Astrocyte polarization in glaucoma: a new opportunity

Introduction

Glaucoma is a neurodegenerative disease characterized by retinal ganglion cell (RGC) death and axonal degeneration. The predominant risk factors for this disease include age and intraocular pressure (IOP) (Quigley, 1993). Currently, glaucoma is mainly treated by reducing IOP; however, the presence of normal-tension glaucoma indicates that there are other pathogenic mechanisms in addition to pathological ocular hypertension (OHT). Neuroinflammation is the main cause of persistent secondary nerve damage after alleviation of high IOP, and has recently attracted significant research attention. However, neuroinflammation is not conventionally considered part of the inflammatory response, which involves only immune cells. Glial cells (microglia and astrocytes) are resident immune monitoring cells in neuroinflammation (Soto and Howell, 2014; Williams et al., 2017). Microglia have been more widely investigated than astrocytes, as they are considered to originate from tissue macrophages, thus exhibiting more immune effects (Ginhoux et al., 2010).

Astrocytes are mainly located in the retinal nerve fiber and ganglion cell layers and the optic nerve (Reichenbach and Bringmann, 2020). Notably, the optic nerve head (ONH) structures and astrocyte components differ between primates and rodents. In primates, the lamina cribrosa is composed mainly of collagen, with abundant astrocytes on the surface and lamina cribrosa cells inside the cribiform plates (Anderson, 1969; Hernandez, 2000; Hernandez et al., 2008). However, in rodents, the structure is known as the glial lamina and is almost entirely composed of astrocytes, without collagen (Johansson, 1987; May and Lütjen-Drecoll, 2002; Howell et al., 2007). Both laminal forms are consistent with the site of neuroinflammation in glaucoma, thus the role of astrocytes requires further exploration (Williams, et al., 2017). Astrocytes are also located in the distal visual pathways, including the lateral geniculate nucleus and visual cortex and are activated under conditions of high IOP, indicating that glaucoma is highly correlated with the central nervous system (Lam et al., 2009; Shimazawa et al., 2012; Fujishiro et al., 2020). Current reviews on neuroinflammation in glaucoma are mainly focused on microglia, and the role of astrocyte polarization in glaucoma has not yet been reported. The purpose of this review is to explore the relationship between astrocyte polarization and glaucoma and explain the feasibility of astrocyte polarization as a therapeutic target for neuroprotection and neural regeneration.

Retrieval Strategy

Articles published from January 1980 to November 2021 were retrieved from PubMed in this narrative review. We used the following search strategy: (A1: astrocyte OR A2: astrocytes OR Astrocytes OR Neuroinflammation) AND (Glaucoma OR Neurodegenerative Disease OR Optic Nerve OR Retina). The final retrieval date was November 29, 2021. The results were screened based on titles and abstracts, and only studies conducted on rodents and primates and published in English were included.

Reactive Astrogliosis

Previous studies reported that resting astrocytes are activated into reactive astrocytes in response to injury through a process known as “reactive astrogliosis”. The process comprises four major changes (Figure 1) (Sofroniew, 2009), which are described below.

Morphological changes

Astrocytes are grouped into two main types based on their morphology including protoplasmic astrocytes in the retina and fibrous astrocytes in the ONH (Büssow, 1980). The two types are in contact with blood vessels and neurons. However, protoplasmic astrocytes are closer to neuronal cell bodies and synapses, whereas fibrous astrocytes are in contact with the nodes of Ranvier on the neuronal axons (Allen and Barres, 2009). Reactive protoplasmic astrocytes in the retina constrict themselves but the structure of the spatial domain is maintained (Figure 2). This situation may be implicated in disrupting neuronal homeostasis and the blood-eye barrier. Reactive fibrous astrocytes in the ONH undergo biphasic morphological changes, based on axonal changes. Astrocytes retract their primary processes

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Reactive astrogliosis is a cascade based on the severity of pathophysiology. Proliferation of astrocytes is initiated by severe irritations, such as chronic neurodegenerative trauma, diffuse ischemia, or consequences of infection (Sofroniew, 2009, 2014). One study using a chronic glaucoma model reported that reactive non-proliferative astrogliosis is prevalent in the retina (Inman and Horner, 2007). Astrocytes proliferate and participate in the remodeling of ONH (structure Hernandez, 2000; Lozano et al., 2009). The explanation may be that the retina, as a whole, distributes the OHT evenly, whereas the ONH as a structurally different region of the retina may be subjected to more pronounced pressure. Significant biomechanical deformation appears in the ONH. Therefore, structural remodeling and astrocytes proliferation can cope with this deformation.

