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# **Circadian clocks, retinogenesis and ocular health in vertebrates: new molecular insights**

**Running title: Circadian clocks and retinal development**

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## **Conflict of interest**

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## **Authors' contribution**

AB and UB and MPFS wrote the manuscript. AAB and MPFS edited the manuscript.

## **ABSTRACT**

Circadian clocks are cell-autonomous, molecular pacemakers regulating a wide variety of behavioural and physiological processes in accordance with the 24 h light/dark cycle. The retina contains a complex network of cell-specific clocks orchestrating many biochemical and cellular parameters to adapt retinal biology and visual function to daily changes in light intensity. The gene regulatory networks controlling proliferation, specification and differentiation of retinal precursors into the diverse retinal cell types are evolutionary conserved among vertebrates. However, how these mechanisms are interconnected with circadian clocks is not well-characterized. Here we explore the existing evidence for the regulation of retinal development by circadian clock-related pathways, throughout vertebrates. We provide evidence for the influence of clock genes, from early to final differentiation steps. In addition, we report that the clock, integrating environmental cues, modulates a number of pathological processes. We highlight its potential role in retinal diseases and its instructive function on eye growth and related disorders.

**Keywords:** differentiation, photoreceptors, rhythms, eye, retinopathy

## **1. INTRODUCTION**

The evolutionary force exerted by the Earth's 24-hour rotation is responsible for the development of circadian clocks in living organisms. It drives rhythms in physiology and behaviour with an approximate period (circa) of 24 h (Pittendrigh, 1993). These rhythms are endogenously generated by conserved cell-autonomous mechanisms occurring in virtually every life-form from algae to mammals. Their chronic disruption predisposes to the failure of optimum physiological functions across a wide range of organs (Takahashi et al., 2008).

In mammals, the anticipation and response to light/dark (LD) and temperature cycles are regulated by daily rhythms in a variety of physiological functions including hormone levels and sleep (Roenneberg and Merrow, 2016). The 24 h rhythms are controlled by the hypothalamic structure named suprachiasmatic nuclei (SCN), acting as the central pacemaker for the whole body. These rhythms are retained in constant environmental conditions such as constant darkness (Hastings et al., 2018). The LD cycle is the most potent circadian synchroniser and acts via a unique light-sensing system located in the retina: the intrinsically photosensitive (melanopsin-expressing) retinal ganglion cells (ipRGC) transmit light-evoked neurochemical signals to the SCN and direct synchronization for peripheral (secondary) clocks. Indeed, cells of many different tissues and organs (skeletal muscle, heart, liver, kidney, bone/cartilage, among others) have such intrinsic secondary circadian clock (Albrecht, 2012). These drive many physiological functions, such as xenobiotic and endobiotic detoxification, carbohydrate and lipid metabolism, renal plasma flow and urine production, cardiovascular parameters, among others. Next to light, both food and body temperature are known to also synchronize circadian rhythms in peripheral tissues (Buhr et al., 2010; Damiola et al., 2000).

### ***1.1. The clock machinery***

Circadian clock organization at the cellular level is conserved across vertebrates (Bell-Pedersen et al., 2005; Dunlap, 1999). The functioning of circadian clocks is directed by clock gene-encoded

