UTSouthwestern
Medical Center

Donor Report to Darrell K Royal Research Fund

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Shaping the Future of Medicine

Dementia interferes with the daily life of patients. Neurodegeneration is a key driver to cause problems with memory, thinking, and behavior. Understanding the molecular mechanisms of neurodegeneration may provide an effective treatment for dementia. Apoptosis-inducing factor (AIF) is a mitochondrial flavoprotein controlling both cell life and death. Interestingly, we recently identified a novel AIF isoform-AIF3. The expression of AIF3 is not detectable under physiological conditions, but increased in neurological diseases. The goal of our study is to understand the role of newly identified AIF3 in neurodegeneration.

Progress

1) Under what disease conditions is AIF3 expression increased? We found that AIF3 was undetectable under normal physiological conditions. It was also not obviously induced in the mouse brain 24 hours following traumatic brain injury. But, its expression was induced following stroke in the brains of both humans and mice.
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 neurodegeneration in multiple brain regions. AIF3 mouse brains showed an enlarged ventricle, and all AIF3 mice showed much earlier aging phenotype. These data indicated that AIF3 plays an essential role in neurodegeneration.
3) What is the underlying mechanism of AIF3-induced neurodegeneration? We found that expression of AIF3 eventually caused mitochondrial biogenesis defects both in vitro and in vivo. AIF3-induced mitochondrial dysfunction contributes to neurodegeneration.

Impact

The Darrell K Royal Fund has promoted our initial study to explore the functions of this new disease-inducible AIF3 isoform. The preliminary data achieved with Darrel K Royal's generous support has allowed us to receive a new funding support to further understand the biological functions of AIF3 in the brain and the deep mechanisms how it contributes to neurodegeneration and dementia.

What's next?

There are still lots of important questions and challenges we need to address in the future. Although we knew AIF3 is a disease-inducible isoform, 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.