**Functional changes**

Functions of resting astrocytes include (1) regulation of the concentrations of ions and neurotransmitters to ensure internal environment balance, (2) nerve nutritional support, (3) synaptic formation, and (4) as a member of the neurovascular unit to form the blood-retinal barrier (Hernandez, 2000; Liddelow and Barres, 2015).

**Astrocyte Polarization**

**A1 astrocytes**

A1 astrocytes are predominantly induced in ischemia and acute trauma models (Anderson et al., 2016). Recent studies reported that primary astrocytes, subjected to oxygen/glucose deprivation are polarized to the A2 phenotype (Su et al., 2019). Interleukin (IL)-4 and IL-10 can also induce A2-like astrocytes in vitro (Chistyakov et al., 2020). Notably, A2 astrocytes can promote neuronal survival as well as tissue repair (Liddelow et al., 2017).

**A2 astrocytes**

A2 astrocytes are predominantly induced in ischemia and acute trauma models (Anderson et al., 2016). Recent studies reported that primary astrocytes, subjected to oxygen/glucose deprivation are polarized to the A2 phenotype (Su et al., 2019). Interleukin (IL)-4 and IL-10 can also induce A2-like astrocytes in vitro (Chistyakov et al., 2020). Notably, A2 astrocytes can promote neuronal survival as well as tissue repair (Liddelow et al., 2017).

**Molecular changes**

Reactive astrocytes upregulate “Pan-reactive” molecules including glial fibrillary acidic protein (GFAP), vimentin and lipocitcin-2, representing the common overlap molecule under neuroinflammation and ischemia (Zamanian et al., 2012). Structurally, GFAP is a cytoskeleton molecule (Middeldorp and Hol EM, 2011) which exhibits increased expression in reactive astrocytes of most species, thus it is often used to label astrocytes to evaluate their functional changes.

Notably, Müller cells also express GFAP (Ramírez et al., 2010; Hol EM, 2011) which exhibits increased expression in reactive astrocytes (Zamanian et al., 2012). Structurally, GFAP is a cytoskeleton molecule (Middeldorp and Hol EM, 2011) which exhibits increased expression in reactive astrocytes of most species, thus it is often used to label astrocytes to evaluate their functional changes.

**Figure 1:** Reactive astrogliosis in glaucoma and regulation of astrocyte polarization.

**Figure 2:** Astrocyte in the stretched preparation of retina labelled by anti-GFAP antibody (green).

This figure is the author’s unpublished data. An OHT mouse model was induced by injecting microbeads into the anterior chamber. Completely untreated mice were included in the control group. Retina was prepared by immunofluorescence. Figures were taken with confocal microscope, each magnified 20×. The expression of GFAP is stronger in eyes with OHT. Astrocytes in eyes with OHT become thinner and their secondary processes are decreased, resulting in reduced synaptic and vascular. GFAP: Glial fibrillary acidic protein; OHT: ocular hypertension.

and redistribute to the edge of the nerve to reduce their spatial coverage during early axon expansion (Cooper et al., 2016). In addition, their fine branches are reoriented (Tehrani et al., 2014). Once axons are lost, astrocytes partially re-extend long processes and restore their uniform distribution from the center to the edge to resume normal morphology and an extensive spatial overlap (Sun et al., 2010; Bosco et al., 2016; Cooper et al., 2018).

Astrocytes close to the myelination transition zone extend characteristically glaucomatous longitudinal processes (Wang et al., 2017).