transcription factors, mainly CLOCK, BMAL1, PER1, PER2, CRY1, CRY2. They interact closely in interlocked transcription/translation feedback loops. The CLOCK and BMAL1 proteins bind the E-box enhancer element of clock genes Period (*Per*) 1-2 (Shearman et al., 1997) and Cryptochrome 1–2 (*Cry* 1–2) (Kume et al., 1999), as well as that of Clock-Controlled Genes (CCG) and stimulate their expression (Koike et al., 2012) (Figure1). The translocation of PER1-2 and CRY1-2 heterodimers back into the nucleus forms the primary core negative feedback loop, thus inhibiting CLOCK/BMAL1 transcriptional activity and hence the expression of *Per* and *Cry* genes [reviewed in (Takahashi, 2017)]. A second feedback loop involves the action of retinoic acid-related orphan nuclear receptor (ROR) and REV-ERB proteins, whose expression is also activated by CLOCK/BMAL1. ROR and REV-ERB factors in turn regulate transcription of *Bmal1* and distribute rhythms to CCG via ROR binding elements (RORE) (Preitner et al., 2002; Sato et al., 2004). In summary, the generation of tissue-specific rhythmic gene expression programs involves a two-branched process: (1) direct transcriptional activation of CCG due to the cumulative response of clock factors and tissue-specific regulators, and (2) indirect effect originating from the transcription factors that are clock targets (Miller et al., 2007). In this complex clockwork, *Bmal1* is the only canonical clock gene whose deletion or mutation causes a complete loss of circadian rhythmicity (Bunger et al., 2000). The circadian core clock machinery is very similar between SCN and secondary oscillators, with slight differences. Besides, it profoundly influences tissue-specific gene expression programs throughout the body. For instance, the diurnal gene expression profiles isolated from 64 different central and peripheral tissues (including the eye) in the young male baboon, established that up to 81.7% protein-encoding genes display daily rhythmic expression in at least one organ (Mure et al., 2018).

Among targets of the molecular clock, genes related to cell cycle regulation have been particularly well documented (Hunt and Sassone-Corsi, 2007). An intimate connection between the circadian clock, the cell cycle, and developmental processes has been reported but this phenomenon remains only partially characterized [reviewed in (Brown, 2014)]. This question has been partly addressed in the vertebrate

retina, a tissue at the interface with the environment, in which the interaction between lighting conditions, clock function and development are particularly interesting to investigate.

### **1.2. *The circadian clock in the retina***

The neural retina is a fascinating heterogeneous tissue composed of a multitude of cell types, including glial cells and very specialized neurons such as the photoreceptors (PR). It is organized into three discreet cellular layers separated by synaptic (plexiform) layers and distinguished by the presence of specific cell types: the Outer Nuclear Layer (ONL) harbours the (cell bodies and nuclei of the) rod and cone PR; the Inner Nuclear Layer (INL) contains bipolar (BC), horizontal (HC), amacrine (AC), and (displaced) ganglion cells as well as nuclei of Müller glial cells (MGC) that stretch over several layers; and the Ganglion Cell Layer (GCL) contains large ganglion and (displaced) AC (Rodieck, 1973). At the back surface of the retina lies the Retinal Pigmented Epithelium (RPE) a non-neural layer of pigmented epithelial cells. All investigated retinal cells were shown to integrate and orchestrate circadian oscillations (Figure 2). Such organisation implicates the retina in anticipating the environmental dawn/dusk cycles. During the early 80s, the circadian clock was found in both frog and avian eye (Besharse and Iuvone, 1983; Underwood et al., 1990). This clock was later shown to be located into light responsive cells of the retina, namely PR, and to drive rhythms of melatonin production, the core hormone of circadian rhythms (Cahill and Besharse, 1993; Thomas et al., 1993). Later, an autonomous clock was also evidenced in chick early embryonic, post-mitotic RGC, based on their capacity to generate self-sustained rhythms in arylalkylamine *N*-acetyltransferase (AA-NAT: the enzyme catalysing the penultimate step in melatonin biosynthesis) expression (Garbarino-Pico et al., 2004b), metabolic labeling (Garbarino-Pico et al., 2004a) and melatonin (Contin et al., 2006).

In mammals, the existence of an independent circadian clock in the retina was suggested by experiments in animals with SCN lesions or severed optic nerves (Reme et al., 1991; Terman et al., 1993). The rhythm of melatonin release in cultured neural retinas of the golden hamster, and the functionalities of this rhythm finally established the mammalian retina as a bonafide circadian pacemaker: free-running in constant darkness, entrainment by light, and temperature compensation

