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## Melanopsin-expressing retinal ganglion cells are resistant to cell injury, but not always

Birgitte Georg<sup>a</sup>, Anna Ghelli<sup>b</sup>, Carla Giordano<sup>c</sup>, Fred N. Ross-Cisneros<sup>d</sup>, Alfredo A. Sadun<sup>d, e</sup>, Valerio Carellif<sup>f, g</sup>, Jens Hannibal<sup>a, \*</sup>, Chiara La Morgia<sup>f, g, \*\*</sup><sup>a</sup> Department of Clinical Biochemistry, Faculty Health Sciences, Bispebjerg Hospital, University of Copenhagen, Denmark<sup>b</sup> Department of Pharmacy and Biotechnology, University of Bologna, Bologna, Italy<sup>c</sup> University La Sapienza, Rome, Italy<sup>d</sup> Doheny Eye Institute, Los Angeles, CA, USA<sup>e</sup> Department of Ophthalmology, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA, USA<sup>f</sup> IRCCS Institute of Neurological Sciences of Bologna, Bellaria Hospital, Bologna, Italy<sup>g</sup> Department of Biomedical and Neuromotor Sciences (DIBINEM), University of Bologna, Bologna, Italy

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### ABSTRACT

Melanopsin retinal ganglion cells (mRGCs) are intrinsically photosensitive RGCs deputed to non-image forming functions of the eye such as synchronization of circadian rhythms to light-dark cycle. These cells are characterized by unique electrophysiological, anatomical and biochemical properties and are usually more resistant than conventional retinal ganglion cells to different insults, such as axotomy and different paradigms of stress. We also demonstrated that these cells are relatively spared compared to conventional RGCs in mitochondrial optic neuropathies, i.e. Leber's hereditary optic neuropathy and Dominant Optic Atrophy. However, these cells are affected in other neurodegenerative conditions, such as glaucoma and Alzheimer's disease. We here review the current evidences that may underlie this dichotomy. We also present our unpublished data on cell experiments demonstrating that melanopsin itself does not explain the robustness of these cells and some preliminary data on immunohistochemical assessment of mitochondria in mRGCs.

### 1. Introduction

Melanopsin-expressing retinal ganglion cells (mRGCs) represent the third class of photoreceptors in the retina, the two other being rods and cones. The mRGCs are mainly involved in the non-image forming functions of the eye, with a crucial role in photoentrainment of circadian rhythms (Hannibal et al., 2002; Hannibal, 2002; Berson et al., 2002; Hattar et al., 2002; Do and Yau, 2010). The discovery of the non-image forming system was prompted by the observation that in mice models of retinal degeneration, light was still able to photoentrain circadian rhythms (Foster et al., 1991; Freedman et al., 1999; Lucas et al., 1999), thus the existence of a novel photoreceptor was postulated. In 2002, after identification of the melanopsin photopigment, a G-protein coupled receptor with structural similarities to the opsin family of photoreceptors (Provencio et al., 1998, 2000), converging evidences showed that a small subset of RGCs express melanopsin in their membrane allowing the cells to be intrinsically photosensitive. The mRGCs project to the

hypothalamic suprachiasmatic nucleus (SCN) through the retino-hypothalamic tract (RHT) (Gooley et al., 2001; Hannibal et al., 2002; Hannibal, 2002; Hattar et al., 2002; Berson et al., 2002). The RHT, a monosynaptic anatomical pathway connecting the eye to the SCN (Moore and Lenn, 1972; Sadun et al., 1984; Moore et al., 1995) is now established to originate from mRGCs (Hannibal et al., 2002; Hannibal, 2002; 2004; 2014; Hattar et al., 2002, 2006; Berson et al., 2002). Besides photoentrainment of circadian rhythms, these cells play a role in other non-image forming functions of the eye such as pupil light response (PLR), regulation of melatonin synthesis, mood, sleep, cognition and light-aversion (Legates et al., 2012). In addition, a possible role in visual functions has been proposed (Estevez et al., 2012).

The mRGCs represent less than 1% of the RGCs in humans (Hannibal et al., 2004, La Morgia et al., 2010, 2016; Liao et al., 2016; Dacey et al., 2005). These cells are characterized by a large soma and in humans approximately equal proportions are located in the retinal ganglion cell and the inner nuclear layer (La Morgia et al., 2010). Studies primarily in mice, based on the level of melanopsin expression, den-

\* Corresponding author.