**Molecular changes**

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Moreover, metabolic molecules in astrocytes undergo redistribution. For example, the transfer of glucose is driven by a concentration gradient, from the non-OHT contralateral eye with a high concentration to the OHT eye with a high demand to support nerve function (Cooper et al., 2020). Astrocytes are highly interconnected by gap junctions which are composed of the protein connexin-43 (Cx43), thus functioning as a broader network (Boal et al., 2021). In OHT models, Cx43-mediated astrocyte network transfers metabolic resources from a non-OHT eye to an OHT eye. Although this may improve axonal function and vision in the OHT eye, it renders the non-OHT eye vulnerable to biological energy stress (Cooper et al., 2020).
Heterogeneity of microglia

Microglia, as an another glial cell involved in neuroinflammation, was introduced to the concept of polarization earlier than astrocytes. Reactive microglia were initially thought to exhibit two opposite activation states (Gordon, 2003). To distinguish these, the term “M1/M2” originally derived from the macrophage is used to describe classical pro-inflammatory (M1) and alternatively activated anti-inflammatory (M2) microglia. Further studies reported that the M2-like phenotype has at least three subtypes, namely, M2a, b and c, with unique functions (Franco and Rodriguez-Suarez, 2015). As research progressed, some of the M2a subtypes were reported in addition to the clear dichotomy, such as disease-associated microglia characterized by ability to promote neurodegeneration in Alzheimer’s disease (AD), as well as SOD1G93A microglia implicated in significant induction of potentially neuroprotective and neurotoxic factors concurrently in amyotrophic lateral sclerosis (ALS) (Chiu et al., 2013; Keren-Shaul et al., 2017). Recent advances in transcriptomics have questioned whether the M1/M2 dichotomy is an oversimplification (Hume and Freeman, 2014; Ransohoff, 2016; Sousa et al., 2016).

Microglia are located in the retina and in the unmyelinated optic nerve. There is an ongoing activation and proliferation during the early stages of chronic glaucoma models (Bosco et al., 2011, 2015). IOP elevation induces transformation of most microglia to their M1-like phenotype, whereas those in the contralateral retinas show multiple phenotypes after activation (Rojas et al., 2015). Thus, microglia usually undergoes a dynamic process, manifested by changes in the ratio of M1 phenotype and M2 phenotype, even the existence of other transition subtypes. So function of microglia is mixed.

Heterogeneity of astrocytes: the possibility of subtypes other than A1/A2

A recent meta-analysis of astrocyte polarized transcriptions was performed based on acute injury and chronic neurodegeneration (Das et al., 2020). The results elucidated that A1-related, A2-related, and pan-reactive genes are upregulated in astrocytes in most acute injury and chronic neurodegeneration mouse models. This indicates two different views: (1) A1 and A2 astrocytes may not be mutually exclusive and may exist as a continuum, their proportions associated with the degree and severity of damage. (2) There may be transition subtypes related to disease, requiring further clarification.

Astrocyte Polarization in Glaucoma

Presence of A1 and A2 astrocytes in glaucoma

There are several reports about astrocyte polarization in glaucoma (Table 1). A1 astrocytes are induced rapidly in the optic nerve crush model, as well as in the microbead high intraocular pressure model (Liddelow et al., 2017; Guttenplan et al., 2020). C3-expressed astrocytes have also been reported to exist in other models, such as laser cataractation and genetic glaucoma models (Kuehn et al., 2006; Harder et al., 2017). Moreover, the three cytokines from microglia that induce A1 polarization, IL-1α, TNF-α, and C1q, are maintained at high levels to ensure existence of A1 astrocytes after the IOP returns to normal (Sterling et al., 2020). Persistent death of RGCs depends on neuronal injury and the presence of reactive A1 astrocytes (Guttenplan et al., 2020).

A2 astrocytes have not yet been reported in glaucoma. However, quantitative polymerase chain reaction results of A2-specific genomes including Clcf1, Pttx3, B3gnt5, Cd14 and Ifi202b, indicate that A2 astrocytes may be present in the retina and ONH in the chronic hypertensive model. This finding provides a basis for further studies on A2 astrocytes in glaucoma (Guttenplan et al., 2020).

Subtype classification of scar-forming astrocytes

In general, activated astrocytes are classified into two categories: reactive astrocytes (RAs) and scar-forming astrocytes (SAs). Reactive astrogliosis is a hierarchical continuum of progressive changes in gene expression and cellular changes. Resting astrocytes undergo reactive astrogliosis to form RAs. Subsequently, RAs overlap their process and form glia scar with SAs (Sofroniew, 2009). Further, these two cell types exhibit different characteristic phenotypes (Hara et al., 2017). Studies report that RAs express Plaur, Mmp2, Mmp13, Axin2, and genes associated with the β-catenin-MMP migration signaling pathway. In contrast, SAs upregulate expression of Chs2, S0K9, axon-directed rejection gene (Slii2), and chondroitin sulfate proteoglycan related genes (CSPG), including Yt1l, Chat11, Csgnact1, Acan, and Pcan.