(Tosini and Menaker, 1996, 1998). Data from the literature suggest that the retinal clock controls the timing of a broad range of essential physiological and metabolic functions in the mature retina, allowing adaptation of vision to the daily changes in light intensity [for review, see (Besharse and McMahon, 2016; Felder-Schmittbuhl et al., 2018)]. More precisely, 90% of the (2670) genes that are rhythmically expressed in mouse eyes under LD condition undergo an alteration of their rhythmic mRNA levels in the *Bmal1* knock out (KO). These results indicate that even in the directly light-sensitive retinal tissue, the circadian clock mediates synchronization of gene expression programs by the LD cycle (Storch et al., 2007). Thus, the retina contains a unique combination of a circadian clock, light-entrainment capacity and multiple clock target outputs. The cellular diversity of the mammalian retina, with significant dissimilarities in the clock gene expression patterns, phasing, and period between cells/layers, renders it challenging to assess the functioning of this network of circadian clocks at the whole tissue level. Kinetics of clock gene expression, at least in mice, showed that circadian rhythms are also generated in the retinal layers distinct from PR, including the retinal pigmented epithelium (RPE) (Baba et al., 2010; Dkhissi-Benyahya et al., 2013; Gekakis et al., 1998; Hwang et al., 2013; Jaeger et al., 2015; Liu et al., 2012; Milicevic et al., 2021; Miyamoto and Sancar, 1998; Ruan et al., 2008; Ruan et al., 2006; Witkovsky et al., 2003; Xu et al., 2016). However, if rhythms of clock gene expression in whole retinas were mainly retained in constant dark conditions, this was less systematic when pure photoreceptor preparations were studied (Hiragaki et al., 2014; Sandu et al., 2011; Schneider et al., 2010; Tosini et al., 2007b). Nevertheless, rhythms in clock protein expression levels were found sustained in cones, in LD and constant darkness, contrasting with all other retinal cell types investigated in that study (Liu et al., 2012). Finally, it should be kept in mind that when comparing the distinct retinal layers, the more sustained clock gene oscillations appear to be generated in the inner retina (comprising the GCL and INL) (Jaeger et al., 2015; Ruan et al., 2008). Another challenge in the field of retinal clocks has been the characterization of their light entrainment pathway. Initial studies by Ruan and coworkers established the importance of dopamine in the phase shifting effect of light (Ruan et al., 2008). Although the signalling pathways have not been completely clarified, it appears

that entrainment of the mouse retinal clock by light primarily involves rods (visible range) but also neuropsin-expressing ganglion cells (UV light) (Buhr et al., 2015; Calligaro et al., 2019).

Hence, the retinal clock is a complex grid of circadian oscillators distinctly located in different cell layers and actively powered by synaptic connections and gap junctions (Jaeger et al., 2015). However, it is not yet known how such an oscillator network arises during retinal development. Conversely, the importance of clock genes and circadian clocks in retinal development has been rarely investigated.

Here we provide first a summarized description of molecular mechanisms regulating retinal development, second an outline of relevant studies that have investigated how circadian clocks intermingle with gene expression and morphogenesis in the developing retina and eye, and finally experimental evidence for the association between clock dysfunction and eye pathology.

## **2. Retinogenesis - an evolutionary perspective**

Eye development and retinogenesis involve complex gene regulatory networks (GRN) that were characterized thanks to the identification of distinct mutants (Figure 3). Multiple well-conserved transcription factors (TF) tightly regulate expansion and differentiation of neural progenitors during retinal neurogenesis until post-natal development (Heavner and Pevny, 2012; Vopalensky and Kozmik, 2009). They cluster into two major classes providing combinatorial influence on cell-fate specification during retinogenesis: the homeobox-containing class (ex.: *Crx*, *Otx2*, *Pax6*, *Rax*, *Six3/6*, *Vsx2*) and the basic helix-loop-helix (bHLH) TF (ex.: *Atoh7*, *Hes1*, *Hes5*, *Mitf*, *NeuroD*). (i) TF from the homeobox-containing class, whose mutation leads to absence of eyes (anophthalmia) or reduced eye size (microphthalmia) in human (Harding and Moosajee, 2019), control the specification of the optic primordium and regulation of cell proliferation and differentiation (Dyer, 2003; Zagozewski et al., 2014b). For instance, pioneering studies from WJ Gehring and coworkers identified the master control gene *Pax6*, which when mutated leads to human Aniridia, mouse Small eye and *Drosophila* eyeless phenotypes (Quiring et al., 1994). (ii) The bHLH TF ensure, in association with other TF, the competence

states of progenitor cells [reviewed in (Hatakeyama and Kageyama, 2004)]. Additional control by *Shh* (Sonic Hedgehog) and *Notch* signalling specifies distinct cellular subtypes, through the symmetric vs. asymmetric division during the cell cycle [reviewed in (Agathocleous and Harris, 2009)].

