Experimental Eye Research 142 (2016) 49–55

Contents lists available at ScienceDirect

Experimental Eye Research

journal homepage: www.elsevier.com/locate/yexer

Review

The role of astrocytes in optic nerve head fibrosis in glaucoma

Magdalena Schneider, Rudolf Fuchshofer*

Institute of Human Anatomy and Embryology, University of Regensburg, Regensburg, Germany

ARTICLE INFO

Article history:
Received 9 February 2015
Received in revised form
3 August 2015
Accepted in revised form 18 August 2015
Available online 29 August 2015

Keywords:
Astrocytes
Glaucoma
Optic nerve head
Fibrosis
Growth factors
Lamina cribrosa

ABSTRACT

Glaucoma is defined as a progressive optic neuropathy and is characterized by an irreversible loss of retinal ganglion cells. The main risk factor to develop glaucoma is an increased intraocular pressure (IOP). During the course of glaucoma structural changes in the optic nerve head (ONH) take place which lead to the characteristic excavation or cupping of the ONH. In this review we will focus on mechanisms and processes involved in structural alterations of the extracellular matrix in the lamina cribrosa (LC) of the ONH, which are associated with astrocytes. In glaucoma, a disordered deposition of elastic and collagen fibers and a typical pronounced thickening of the connective tissue septae surrounding the nerve fibers can be observed in the LC region. The remodeling process of the LC and the loss of ON axons are associated with a conversion of astrocytes from quiescent to a reactivated state. The extracellular matrix changes in the LC are thought to be due to a disturbed homeostatic balance of growth factors and the reactivated astrocytes are part of this process. Reactivated astrocytes, remodeling of the ECM within the LC and an elevated IOP are taking part in the retinal ganglion cell loss in glaucoma.

Glaucoma, one of the leading causes for blindness in the western world, is defined as a progressive optic neuropathy and is characterized by an irreversible loss of retinal ganglion cells. The main risk factor to develop glaucoma is an increased intraocular pressure (IOP) (Collaborative-Normal-Tension-Glaucoma-Study-Group, 1998a, b; Gordon et al., 2002; Johnson et al., 2002; Leske et al., 2003). In most patients the optic nerve head (ONH) shows characteristic excavation and cupping (Quigley, 1996). During the course of glaucoma, degeneration of optic nerve axons and loss of retinal ganglion cells occur, leading to visual field defects (Quigley, 1998). The cause of retinal ganglion cells loss is not completely understood, but it is associated with structural changes of the extracellular matrix (ECM) in the ONH region. In the prelaminar region of the ONH the connective tissue sheaths around the capillaries are significantly thickened in glaucoma patients (Tektas et al., 2010). The main histopathological findings in glaucoma are described in the lamina cribrosa (LC) region of the ONH. The LC is a sieve-like structure of connective tissue plates, where the axons of the retinal ganglion cells pass through to exit the eye. The laminar beams are mainly composed of optic nerve astrocytes and LC cells (Quigley, 2011). In glaucoma, the ECM in the region of the LC is extremely reorganized. ECM remodeling of the LC is mainly due to altered expression patterns of astrocytes and LC cells. The role of LC cells in glaucoma is not a topic of the review, but is described by Wallace and O'Brien in this special issue. ECM changes within the LC are due to enhanced elastosis and a disruption of the regular collagen structure in glaucomatous eyes in comparison to control patients (Hernandez, 1992; Netland et al., 1995; Pena et al., 1998). The ECM changes might contribute to the retinal ganglion cell loss, due to an impaired nutrition of the neuronal tissue by the thickened connective tissue sheaths in the prelaminar region (Tektas et al., 2010). Further the ECM restructuring in the LC region could enhance the effect of the axonal compression at the ONH by the increased IOP, leading to an impaired antero- and retrograde axonal transport of neurotrophic factors (Anderson and Hendrickson, 1974). The astrocytes of the ONH undergo a reactivation during the pathogenesis of glaucoma, which is characterized by morphologic alterations and expression changes (Hernandez, 2000; Hernandez et al., 2002; Pena et al., 1999b). This review focuses on the current knowledge of the role of astrocytes in the ECM remodeling process in the LC and on the underlying molecular mechanisms.

* Corresponding author.
E-mail addresses: magdalena.schneider@vkl.uni-regenburg.de (M. Schneider), rudolf.fuchshofer@vkl.uni-regensburg.de (R. Fuchshofer).

http://dx.doi.org/10.1016/j.exer.2015.08.014
0014-4835/

1. Astrocytes in the ONH

Astrocytes are the most common glial cells in the ONH and are vital for retinal ganglion cell health. Rudolf Virchow has first described them in the mid-19th century (Von Virchow, 1846). Astrocytes maintain the homeostatic balance of the extracellular environment by absorbing or degrading substances dispensed by neurons. As an essential part of the blood–brain and blood–retina barrier (Ransom et al., 2003) astrocytes supply neurons with nutrients by clasping around blood vessels and connecting them to neurons (Bouzier-Sore and Pellerin, 2013). After injury to neuronal tissues astrocytes migrate into the tissue to curtail lesion or inflammation by forming a so-called glial scar that does not support axonal regrowth (Hernandez, 2000; Ridet et al., 1997). Further astrocytes influence neuronal tissue by restructuring the ECM and releasing growth factors, cytokines and other cellular mediators under normal and pathologic conditions (Hernandez, 1992, 2000; Hernandez et al., 1994a; Kirsch et al., 1998; Schwab et al., 2000; Stockli et al., 1989).