\*\* Correspondence to: C. La Morgia, IRCCS Institute of Neurological Sciences of Bologna, Bellaria Hospital, Italy.

Email addresses: Jens.Hannibal@regionh.dk, j.hannibal@dadlnet.dk (J. Hannibal); chiara.lamorgia@unibo.it (C. La Morgia)

dritic field arborization, physiology and central projections, classified the mRGCs into five subtypes (Baver et al., 2008; Ecker et al., 2010; Schmidt et al., 2011a, 2011b). The best characterized are M1, stratifying in the outermost sublamina of the inner plexiform layer (IPL), the M2 stratifying in the innermost sublamina of the IPL and the bi-stratifying M3 cells with dendrites in both inner and outer sublamina (Schmidt et al., 2011a, 2011b). Melanopsin is expressed primarily in the membrane of the soma and dendrites and even in the axons running within the retinal nerve fiber layer, and the large and imbricated dendritic fields constitute a photoreceptive net in the retina (Provencio et al., 2002; Hannibal et al., 2014, Liao et al., 2016; Hannibal et al., 2017; Nasir-Ahmad et al., 2017).

The mRGCs are characterized by unique photoreceptive properties resembling invertebrate photoreceptors e.g. by depolarization in response to light stimuli and possibly displaying bi- or tristability i.e. not being dependent on other cells for chromophore isomerization (Isoldi et al., 2005; Do and Yau, 2010; Brown, 2016). Melanopsin is maximally sensitive to short wavelength blue light (peak response at 480 nm), and mRGCs present a sustained response to light, which can persist even after the light has been switched off (Do and Yau, 2010). Although mRGCs are independently functioning photoreceptor cells, they receive inputs from rods and cones through amacrine and bipolar cells (Viney et al., 2007; Belenky et al., 2003), thus constituting an "irradiance-detector" system in the eye (Viney et al., 2007; Jusuf et al., 2007; Do and Yau, 2010).

The phylogenetic and ontogenic importance of this cellular system is demonstrated by the fact that melanopsin has been discovered in a number of vertebrate organisms, and that in rodents these cells respond to light at post-natal day 0, long before the classic photoreceptors, i.e. rods and cones are functional (Hannibal and Fahrenkrug, 2004; Sekaran et al., 2005; Tu et al., 2005; Koyanagi and Terakita, 2008; Davies et al., 2010; González-Menéndez et al., 2010). The importance of the melanopsin-based system is supported by the observation that in the subterranean blind mole rat, the circadian photoentrainment persists due to residual presence of mRGCs projecting to brain structures deputed to control circadian rhythms (Cooper et al., 1993; Hannibal et al., 2002; Esquivia et al., 2016). Moreover, there is consistent evidence that mRGCs are more resistant to injury such as axotomy and survive different paradigms of stress (Cui et al., 2015; Rovere et al., 2016) and metabolic dysfunction such as in mitochondrial optic neuropathies (La Morgia et al., 2011). However, in other pathological conditions such as Alzheimer's disease and glaucoma, these cells are affected (La Morgia et al., 2016; Drouyer et al., 2008; Pérez-Rico et al., 2010; Obara et al., 2016; Valiente-Soriano et al., 2015). In this paper, we will review this dichotomy, in addition to present unpublished data on the topic.

## 2. Models of stress and robustness of mRGCs

### 2.1. Optic nerve transection

Hollander and colleagues (Holländer et al., 1985) and von Bussman and colleagues (von Bussmann et al., 1993) reported that a small subset of RGCs survived optic nerve transection. In particular, von Bussman and colleagues demonstrated that this subset (about 1%) of cells had large bodies and were intensively stained with cytochrome *c* oxidase (COX) (von Bussmann et al., 1993), which suggests that mRGCs are the surviving cells; subsequent studies have indeed demonstrated increased resistance of mRGCs to optic nerve transection in rodents (Robinson and Madison, 2004; Li et al., 2008; Nadal-Nicolás et al., 2015; Pérez de Sevilla Müller et al., 2014).

### 2.2. Mitochondrial optic neuropathies

In humans, it has been demonstrated that patients suffering blinding disorders with either extensive damage of rods and cones, as seen in outer retinopathies or certain optic neuropathies, maintained the melatonin suppression response induced by light and the circadian entrainment to the light/dark cycle (Zaidi et al., 2007; Czeisler et al., 1995; Pérez-Rico et al., 2009).

