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Müller glial cell photosensitivity: A novel function bringing higher complexity to vertebrate retinal physiology

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ABSTRACT

The retina of vertebrates is responsible for detecting and capturing ambient light for image and non-image forming (NIF) functions through diverse projections to the brain which regulate visual processing, pupillary light responses, photic synchronization of circadian rhythms and suppression of pineal melatonin, among others. For this, vertebrates have retained through evolution at least two sets of photoreceptors specialized primarily in such visual and NIF tasks: visual photoreceptors cones and rods responsible for day/night vision, and intrinsically photosensitive retinal ganglion cells (ipRGC) together with horizontal cells in some vertebrates, expressing melanopsin (Opn4). Interestingly, Opn4 as well as encephalopsin (Opn3) and neuropsin (Opn5), responding to blue and UV light, respectively, are expressed in the inner retina and command light detection in the blue range of the visible spectra; they are responsible for a number of NIF functions still lacking characterization. Though most retinal photoreceptors are derived from ciliary or neuronal progenitor cells, in recent years Müller glial cells (MCs), the most abundant retinal glial cell type, have been shown to express different blue opsins (Opn3 and Opn5) and the photoisomerase retinal G protein-coupled receptor (RGR), and to respond directly to light. MCs display different essential functions to maintain the homeostasis and cell survival of the whole retina, contributing to glutamate metabolism and chromophore recycling. The novel photoreceptive capacity of MCs, mainly in the blue region, offers several highly intriguing possibilities that increase the complexity levels for light detection in the retina and its light-activated circuits, calling for further investigation. The goal of the present review is to discuss the state of the art of research on **the principal macroglial cells in the retina,** focusing mainly on the novel photic responses driven by MCs, the biochemical mechanisms triggered after light stimulation and their putative functions and implications.

1. Introduction

Forming a part of the central nervous system (CNS), the retina in vertebrates is a fundamental component of the visual system with specific responsibility for light detection from the environment in terms of color, wavelength, intensity and duration. The retina controls two major light-regulated activities of essential importance: vision associated with image forming tasks and non-image forming (NIF) functions

Abbreviations: **ARAT**, 11-cis acylretinol acyltransferase; **ATP**, Adenosine triphosphate; **CAMKII**, calcium/calmodulin-dependent protein kinase II; **cAMP**, Cyclic adenosine monophosphate; **CNS**, central nervous system; **CRALBP**, cellular retinaldehyde-binding protein; **CRBP**, cellular retinol binding protein; **CREB**, cAMP response element-binding protein; **EGTA**, 3,12-Bis(carboxymethyl)-6,9-dioxa-3,12-diazatetradecane-1,14-dioic acid; **ERG**, electroretinogram; **ERK**, Extracellular signal-regulated kinases; **GABA**, γ-Aminobutyric acid; **GCL**, ganglion cell layer; **GFAP**, glial fibrillary acidic protein; **GLAST-1**, glutamate-aspartate transporter 1; **GPCR**, G protein-coupled receptors; **GS**, glutamine synthase; **IF**, intermediate filaments; **INL**, inner nuclear layer; **IP3**, inositol 1,4,5-trisphosphate; **IPL**, inner plexiform layer; **ipRGC**, intrinsically photosensitive retinal ganglion cells; **JUNK**, c-jun N-terminal kinase; **MCs**, Müller glial cells; **MFAT**, multifunctional O-acyltransferase; **MIO-M1**, Moorfields/Institute of Ophthalmology-Müller 1; **mRNA**, messenger ribonucleic acid; **NES**, Nestin; **NIF**, non-image forming; **ONL**, outer nuclear layer; **p38**, p38 mitogen-activated protein kinase; **PLC**, phospholipase; **PRCs**, photoreceptors cells; **RDH**, retinol dehydrogenases; **RES**, retinyl ester synthase; **RGC**, retinal ganglion cells; **RGR**, retinal G protein-coupled receptor; **RPC**, retinal progenitor cells; **RPE**, retinal pigment epithelium; **RRH**, peropsin; **TMT**, teleost multiple tissue; **TRP**, transient receptor potential.

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mainly related to day and night duration, measuring time through daily changes in ambient illumination and consequently driving pupillary light responses, photic synchronization of circadian rhythms, masking, sleep, suppression of pineal melatonin, mood and learning, among others (see [1–3] for review). The retina is a highly ordered, multilayer-organized structure composed of three nuclear layers: the outer nuclear layer (ONL), comprising photoreceptor cells (cones and rods), the inner nuclear layer (INL), made up of horizontal, bipolar and amacrine cells serving as interneurons, and the **ganglion cell layer (GCL)** containing retinal ganglion cells (**RGC**). Two layers of projections connect the nuclear layers: the outer plexiform layer connects cells of the ONL with the INL and the inner plexiform layer connects the INL cells with the GCL (Fig. 1) [4]. RGC axons in the GCL project via the optic nerve to diverse brain areas related to vision and image-forming areas and to NIF regions controlling diverse light-regulated activities [5,6]. **For this to occur, vertebrates have retained through evolution different sets of photoreceptors primarily specialized in such visual and NIF tasks: the visual photoreceptors cones and rods responsible for day/night vision derived from ancestral canonical C-opsins, and the intrinsically photosensitive retinal ganglion cells (ipRGC) [7–11] together with horizontal cells in some vertebrates [12–15], likely derived from a common ancestor and belonging to the canonical R-opsins clade** [16,17]. Most of these nonvisual photoreceptors express melanopsin (Opn4), a blue light photopigment [18,19] shown to be responsible for driving NIF activities (see 2,3,5,20 for review). Photic responses were retained even in some non-cone, non-rod mammalian models of retinal degeneration [21–23] or in blind GUCY1 chicks lacking functional visual photoreceptors since hatching [24–26]; however, these responses were lost after enucleation or triple knockout for rod and cone genes and Opn4 of ipRGCs [11,27]. Light responses in these cases required a functional photopigment and retinaldehyde as chromophore [28] and operated through a photocascade involving the Gq protein, activation of phospholipase C (PLC), calcium mobilization, opening of transient receptor potential (TRP) channels, membrane depolarization, and in some cases, GABA release [3,8,9,14,20,29,30]. **More recently, it has been shown that the photocascade in mouse ipRGC subtypes may rely on a mechanism involving cyclic nucleotide and hyperpolarization-activated and cyclic nucleotide-gated channels [31], as well as closure of potassium leak channels by Gq protein activation [32]; observations that strongly suggest the coexistence of both types of mechanisms in nonvisual photoreceptors which still remains as an open question [33,34]. Furthermore, light responses appeared very early in development, even before the occurrence of any formal sign of vision in vertebrates [8,9,14,35,36], while the characterization of different subtypes of RGCs in mammals showed diverse cellular size, opsin expression, electric properties, morphology, cellular connectivity within the inner retina and projections to brain areas, thus conforming different Opn4-expressing RGCs subpopulations, such as M1-M6 in mice, that sustain their participation in different visual and NIF activities [1,6,37–39].** Interestingly, Opn4 together with the blue/UV opsins encephalopsin (Opn3) and neuropsin (Opn5) and the photoisomerase retinal G protein-coupled receptor (RGR) are expressed in different cells of the inner retina of vertebrates and may conform a network of specialized opsins commanding light detection in the blue range of the visible spectra (reviewed in 3). This additional feature may confer on the vertebrate retina the capacity to regulate several additional NIF functions triggered by light such as setting the retinal clock, cell-to-cell communication and chromophore recycling [35,40–42]. **In recent years the most abundant retinal glial cell type, Müller glial cells (MCs), have been shown to express different blue opsins (Opn3 and Opn5) and the photoisomerase RGR, and to respond directly to light stimulation [35,43,44].** MCs display different essential functions within the retina to maintain retinal homeostasis and cell survival and have also been shown to regulate glutamate uptake and metabolism, chromophore recycling, neuronal regeneration and to be a putative target for cell therapy (reviewed in [45–47], see next section for further detail). The recently described novel photoreceptive feature of MCs with responses centered at the blue region opens the possibility of a higher level of complexity for light detection in the retina involving light-regulated circuits and pathways, to be further discussed in the following sections of this review.

