The head of the optic nerve (ON) is made up of the superficial nerve fibre layer (SNFL), the pre-laminary region (PLR), the lamina cribosa region (LCR) and the retro-laminary region (RLR).

Although the axons of the ganglion cells are the fundamental element of the ON, the rest of its components help to maintain the physiological balance that allows it to work properly. These other cell components include the noteworthy astroglial cells or astroglia.

Depending on their location, astroglia fulfill various functions. In the SNFL, they isolate the axons of the vitreous whereas in the pre-laminary region they organize and control the arrangement of nerve fibres. This is brought about through a special grouping of astrocytes to form baskets at the most anterior level and tubes at the most posterior level of the pre-laminary area (1).

In the lamina cribosa, astrocytes coat the sieve-like holes and in the retro-laminary region share the space with oligodendroglial cells, which then start to myelinize the axons (1).

Structurally, the lamina cribosa is a complex tissue making up multiple pores through which the axons have to pass. The size of these pores varies between ten and one hundred microns and their distribution is uneven, so the nasal and temporal regions of the ON are smaller and denser, thus rendering them more resistant. The superior and inferior regions of the ON, on the other hand, have fewer holes as they are larger in diameter, which induces less resistance.

The lamina cribosa has two components: the cells themselves and the extracellular matrix (ECM). The first comprises astrocytes to provide support, contribute to the maintenance of the extracellular area and absorb mechanical and ischemic damage. All of them are GFAP positive as that is the protein making up their cytoskeleton, but at the same time they may be NCAM (neural cell adhesion molecule) positive if they are related to axons (type 1B astrocytes) or NCAM negative if they are not (type 1A astrocytes). Other cells present, albeit less well known, seem to be associated with fibroblasts and are GFAP negative. Finally, there are microglial cells that, as well as being GFAP negative, are positive for HLA-DR and CD45 (2,3).

The other fundamental component of the lamina cribosa, the ECM, is made up of specific macromolecules assembled to provide the tissue with strength, flexibility and elasticity. Its components include various types of collagen (I, III, IV, V, VI), elastin, basal filament-like membranes, dermatan sulphate, condroitin sulphate 4 and 6, hyaluronic acid, decorin, laminin and heparan sulphate.

The importance of the lamina cribosa lies in the fact that it represents a key site for the maintenance of the pressure gradient between the intra- and extra-ocular spaces and it is currently considered to be the target area for glaucomatous damage. In addition, as it is only nourished by branches derived from the Zinn-Haller circle (part of the ciliary system), it may be even more vulnerable, since we know it operates with a lower perfusion pressure than the ACR system.

The wealth of cell content in the lamina cribosa, closely tied to vessels and axons, allows an increase in both intraocular pressure and also a reduction
in the flow of the Zinn-Haller circle and these circumstances are capable of modifying their physiology, which translates into cell reactivation that gives rise to remodeling of the ECM.

In primary open-angle glaucoma, these changes constrain an increase in type VI collagen and a reduction in the collagen fibres around the elastic fibres, thus determining a considerable alteration in the mechanical properties at this level. In addition, type IV collagen, a constituent of the basal astrocyte membrane, is also extraordinarily increased in the pre-laminary and laminary regions, modifying the original structure of the sieve-like holes. If we add to this the alteration in the proteoglycans and glycosaminoglycans, and the degeneration of the elastic fibres, it is tempting to think that an alteration of the biomechanical properties of the area might explain why there is less ability to dampen the pressure gradient in this pathology (4).

As one of the most numerous cell types in the ON head, astroglia fulfill key functions to maintain its physiology (1). Because of their relationship with vessels and axons, they can store glucose in the form of glycogen for later supply in situations of neuronal stress. They are also involved in the maintenance of the sodium and potassium ion balance and in the metabolism of neurotransmitters such as glutamate. They produce laminin, fibronectin and tropoelastin, the precursor of elastin, as well as growth factors including the basic fibroblastic growth factor (bFGF), the transformation growth factor beta (TGFb) or neuronal survival factors such as nerve growth factor (NGF) (5).

In situations of stress, astroglial cells are reactivated to form a barrier that isolates the damaged area, keeping it separate from the intact area. The cell reactivation condition is manifested by hyper trophy of the cell through an increase in the expression of GFAP around the vessels and of N-CAM 180. In addition, during reactivation, the integrin b1 associated with astrocytes increases, tenasin is synthesized and the metalloproteinases (MMPs) increase, thus degrading the adhesion molecules and allowing their mobilization. Furthermore, the astroglia are able to present antigens (2,3).

At our laboratory, we have been able to verify, after provoking an experimental glaucoma in a rat, that there is an increase fifteen days into the condition of immunoreactivity for GFAP in the cells located on the vessels. Simultaneously, there is a reduction in the astrocytes located between the vessels (intervascular) and Müller’s glia become immunoreactive for GFAP. After a course of about a month and a half, the astrocytes in the peripheral retina have notably diminished and the most intense immune staining for GFAP can be seen on the margins of the optical disc, which would speak to cell mobilization from the more anterior regions of the head of the ON. The increased immunoreactivity for GFAP in reactive astrocytes corresponds, under a scanning electron beam microscope, to a large increase in the glial filaments forming their cytoskeleton (6,7).

Under normal conditions, astrocytes communicate with each other by using nitric oxide (NO) as a neurotransmitter, therefore they express NOS-1 (nitric oxide synthetase). In contrast, in situations of stress, either by an increase in IOP or due to ischemia, they produce inducible NOS-2, causing the formation of peroxynitrites and hydroxyl radicals that are toxic for axons (3). On top of this, we must add that the change in the cell geometry secondary to their reactivity favors the accumulation of glutamate in the intercellular space, H+ and K+ that will later be inserted in the astrocyte cytoplasm, causing cell edema. This edema leads to the disinsertion of the intermediate filaments and the death of the astrogial cells, leaving the axon unprotected and finishing with the death of the neuron. The irreversibility of glaucomatous disease lies precisely in the death of the ganglionary cells that are responsible for the receptor fields in the retina.

Therefore, it can be said that the collapse of the lamina cribosa does not indicate the start of axon loss but rather the result of the failure of the astrocyte providing it with a support function: the neuronal protection mechanisms are altered and a direct toxic effect is induced by the increase of nitric oxide in the nerve tissue.

Only an ever more accurate understanding of the mechanisms involving the different components of the head of the optical nerve will allow us to harbor, for the near future, any expectation of the emergence of new therapies, probably very different from those we use today.

REFERENCES


