Targeting Dual Leucine Zipper Kinase as a Therapeutic Strategy for Traumatic Optic Neuropathy and Brain Injury

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PUBLIC ABSTRACT

Service members are at risk for combat and non-combat forms of trauma that can lead to vision loss. Injuries to the head that are hard enough to cause a brief loss of consciousness or memory, known as traumatic brain injuries or "TBIs" (often called "concussions" in the popular media), often lead to problems with vision later in life. In the last decade, there were more than 250,000 TBIs diagnosed in the Armed Forces and more than 50% will go on to develop vague, and sometimes difficult-to-objectively-measure, complaints such as trouble with reading. The exact part of the brain that gets damaged and causes these abnormalities is not known. Generally, however, it is known that the way in which TBI causes any neurologic disability is by quickly accelerating and then decelerating the nerve cells of the brain, shearing the long delicate fibers, known as axons, that emanate from them and connect them to neighboring nerve cells. At the very least, this results in lost connections and, in other cases, leads to the death of the injured nerve cells. Another way in which trauma can lead to vision loss is through direct injury to the eye. Nearly 20% of soldiers who sustain a serious eye injury will suffer an irreversible injury to the optic nerve. This nerve is made up of approximately one million axons originating from a corresponding number of retinal ganglion cells (RGCs). RGCs are specialized nerve cells that line the inside of the eye and are responsible for transmitting "vision" from a given spot in the eye, down the optic nerve to the vision centers of the brain. Similar to the case above, trauma damages these long delicate fibers and disconnects that part of the eye from the brain, leading to permanent blank spots in a patient's vision -- a disease called optic neuropathy. Moreover, disconnecting a RGC causes it to commit suicide, a process known as apoptosis (which is useful developmentally as people start off with nearly four million RGCs, many of which are miswired, and the process pares down the number to include only the correctly connected cells). This complicates the disease because once nerve cells are lost, there is no capability to regenerate and replace them, making the vision loss permanent and irreversible. Unfortunately, for both TBI and traumatic optic neuropathy, there are no treatments. The field needs neuroprotective medications that make the axons resistant to degeneration or the nerve cells less likely to die.

In order to identify such a neuroprotective drug, we used mouse RGCs with injured axons to search through over 6,000 medications and 600 proteins (the cellular machines that are the targets of medications) for drugs/drug targets that improve RGC survival. Although labor intensive, this approach has the advantage of not having preconceived notions about what drugs/drug target should be important and allows us to make novel discoveries. We found a drug/drug target pair -- inhibition of a protein called dual leucine zipper kinase (DLK) by a cancer drug called sunitinib -- that potently protects RGCs. For instance, after crushing the optic nerve in mice (simulating traumatic optic nerve damage), 50%-75% of RGCs will die by two weeks. In mice treated with sunitinib or in which the DLK protein is deleted, RGC death can be reduced by 75%. These results highlight the usefulness of our screen as no one would have expected a cancer drug (that
normally kills cells) to be so effective at promoting nerve cell survival. Even more exciting, sunitinib happens to have Food and Drug Administration approval (for cancer), meaning that doctors today could use it for traumatic optic neuropathy and TBI ("off-label use") if there was a compelling reason. While our basic science work is very suggestive that sunitinib should be studied in human clinical trials, there are some unresolved translational questions that first need to be answered. This proposal seeks to finish laying the foundation for the use of sunitinib as a neuroprotective therapy to reduce vision loss in TBI and traumatic optic neuropathy.

First, our work is in rodents and while this is able to predict success in people, it is not perfect. Our first aim is to use eyes from soldiers, surgically removed following a serious eye injury, and pathology techniques to determine whether DLK plays a role in human RGC cell death. Second, the timing of when the drug needs to be given and the minimum duration of treatment still needs to be evaluated. Thus, our second aim uses a set of experiments in which DLK inhibition is started and stopped at various times to determine this critical window. Third, although DLK inhibition clearly is protective in traumatic optic neuropathy (at least in rodents) and it is reasonable to expect that it might have a role in TBI (since they share a similar mechanism of axon damage), we have not yet tested sunitinib in models of TBI. Our third aim proposes to evaluate DLK inhibition by sunitinib in rodent models of TBI. Finally, although we have shown that DLK inhibition by sunitinib keeps RGCs alive, we have not shown that this translates into better vision. As such, our fourth aim looks whether blocking DLK, including with the drug sunitinib, translates into better visual outcomes in our rodent models of traumatic optic neuropathy and TBI. Together, the answers to these questions will set the stage for designing clinical trials to evaluate sunitinib as the first neuroprotective therapy for traumatic optic neuropathy and TBI.