Inherited optic neuropathies due to mitochondrial dysfunction such as Leber's hereditary optic neuropathy (LHON) and dominant optic atrophy (DOA) are both characterized by selective loss of RGCs (Carelli et al., 2004; Yu-Wai-Man et al., 2011). We have studied the mRGC system in these optic neuropathies by evaluating the melatonin suppression response to light in affected LHON and DOA patients. In addition, we have immunohistochemically stained the mRGCs in postmortem retinal and optic nerve specimens from LHON and DOA patients and controls. Both LHON and DOA patients had a melatonin suppression response induced by light comparable to controls, and the immunohistochemistry of retinal and optic nerve specimens revealed that mRGCs were preferentially spared compared to non-mRGCs (La Morgia et al., 2010). The observation that mRGCs are relatively spared in mitochondrial optic neuropathies explains the maintenance of the pupillary light reflex (PLR), a peculiar and previously unexplained clinical feature of LHON (Bremner et al., 1999; La Morgia et al., 2010, 2011). Other studies have subsequently confirmed these findings by assessing the PLR (Kawasaki et al., 2010; Moura et al., 2013; Nissen et al., 2015). Furthermore, a mouse model with rotenone-induced optic neuropathy mimicking LHON was also shown to maintain the PLR (Zhang et al., 2006).

Perganta and colleagues showed preservation of mRGCs in a mouse model of DOA (B6; C3-*Opa1*<sup>Q285STOP</sup>) (Perganta et al., 2013). Strikingly, the mRGC preservation in another DOA mouse model (B6;C3-*Opa1*<sup>329-355del</sup>) persisted after breeding with melanopsin deficient mice (*OPN4*<sup>-/-</sup>) proving that mRGC resistance seems to be independent from melanopsin expression (González-Menéndez et al., 2015).

Overall, these observations suggest that mRGCs may have specific properties that make them more resistant to neurodegeneration in mitochondrial optic neuropathies.

### 2.3. Other injuries

Other evidences of mRGC robustness are provided by studies on cell toxicity to monosodium glutamate (Chambille and Serviere, 1993; Hannibal et al., 2001) and NMDA-induced excitotoxicity (DeParis et al., 2012). The robustness of mRGCs to other different stressful insults remains, however, an open question, which needs specifically dedicated studies.

## 3. Models of mRGC vulnerability and loss

### 3.1. Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the occurrence of circadian and sleep dysfunction even in the early stages (Mattis and Sehgal, 2016). The presence of neuronal loss and AD pathology has been reported in the SCN of AD patients (Swaab et al., 1985; Stopa et al., 1999; Harper et al., 2008). Moreover, a recent longitudinal study demonstrated that sleep fragmentation is correlated to neuronal loss in the SCN in AD patients (Lim et al., 2014).

Optic neuropathy has also been described in AD, as confirmed by both histological and optical coherence tomography (OCT) studies (Hinton et al., 1986; Coppola et al., 2015). We recently demonstrated that mRGCs are lost and affected by amyloid AD pathology in post-

mortem retinas of AD patients, possibly contributing to the circadian dysfunction observed in AD (La Morgia et al., 2016). Thus, in AD mRGCs are vulnerable to amyloid pathology. Interestingly, the mRGC loss in AD occurred even with a completely normal count of conventional RGCs, pointing to a primary AD pathology selectively affecting these cells (La Morgia et al., 2016).

### 3.2. Glaucoma

Glaucoma is a common ocular degenerative disease that affects primarily the inner retina. Reports on mRGCs in glaucoma are contradictory. An initial study pointed to mRGC resistance in an animal model of glaucoma (Li et al., 2006), while another study reported that mRGC are lost with disease progression, possibly in relation to increased intraocular pressure (IOP) in older animals (Zhang et al., 2013). However, in other rodent models mRGCs are reported to be vulnerable to IOP damage to the same extent as conventional RGCs (Drouyer et al., 2008; de Zavalía et al., 2011) and recently, in experimental rat and mouse glaucoma models, a 50% loss of mRGCs was described (Vidal-Sanz et al., 2015). Similarly, human functional studies investigating PLR and light-induced nocturnal melatonin suppression in glaucoma patients have reported reduced responses in patients compared to controls suggesting a vulnerability of mRGCs in glaucoma (Gracitelli et al., 2016, 2015, 2014; Kelbsch et al., 2016; Pérez-Rico et al., 2010; Nissen et al., 2014; Rukmini et al., 2015). However, in a severely affected glaucoma patient Zhou and colleagues showed persistence of the PLR implicating the survival of mRGCs despite the severe optic neuropathy (Zhou et al., 2014). We have recently shown, that mRGCs are reduced in severe glaucoma compared to age-matched controls, but with a relative sparing of displaced mRGCs (Obara et al., 2016).

