● PERSPECTIVE

Indirect traumatic optic neuropathy: modeling optic nerve injury in the context of closed head trauma

Traumatic optic neuropathy: Traumatic brain injury is one of the leading causes of disability and mortality in the United States. It impacts people of all ages and demographics, particularly younger males and members of the military. Vision loss is commonly associated with traumatic brain injuries of all severities and can leave patients permanently disabled. This vision loss can be caused by injury to the visual system at multiple levels, including the eyes, optic nerves, and many different sites in the brain and brainstem (Sen, 2017). Despite the far-reaching effects of visual impairment after traumatic brain injury, its incidence after traumatic brain injury is not well measured, and few successful treatments have been identified or implemented.

Traumatic optic neuropathy is a condition characterized by visual impairment after indirect or direct injury to the optic nerve (Steinsapir and Goldberg, 2011). While the latter mode of injury is caused by penetrating trauma, indirect traumatic optic neuropathy is caused by force transmission into the optic nerve during head injury, or by secondary effects of brain injury such as hemorrhage or edema (Steinsapir and Goldberg, 2011). The intracanalicular portion of the optic nerve is most vulnerable to injury and is a common site for compression and ischemia (Sen, 2017). Common symptoms of traumatic optic neuropathy include reduction in sharpness, field of vision, or color vision (Singman et al., 2016).

It is estimated that at least 0.5–2% of patients have traumatic optic neuropathy resulting from the forces sustained during traumatic brain injury (Steinsapir and Goldberg, 2011). However, it can be difficult to diagnose traumatic optic neuropathy, particularly in patients presenting with low Glasgow Coma Scores due to traumatic brain injury (Steinsapir and Goldberg, 2005). In such patients, direct ophthalmology is an appropriate diagnostic procedure because it can be done in an unconscious patient. However, the optic nerve frequently appears normal in traumatic optic neuropathy cases; and, because unconsciousness occurs in 40–72% of diagnosed traumatic optic neuropathy cases (Steinsapir and Goldberg, 2005), it is likely that there is underdiagnosis of traumatic optic neuropathy in obtunded patients. In less severely affected patients, visual acuity loss with traumatic optic neuropathy can be mild (Steinsapir and Goldberg, 2005), and there is evidence that visual function after optic nerve injury may recover at least partly, due to adaptive neuroplasticity (Wang et al., 2011). Still, it is possible that milder cases of traumatic optic neuropathy go undiagnosed and that the actual incidence of traumatic optic neuropathy may be higher than has been reported.

In addition to difficulty with diagnosing traumatic optic neuropathy (particularly more mild injuries), treatment options are not clear. Current treatment possibilities include surgical decompression of the optic nerve, corticosteroid therapy, and combinations of the two (Steinsapir and Goldberg, 2005). However, large-scale studies have not supported efficacy of these methods (Steinsapir and Goldberg, 2005). Of traumatic optic neuropathy cases that are diagnosed, up to 48% will improve without treatment (Levin et al., 1999), and it is not clear whether there are circumstances in which treatment should be attempted. Ongoing uncertainties surrounding diagnosis and treatment of traumatic optic neuropathy, as well as the current lack of effective treatment options, suggest that further research on pathologic processes is needed.

Traumatic optic neuropathy pathology is driven by primary and secondary injury mechanisms (Steinsapir and Goldberg, 2005). Primary injury is thought to consist mainly of the effects of direct trauma to the nerve, such as axonal shear and contusion necrosis (Steinsapir and Goldberg, 2005). Secondary injury, on the other hand, is driven by processes like neuroinflammation, oxidative stress, free radicals, and gliosis. Much of what is known about these pathophysiologic processes comes from studies done using animal models (Levkovitch-Verbin, 2004).

Experimental models of traumatic optic neuropathy: Several animal models have been developed for studying traumatic injury to retinal ganglion cells and the optic nerve (Levkovitch-Verbin, 2004). Most commonly, this is done using partial or complete optic nerve crush, or optic nerve transection approaches. Other methods, such as blast injury and ultrasound methods have also been developed. Both optic nerve crush and transection models are models of direct traumatic optic neuropathy, by virtue of a foreign body (*e.g.*, scalpel or forceps) directly injuring the nerve, by crushing or cutting, respectively. Transection models typically involve complete injury of the optic nerve and, therefore, interruption of all axons travelling in the nerve. Optic nerve crush, on the other hand, can be either a complete or incomplete injury, depending on the amount of force applied and the duration of application. Both of these approaches lead to death of retinal ganglion cells and degeneration of their axons. Because of this, both have been used as models for retinal injury, including traumatic optic neuropathy and glaucoma (Levkovitch-Verbin, 2004).

Many of the features that make these surgical models appropriate for the study of direct traumatic optic neuropathy also make these approaches less ideal for the study of indirect traumatic optic neuropathy. As noted above, indirect traumatic optic neuropathy results from the focusing of traumatic force into the optic nerve, commonly at the optic canal (Steinsapir and Goldberg, 2011). Typically, this kind of injury occurs in conjunction with head and/or facial trauma, and does not involve open penetration of the optic nerve. Ultrasound and blast injury approaches have been used to more closely model indirect traumatic optic neuropathy. The ultrasound model involves pulsed ultrasound, which causes an injury to the optic nerve as it traverses the optic canal, without requiring a penetrating injury or surgical procedure (Tao et al., 2017). Blast models, on the other hand, work by subjecting the animal to a pressure wave (often focused on one eye), which has been shown to cause decrements in eye function, as well as injury to the eye itself (Mohan et al., 2013).