Several studies have emphasized that it is inadequate to describe only RAs in astrocyte polarization exploration. Initially, SAs were thought to inhibit axon regeneration by physical forming glial scars with regenerated axons forming so-called dystrophic endbulbs or by chemically blocking axon regeneration (Liuzzi and Lasek, 1987; Silver and Miller, 2004). Further studies explored the beneficial effects of SAs, which can repair the blood-brain barrier, prevent overexpression of inflammatory response genes and inhibit cell cycle, and limit cellular degeneration (Bush et al., 1999; Faulkner et al., 2004; Sofroniew, 2015). In addition, SAs up-regulate two CSPGs fRNAs (CSPG4 and CSPG5) that supports axon growth, thus contributing to axon regeneration (Li et al., 2018).

Review

Current therapeutic strategies for neuroinflammation mainly target microglia and are aimed at reducing infiltrating immune cells. Regulation of astrocyte polarization to promote the protective effect of A2 astrocytes and reduce the adverse effect of A1 astrocytes is a potential alternative therapy approach for treatment of neuroinflammation. Regulation of astrocyte polarization can be achieved via the extracellular microglia-related pathway and the intracellular pathway (Figure 1).
so the ratio of M1 to M2 microglia also directly affects astrocyte polarization. Current neuroprotective approaches in other diseases via the extracellular microglia-related pathway mainly focus on three strategies: (1) Inhibition of M1 microglia activation to reduce the three factors and thus the number of A1 astrocytes; (2) Polarization of microglia to M2 subtype so that astrocyte polarization is skewed toward the A2 subtype; (3) Inhibition of inflammatory factors from microglia alone, such as NLRP3-inflammasome, to reduce A1 astrocytes (Table 2).

### Table 2 | Influence of astrocyte polarization through the extracellular microglia-related pathway

| Mechanism                  | Disease          | Animal     | Method                     | Reference                  |
|----------------------------|------------------|------------|----------------------------|----------------------------|
| Inhibition of NLRP3-inflammasome released from microglia | M1 | Mice | MCC950 | an inhibitor of the NLRP3 inflammasome | Hou et al., 2020 |
| Inhibition of microglia activation (to M1 subtype) | MS | Mice | Ac2-26 | a mimetic peptide of Annexin-A1 | Song et al., 2020 |
| SCI | Rats | Minocycline | a non-specific microbial inhibitor | Liu et al., 2019 |
| SCI | CS | Rats | BMSCs-Exos | a specific microglial inhibitor | Li et al., 2020 |
| Ischemic stroke injury | Rats | Cottonseed oil | an inhibitor of microglial activator | Liu et al., 2020 |
| Regulation of microglia polarization to M2 subtype | SCI | Mice | The NEAT1/miR-224-5p | Li et al., 2021 |

Intracellular pathway

It has been demonstrated that A1 astrocyte activation does not always take place through the classic extracellular microglia pathway, and that microglia activation in some models occurs after the polarization of A1 astrocytes (Clark et al., 2019; Carroll et al., 2020). This implies that intracellular pathways may be more inclusive targets (Sofroniew, 2009).

The nuclear factor kappa-B (NF-κB) signal plays a crucial role in this process. In addition to releasing pro-inflammatory cytokines, increased NF-κB gene expression leads to the expression of other pro-inflammatory proteins such as IL-1β, IL-6, and TNFα (Zamanian et al., 2012; Lian et al., 2015). Previous studies have shown that inhibition of the NF-κB signal plays a protective role following injury (Brambilla et al., 1997; Davis et al., 2014).