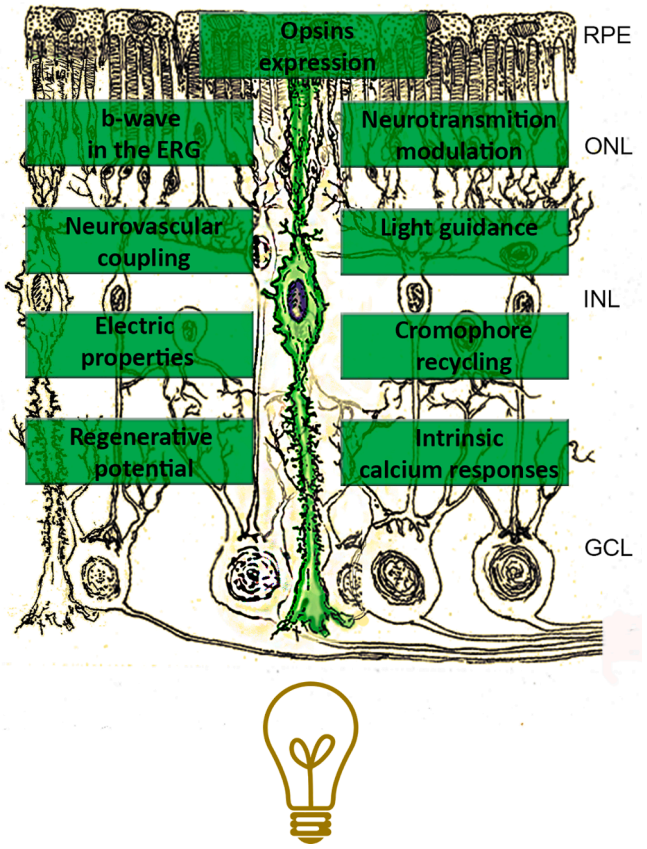

Fig. 1. Müller glial cell contributions in light-driven events. Müller glial cells (in green) represent the main glial component in vertebrate retina, spanning the whole structure and being in contact with all its neuronal cell types. From their perykaria in the inner nuclear layer (INL), two stem processes run in opposite directions: towards the subretinal space, contacting photoreceptors in the outer plexiform and outer nuclear (ONL) layers and conforming the outer limiting membrane; and towards the ganglion cell layer (GCL) as a funnel-shaped endfoot defining the inner limiting membrane. Conventional and unconventional participation of MCs in light-evoked responses within the retina are listed (green boxes) and further detailed in the main text. RPE: retinal pigment epithelium.

2. Müller glial cells

After their initial description by Ramón y Cajal at the end of the 19th century, glial cells gained relevance over the years as their multiple roles began to be reported. Along with the fine anatomical and morphological descriptions, several aspects of the putative functions of glial cells proposed by this outstanding Spanish neuroscientist have underpinned glial research ever since. As new techniques have become available, this non-excitable cell type has been shown to be a complex and dynamic system that spatially and temporally regulates ion-mediated signals to enable them to respond biochemically to stimuli within their environment [49–51]. By 1851 the work of Heinrich Müller (1820–1684) had also made fundamental contributions to the histology and anatomy of the visual system. Along with a pioneer description of rhodopsin, Müller provided a precise representation of retinal vasculature and deduced that vision initiates at the back of the retina, where he identified “radial

fibers'' that traverse the entire thickness of the retina, known nowadays as MCs, the main glial cell type within the vertebrate retina [48,52,53].

MCs, unlike other retinal glial components, are derived from neural crest cells showing developmental characteristics highly conserved across species [54]. From an initial pool of mitotic pluripotent retinal progenitor cells, all retinal neurons are produced in an ordered, overlapping sequence involving early differentiation of **RGC,** followed by horizontal cells, amacrine cells and cones, and a final stage with bipolar cells and rods that culminates in MCs differentiation [48,54]. During the four stages of this process, which includes sequential synaptic formation and pruning whose duration can vary from hours to days across species, lateral and vertical neuronal networks are shaped along the different retinal layers [54]. Even though the fate of MCs is defined at late developmental stages, they play fundamental roles along a process spanning cellular organization across the retina, release of trophic factors affecting neuronal survival, refinement of synaptic connectivity, release of synaptogenic and anti-synaptogenic molecules, cellular debris clearance, and neuronal activity-evoked responses (reviewed in [55]). Initially resembling progenitor cells with apical and basal processes, MCs show a regular distribution pattern across the retina - except at the transcriptional level as observed in chicken retina – with non-overlapping territories [56–58]. MCs undergo substantial morphological changes across the different developmental stages, including extension of basal processes to ensheath **RGC** soma, dynamic branching of fine lateral processes to contact the different synaptic layers, enlargement of the apical section towards the ONL to enwrap photoreceptor soma and to form microvilli projections that contact outer segments of photoreceptors, and projections to reach blood vessels in vascular retinas [54].