Although retinogenesis is highly similar during eye development in many organisms, including chick, mouse and human, the percentage of each cell type in the fully-differentiated retina varies from species to species, suggesting that retinal organization enables species-dependent visual adaptations [reviewed in (Lamb, 2009; Lamb et al., 2009)]. The present chapter describes principal steps leading to the determination of each cell type, based mainly on mouse model [reviewed in (Zagozewski et al., 2014a; Zhang et al., 2011)], with the mention of alternative processes in distinct vertebrates, when applicable. The intermingled GRN of rods and cones will be discussed in a subsequent section. Figure 4 summarizes the information contained in chapter 2.

### **2.1. Towards mature retina: retinal cell fate determination**

The seven major retinal cell types are generated from common progenitors in an extensively conserved order, from ganglion cells (first) to MGC (last). The underlying genetic program is also well conserved among vertebrates and proceeds through a series of steps that increasingly restrict lineage choices and commit cells to a particular fate. One key event is the transition from the proliferating progenitors to cell fate specification. Especially, dynamics of variable *Pax6* expression during the cell cycle appear to play an instructive role in these processes, thus suggesting the cellular diversity in the retina essentially results from the modulation of key TF by extrinsic signalling cues.

The specification of **retinal ganglion cells (RGCs)** requires *Pax6*, *Atoh7/Math5* signalling, *Pou4f2/Brn3b* and *Isl1* activity (Marquardt et al., 2001; Pan et al., 2008; Riesenberger et al., 2009). *Atoh7* turns on ganglion cell development, while repressing the other retinal cell fates through repression of other proneural genes (*Math3*, *NeuroD*, *Ngn2*) (Le et al., 2006; Mu et al., 2005; Stenkamp, 2007; Yang et al., 2003). *Pou4f2* and *Isl1* together drive the ganglion cell differentiation program and also upregulate *Shh*, which maintains RPC proliferation in mice, in contrast with its pro-RGC differentiation effect in

zebrafish (Wang et al., 2005). RGC development also involves the *Dlx1* and *Dlx2* homeobox genes, since their absence leads to increased apoptosis of late born RGC (de Melo et al., 2005). Finally, *Pou4f2* promotes RGC development via an *Atoh7*-independent pathway and induces RGC maturation and survival in the mouse via *Barhl2* activation (Ding et al., 2009).

**Horizontal cell (HC) specification** depends on *Foxn4* ((Li et al., 2004; Marquardt and Gruss, 2002) which provides RPC competence to become HC or AC. Downstream of *Foxn4*, *Ptf1a* and *Hnf6/Oc1* (Onecut1) act together to specify the HC fate (Fujitani 2006, Li 2004, Wu 2013). HC specification also requires *Prox1*, a gene essential for cell cycle exit of early RPCs (Dyer et al., 2003). This followed from depletion of HCs in the *Prox1*-null mouse, and enhanced HC production when misexpressing *Prox1* (Dyer et al., 2003). Additional regulation by *Lim1/Lhx1* appears to control HC positioning (Fujitani et al., 2006; Li et al., 2004; Poche et al., 2007). A similar cascade was reported in zebrafish (Jusuf et al., 2011), frog (Dullin et al., 2007) and chicken retina (Boije et al., 2013; Suga et al., 2009). In particular, the appropriate positioning of HC in the INL involves the *Spalt* family TF *Sall3* (de Melo et al., 2011).

The specification of **amacrine cells (ACs)** depends on *Foxn4* and its downstream targets *Math3* that works along with *NeuroD* (Li et al., 2004). *Math3* and *NeuroD* are essential, yet not sufficient for AC induction (Inoue et al., 2002). Downstream of *Foxn4* AC specification also involves *Ptf1a* (Fujitani et al., 2006; Nakhai et al., 2007). AC differentiation is also regulated by *Pax6* and its activator *Sox2*, which sustain early progenitor populations (Lin et al., 2009). Finally, differentiation of AC subpopulations involves notably *Ptf1a* and *Barhl2* for GABA-ergic cells and glycinergic cells (Ding et al., 2009; Nakhai et al., 2007) and *Isl1* for cholinergic cells (Elshatory et al., 2007).

