Study advances new target for CNS drug development

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A breakthrough discovery by scientists at the University of Kentucky could someday lead to new treatments for a variety of diseases of the brain, spinal cord and the eye.

Researchers led by Royce Mohan, associate professor of ophthalmology and visual science in the UK College of Medicine, found that the small molecule withaferin A can simultaneously target two key proteins — vimentin and glial fibrillary acidic protein (GFAP) — implicated in a damaging biological process called reactive gliosis.

Both vimentin and GFAP, members of a family of proteins called intermediate filaments, are important factors in the stress response of the central nervous system (CNS). But pathology in the CNS from a traumatic injury or neurodegenerative disease can cause overexpression of vimentin and GFAP and lead to reactive gliosis.

During gliosis, astrocyte cells that express vimentin and GFAP accumulate into dense, fibrous patches called glial scars, which interfere with normal functioning of the CNS. Gliosis is a significant feature of many disorders of the CNS, including multiple sclerosis, Alzheimer's disease, stroke, and traumatic brain and spinal cord injury, and it is also central to major retinal diseases such as age-related macular degeneration, diabetic retinopathy and glaucoma.

Mohan's lab discovered that withaferin A binds to both vimentin and GFAP within an unique pocket when these proteins are in their soluble,

tetrameric form. This finding makes withaferin A an appealing therapeutic lead for drug-development research, Mohan said, and he owes great credit to the interdisciplinary team of collaborators who contributed to extending this finding.

Mohan describes the discovery as serendipitous. Originally, his team was investigating withaferin A as an angiogenesis inhibitor, a type of drug used to slow the development and growth of new blood vessels. Such drugs are useful in treating cancers and various conditions of the eye, such as corneal neovascularization, wet-stage macular degeneration and glaucoma.

Using an approach called reverse chemical genetics, Mohan's lab started with the identification of withaferin A as a vimentin probe, and then looked for CNS pathological indications where the related type III intermediate filament GFAP is critically involved.

"It was fortuitous that we looked at the retina of injured mice," Mohan said. "This drug was causing simultaneous inhibition of both corneal angiogenesis and retinal gliosis, a finding that is relevant to combat ocular trauma from the alarming incidence of blast injuries. Rarely does one get the opportunity to make an important discovery that advances on two drug targets at once."

More information: The study, "Withaferin A Targets Intermediate Filaments GFAP and Vimentin in a Model of Retinal Gliosis," was published online Jan. 4 in the *Journal of Biological Chemistry*.

Provided by University of Kentucky