In adult vertebrate retina, MCs therefore constitute unique functional elements that transverse the whole structure and directly interact with all cell types within the inner retina (Fig. 1). Indeed, MCs are considered the core of the retina's functional unit, with a restricted number of photoreceptors and neurons anatomically and functionally linked to central MCs for "forward information processing" (Fig. 1) [59,60]. In this context it is not surprising that MCs assume such a broad span of physiological functions including neurotransmitter recycling and synthesis along with gliotransmitters release, therefore affecting synaptic activity and limiting glutamate toxicity; trophic, metabolic and antioxidant support to neurons and photoreceptor cells (PRCs); K+ siphoning; water clearance; and biomechanical guidance (reviewed in [48,61,62]); and others to be discussed in greater depth below.

2.1. Light-evoked activity

The involvement of MCs in light-driven responses in the retina has long been under the spotlight. Early work by Miller [62] proposed the essential contribution of MCs activity to the electroretinogram (ERG), the light-induced potential change related to the electrical activity within the retina in response to light. Along with their description of MCs morphology in the mudpuppy retina, the authors showed that the slow depolarizing potentials of MCs in response to light stimulation correlate in intensity and time lapse with the b-wave, thus proposing MCs as one of the current paths associated with the b-wave of the ERG [62]. When the retina was treated with gliotoxin DL-a-aminoadipic acid, the b-wave amplitude was absent or markedly reduced compared to controls [63]. Changes in extracellular K+ concentration could thus depolarize MCs membranes as this cation is transported across them, which is later reflected in the generation of the b-wave [64,65]. The "Müller cell-Hypothesis" was subsequently upheld in several reports on different species [66–71], though it remains a matter of debate [72]. **Weather the implication of MCs in the b-wave generation reflects a direct change in MCs membrane potential or an indirect effect, given their crucial participation in K+ buffering after neurotransmission, is not specified; nevertheless Miller's work envisioned MCs as active elements participating in light-driven responses in the retina.**

Advanced optical imaging techniques for visualizing intracellular calcium concentrations extended the understanding of glial cell physiology, showing this electrically non-excitable cell type to be a complex responding system in which ion-mediated signals are highly regulated in space and time [51]. Indeed, intracellular calcium signaling was initially described as part of the complex dialog between neuron and glial cells since pharmacological or mechanical stimulus evoked calcium elevation in glial cells, which spread to neighboring glia and activated calcium signaling in neuronal cells [73,74]. Similarly, by monitoring calcium signaling in the intact retina of rat, Newman and Zahs [75] showed changes in neuron firing rates that correlated with the onset of glial calcium waves after light stimulation. The neuronal modulation was mainly inhibitory, correlating in time and magnitude with the light-elicited calcium wave in MCs, and partially depended on calcium availability from internal stores [75]. Moreover, the authors showed that glial release of neurotransmitters mediated the reinforcement or dampening of neuronal activity, possibly depending on the prominence of inhibitory interneurons in the feedback circuit [75].

Other released signaling molecules such as adenosine triphosphate (ATP) could also be related to glial modulation of neuronal activity, as mechanical stimulation of MCs promotes ATP release after calcium increase and inhibits neurons by activating adenosine A1 receptors [76]. Indeed, ATP was shown to mediate two-way signaling between neurons and glia [77]. Calcium release from internal stores in MCs is potentiated by adenosine and blocked when synaptic transmission is abolished by pharmacological agents [77]. Interestingly, calcium waves in MCs, elicited by light stimulation and potentiated by adenosine, show changes along the retina, originating in inner regions of the inner plexiform layer (IPL) and then spreading distally towards MCs endfeet to finally reach the outer IPL and GCL [77]. In line with these observations, MCs in guinea pig retina displayed a light-evoked calcium increase consisting of a fast and a slow response [78]. The slow calcium response occurred simultaneously with the onset of light stimulation and lasted for several minutes, whereas the fast calcium response showed different onsets and began with a latency of minutes after the stimulus at the endfeet of 60% of the MCs population [78]. Interestingly, the two light-evoked calcium responses showed different dependencies on light intensity, further suggesting that they are generated by different mechanisms [78]. The slow calcium response would be evoked by photoreceptor signaling to MCs, changing their membrane potential and allowing calcium influx from the extracellular space; fast calcium responses, restricted to the GCL, would imply calcium release from internal stores with a small contribution from ATP signaling [78].

A novel perception of glial multiple functions in the CNS arose within the context of the brain neurovascular unit as an anatomically and functionally integrated compartment conformed by neurons, astrocytes and endothelial cells [79–81]. The coordinated activity between these cell types is essential for the maintenance of brain homeostasis and implies astrocytic calcium waves in response to neuronal activity, these in turn promoting the release of vasoactive agents that induce changes in vascular tone [80,82,83]. In this manner, increases in neuronal activity are accompanied by a local enhanced supply of glucose and oxygen and removal of metabolites, a concept known as functional hyperemia [79–81]. In the retina, the high metabolic demand of photoreceptor activity is met by choroid circulation in most invertebrate and vertebrate species, leading to the term avascular retinae; however, in mammals the retinal vasculature constitutes an additional system for nutrient and oxygen delivery for the inner retina, therefore presenting vascular retinae [84]. This system innervates the inner two thirds of the retina and lacks autonomic control, for which reason it is proposed that several local intrinsic mechanisms regulate vascular tone and neurovascular coupling in the retinal vasculature, with MCs contributing to both vascular regulatory events [84,85]. ATP is a vasoactive compound mediating vessel constriction and relaxation subject to the activation of P2X or P2Y receptors [86]. Indeed, tonic ATP regulates vascular tone in

the retinal vasculature [87]. When manipulation of ecto-enzyme activity in the rat retina causes endogenous levels of ATP to decrease or increase, vessels dilate or constrict, respectively [87]. Interestingly, flourocitrate treatment -which selectively alters MCs metabolism by inhibiting the Krebs cycle- resulted in blood vessel dilatation, pointing to a glial origin of ATP-mediated tonic vasoconstriction [87]. Given the proximity of MCs endfeet to the vessels, it is plausible that glial release of ATP occurs, after which the ATP is further converted to adenosine and finally leads purinergic-mediated vasoconstriction [87]. In addition, calcium signaling up regulation in glia actively promotes vasodilation and vasoconstriction independently of neuronal activity [88]. Given the similarity in the vascular responses elicited by light and by calcium increases in MCs, it can be hypothesized that neurovascular coupling in retinal tissue is mediated by MCs activity, through calcium signaling and release of arachidonic acid metabolites [88]. In this way, MCs in vascular retinas would constitute a bridge between neuronal activity and blood supply to sustain the functioning of the illuminated retina.