Astrocytes can be sub classified into ~11 distinct phenotypes that can be readily distinguished regarding their expression profile and morphology (Abbott et al., 2006). In the human ON three subtypes of astrocytes were identified. Type 2 astrocytes are the dominant subtype in the myelinated postlaminar part of the ON and type 1 astrocytes are the main subtype in the unmyelinated laminar and prelaminar region of the ON (Kobayashi et al., 1997; Ye and Hernandez, 1995). Type 1 astrocytes are characterized by the expression of GFAP and can be distinguished in type 1A and B astrocytes. Type 1A astrocytes express GFAP, but are neural cell adhesion molecule (NCAM) negative. Type 1B astrocytes on the other hand express GFAP and NCAM. Type 1B astrocytes are the major astrocyte subtype in the ONH and are distributed throughout the prelaminar and laminar regions of the ONH. The type 1B astrocytes and the LC cells form the cribriform plates of the LC. The processes of Type 1B astrocytes are separated from the underlying fibroelastic ECM core of the cribriform plates by a continuous basement membrane, whereas the LC cells are located inside the plates of the LC (Hernandez, 1992, 2000; Kobayashi et al., 1997). In the LC and in the prelaminar region the processes of the astrocytes ensheath axon bundles, surround blood vessels and link connective tissue surfaces (Anderson, 1969).

In rodent models the classification is mainly based on the anatomical characterization and not on the antigenic phenotype. Rodent astrocytes are divided into protoplasmic and fibrous subtypes. The protoplasmic astrocytes are not present in the ONH, as they are mainly localized in the gray matter (Oberheim et al., 2009). The fibrous astrocytes of the rodent ON are classified into random, transverse and longitudinal types, based on the orientation of their primary processes to the long axis of the nerve. The transverse phenotype is the dominant form in the unmyelinated ONH region (Sun et al., 2009) and is of a pivotal role for the structural architecture of the rodent ON. The mouse ONH shows distinct structural differences to that of humans and monkeys. The exit canal of the ON is surrounded by peripapillary sclera, but contains no connective tissue beams (May and Lutjen-Drecoll, 2002). Behind the peripapillary sclera, the fibrous astrocytes form an enmeshing network termed “glial lamina” through which the retinal ganglion cell axons pass (Howell et al., 2007; Sun et al., 2009). Within the glial lamina, astrocyte processes compartmentalize ganglion cell axons into bundles, forming “glial tubes” and giving the glial architecture of the ONH in transverse section a honeycomb appearance, not unlike to that seen in species with a connective tissue LC (Sun et al., 2009).

2. Response of ONH astrocytes to glaucomatous damage

Astrocytes of the ONH respond strongly to glaucomatous damage. While astrocytes are in a quiescent state under normal conditions, it is widely acknowledged that astrocytes undergo a process of reactivation during the course of glaucoma, called astrogliosis. Astrogliosis is characterized by alterations in astrocytic morphology, like thickened processes and hypertrophy of the cell body, and in protein expression patterns in the prelaminar region of the ONH. In the LC region the astrocytes show round shaped cell bodies and a loss of cell processes (Varela and Hernandez, 1997). In addition to the morphological changes, ONH astrocytes of the prelaminar and LC region have an increased immunoreactivity for GFAP in human ONH with a chronic elevated IOP and a moderate or advanced glauomatous axonal damage (Hernandez and Pena, 1997; Wang et al., 2002). The changes observed in glaucomatous ONH from human donors prove that astrocytes are reactivated, but this is mostly an end-stage description of the disease. To gain further information about the progression of astrocytic changes occurring during the pathogenesis of glaucoma, different animal models were developed. Most glaucoma models are based on rodents, in the majority of cases rats or mice, as established primate models are usually not affordable to most laboratories. Rodent models have limitations in the homology to human ONH anatomy in respect to the lamina cribrosa and/or to experimental settings. Rat glaucoma models have the advantage that rats have a LC with many similarities to the primate LC (Hildebrand et al., 1985; Johansson, 1987; May, 2003; Morrison et al., 1995), but have the restriction of a limited availability of genetic models, whereas genetic mouse models are available in a great variety, but miss a connective tissue LC. Commonly used glaucoma models are DBA/2J mice and mice or rat ocular hypertension models. All models show clear signs of astrocyte reactivation like hypertrophia and thickening of cell processes, which is associated with axon loss (Lye-Barthel et al., 2013; Son et al., 2010).

In respect to astrocytic GFAP expression after experimentally increased IOP the data is quite conflicting between the different models regarding short-term treatments. Data range from reduced to significantly increased GFAP levels (Johnson et al., 2000; Lam et al., 2003; Sun et al., 2013). The comparison of all models is difficult, as no standard settings were used. Procedures vary in experimental duration, experimental settings, pressure changes and observation methods. In contrast, long-term studies with a genetic model, like the DBA/2J mice, show a constantly significant increased GFAP expression in the ONH, hinting at an association of the reactive phenotype with severe axon loss and a relation to other occurrences during the pathological changes (e.g. microglia activation, monocyte invasion). This suggestion is supported by findings that the recovery of the astrocytic organization is dependent on the grade of axon loss. Astrocytes, after a moderate axon loss, have the capability to re-establish the honeycomb arrangement in the glial lamina (Sun et al., 2013), whereas after an optic nerve crush, astrocytes do not regain the structure of a glial lamina and lead to the formation of a glial scar (Sun et al., 2010). It is tempting to speculate that the reactivation of astrocytes has, in the initial phase of the disease, a beneficial protective effect on the survival of axons, but with a progression of the disease the effects of reactive astrocytes become more and more detrimental (Sun et al., 2013).

3. ECM remodeling in glaucomatous patients

During the pathogenesis of glaucoma an ECM remodeling process occurs in the ONH region, leading to a stiffening of the