Overall, the large majority of studies point to some vulnerability of mRGCs to glaucomatous damage leading to the occurrence of circadian rhythm dysfunction. Noticeably, a higher prevalence of glaucoma has been reported in AD (Bayer et al., 2002) compared to controls, and the pattern of optic nerve fiber loss in AD resembles that described in glaucoma (La Morgia et al., 2016).

### 4. Hypothetical mechanisms of mRGC resistance in mitochondrial optic neuropathies

The specific vulnerability of conventional RGCs in mitochondrial optic neuropathies, leading to optic atrophy, is currently ascribed to the long intraretinal unmyelinated axonal segment of the RGCs (Carelli et al., 2004; Yu-Wai-Man et al., 2011; Sadun et al., 2013). In humans, this unmyelinated axonal segment is needed for transparency of the retina to light. It has been argued that a byproduct of this anatomical feature is the exposure of RGCs to the damaging effect of light, in particular to short wavelength blue light (Osborne et al., 2014). However, there is more compelling evidence that non-myelinated membrane is metabolically expensive and the rate of RGC axonal degeneration can be mathematically modeled precisely taking these features into account (Pan et al., 2012). Within the RGC population, the subset of mRGCs may better cope with light due to the expression of melanopsin. Thus, a logical first hypothesis for mRGC resistance to mitochondrial dysfunction is the natural protection provided by the melanopsin photopigment. However, a recent study by Gonzalez-Menendez and collaborators provided evidence that mRGC resistance persists in an animal model of DOA despite the lack of melanopsin expression (González-Menéndez et al., 2015). We also tested the possible protective role of melanopsin using an in-vitro human cell model and here report these previously unpublished results. In addition, we evaluated the mitochondrial abundance in mRGCs and conventional RGCs by immunohistochemistry on human retinal sections.

#### 4.1. Experiments with HEK-hMel cells

We hypothesized that expression of melanopsin, specific to mRGCs, may be responsible for their metabolic robustness. To test if melanopsin expression indeed influences cell viability in different stressful paradigms, we used the human embryonic kidney cell line HEK-293 modified to stably express human melanopsin under the control of a tetracycline-sensitive promoter (HEK-hMel) (Georg et al., 2014). The experiment was performed with cells either in the presence or absence of 1 µg/mL tetracycline that elicits maximal melanopsin expression. The cells grown in absence of tetracycline and, thus, not expressing melanopsin served as controls. The effect of pro-oxidant challenge with rotenone or tert-butyl-hydroperoxide (TBH) on survival of the cells was evaluated by the sulforhodamine B (SRB) absorbance, as previously described (Porcelli et al., 2009). Rotenone is a respiratory complex I inhibitor, which induces ROS production within mitochondria, thus simulating the pathological condition determined by the LHON mtDNA mutations. TBH induces a cytoplasmic increase of ROS, representing a different paradigm of ROS exposure. Fig. 1 shows results of experiments ( $n = 3$ ) performed during darkness. We applied increasing concentrations of rotenone (0.5 µM; 2.5 µM; 5 µM) or TBH (50 µM; 200 µM) to the cells either expressing or not melanopsin, and both in the presence or absence of the chromophore retinal (5 µM). Fig. 1 shows that increasing concentration of both rotenone and TBH, as expected, affected cell survival negatively. However, expression of melanopsin did not influence significantly cell survival nor did the presence of the chromophore retinal.