2.2. Light guidance

Cells are defined as being translucent; however, in the case of multiple cell layers, as in tissues, the light path in the cell is subjected to optical and geometrical elements whose length scales are in the order of the wavelength of visible light (380–770 nm) [89,90]. Such elements constitute phase objects that reflect and scatter light. The fact that the vertebrate retina is inverted (Fig. 1) reduces its visual sensitivity and acuity and decreases the signal-to-noise ratio of the transmitted image [89]. Among the irregularly shaped and randomly oriented cells of the retina, MCs constitute a unique component with a cylindrical, fiber-like shape, showing a regular distribution pattern along the retina, with the exception of the fovea, and bridging the light path through the inner retina from the vitreous, where light enters the tissue, to the outer limiting membrane, where photoreceptor cells receive the incident light (Fig. 1) [89,91]. The pioneering work by Franze et al. [90] revealed that light transmission and reflection through guinea pig retina shows a regular pattern of spots, indicating the presence of tubular structures along the retina that transmit significantly more light than their surrounding tissue. Despite their complex morphology, MCs show cylindrical geometry and constant light-guiding capability along the retina, strongly suggesting that these cells could function as **waveguides for visible light** [90]. Subsequent evidence obtained in intact retinal tissue of the guinea pig indicated that transretinal light propagation changed as a light beam moved in front of a tubular-shaped MC [92]. When illuminating the retina, the prominent scattering observed at the end of the light path decreased from a position not in front of a MC center (where light is transmitted as a diffusely distributed wide spot) to a position where fiber and MC were coaligned and the transmitted light spot became smaller and more intense [92]. Thus, the authors proposed a non-overlapping illuminated receptor-field for each MC with an average of 10–12 adjacent photoreceptor cells, which matches with the described ontogenetically organized functional retinal microcolumns; each cone would couple to one of the MCs as an individual light guide [60,89,92,93]. In this way, MCs channel virtually all light from one side of the retina to the other, doing so by separating different wavelengths [93,94]. The spectral distribution of light transmitted inside guinea pig MCs showed enhancement for wavelengths along 550–700 nm; whereas light intensity propagating inside the MCs reached its peak at 575 nm [93]. Thus, MCs concentrate the red-green part of the visible spectrum, so it reaches the cones and leak the blue-violet light to illuminate the surrounding rods [93]. It is currently proposed that MCs transfer light throughout the retina with low scattering and wavelength sorting, possibly contributing to higher sensitivity of rods during night vision and improving contrast sensitivity of cones along daytime [90,92,93]. These anatomical light guidance capabilities of MCs are in line with other cellular modifications in retinal cells that are assumed to favor the amount of light reaching the PRCs [90,95–97].

A new perspective on MCs implication in light transmission has arisen in terms of **their electrical properties for transferring energy**. A morphological description by electron microscopy indicates that intermediate filaments (IF) run all through the length of MCs, organized into bundles, following the geometry of the cell, and directly interacting with photoreceptor membranes [98]. **These structures that resembles a bundle of parallel IFs with the outer diameter of 10 nm (varying within 8 to 13 nm, with each filament typically built of eight protofibrils), with some smaller microparticles organized around the filaments which are usually found to stabilize long filaments. The filamentary structure spans almost the entire MC length (400 to 500 μm), from the endfoot to the photoreceptor (the outer membrane), whereas it is absent in the MC endfeet** [99]**. Although the identity of these IFs remains unknown, it could be suggested that these filaments are vimentin and not GFAP as observed in the adult healthy retina** [48]. This finding has provided the basis for a quantum mechanism model that proposes electromagnetic field energy transmission by a waveguide in the form of a nano-capillary with conductive walls [100]. In this system, photons of light are absorbed by IFs in the MC endfeet into discrete excited states to induce excitons that propagate axially along the IFs to the respective PRCs [99,101,102]. Furthermore, numerical analyses point to an energy exchange mechanism between an electronically excited IF (energy donor) and a photoreceptor containing 11-cis-retinal bound to an opsin molecule (energy acceptor), only when the opsin molecules were located close to the extremity of the IF [103]. This body of evidence shows that MCs within the retina may work as waveguides for visible light and energy transfer units to improve light transmission and favor adequate retinal physiology in response to light of different wavelengths, intensities, and durations.

2.3. Chromophore recycling

Visual PRCs, rod and cones, are specialized cell types within the retina with substantial differences in terms of light detection. Besides their morphological dissimilitude, rod and cones differ in lighting condition sensitivity (scotopic and photopic vision), opsin specific expression (type and number of variants), and chromophore recycling pathways [3]. The “visual or retinoid cycle” was first proposed by George Wald (Nobel Prize, 1967) and colleagues to describe the sequence of chemical reactions taking place after light exposure, involving visual perception (which results in an 11-cis to an all-trans isomerization of the visual chromophore 11-cis-retinal) and chromophore recycling [104]. In order to maintain visual functioning after light stimulation, visual PRCs therefore depend on the recycling of retinaldehyde to regenerate bleached visual photopigments [3,20,105]. Over the years, two different mechanisms of retinoid recycling for rods and cones have been proposed [3,106,107].

The canonical visual cycle implies cytosolic enzymatic reactions and retinoid transport between rods and the retinal pigment epithelium (RPE). Upon light absorption and chromophore isomerization the conformational change in the G-protein coupled opsin releases the all-trans-retinal, which is reduced to alcohol by multiple membrane-bound retinol dehydrogenases (RDH5, RDH8 or RDH12) [108]. Once the all-trans-retinol is formed, it is shuttled to the RPE by interphotoreceptor retinoid-binding protein where it encounters cellular retinol binding protein (CRBP). In the RPE, retinol is subsequently esterified to ester, isomerized into 11-cis-retinol by RPE65, and then oxidized into 11- cis-retinal [3,20,105,109]. The reactions in the RPE depend on cellular retinaldehyde-binding protein (CRALBP), a **retinoid** transporter acting as a chaperone carrier in an aqueous milieu. Finally, the recycled 11-cis retinal is transported back to rod outer segments to re-assemble with the opsin and thus restore the functional visual pigment [3,20,105,109].