Specification of the late-born **Bipolar Cells (BCs)** requires both *Mash1* and *Math3* (Tomita et al., 2000). For the sake of completeness, it should be noted here that, before BC development, *Mash1* interacts with *Math3* in RPCs to control the neurogenic-gliogenic balance. In retinal explants, deletion of *Mash1* delays the production of BCs, rods and MGCs, and reduces the number of BCs at the expense of MGCs (Tomita et al., 1996). Another factor playing a crucial role in BC differentiation is a target of *Otx2* (Kim et al., 2008), *Vsx2/Chx10*, as shown by studies based on its mutation in mice (Burmeister et al., 1996;

Koike et al., 2007) and its down-regulation in zebrafish [reviewed in (Boije et al., 2015; Vitorino et al., 2009)].

The most numerous glial cells in the retina, **Müller glial cells (MGC)**, arise from progenitor cells that followed the gliogenesis, not the neurogenesis pathway. A central cue in this process is *Notch* signalling, where *Hes5* promotes glial cell production, whereas *Hes1* maintains progenitor cell fate, notably by inhibiting the proneural *Mash1* gene (Hojo et al., 2000; Takatsuka et al., 2004; Tomita et al., 1996). In addition, *Notch* and *Hes1* are induced early in development by *Rax*, which controls early precursor proliferation and enables differentiation of late born cells (MGC, rods, BC) (Furukawa et al., 2000; Rodgers et al., 2018). The hierarchy of events required for MGC production further involves *Sox8* and *Sox9*, being induced downstream of Notch signalling (Muto et al., 2009). Interestingly, MGC have the capacity to regenerate retinal neurons in amphibians and zebrafish [reviewed in (Hamon et al., 2016)].

## **2.2. Photoreceptor differentiation**

Mature PR handle phototransduction, converting photons to electrical and subsequent neurochemical signals. The general morphology of PR includes the outer segment (OS), the inner segment (IS), the cell body, and the synaptic terminal. Rods and cones are named according to their OS morphology and differ in electrophysiological properties. Both express visual protein pigments, the opsins. Vertebrates have five classes of opsins, a single rod class (RH1) and four cone opsin classes (SWS1, SWS2, RHB/RH2, LWS) that are all expressed in fish and exist in all lineages [reviewed in (Davies et al., 2012)]. Rods are responsible for vision at low light levels/dim light (scotopic vision) and display low spatial acuity. On the contrary, cones are active at higher light intensities (photopic vision) and provide high spatial acuity and color vision. Devoid of red or L-cones, the mouse retina has 5% of “pure” S-cones distributed across the whole retina whereas 95% cones express both M- and S-opsin in a dorso-ventral gradient (primarily S-opsin in the ventral part and M-opsin in the dorsal one) (S, M and L account for Short, Middle and Long-wavelength-sensitive, respectively) (Applebury et al., 2000; Haverkamp et al., 2005).

Evolution has led to strong adaptations of vision. Especially, number, shape and size of PR sub-types, and molecular evolution of opsins differ among vertebrates, in line with the distinct demands of their operating environments. Hence, the timing of specification and differentiation, from PR precursors to distinct mature PR types, may slightly differ from species to species. In mice, cones are generated prenatally, peaking around E15. Rod generation takes place around birth (Brzezinski and Reh, 2015), their differentiation starting from postnatal stage 5 (P5), and rhodopsin expression increasing rapidly. At around P10 OS form and eyes open by P13, after which the retinal visual activity matures (Findlater et al., 1993; Shen and Colonnese, 2016). Despite the functional differences between rods and cones, they share TF and cofactors that mutually regulate each other during specification and differentiation (ex: *NeuroD*, *Otx2*, *Crx*, *Nrl*, *Nr2e3*, *Nrl*, retinoic acid and thyroid hormones). For that reason, this chapter is organized according to the different TF and cofactors involved in the specification of both PR subtypes (reported in Figure 4).

