UT Southwestern
Medical Center

Donor Report to Darrell K Royal Research Fund

Prepared by: Yingfei Wang, Ph.D., Principal Investigator
Assistant Professor, Departments of Pathology, Neurology and Neurotherapeutics
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Shaping the Future of Medicine

Dementia severely interferes with the daily life of patients. Neuronal cell death is a key feature in dementia and causes problems with memory, thinking, and behavior. Understanding the underlying mechanisms of neuronal cell death in dementia may provide an effective treatment for dementia. Apoptosis-inducing factor (AIF) is a mitochondrial flavoprotein controlling both cell life and death. Although it is clear that AIF plays an essential role in embryo development, the role of AIF in the adult brain remains obscure. Interestingly, we recently identified a novel AIF isoform – AIF3. As reported previously, the expression of AIF3 is not detectable under normal physiological conditions, but increased in dementia-associated, progressive neurodegenerative diseases, including Parkinson's disease (PD) and Alzheimer's disease (AD). Our study continues to elucidate the role of AIF3 in dementia. Ongoing support from Darrell K Royal helps us better understand AIF3 functions in neurodegeneration and dementia, which might yield a new therapeutic target for the treatment of dementia.

Progress

1) Under what disease conditions is AIF3 expression increased? We found that AIF3 was undetectable under normal physiological conditions, and it was not increased in cortical neurons when exposure to glutamate toxicity, glucose-oxygen deprivation, or hypoxia in vitro. It was also not obviously induced in the mouse brain 24 hours following traumatic brain injury. Interestingly, we found it was clearly induced following stroke in the brains of both humans and mice, which has been confirmed at both mRNA and protein levels. In addition, we found that AIF3 expression was also increased in PD patients with dementia as well as AD patients in the cortex and hippocampus tissues. The expression of AIF3 in human AD patients was also further confirmed at both mRNA and protein levels.
2) What is the biological function of AIF3 in the brain? In order to study the biological functions of AIF3 in vivo, we have successfully established a mouse model that expresses AIF3 in the brain. We found that AIF3 expression caused severe neurodegeneration in multiple brain regions, especially in the somatosensory cortex, hippocampus, piriform cortex, thalamus, and the cerebellum. AIF3 mouse brains showed an enlarged ventricle, and all AIF3 mice died between two and four months after birth, whereas AIF mice from the same litter grew normally. These data indicated that AIF3 functions differently from AIF, and its expression may contribute to the pathogenesis of neurodegeneration.
3) What is the underlying mechanism of AIF3-induced neurodegeneration? We characterized AIF and AIF3 in vitro biochemical properties. We found that AIF3 lacks NADH oxidase activity. Using cortical neuron cultures and an AIF3 mouse model, we further found that expression of AIF3 eliminated ATP synthesis, and reduced oxygen consumption, eventually causing mitochondrial biogenesis defects both in vitro and in vivo. In addition, expression of AIF3 significantly caused chromatin condensation and nuclear shrinkage in the mouse brain.

   Our progress data continue to support our hypothesis that AIF3 is induced in dementia-related human diseases and might promote dementia pathogenesis.

Impact

The Darrell K Royal Fund promotes our collaboration with the Alzheimer's Disease Center at UT Southwestern, which provided human AD samples, and promotes our collaboration with the pathologist in our Department who provided human stroke patient samples. Darrell K Royal Fund support has allowed us to check under what disease conditions AIF3 was increased. This funding has enabled us to look more deeply at the underlying mechanisms of AIF3-induced neurodegeneration, which involves AIF3-induced mitochondrial dysfunction and nuclear condensation.

What's next?

There are still many important questions and challenges we need to address in the future. Although we knew AIF3 expression was increased following stroke and in cases of AD and PD with dementia, it is not clear if AIF3 expression is specific for aging-related neurologic diseases or specific to mitochondrial dysfunction-related neurologic diseases. It is not clear what the impact of AIF3 expression on the pathogenesis of these diseases is. We also still need to discover how AIF3 splicing is regulated under these disease conditions and how we can target AIF3 splicing to prevent neurodegeneration. Continued support from Darrell K Royal and other grants are extremely important in order to further address these key questions.

For a long time, beta-amyloid (Aβ) plaques and neurofibrillary tangles have been considered the prime suspects in damaging and killing neurons in AD. Our group has newly identified AIF3 as a splicing form. It has never been linked to dementia, although we have strong evidence that expression of AIF3 in the mouse brain caused progressive neurodegeneration. The proposed project is highly promising and simultaneously a high risk. If it is successful, our discovery of the novel AIF3 isoform and its critical roles in neurodegeneration may provide a significant new therapeutic target for mitochondrial dysfunction-related neurologic diseases, including AD and dementia. We are extremely thankful for Darrel K Royal's generous support, which has allowed us to further understand the biological functions of AIF3 in the brain and how it contributes to neurodegeneration.