The intra-retinal visual cycle is proposed as a cone-specific pathway in cone-dominant retinas, such as in birds and amphibians [20,105]. The distribution of retinoids in cone-dominated species shows enrichment of

11-cis-retinyl esters in the retina, whereas rod-dominated retinas show all-trans-retinyl ester stores in the RPE [20]. Although the idea of an alternative visual cycle had been around for decades, it was not until the beginning of this century that the enzymatic pathway was identified in chicken and ground squirrel retina [110]. In this pathway, all-trans-retinol produced in the cone outer segment is processed for regeneration of photoreceptor visual pigments. The first enzymatic activity by Isomerase II catalyzes isomerization of all-trans to 11-cis retinol, possibly requiring the chaperon activity of CRALBP and CRBPI, akin to the role they play in the isomerase reaction in RPE. The second enzymatic step is that of retinyl ester synthase (RES), particularly by action of the 11-cis acylretinol acyltransferase (ARAT), catalyzing the production of retinil-esters from retinol. The 11-cis-retinol thus formed can then be stored as 11-cis-retinyl ester, and the 11-cis-retinyl ester can be later hydrolyzed to 11-cis-retinol. This latter enzymatic activity is that of RDH, localized in cones, strongly suggesting that the chromophore supplied by this alternative pathway would only supply cone demand, and not that of rods [20,105,110–113].

As with the canonical visual cycle, a second cell compartment for cone chromophore recycling is proposed to comprise MCs [20,105,111]. Initial reports described the expression of the retinoid binding proteins CRBP and CRALBP in MCs [114,115]. Later on, Das [116] reported a high proportion of retinoid pools in both the neural and epithelial compartments of cone-dominant chicken retina. Indeed, chicken MCs in culture take up supplied all-trans-retinol, esterify it to all-trans-retinyl palmitate and convert it into 11-cis-retinol, indicating that chicken MCs have isomerase and RES activities [116]. In 2006, Muniz et al. confirmed ARAT activity in MC cultures to produce 11-cis retinyl ester, whose activity is enhanced in the presence of CRALBP [117]. Furthermore, it had already been shown that apo-CRALBP strongly stimulates the synthesis of 11-cis retinol from all-trans retinol in the retina fraction [110]; and that knockdown of the CRALBP b isoform in MCs of zebrafish retina has a pronounced effect on photoreceptor function, causing reduction of 11-cis-retinal levels and deficits in visual behavior tests [118]. Similarly, studies performed in salamander and mice confirmed that CRALBP in MCs is essential for recycling and supplying 11-cis -and not 9-cis- chromophore exclusively to red and blue cones [119]. This is in line with previous *in vivo* evidence obtained by Wang and Kefalov [112], showing cone dark adaptation and pigment regeneration in isolated or whole-retina to be affected by MC disturbance, either via L-α-AAA gliotoxin or by physical disruption of MC-cone cell contact [112]. In fact, this visual cycle continues to be expanded to include new components such as 11-cis-specific retinyl-ester synthase, which was discovered in retinal MCs, characterized as the multifunctional O-acyltransferase (MFAT) and proposed to act cooperatively with Isomerase II to produce 11-cis-retinoids in MCs [120].

From an evolutionary perspective, the coexistence of the two visual cycles would solve the competition for chromophore availability between cones and rods under photopic conditions. In this scenario, rods have a high demand for 11-cis retinal and show a thermodynamic advantage in being able to combine the chromophore and the apoprotein [105,110], thus giving rise to an alternative visual cycle for chromophore supply to cones. By means of the expression of an 11-cis--retinol dehydrogenase, cones gained exclusive access to 11-cis retinal production from the 11-cis retinol supplied by MCs [105,110]. Cones appear earlier along evolution and development than rods, although cone-rich retinas like those in diurnal animals are derived from duplex-retina (similar rod/cone ratio). Thus, there remain unknown aspects of coexistence and interaction between these two visual cycles under bright and dim light conditions [20,121].

In the context of the intricate mechanisms of chromophore recycling, the precise role of MCs in retinoid availability to retinal cells expressing non-visual opsins remains to be elucidated. It should be noted that MCs, like the RPE, express the RGR that together with retinochrome constitutes a distinctive subclade in the opsin family [3,106]. RGR has been linked to the rod visual cycle as an alternative pathway to obtain cis-retinoids, by combining with RDH activity and the photoisomerization of all-trans retinal to 11-cis-retinal [106,121]. Strikingly, RGR is expressed at the endoplasmic reticulum membrane in MCs at the inner nuclear layer and the endfeet, matching CRBP and CRALBP distribution and enclosing Opn4-expressing neurons [35,106,122]. Beyond Opn4 bi/tri stability, our group has proposed that RGR in MCs may contribute to a novel alternative modulation of retinoids pools (retinals, retinols and retinyl esters) in light, maintaining the retinoid balance for Opn4-expressing ipRGCs/horizontal cells for further use upon light exposure [3,14,35]. The fact that MCs are in close contact with ipRGCs, together with the presence of novel visual-cycle enzymes within the inner retina specifically localized in the GCL as described by Kaylor and colleagues [120,123,124] and of RGR [35] strongly suggests that MCs act as a second cell-type supporting the alternative visual cycle in the inner retina, operating to supply the pool of retinoids to ipRGCs and Opn4x-horizontal cells [3,14,35]. In this regard, an alternative retinoid isomerization from all-*trans*-retinol to 11-*cis*-retinol was shown to be catalyzed by the retinol isomerase dihydroceramide desaturase-1, identified as a putative Isomerase II [124] present in the GCL where the endfeet of MCs are attached. The 11-*cis*-retinol thus formed can be stored as 11-*cis*-retinyl ester by action of the 11-*cis* ARAT. For this, two 11-cis-specific retinyl-ester synthases have been identified within the retina: the MFAT [120] and diacylglycerol O-acyltransferase-1 [123], both shown to be expressed in MCs and in the GCL. Nevertheless, the exact nature of this alternative cycle for non-visual photoreceptors has yet to be revealed.

