Astrocytic contributions to endogenous neuroprotection: Can astrocytes point the way to neuroprotective treatments?

Stroke is a sudden, localized disruption of blood flow in the brain, leading to the death of neuronal cells. Despite significant progress in understanding the mechanisms of brain injury during stroke, the development of effective therapies that support regeneration remains a major challenge. As a result, stroke continues to be one of the leading causes of death and long-term disability worldwide.

Currently, the most effective treatment for stroke is reperfusion—restoring blood flow to the affected area of the brain as quickly as possible. While this procedure significantly reduces the extent of damage, there are still no therapies that support neurons in adapting to ischemic stress or preventing the progression of injury. This therapeutic approach, known as neuroprotection, remains one of the most important yet unmet goals in modern neurology.

One of the most promising directions in the search for effective neuroprotection is to harness the brain's own natural defense mechanisms—so-called endogenous neuroprotection. Some brain regions are naturally more resistant to ischemia, not because of better blood supply or higher oxygen and glucose availability, but due to the activation of intrinsic processes that protect neurons from damage. This "natural shield" is the result of complex, local mechanisms that may also play a crucial role in the course of stroke. We believe that identifying and understanding these mechanisms—especially their cellular components—will allow for their targeted activation in clinical settings.

Our research focuses on the hippocampus—a brain region involved, among others, in memory processing. After ischemia, its various regions respond differently: the CA1 area is highly vulnerable, while the CA2–4 regions and the dentate gyrus (DG) show much greater resistance. Our hypothesis is that astrocytes—glial cells once considered passive scaffolding for neurons—are, at least in part, responsible for this difference. Today, astrocytes are recognized as active regulators of brain function. They maintain chemical homeostasis, participate in the inflammatory response, and communicate with other cells. Following ischemia, they can adopt different phenotypes—some support neurons and promote regeneration, while others exacerbate injury.

In our project, we will compare astrocytes from ischemia-sensitive and -resistant hippocampal regions, analyzing their activity, transcriptional profiles, and the composition of extracellular vesicles (EVs), which are key mediators of intercellular communication. By employing advanced techniques in molecular biology, microscopy, and cell culture, we aim to determine the nature of the signals released by astrocytes and their impact on neuronal survival.

Our findings may pave the way for new neuroprotective strategies that highlight the role of astrocytes alongside neurons. This approach may not only deepen our understanding of brain function but also provide a foundation for the development of effective therapies to protect the brain after stroke and in other neurodegenerative conditions.