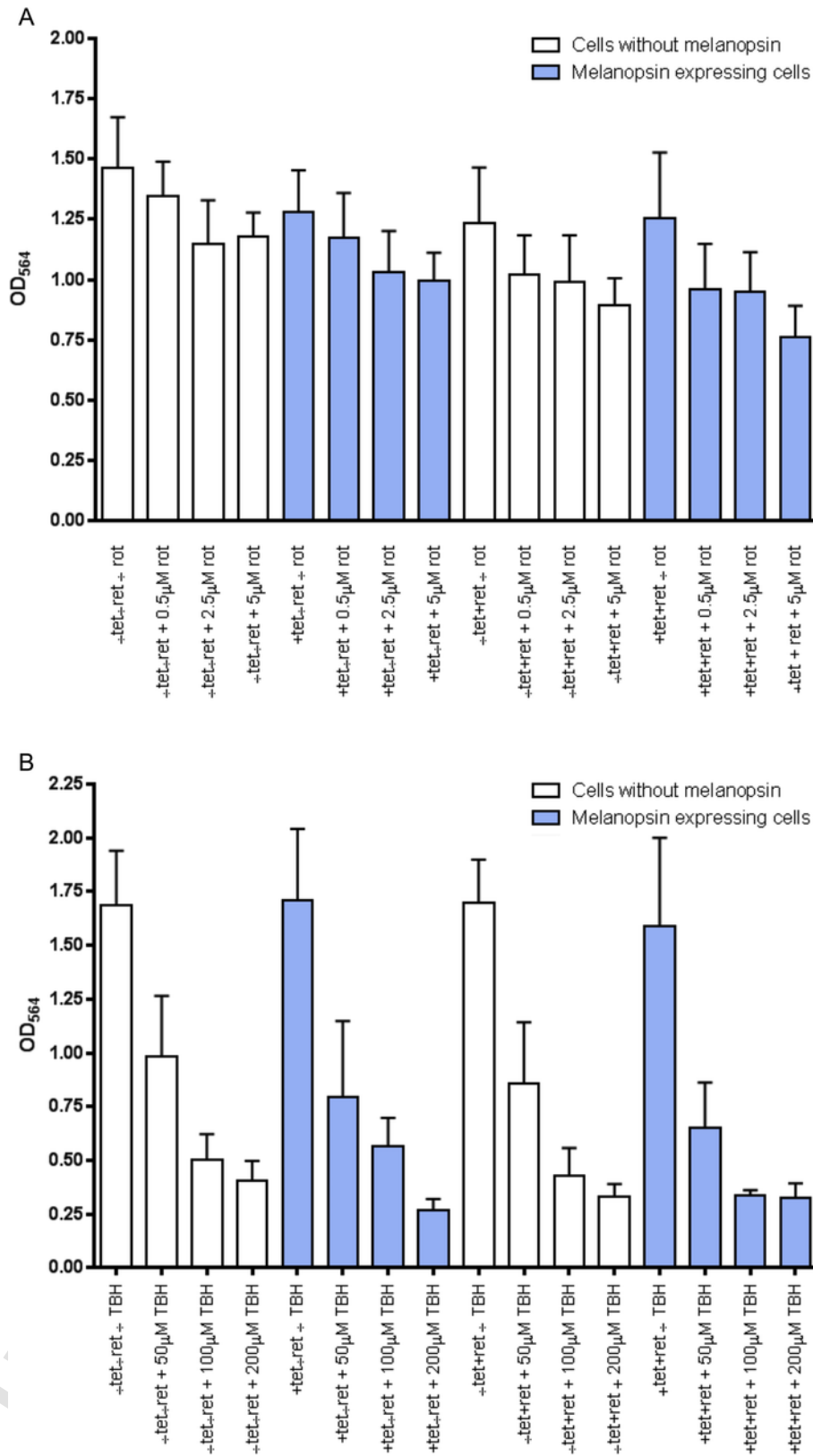
To test whether exposure to light affected cell viability during oxidative stress, we exposed the cells to either white or blue (480 nm) light for 30 min during rotenone or TBH challenge. We obtained similar results irrespective of wavelength. Fig. 2 shows the results obtained by exposing the cells to blue light. Fig. 2A shows the results obtained with rotenone and 2B those with TBH.