2.4. Opsin-expressing müller cells

Opsins are a complex family of photosensitive G protein-coupled receptors (GPCR) for which seven subfamilies of opsins have been phylogenetically described: the vertebrate visual (Gt-coupled opsin) and the non-visual opsin subfamily encephalopsin (Opn3)/tmt-opsin; the melanopsin Gq-coupled (Opn4); the Go-coupled opsin, neuropsin (Opn5); and the peropsin (RRH) and retinal photoisomerase (RGR) subfamily, which has lost its coupling with G protein [3,125]. In their **light-receptive** form, opsins bind 11-cis retinal as chromophore, the light absorption resulting in the photo isomerization from 11-cis to all-trans retinal, which leads to the activation of the corresponding G-protein. The intricate lineage of the opsin family in terms of molecular and biochemical properties ensures light detection throughout the whole spectra [3,126]. In this sense, the non-visual opsins are highly (Opn5) and moderately (Opn3) conserved in all mammalian lineages, whereas the sequence of Opn4 is highly variable in mammalian species [126]. Furthermore, opsins are not limited to the retina and visual functions. In vertebrates, apart from the retina, the non-visual photopigments Opn4, Opn5 and Opn3 have also been found to participate in NIF functions [5,37,42] and to be expressed in many extra ocular tissues as in brain, skin and adipose tissue [41,127–131] mainly in relation to seasonal rhythm entrainment, migration, reproduction, and metabolic responses [41,132–134], among other functions still not fully elucidated.

Within the inner retina, our group has contributed to the characterization of new populations of intrinsically photosensitive cells. Horizontal cells expressing the Xenopus ortholog (Opn4x) in the chick retina were identified as new intrinsic photoreceptors responding to light through a cascade involving Gq protein, PLC activation and intracellular calcium rises with the consequent release of the inhibitory neurotransmitter GABA [14]. In **RGC**, intrinsic light-driven responses activate the phosphoinositide cycle and give rise to an increase in intracellular calcium levels [8,9,29]. Activation of Opn4x in chick **RGC** along with RGR in MCs modulate retinaldehyde levels in response to light and maintain the balance of inner retinal retinoid stores [35]. Activation of Opn4x in cultured chick **RGC** thus directs the photoisomerization of exogenous all-trans to 11-cis retinal and other retinoids [35]. Knocking down RGR, on the other hand, modified the retinoid pool in response to light

towards higher levels of 11-cis, all-trans retinal and all-trans retinol, and lower levels for all-trans retinyl esters, compared to dark controls. This reveals a novel role for RGR in modulating retinaldehyde levels in **ipRGC** in response to light and in maintaining the balance of inner retinal/retinoid stores [35]. In this regard, RGR was identified in the developing retina of the chick and in primary MCs avian cultures (Fig. 2) [35].

In our most recent work we furthered our understanding of non-canonical light responses in the avian inner retina, particularly in relation to MCs. We identified ubiquitous expression of the non-visual opsins Opn3 and Opn5 in the chick inner retina from early embryonic stages (E7/8); in the case of Opn3, an increase in its transcription and expression was observed throughout development up to the time of hatching [44]. This staggering of opsin expression overlaps with the increase in classical glial markers such as glial fibrillary acidic protein (GFAP) and glutamine synthase (GS), which together with Opn3-GS immunohistochemical double labeling in the developing retina initially suggested non-visual opsin expression by MCs. This idea was subsequently reinforced by studies performed on enriched MCs primary cultures expressing GS, GFAP, vimentin and the glutamate-aspartate transporter 1 (GLAST-1) [43,44]. Avian MCs in culture express three types of non-visual opsins: Opn3, Opn5 and RGR (Fig. 2) [35,43,44]. Opn3 expression was found to be photic regulated as its expression increased after 1 h of blue light stimulation and was maintained up to 1 h after the end of the stimulus [44]. This change in expression levels was accompanied by a change in the subcellular localization of the opsin, evidenced at 1 h of blue light exposure as a mobilization from intranuclear-like compartments towards the cellular edges. Remarkably, intranuclear compartments were refilled upon 1 h of darkness after the blue light stimulus [44]. This pattern of intranuclear expression

