Lenora Volk, Ph.D.
Assistant Professor
Department of Neuroscience

UT Southwestern Medical Center

Our lab studies how experience modifies communication between brain cells. This modification, called synaptic plasticity, is widely believed to be a fundamental mechanism by which memories are formed and stored in brain cells. Abnormal synaptic plasticity is extensively linked to disorders of learning and memory, and is implicated in the early stages of Alzheimer's disease (AD). Amyloid beta and tau are the major pathological molecules clinically associated with AD, but it is still unclear how these molecules impair memory and affect the function of brain cells, particularly early in the disease before widespread cell death occurs. We study a group of proteins that regulate synaptic plasticity and memory. Two of these proteins, KIBRA and PICK1, are disrupted by pathological tau and amyloid beta. Our research seeks to understand how these proteins regulate experience-dependent changes in communication between brain cells to support memory. Our previous work suggested that the adult brain may be particularly susceptible to the loss of KIBRA or PICK1. Therefore, our research also aims to understand if and why the young brain is resilient and the adult brain is vulnerable to disruption of this complex, as this may help us understand how to make "old" brains more resilient to pathological conditions like AD that disrupt the function of this protein complex.

In studies supported by the Darrell K Royal foundation, we selectively deleted KIBRA from young or adult brain cells (neurons) in mice. We find that loss of KIBRA from adult brain cells impairs synaptic plasticity, whereas young brain cells are unaffected. We have also uncovered a novel molecular mechanism that may help to explain why brain cells without KIBRA are unable to express robust synaptic plasticity or support normal memory function. AMPA receptors are the primary neurotransmitter receptors responsible for rapid communication between brain cells, and synaptic plasticity changes the availability of AMPARs. We have exciting preliminary data suggesting that loss of KIBRA decreases the availability of AMPARs selectively in adult but not young neurons, and that experience fails to regulate AMPARs appropriately in adult neurons.

While brain cells are the site for molecular modifications that create memories, no single brain cell encodes an entire memory. Communication between many hundreds to thousands of neurons compose "brain circuits" that are ultimately responsible for higher cognitive functions like memory. The DKR funds have also allowed us to examine how loss of KIBRA from adult neurons affects circuit function in brain regions critical for forming and storing memories. Intriguingly, we find that baseline circuit function is largely normal without KIBRA, but the brain's ability to respond to new experiences by coordinating information flow in memory-relevant circuits is substantially impaired.

Acetylated tau has been linked to dementia and early stages of disease pathology in AD. Loss of KIBRA is associated with pathological tau acetylation and cognitive decline in AD patients, suggesting that decreased KIBRA protein could contribute to impaired brain function, but such human studies are necessarily correlational and mechanistically complex, thus it is hard to distinguish cause and effect. Our data supports that idea that disruption of KIBRA in the adult brain can contribute to neural dysfunction and memory impairment. Future studies will determine if reintroducing KIBRA in adult brains can rescue synaptic plasticity and memory. While much of our work thus far has focused on KIBRA, we are also beginning to examine how loss of PICK1 affects circuit function.

As a new investigator, my Darrell K Royal grant has been essential for providing resources to establish a successful research program. It has allowed us to take some risks and make new discoveries that we did not anticipate. Support from the Darrell K Royal grant was also instrumental in allowing us to obtain additional NIH funding to continue our research. More than that, as one of the millions of people that has watched a loved one slowly disappear to the devastating effects of Alzheimer's disease, I am grateful to the DKR fund for supporting talented researchers across the state of Texas.