#### 4.2. Immunohistochemistry assessment of mitochondria in mRGCs

To assess the abundance of mitochondria in mRGCs and conventional RGCs we performed immunohistochemical analysis on post-mortem ocular specimens from a LHON (male, aged 52) and a control (male, aged 59). Serial formalin-fixed paraffin-embedded retinal sections were stained either with antibodies against melanopsin (La Morgia et al., 2010) or against a mitochondrial extract (UCS Diagnostic), the mitochondrial respiratory chain enzyme subunits ND6 (Mitosciences) and the mitochondrial anti-oxidant enzyme superoxide dismutase (SOD2, Stressgene). As we show in Fig. 3, the mRGCs were heavily stained with antibodies against mitochondrial proteins, suggesting a high cellular content of mitochondria, perhaps even higher than conventional RGCs.

### 5. Conclusions and future directions

The photopigment melanopsin was our initial candidate for conferring mRGC resistance to metabolic injury, associated with mitochondrial dysfunction in inherited optic neuropathies such as LHON and DOA. According to the hypothesis put forward by Osborne and colleagues (Osborne et al., 2014), the melanopsin that allows for the intrinsic photosensitivity of mRGCs, may also protect the cells by quenching against damaging effects of light. The conventional RGCs may be more vulnerable in conditions characterized by mitochondrial dysfunction. However, there are accumulating evidences against a major role of melanopsin in mRGC resistance to injury. In fact, the DOA mouse model crossed with *OPN4*<sup>-/-</sup> mouse, thus lacking melanopsin expression, still maintains intact the mRGC subpopulation, which survives mi-



**Fig. 1.** Effect of Rotenone and TBH on HEK cell survival during darkness. Panel A shows the effect of increasing concentrations (0.5 μM, 2.5 μM and 5 μM) of rotenone on cell survival. White and blue bars are results of control cells and melanopsin expressing cells, respectively. Left and right half of the figure shows results obtained in the presence or absence of the chromophore retinal, respectively. Panel B shows the effect of increasing concentrations (50 μM, 100 μM and 200 μM) of TBH on cell survival. White and blue bars are results of control cells and melanopsin expressing cells, respectively. Left and right half of the figure shows results obtained in the presence or absence of the chromophore retinal, respectively. Each bar shows the mean ± SEM (n = 3). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

