Commentary: A therapeutic Jedi mind trick: A neuroprotective target to counteract deep hypothermic circulatory arrest

Nicholas D. Andersen, MD, Mohammed K. Alsarraj, BS, and Joseph W. Turek, MD, PhD

From the Duke Congenital Heart Research & Training Laboratory, Duke University, Durham, NC.

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Address for reprints: Joseph W. Turek, MD, PhD, Division of Cardiovascular and Thoracic Surgery, Duke University Medical Center, 2301 Erwin Rd, DUMC 3474, Durham, NC 27710 (E-mail: joseph.turek@duke.edu).

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Neuroinflammation promoting neuronal damage after deep hypothermic circulatory arrest (DHCA) has been well characterized.^{1,2} Unfortunately, finding a remedy has remained a challenge, with underlying molecular mechanisms not clearly delineated. In the current issue of the *Journal*, Liu and colleagues³ have described the possible role of cold-inducible RNA-binding protein (CIRP) in promoting neuroinflammation after DHCA. Specifically, under conditions of deep hypothermia, oxidative stress, and hypoxia lead to overactivation of microglial cells in the brain, promoting increased proinflammatory gene transcription and subsequent neuronal injury (Figure 1).

Liu and colleagues³ were able to identify bromodomain and extra terminal domain proteins, such as the transcriptional activator Brd2, as key mediators of the inflammatory response induced by microglial cells. The experimental strategy used an established rat model of hypothermia and hypoxia with normal and CIRP knockout animals.⁴ The results showed CIRP levels to be significantly increased in the normal, DHCA-treated group compared with the sham group. The neuronal injury inflicted by CIRP in the normal, DHCA group demonstrated characteristics of ischemic cell death, as well as elevated cerebral injury markers in the plasma, such as tumor necrosis factor- α , interleukin-5, and interleukin-13, that were not present in the DHCA, CIRP knockout rats. Through RNA-sequencing analysis, it was shown that the expression of the protein Brd2 was greatly reduced in the hippocampus of DHCA, CIRP knockout rats.

An inhibitor of bromodomain and extra terminal domain proteins (JQ1) was administered that blocks the acetylated lysine binding pockets, which limits the downstream effects of the proinflammatory cytokines released by microglial cells. Under experimental conditions of hypothermia and oxidative stress, both Brd2 proteins and the nuclear factor-kB proinflammatory pathway were significantly downregulated upon CIRP removal. Thus, the inhibition

Mechanism of CIRP on brain injury in deep hypothermic circulatory arrest.

Central Message

A neuroprotective strategy blocking CIRP shows promise in a rat model of deep hypothermic circulatory arrest.

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of the nuclear factor-kB transcription pathway in microglia through the inhibition of CIRP activity can lead to the downregulation of neuronal damage, and therefore may have therapeutic implications in treating DHCA-induced cerebral injury.

This article offers compelling support for CIRP, largely through the Brd2 protein, as a pivotal initiator of microglial activation, inflammatory gene transcription, and the devastating effects of neuroinflammation after exposure to DHCA. Furthermore, this knowledge introduces promising therapeutic targets (inhibitors of CIRP and Brd2) to “trick” microglia into not activating, thereby protecting the mind from inflammation-related neuronal damage during deep hypothermia. In essence, this strategy tells microglia, “these aren’t the neurons you’re looking for.”

References

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FIGURE 1. Mechanism of cold-inducible RNA-binding protein on brain injury in deep hypothermic circulatory arrest.