Most of the current literature on traumatic optic neuropathy utilizes direct approaches, likely due in part to the earlier establishment of those models. While these approaches do allow study of retinal ganglion cell responses to optic nerve axonal injury, they limit our understanding of indirect and more diffuse injuries often seen with indirect traumatic optic neuropathy in the context of head trauma. This is an important consideration, given that traumatic optic neuropathy, both direct and indirect, is usually associated with traumatic head injury (Sen, 2017). In any case, it appears that other models of traumatic optic neuropathy are needed in order to complement existing models, and broaden our understanding of the pathophysiology and potential treatment of traumatic optic neuropathy.

We recently published a description of a murine closed head traumatic brain injury model, performed with scalp intact, in which there is selective injury to the optic nerve. In this model, experimental traumatic brain injury is induced in an anesthetized mouse, using a 400 g rod dropped 1.5 cm vertically onto the intact scalp, centered approximately over bregma (Evanson et al., 2018). Many other rodent models of traumatic brain injury are in common use, utilizing a variety of injury mechanisms. Existing models include numerous variations of closed head injury with or without an intact scalp, controlled cortical impact (which uses a calibrated blow using a motorized piston, usually through a craniotomy onto the intact dura mater), fluid percussion injury (using intracranial injection of a pressurized fluid wave to induce a diffuse brain injury), and blast injury, among others (Levin and Robertson, 2013). Optic nerve and/or optic tract injuries have been reported in some of these models, although uniformly with damage to other brain regions also present (Evanson et al., 2018).

The optic nerve injury in our model is potentially caused by pinching of the nerve within the optic canal (as evidenced by decrease in the diameter of the canal under dorsal-ventral loading of the skull). We found neuroinflammation, gliosis, and axonal degeneration in the optic tract and major axonal targets of the optic nerve axons such as the superior colliculus and lateral geniculate thalamic nucleus (Evanson et al., 2018). In addition, there is evidence from optomotor function assessments that there is decreased visual acuity after this injury (unpublished results). As this model does not involve penetra-

tion of the animal's body, but rather injury of the optic tract within the intact head, it provides a way to study indirect traumatic optic neuropathy. In addition, because this method induces optic nerve injury using head trauma, it may be more relevant to traumatic optic neuropathy associated with traumatic brain injury.

The multifaceted damage associated with traumatic brain injury produces multi-system injury to the brain, resulting in more wide-ranging damage than seen in isolated optic nerve trauma. Traumatic brain injury is known to lead to multi-systemic sequelae, such as effects on the respiratory, cardiovascular, endocrine and immune systems (Wijayatilake et al., 2015). Particularly important in the context of axonal injury are effects on the immune system and stress responses, either of which could significantly influence the progression of optic nerve injury. Further, indirect traumatic optic neuropathy can be associated with other side-effects of head trauma like hemorrhage (Steinsapir and Goldberg, 2011), blood brain barrier disruption and edema (Wang et al., 2011), or increased intracranial pressure leading to changes in optic nerve sheath diameter (Sen, 2017), all of which could interact with primary and secondary injury mechanisms to influence the progression of an optic nerve injury (**Figure 1**). Thus, although focal direct and indirect models of traumatic optic neuropathy continue to provide important understanding of the pathophysiology of axon injury, it is also valuable to investigate traumatic optic neuropathy in the context of a more global head trauma.

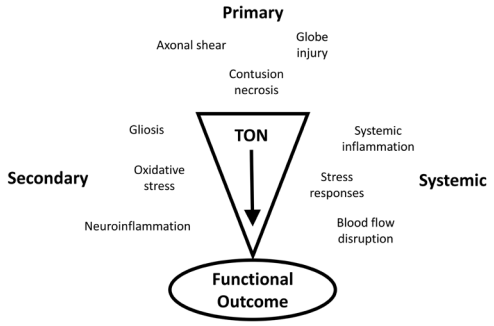

Figure 1 Factors that influence progression of optic nerve injury.
Traumatic optic neuropathy (TON) outcomes are driven by primary and secondary injury. In addition, systemic effects, particularly those associated with trauma in general and head trauma specifically could potentially influence the progression of secondary injury and thus the functional outcome after TON.

Many questions remain to be answered with respect to traumatic optic neuropathy. These include whether – and to what extent – inflammation, altered metabolism, or other processes occurring outside the optic nerve or retina influence optic nerve injury, degeneration, and/or recovery? To what degree do other neurologic deficits after traumatic brain injury influence recovery? What are possible approaches that could be used to provide effective treatment for traumatic optic neuropathy directly, or for secondary processes that contribute to worsening optic nerve injury after head trauma? Given the complex nature of traumatic optic neuropathy, it is likely that not all of these questions can be answered using targeted optic nerve injury as is seen in most animal models of traumatic optic neuropathy. Our approach, using closed head trauma in mice, shows promise in recapitulating some of these parallel pathologic processes. In particular, our approach allows us to study the influence of head trauma-associated processes occurring outside the optic system on pathology and recovery of indirect traumatic optic neuropathy. Because this is done in a mouse model, it is possible to use powerful techniques such as transgenic and knockout mouse models, genetic or epigenetic studies requiring tissues samples, or initial testing of invasive experimental interventions.

Summary: Several models of optic nerve injury have been used for the study of traumatic optic neuropathy. For the most part, the published research uses optic nerve transection or crush models, which have face validity for direct traumatic optic neuropathy, but have some shortcomings with respect to the study of indirect traumatic optic neuropathy. We have recently published a closed head traumatic brain injury model that appears to replicate key features of human indirect traumatic optic neuropathy in a murine model of head trauma. This model places optic nerve trauma within an experimental context that reproduces other aspects head trauma that likely influence the pathophysiology and progression of traumatic optic neuropathy. It further presents opportunities for exploring the complex pathophysiology of such injuries and, by corollary, for evaluating potential treatment approaches for these injuries.

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