that knockout of PSAP improved walking ability and prevented incontinence in SOD1G93A mice raises the possibility that understanding the molecular mechanism by which PSAP contributes to the pathogenesis of ALS may lead to the identification of a novel therapeutic target and development of methods of treatment to improve the quality of life of human patients.

Further information available at:

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