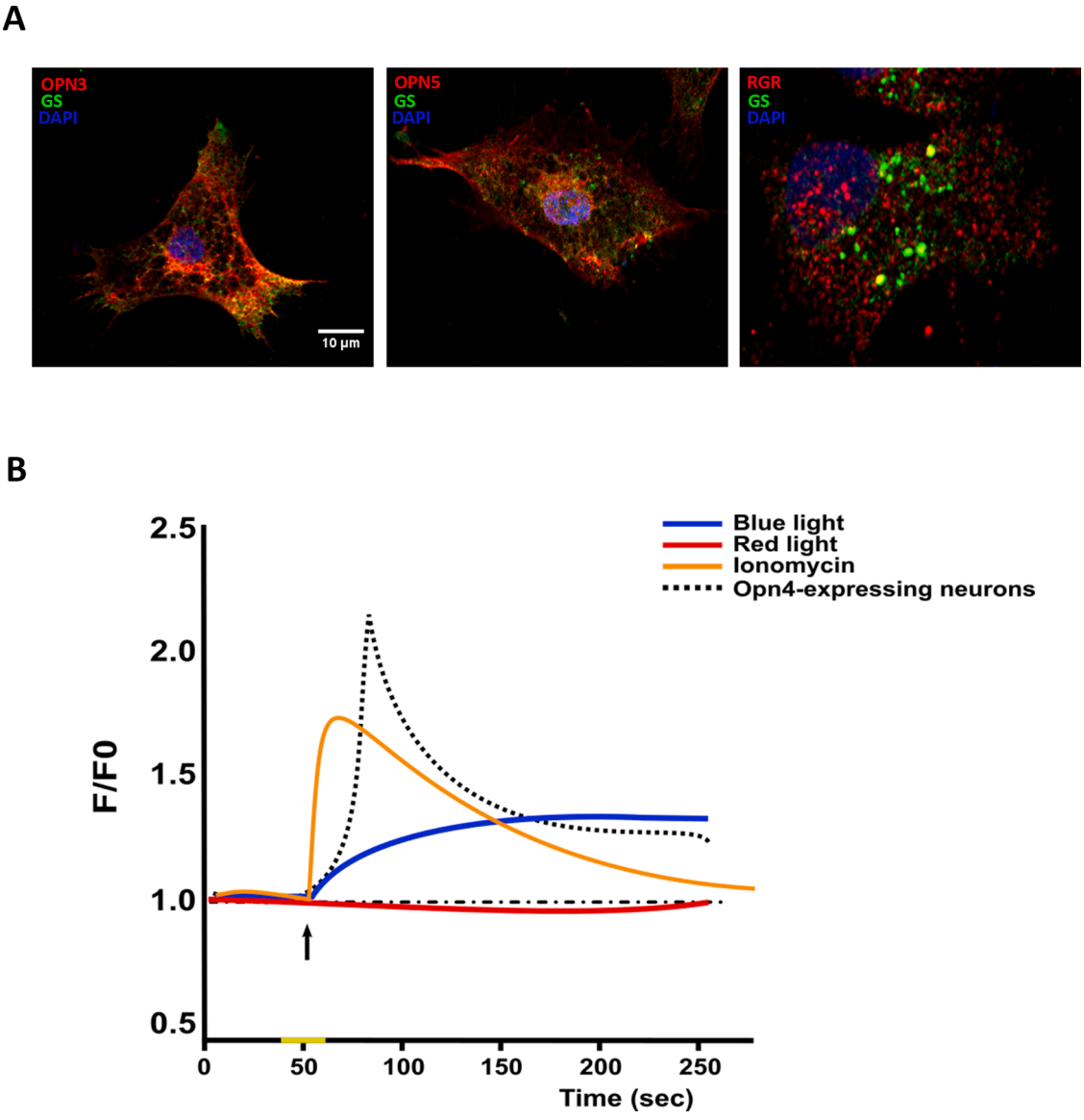

Fig. 2. Intrinsic photosensitivity of Müller glial cells. (**A**) Highly enriched primary cultures of Müller glial cells (MCs) from embryonic chicken retina express the non-visual opsins Opn3, Opn5 and RGR (in red), co-immunolabeled for the specific glial marker Glutamine **Synthase** (GS, in green) and DNA staining by DAPI (in blue) (3 µM). Scale bar 10 µm. (**B**) Different calcium responses elicited in MCs cultures are shown in the bottom panel (continuous lines). The ionophore ionomycin effectively elicits a large and fast calcium increase for a generalized depletion of calcium internal stores (orange line); whereas a blue light pulse promotes a slower and sustained increase in cytosolic calcium levels (blue line) as it is released from endoplasmic reticulum. The MCs responses (blue line) differ from those elicited by light in retinal horizontal neurons and ganglion cells expressing the non-visual opsin Opn4 in terms of their distinct high amplitude and transient characteristics (dashed lines). Red light has no effect on calcium levels (Red line). Dot-and-dash line indicates relative values=1 (no change in calcium levels). Yellow line in the X axis: duration of light stimulus. Arrow: Ionomycin stimulus.

coincides with Opn3 immunolabeling in other cell lines [135,136]. It is important to note that both described events for Opn3 in MCs are part of a same protein synthesis- dependent response, since the increase in and re-localization of Opn3 were not observed in the presence of the protein synthesis inhibitor cycloheximide [44].

Studies on glial cells and opsins are scarce and have been mainly performed using immortalized cell lines. The human immortalized cell line MIO-M1 expresses glial markers such as GS, GFAP, vimentin, together with neuronal progenitor markers such as Nestin (NES), paired-type homeobox transcription Factor (Pax6), and neurogenic locus notch homolog 1 (NOTCH1). Interestingly, these cells become depolarized in response to L-glutamate [137–139]. Furthermore, MIO-M1 cells also contain the mRNA of multiple opsins such as blue cone opsin (OPN1SW), rhodopsin, OPN3, OPN4, OPN5, RRH and the G protein transducin. In addition, the murine glial cell line MU-PH1, which expresses both glial and neuronal progenitor markers like MIO-M1 cells, also expresses photoreceptor markers such as transducin, rhodopsin, blue and red/green cone opsins together with the non-visual photopigment Opn4 [140]. These lines of investigation pursue the differentiation of glial cells into retinal progenitor cells (RPC) to be used for the treatment of retinal degenerative diseases such as retinitis pigmentosa [141]. The potential of MCs to regenerate retinal structure and functionality after an injury event is an amazing phenomenon to study from an evolutionary point of view as well as for the development of new therapies for neurodegenerative diseases. Regenerative processes have been studied mainly in vertebrate models such as teleost fish and birds [142–144]. The zebrafish retina has the capacity to fully recover in response to various forms of damage. In order for MCs to act in retinal repair the gliotic response must be balanced, implicating three important events: MC reprogramming into a stem cell, proliferation of a derived population of multi-potent glial cells, cell cycle exit and neuronal differentiation [143–145]. The ability of MCs to participate in repairing retinal injury and in regenerating new neurons remains active in postnatal days in chick retina but has been lost in adult birds [142]. Though there has been no in-depth study of the expression of opsins in MCs during regeneration processes in the different models, in fish there is a two-dimensional topographic reconstruction of stereotyped patterns and functionalized regions with expression of cone opsins [146]. Unlike in fish and chick retina, mammalian glia become reactive after injury, leading to damage and vision loss and limited *in vivo* reprogramming capacity; nevertheless, they present progenitor markers and proliferative capacity in culture [143].

The precise role of non-visual opsins in glial cells remains unknown; whether it is associated with a physiological function or with these cells' potential to dedifferentiate into RPC and form new neuronal photoreceptor cells, it opens an interesting avenue of research. As discussed in the following section, all these opsin-expressing MCs show cellular calcium increases in response to light stimulation.

2.5. Müller cells as photodetectors

Opsins have two main components: the chromophore and the apoprotein, the first being a retinaldehyde derived from vitamin A which undergoes photo-isomerization and promotes a conformational change in the second component, a GPCR. Although opsins constitute a monophyletic branch within the GPCR superfamily, the specific type of coupled G protein may vary across different cell types, tissues and species [3,147]. The blue-light sensitive Opn3 is phylogenetically linked to vertebrate visual opsins and teleost multiple tissue (TMT) opsin, which is expressed in teleosts, and both are known to activate the Gi protein cascade, thus decreasing cAMP values [148]. In agreement with this, the expression of chimeric proteins for Opn3 suggests that these opsins could directly modify cAMP concentration [149]; however, Opn3 stimulation in dermal cell types implies PLC activation, intracellular calcium increase and downstream activation of the signaling cascade involving CAMKII, JUNK, p38, ERK and CREB [130,131,135]. Significant changes in somatic calcium levels upon light stimulation reflect a typical characteristic of vertebrate photosensitivity that has been reported in diverse retinal cells such as visual PRCs, ipRGCs and Opn4x-expressing horizontal cells [9,14,20,150–152].