***TF1: Early bHLH gene NeuroD is required for both rods and cones development***

First involved in the neurogenic-gliogenic balance (Morrow et al., 1999), *NeuroD* is essential for rod development in the mouse, as shown by reduction of rods in *NeuroD* deficient mice and enhanced rod differentiation at the expense of BCs after misexpressing *NeuroD* (Morrow et al., 1999). *NeuroD* also regulates cone differentiation, especially by modulating expression of the TR $\beta$ 2 (beta-2 subunit of thyroid receptor) encoding gene (see below) (Liu et al., 2008).

***TF2: Downstream of Otx2, the cone-rod homeobox gene, Crx, is central to PR differentiation***

*Otx2* triggers PR specification and activates *Crx* that will drive the formation of OS and expression of both cone- and rod-specific genes (Furukawa et al., 1999; Livesey et al., 2000; Nishida et al., 2003). In particular, *Crx* activation triggers a transcriptional cascade with consecutive activation of *Rorb* (encoding ROR $\beta$ ), *Nrl*, and *Nr2e3*, which leads to rod production (Corbo and Cepko, 2005; Haider et al., 2001; Jia et al., 2009; Kautzmann et al., 2011; Oh et al., 2007). Interestingly the development of the pineal gland, whose principal melatonin-synthetizing cells are very similar to retinal PR, also involves *Otx2* and *Crx*, thus suggesting a common ancestral origin (Furukawa et al., 1999; Nishida et al., 2003).

Finally the stabilization of the (late-born) rod phenotype involves *Prdm1*, another downstream target of *Otx2* (Brzezinski et al., 2010; Mills et al., 2017; Wang et al., 2014).

**TF3: *Nrl*, a rod specific gene with an evolutionary divergent role**

*Nrl* (neural retina leucine zipper) is a *Maf* family member that is fully rod-specific. In *Nrl*-deficient retinas prospective rods switch cell-fate to become S-cones (Mears et al., 2001). Further studies have emphasized that *Nrl* is responsible for rhodopsin expression (Kumar et al., 1996; Rehemtulla et al., 1996) and activates *Nr2e3* to suppress the expression of cone-specific genes, promoting rod development (Mears et al., 2001; Oh et al., 2008). Unlike human *NRL*, *Xenopus Nrl*, and likely zebrafish *Nrl*, are responsible for lens development (Coolen et al., 2005; McIlvain and Knox, 2007). In the avian lineage *Nrl* has been lost, hence PR differentiation (at least in chicken) involves other members of the *Maf* family: *MafA* for the regulation of the opsin in rods and *MafB* for one of the avian green opsins (Enright et al., 2015). Finally, characterization of the *Nrl* KO mice showed a strong relationship between blue cones and rods specifically in mammals and suggested that *Nrl* evolution was instrumental in the advent of (nocturnal and rod-rich) mammals (Kim et al., 2016).

**TF4: Function of the nuclear receptor *Nr2e3* in PR differentiation**

Rod differentiation relies on *Nrl* and its downstream target *Nr2e3*. Indeed, human *Nr2e3* or *Nrl* induce the differentiation of PR into rods after *in vivo* transfection in *Xenopus*, maximal effect being reached upon co-expression of both factors (McIlvain and Knox, 2007). Some studies in mice reported also that the NR2E3-CRX complex activates rhodopsin, whereas *Nr2e3* alone repressed cone-specific genes (for instance S-opsin) in rods (Chen et al., 2005; Peng et al., 2005). Accordingly, human *NR2E3* mutation leads to enhanced S-cone syndrome (ESCS) associated with blue light hypersensitivity, early onset night blindness, varying degrees of L and M cone vision-loss and retinal degeneration (Haider et al., 2000). A similar phenotype was described in the *rd7* mouse model with *Nr2e3* deficiency: extra S-cones followed by degeneration of both cones and rods, plus other retinal abnormalities (Corbo and Cepko, 2005; Haider et al., 2001).

**TF5-6: Regulation of PR development by Retinoic acid and Thyroid hormones**

Precise timing of PR production and maturation is regulated by members of the nuclear receptor TF family, especially receptors for retinoids and thyroid hormones.

