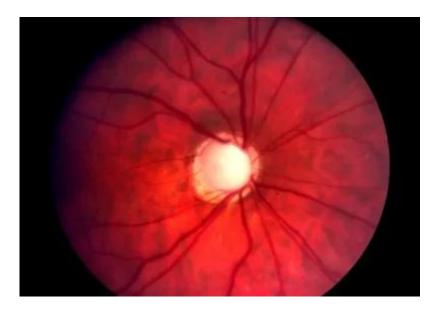


## A possible role of tau protein dysregulation in the pathogenesis of glaucoma | 1

Glaucoma is a heterogeneous group of diseases characterized by chronic progressive damage to the optic nerve, resulting from a slowly progressive degeneration of retinal ganglion cells. It is the most frequent cause of irreversible blindness worldwide. In this review article, Italian authors analyze the new perspective of glaucoma as a tau-associated disorder and recent findings on the link between tau protein dysregulation and glaucomatous neurodegeneration. They also discuss the possible role of tau protein in the pathogenesis of glaucoma and its effects on retinal ganglion cells.

Even though glaucoma is recognized as a chronic neurodegenerative disease, the mechanisms of pathogenesis are still unknown. A reduction in intraocular pressure is the only proven treatable risk factor. In patients with elevated intraocular pressure, mechanical stress and tension on the posterior eye structures, particularly the lamina cribrosa, can result in damage to retinal ganglion cells and disruption of axonal transport. This leads to the accumulation of vesicles and disorganization of microtubules and neurofilaments in the prelaminar and postlaminar regions.

However, glaucomatous optic neuropathy may also occur when intraocular pressure levels are within normal range. This form is known as normal-tension glaucoma, and the probable pathogenesis is vascular. This confirms that other factors can contribute to glaucomatous optic neuropathy, such as impaired microcirculation and altered immunity.



Tau protein is predominantly expressed in neurons, where it plays a crucial role in



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microtubule assembly, stability, and dynamics, forming the neuronal microtubule network. Under physiological conditions, tau protein is primarily localized in axons. Its function is regulated through phosphorylation at numerous sites. A dysregulation in the phosphorylation of the tau protein is responsible for a group of neurodegenerative disorders referred to as tauopathies. Hyperphosphorylation of tau protein decreases its binding affinity, which ultimately leads to the destabilization of microtubules and the formation of aberrant fibrillar polymers.

The evidence also suggests that tau protein may play a significant role in the regulation of axonal transport, which is crucial for the preservation of retinal ganglion cells and their axons. Retinal ganglion cells are particularly sensitive to the impairment of axonal transport because the function of these neuronal cells is dependent on retrograde trophic support.

"Tauopathies" is a collective term that refers to a group of neurodegenerative diseases characterized by the deposition of tau protein in the brain as neurofibrillary tangles and paired helical filaments. The deposition occurs primarily in neurons, however, it can also be observed in glial cells and the extracellular space. The spectrum of tauopathies encompasses frontotemporal dementias, progressive supranuclear palsy, chronic traumatic encephalopathy, and Alzheimer's disease. Nonetheless, the precise mechanism by which tau contributes to neurodegeneration remains to be fully elucidated. Numerous mechanisms have been proposed, suggesting that tau may exert its pathological effects through a variety of mechanisms.

The authors emphasized that in recent decades, increasing evidence supports the possibility that glaucoma may have features of tauopathy.

#### These findings include:

- 1. In glaucoma patients, aggregated tau inclusions are present in the somatodendritic compartment of retinal ganglion cells. Animal models and human studies have demonstrated the presence of hyperphosphorylated tau in the retina.
- 2. Glaucoma exhibits pathological traits typical of tauopathies, such as tau accumulation, dysregulation of axonal transport, and the interaction with amyloid beta (AB) deposits. The tau protein interacts with AB protein, and, deposits of AB were found in all layers of the retina, including the ganglion cells, nerve fibers, and photoreceptor layers. Pathological deposits of AB protein cause the death of retinal ganglion cells and the thinning of the retinal nerve fiber layer.



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- 3. The pathogenesis of the disease may involve tau splicing, phosphorylation, oligomerization, and subcellular localization.
- 4. Short interfering RNAs against tau, administered intraocularly, significantly decreased retinal tau accumulation and enhanced survival of retinal ganglion cells somas, and axons.
- 5. A decrease in cognitive scores and an increased risk of dementia were found in patients with glaucoma, and, conversely, patients with Alzheimer's disease have been shown to have an increased incidence of glaucoma.

The authors also discussed oxidative damage, a common feature in both, glaucoma and tauopathies, and a vicious cycle between oxidative stress and tau hyperphosphorylation. They analyzed the impairment of axonal transport resulting from tau protein dysregulation leading to the degeneration of retinal ganglion cells in glaucoma. They also discussed the relationship between tau protein, Aß protein, and glaucoma.

#### Conclusion

The intraocular pressure is the only known major modifiable risk factor for glaucoma. Other factors, which are unrelated to intraocular pressure, contribute to vision loss. They include neuroinflammation, oxidative stress, the dysregulation of calcium-dependent processes, defective autophagy, reactive gliosis, differences in the pressure on the lamina cribrosa, and, possibly, the dissemination of misfolded proteins.

The role of tau in glaucoma is still unclear, but, the accumulation of tau in the retina could be another contributing factor. The authors suggested that further research is needed to prove that tau protein dysregulation is involved in glaucomatous neurodegeneration.

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