Our attention was drawn to opsin photo-modulation of non-neuronal cell physiology in the context of MC functions and their putative involvement in light detection, since we described the expression of Opn3 and Opn5 in developing chick retina MCs and derived primary MCs cultures [44]. Indeed, by means of intracellular calcium level detection with fluorescent probes and real-time microscopy, we identified for the first time a direct photic response in MCs. In this case, responses to a blue light pulse (20 s, peak at 480 nm) were observed as a >20% increase in intracellular calcium levels, maintained for several minutes after the stimulus (Fig. 2) [44]. The response was shown to be dependent on opsin activation since it could be abolished with the nonspecific opsin antagonist hydroxylamine. Moreover, this response is specific to blue light stimulation, with no increases in calcium levels being observed after red light stimulation (Fig. 2) [43,44]. In accordance with our findings, light stimulation at 480 nm specifically evokes calcium responses in MIO-M1 cells, with no detectable calcium increases after red light stimulation [137], whereas the same blue light stimulus in MU-PH1 cultures evokes heterogeneous calcium increases reaching similar values to those described by our group [140]. Strikingly, blue light activation of astrocytes viral transfected with Opn4 elicits similar responses after at least 20 s of irradiance and lasting for several minutes [153], constituting a new optogenetic research tool for modifying calcium levels in glial cells, resembling the physiological characteristics of calcium mobilization by GPCR in this cell type.

The described intrinsic photic response in MCs is not homogeneous, as three subpopulations within the cultured MCs were identified: High responders (calcium increase greater than 20% of pre-stimulus values), low responders (calcium increase between 10 and 20%); and non-responders (those not responding with an intracellular calcium increase) [43,44]. The majority of cells analyzed (45–50%) were high responders, 40% were non-responders and the remainder low responders. Since our observations indicate that most of the cells express non-visual opsins, the MCs subpopulation responding to light could rely on different active states for the opsin or different signaling cascades not only involving calcium increase (i.e. cyclic nucleotides as described for heterologous expression of opn3 chimeras by Sugihara et al. [149]). Nevertheless, mixed MCs responding/non-responding populations have been described in retinal tissue along development and particularly for calcium responses in MCs. In this sense, the percentage of MCs showing increased calcium levels differs among embryonic stages for different stimuli: glutamate, acetylcholine, and ATP [154,155]. The work by Rosa et al. [154] provides a complete description of a switch in MC responsiveness along retinal development in mice; the two neurotransmitters evaluated (glutamate and acetylcholine) promote differential responses in MCs ranging from no increase to up to a calcium increase of 20% (similar magnitudes to those described in our papers, [43,44]). In line with this evidence, Uckerman et al. [155] indicate a decreased responsiveness in MCs to ATP stimulation along rabbit retinal development. In view of these results, a mixed population of MCs at the embryonic stage considered for our experimental model (E8) cannot be discarded. In addition, different percentages are observed in other non-visual cells with heterologous expression of the non-visual opsin Opn5 [156] or in viral-transfected astrocytes for Opn4 expression [153]. Freitas et al. [157] reported increased calcium levels and high percentages of responding MCs in primary cultures when stimulated specifically with glutathione in the millimolar range. Similarly, we observed a high percentage of MCs responding to the generalized calcium mobilization induced by the ionophore ionomycin (Fig. 2), indicating that differences in MC populations may be related to stimulus specificity. Bearing in mind that we selected the minimum stimulus promoting calcium responses in MCs (20 s 85 μWatt/cm^2; no responses were detected after 10 s illumination, [44]), the presence of different MCs populations could

depend on stimulus characteristics such as duration and energy.

Calcium signaling constitutes an elementary part of glial physiology and cell to cell communication, allowing direct glia-glia signaling via gap junctions and glia-neuron interplay through GPCR-mediated responses [49]. The activation of Gq protein leads to the production of inositol 1,4,5-trisphosphate (IP3) which binds to IP3 receptors on the endoplasmic reticulum membrane, thereby releasing calcium from intracellular stores [49,158]. Nevertheless, calcium increase in glial cells can also be linked to Gi signaling, as is the case with the registered responses after GABA stimulation in astrocytes [159]. Notably, light-evoked responses in MC cultures were suppressed by up to 50% after prolonged incubation with thapsigargin, which inhibits endoplasmic reticulum calcium -ATPase activity and thus depletes endoplasmic reticulum calcium stores; no significant inhibition was achieved by modifying extracellular calcium availability with the calcium chelator EGTA [43]. This would indicate that blue light stimulation in MCs promotes increases in calcium intracellular levels by calcium mobilization from internal stores. Indeed, by combining cytosolic and endoplasmic reticulum calcium fluorescent dyes, we showed a time correspondence for calcium mobilization from internal stores observed as an increase in cytosolic calcium levels along with a calcium decrease in the endoplasmic reticulum [43]. Given that mitochondrial calcium levels were not affected by photic stimulation, light induction of calcium increase in MCs can be clearly confined to a signaling cascade that mobilizes calcium from endoplasmic reticulum [43], and possibly relates to a physiological photo-detection role, as calcium increase in mitochondria has been related to oxidative stress events and apoptotic signaling [160,161].

Overall, the intrinsic photosensitivity of MCs may open a whole new chapter on light-driven responses in retinal physiology and the role of MCs in light-related responses. Indeed, recent evidence indicating pigment regeneration via direct RGR-light detection in MCs points to intrinsic glial photosensitivity controlling retinoids pools independently of the already known metabolic pathways [162]. It is thus plausible to suggest that light-driven intrinsic calcium responses in MCs likely involve a blue-light sensitive opsin that signals for calcium release from the endoplasmic reticulum, though more evidence is required to be able to clearly identify such opsin, the G protein and the signaling cascade mediating blue light responses in MCs.

3. Final considerations

In summary, the stunning diversity of the functional implications of MCs in retinal homeostasis includes their capacity to interact with light; up to now these interactions contemplated only metabolic and physical aspects. We thus propose a novel aspect considering MCs as new light-sensitive components in the chick inner retina like ipRGCs and intrinsically photosensitive horizontal cells., expressing non-visual opsins and therefore intrinsically responding to blue light with calcium mobilization. The functional significance of these calcium-mediated responses remains unclear, along with other open questions: is this intrinsic capacity linked to development or is it retained in the adult retina?; is it related to photopic habits and therefore restricted to diurnal vertebrates?; is it sustained in mammals?; could it represent a new component in retinal circadian entrainment as is the case with astrocytes in the suprachiasmatic nucleus [163]?; would this intrinsic photosensitivity add new aspects to an already known physiological role or does it underpin a whole new chapter of MC functions within the retina? Coming up with answers to these incognita certainly provides an interesting challenge for future research in the field.

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CRediT authorship contribution statement

Natalia A. Marchese: Writing – original draft, Investigation, Formal analysis, Writing – review & editing, Visualization. **Maximiliano N. Ríos:** Writing – original draft, Investigation, Formal analysis, Writing – review & editing, Visualization. **Mario E. Guido:** Writing – original draft, Investigation, Formal analysis, Writing – review & editing.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability

No data was used for the research described in the article.

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