Binding of retinoic acid (RA) to the RA nuclear receptor (RAR) triggers rod specification (Kelley et al., 1994). Closely related to RAR, the orphan nuclear receptors of the ROR family also control PR development: ROR $\alpha$  (encoded by *Rora*), synergistically with CRX, activates transcription of S-opsin gene (Fujieda et al., 2009); *Rorb* gene is required for rod differentiation and function since its absence led to complete rod depletion and over-production of S-cones (Jia et al., 2009). *Rorb* induces expression of *Nrl*, which in turn feeds back positively on *Rorb* (Fu et al., 2014), and expression of *Prdm1* (Wang et al., 2014). *Rorc* gene, as a target of *Rev-Erba/Nr1d1*, is potentially involved in retinal differentiation at E18.5 in the mouse (Haider et al., 2009; Mollema et al., 2011).

The thyroid hormone (TH) plays a crucial role during cone development, since the lack of TR $\beta$ 2 in the mouse leads to depletion of M-opsin expression and concomitant widespread expression of S-opsin in cones (Ng et al., 2001). Hence, TH appears to activate the M-opsin gene and repress the S-opsin gene [as also does RXR $\gamma$  (Roberts et al., 2005)]. In addition, the TH gradient occurring at the latest stages of cone development corresponds to the dorso-ventral gradient of M/S-opsins expression in cones (Roberts et al., 2006). Finally, M-cone development is also regulated by earlier activators of *Thrb*, such as *NeuroD* (Liu et al., 2008) or *Otx2*, which acts in combination with *Hnf6/Oc1* (Emerson et al., 2013). However, the factor inducing cone fate, if any, remains to be identified.

To conclude, retinogenesis is regulated through a finely tuned GRN that is based on an ON/OFF program of several growth factors, TF and hormone signalling pathways. The general mechanism is well conserved among vertebrates, but some features differ between species and reflect species-specific development strategy, adaptations to environment and lifestyle, especially diurnal versus nocturnal animals. For example, AC subtypes are determined by *BhlhB5*, *Isl1* and *Barhl2* in *Xenopus* and mouse (Feng et al., 2006), whereas in human *BHLHB5/BHLHE22* expression is associated with emergence of human BC, thus suggesting divergence of evolutionary pathways between tetrapods and

primates (Mellough et al., 2019). Furthermore, *Nrl* function is required for the development of mammalian rods, whereas it has been lost in the avian lineage and inversely *Nrl* is an important driver of ocular features in both *Xenopus* and zebrafish. Consequently, evolutionary divergence of molecular mechanisms exists during retinal cell differentiation and might be the result of circadian clock-related mechanisms, which are known to be involved in adaptation to environmental lighting conditions.

### **3. Clock genes and clock-controlled genes (CCG) during retinal development**

Much is known presently about the functionality of circadian clocks during adult stem cell renewal, including neurogenesis (Terzibasi-Tozzini et al., 2017). However, when the circadian clock arises during development and how it acts have been long-standing questions (Agrawal et al., 2017; Landgraf et al., 2014; Seron-Ferre et al., 2012; Umemura et al., 2017; Yagita et al., 2010). Clock gene transcripts were repeatedly shown to be maternally inherited but their levels were not rhythmic (Amano et al., 2009; Curran et al., 2008; Dekens and Whitmore, 2008; Hamatani et al., 2004; Johnson et al., 2002).

In zebrafish, asynchronous, endogenously-driven cellular oscillations of the zygotic *Per1* transcript were shown to start by 1 day post-fertilization (dpf). However, global rhythms of *Per1* expression in embryos were only observed when they were exposed to (synchronizing) LD cycles (Dekens and Whitmore, 2008). At these developmental stages, the induction of *Per1* rhythmicity required *Clock* gene, though *Clock* expression levels were constant (Dekens and Whitmore, 2008).

During early stages of development in mice, clock gene expression data indicate that their expression products are not fully matured yet to form a functional circadian circuit (Amano et al., 2009; Dolatshad et al., 2010). Interestingly, in mouse embryonic stem cells (ESC), the all-trans retinoic acid induction towards a differentiated neural fate generates circadian oscillations. Conversely, loss of circadian oscillation is seen during the dedifferentiation of neural stem cells by the four major reprogramming factors (*Oct3/4*, *Sox2*, *Klf4*, and *c-Myc*) (Yagita et al., 2010). Thus, the current idea is that the functional

clockwork machinery begins to operate as soon as embryonic differentiation starts (Umemura et al., 2017).