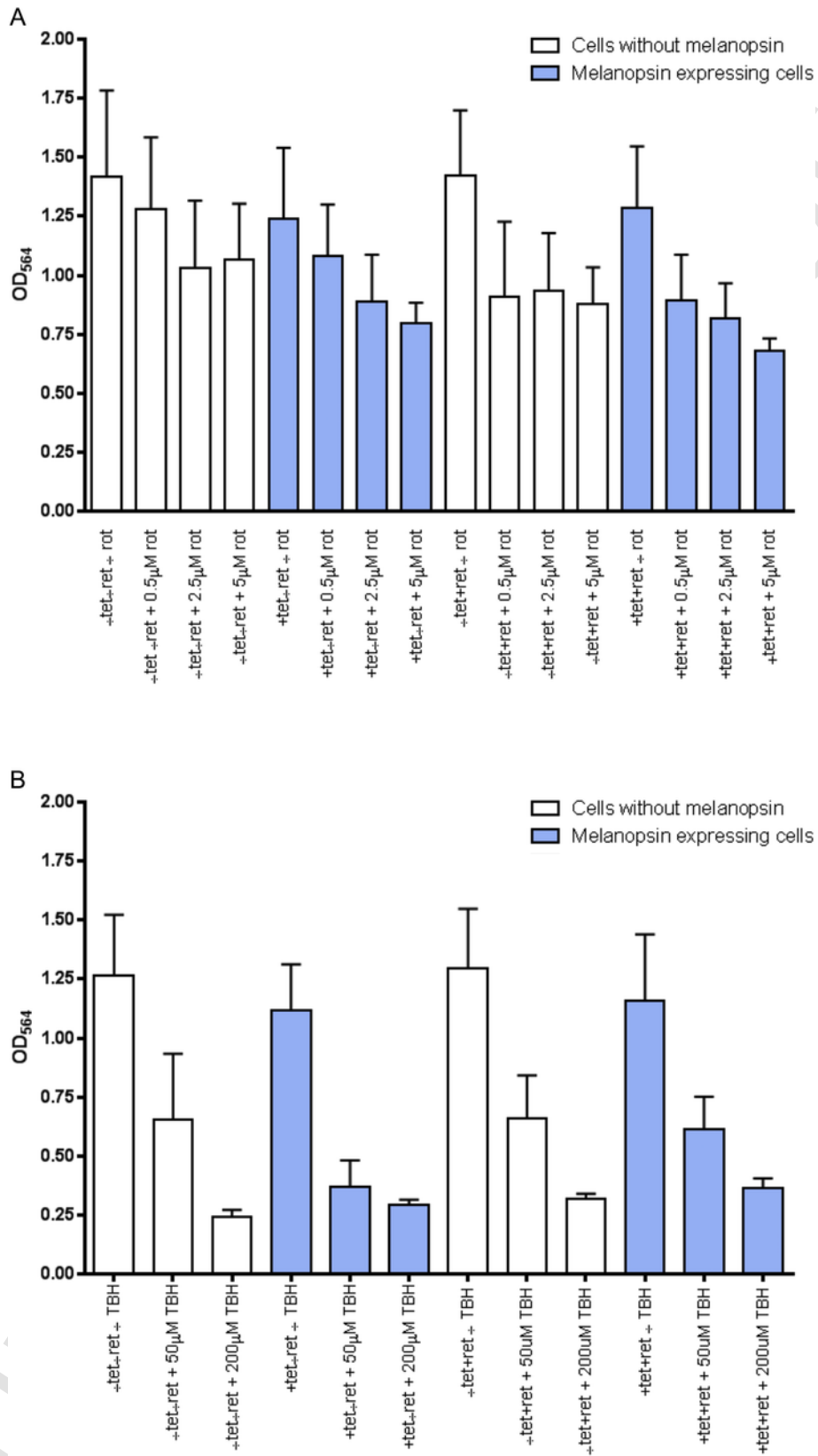
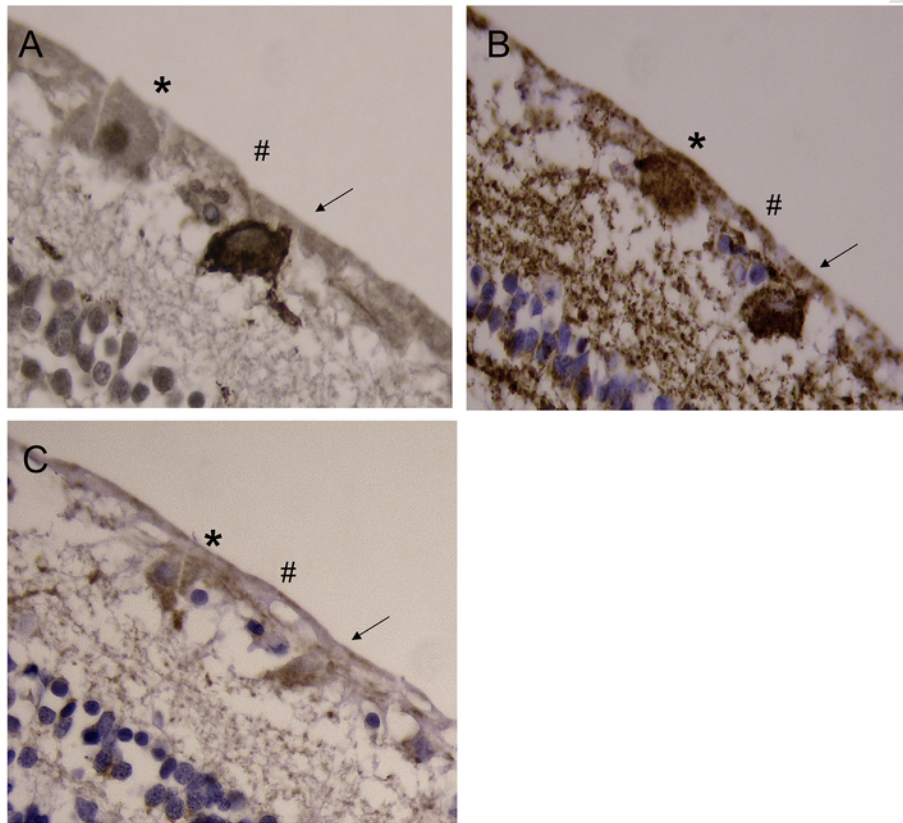