### Table 3 | Mechanisms other than the The nuclear factor kappa-B (NF-κB) signal pathway that can regulate astrocyte polarization through the intracellular pathway, including physical and physiological changes such as cytokine increase and regulatory protein expression

| Mechanism                              | Disease          | Animal     | Method                     | Reference                               |
|-----------------------------------------|------------------|------------|----------------------------|-----------------------------------------|
| Inhibit astrocytes activation to A1 subtype | Infrasound Exposure | Rats       | FGFR2/FGFR1 pathway ↑      | Zou et al., 2019                      |
| Depression                              | Mice | Mice | TUDCA directly prevents A1 polarization in a dose-dependent manner | Bhardwaj et al., 2020 |
| ALS                                     | Mice | Mice | TGFβ3 ↑ | Gottiapi et al., 2020 |
| Pain                                    | Mice | Mice | Ac2-26 ↑ | Luo et al., 2020  |
| Subarachnoid hemorrhage                  | Mice | Mice | Ponesimod ↑ | Zhang et al., 2021 |

| Induce astrocyte polarization to A2 subtype | PD and Subarachnoid hemorrhage | Mice | Cx30 ↑ | Fujita et al., 2018 |
| Chronic hypoperfusion                    | SCI | Mice | mir-21 ↓ | Su et al., 2019 |

Conclusions

Astrocyte polarization is a novel concept that has not fully been reported in glaucoma. Further studies are required to fully explore the concept of astrocyte polarization as a new potential therapeutic strategy for the treatment of glaucoma. The following research directions may help to further understand the role of astrocyte polarization in glaucoma.

(1) Drug development programs should target astrocyte polarization. It is imperative to explore whether known astrocyte polarization-related drugs in other diseases are also effective in glaucoma, or whether anti-glaucoma drugs exert their effect by regulating astrocyte polarization.

For example, omega (n)-3 polyunsaturated fatty acids (PUFAs) reportedly attenuate adverse outcome in other diseases by balancing the A1/A2 phenotype of astrocyte polarization (Nguyen et al., 2007; Kalogerou et al., 2018). PUFAs induce the synthesis of astrocyte polarization-related proteins such as β3 integrin (Sheetz et al., 2018).

### Table 4 | Functions of astrocyte polarization-related drugs

| Mechanism                  | Disease          | Animal     | Method                     | Reference                  |
|----------------------------|------------------|------------|----------------------------|----------------------------|
| Inhibit astrocytes activation to A1 subtype | Infrasound Exposure | Rats | FGFR2/FGFR1 pathway ↑      | Zou et al., 2019                      |
| Depression                              | Mice | Mice | TUDCA directly prevents A1 polarization in a dose-dependent manner | Bhardwaj et al., 2020 |
| ALS                                     | Mice | Mice | TGFβ3 ↑ | Gottiapi et al., 2020 |
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| Chronic hypoperfusion                    | SCI | Mice | mir-21 ↓ | Su et al., 2019 |

### Limitations

Although astrocyte polarization has been widely researched in recent years, it remains relatively poorly understood in glaucoma. In this review, the characteristics of astrocyte polarization in the visual nervous system are inferred based on knowledge of astrocyte polarization in the central and peripheral nervous systems. The study has some limitations.

First, while the visual nervous system and the central nervous system (brain and spinal cord) have broadly similar cell populations, including neuronal cells and glial cells, their organizational structures, cell connections and interactions differ. Therefore, astrocyte polarization in glaucoma and the central nervous system may not be directly comparable. Second, although glaucoma is considered a neurodegenerative disease, its pathogenesis differs from that of neurodegenerative diseases in the central nervous system. Therefore, the role of astrocyte polarization in glaucoma may be disease-specific.
Astrocyte polarization is a potential target for the prevention of glaucoma in people with OHT and without glaucomatous neurodegeneration. Activation of astrocytes precedes axonal injury and A1 astrocytes do not cause damage to unimpaired RGCs, thus it is possible that A1 astrocytes are present in these patients (Guttenplan, et al., 2020) and may explain their predisposition to glaucoma. Prophylactic downregulation of A1 astrocytes or adjustment of the ratio between activated A1 and A2 astrocytes may effectively reduce the incidence of glaucoma in patients with high IOP. This would be a major breakthrough since currently there is no effective preventive therapeutic target for glaucoma.

**Author contributions:** Design of manuscript: YXL, HS, WYG; literature review and drafting of manuscript: YXL; critically editing the manuscript: HS, WYG. All authors read and approved the final version of this manuscript.

**Conflicts of interest:** The authors declare that there are no conflicts of interest associated with this manuscript.

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**Open peer reviewer:** Sanjeev K. Bhattacharya, University of Miami School of Medicine, USA.

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