

Efficient brain function requires optimal energy metabolism in neurons, and its disruption is linked to neurodegenerative and mental disorders. Astrocytes provide energy support for neurons. However, we still do not fully understand how neurons regulate their own energy production and communicate their energy states to astrocytes.

The transcription factor TCF7L2 is known for its role in regulating energy metabolism in the pancreas and the development of diabetes, while its mutations are also associated with autism spectrum disorder and schizophrenia. But does it also regulate energy metabolism in the brain? And could this regulation influence behavior? This project aims to answer these questions, with a particular focus on the thalamus, a brain region that plays a key role in sensory processing and is often impaired in autism and schizophrenia.

We discovered that when TCF7L2 is absent from thalamic neurons, there is a dramatic shift in the balance between the efficiency of pyruvate oxidation, the energy substrate preferentially utilized by neurons, and the oxidation of lipid substrates, including those typical of neurons and astrocytes. We propose three main ideas: 1) TCF7L2 enhances pyruvate oxidation in thalamic neurons and indirectly affects astrocyte metabolism; 2) TCF7L2 influences metabolism in neurons by controlling genes in a pathway that activates an enzymatic switch between pyruvate and lipid oxidation; 3) Restoring the activity of this pathway may help reverse the behavioral problems in mice lacking TCF7L2 in thalamic neurons.

To investigate these hypotheses in mice, we will induce cell-specific mutations in the TCF7L2 gene and the gene encoding the main metabolic switch, and pharmacologically manipulate the activity of metabolic pathways. We will then examine the effects of these manipulations on gene expression and mitochondrial function separately in neurons and astrocytes derived from the thalamus. Simultaneously, we will study the impact of these manipulations on the animals' behavior, including in tests assessing social behaviors.

Our research will enhance understanding of how intracellular factors and intercellular neuronal-astrocytic communication regulate brain energy metabolism and could reveal potential links between metabolic disorders and mental health conditions.