Fig. 2. Effect of Rotenone and TBH on HEK cell survival after light exposure. Panel A shows the effect on cell survival of increasing concentrations (0.5 μM, 2.5 μM and 5 μM) of rotenone. White and blue bars are results of control cells and melanopsin expressing cells, respectively. Left and right half of the figure shows results obtained in the presence or absence

of the chromophore retinal, respectively. Each bar shows the mean  $\pm$  SEM ( $n = 3$ ). Panel B shows the effect on cell survival of increasing concentrations (50  $\mu$ M, 100  $\mu$ M and 200  $\mu$ M) of TBH. White and blue bars are results of control cells and melanopsin expressing cells, respectively. Each bar shows the mean  $\pm$  SEM ( $n = 6$ ). To test whether melanopsin affected cell survival during oxidative stress, we exposed cells to light for 24 h. Similarly to the previous experiment, cellular expression of melanopsin did not change cell viability during long light exposures (data not shown). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



**Fig. 3.** Immunohistochemistry assessment of mitochondria in mRGCs. Serial retinal sections immunostained with antibodies against melanopsin (A), a mitochondrial extract (B), and the mitochondrial respiratory chain subunit ND6 (C), counterstained by haematoxylin to highlight the nuclei. Asterisk and hash indicates respectively large and small conventional RGCs, mRGCs are highlighted by arrow. Both large conventional RGCs and mRGCs stain heavily with mitochondrial antibodies (original magnification 40  $\times$ ).

tochondrial dysfunction without melanopsin (González-Menéndez et al., 2015). Similarly, our in-vitro results using the HEK-hMel cell model with inducible expression of melanopsin and under different paradigms of light and stress exposure, clearly showed a lack of protective effects of melanopsin on cell viability. Thus, the mechanisms providing mRGC robustness to injury, in particular to mitochondrial dysfunction, must be different. Furthermore, our data on human retinal specimens showing that mRGCs are metabolically active with abundant mitochondrial mass may have another interpretation. The abundant mitochondrial population may reflect some compensatory and possibly even protective effect in impaired mitochondria. This has been recently suggested by the compensatory role exerted by mitochondrial biogenesis in regulating LHON penetrance (Giordano et al., 2014). Alternatively, the high mitochondrial activity in mRGCs may also indicate that they are deeply energy-dependent and, thus, potentially vulnerable to mitochondrial dysfunction, as suggested by the reported role of calcium management in mRGCs (Peinado et al., 2015; Kumbalasiri et al., 2007; Hartwick et al., 2007). A further point of discussion relates to the differential vulnerability of mRGCs in view of the vulnerability of small axons in mitochondrial optic neuropathies (Pan et al., 2012). Remarkably, the vast majority of mRGCs are characterized by large cell bodies (Hannibal et al., 2004) putting them in the category that is naturally preferentially spared in LHON and DOA (Sadun et al., 2000). There is clearly a need for further studies specifically addressing mitochondrial metabolism in mRGCs and its relationship with calcium and photoreception.

Another natural candidate, besides melanopsin, for mRGC neuroprotection, is the neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP). This neuropeptide is selectively expressed by mRGCs and not by conventional RGCs (Hannibal et al., 2002; Hannibal, 2006) and there is evidence for its possible role in mRGCs robustness.

Recently, one more hypothesis has been put forward to explain mRGC robustness specific to injuries such as axonal transection. Such survival seems to be limited to selective subtypes of mRGCs, in particular the M1 subpopulation, which has collateral projections into the retina, iris and ciliary marginal zone (Joo et al., 2013; Schmidt et al., 2013; Semo et al., 2014). These collateral axons may provide a reservoir for trophic support of the mRGCs after transection of the main axon. The corollary of this hypothesis would be that surviving mRGCs should be mostly M1 also in mitochondrial optic neuropathies, thus we are currently investigating this issue in retinas from LHON and DOA patients.

The proven vulnerability of mRGCs in AD may turn out to be a more general feature of neurodegeneration associated with accumulation of misfolded proteins. In this regard, Parkinson's disease (PD) may provide a further model of this pathogenic mechanism, as there is some evidence of alpha-synuclein retinal deposition and circadian disturbances amongst PD patients with non-motor symptoms.

In conclusion, the mRGC system is a fascinating model to further investigate for factors that may mitigate neuronal death in degenerative neurological conditions. We should take advantage of the vagaries of



human diseases to better understand the functions of mRGCs and especially to explore their robustness and vulnerability to injury and neurodegeneration.

## Uncited references

Denis and Cooper, 2008  
Foster, 2005  
Hannibal and Fahrenkrug, 2002

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