Nevertheless, a bidirectional co-regulation of the cell cycle and the circadian clock has also been proposed (Feillet et al., 2015). Furthermore, several cell cycle regulators are well-known to be clock-controlled: tumor suppressor *p53*, cyclins (such as *Ccnd1* and *Ccnd1b*), oncogenes like *c-Myc* and *Mdm2*, and *Sox9*, *Itga6*, *Wnt3*, *Smad7*, *Cdk4*, *Lhx2*, *Tcf4*,  $\beta$ -catenin (Fu and Kettner, 2013). It was proposed in zebrafish that the early cycling of the circadian clock, synchronized by the LD cycle, controls the timing of cell division (for instance in the gut and skin (Dekens et al., 2003)). This is also likely mediated by the circadian clock control of cell cycle genes (such as p20 and p21 during the G1 phase and genes expressed at G2/M checkpoint) [reviewed in (Brown, 2014; Laranjeiro and Whitmore, 2014)]. Perhaps surprisingly, the link between cell proliferation and the clock during organ development has been rarely reported in mammals (Bagchi et al., 2020; Li et al., 2007). Hence, the exact mechanisms for clocks to start ticking in early life are yet to be unravelled and the question remains whether circadian clocks are simply an evolutionary or also a developmental process, or both (Brown, 2014; Vallone et al., 2007).

Several cellular processes within the wild-type retina are regulated by clock genes (Figure 2) but the relevance of circadian rhythms during retinogenesis has only been rarely reported. Below we review the studies that have investigated the role of clock genes in the successive stages of retinal development in diverse vertebrates and the potential contribution of the circadian clock in generating the eye and retina.

### **3.1. Clock and clock-controlled genes in retinal progenitors and during cell fate determination**

#### **3.1.1. Clock in early eye development in *Xenopus* and zebrafish**

Insight into very early expression of clock factors has mainly been obtained in vertebrates with embryo transparency and external development such as amphibians and fish, and more recently in human thanks to the development of organoids (Sridhar et al., 2020; Wagstaff et al., 2021).

In *Xenopus*, expression of the *XClock* gene was detected early during gastrulation in the anterior neural plate. It was later found expressed in the neural tube, with highest expression in its anterior part, including developing eyes (Green et al., 2001). Expression of a dominant-negative mutant form of *XClock* during early development in *Xenopus* induced abnormal eye and head development, together with the down-regulation of *Pax6* and *Otx2*, two (in-)direct transcriptional targets [(Morgan, 2002, 2004) also reviewed in (Vallone et al., 2007)]. Conversely, the overexpression of *XClock* gene in this dominant negative *XClock* mutant rescued *Otx2* levels and normal development (Morgan, 2002). Surprisingly, *XClock* expression is also directly upregulated by *Otx2* in *Xenopus* embryos (Green et al., 2001), suggesting a positive feedback loop between the two (Green et al., 2001; Morgan, 2002). Besides *Clock*, expression of *Per* genes was detected in the eye at the late *Xenopus* tailbud stage (stage 31, production of AC and BC), and rhythmic expression of *XBmal1* was determined at stage 41 (when the retina is differentiated and strong expression of rhodopsin is detected in PR layer) (Curran et al., 2008). Whether the early expression of *XClock* in the anterior embryonic region of *Xenopus* helps to coordinate local ontogenesis of the circadian clock with neural patterning remains to be established. Intriguingly, (rhythmic) expression of clock genes *Per3* and *Rev-Erba* was also described in the anterior neural region of the zebrafish embryo including the retina, already during the second to fifth day post fecundation (dpf) (when pigments are produced in the RPE) (Delaunay et al., 2000). Similarly, highest expression of *Clock1* and *Per1* transcripts occurred in the anterior region of embryos on second dpf (Dekens and Whitmore, 2008).

### **3.1.2. The clock during cell cycle and cell fate determination in the developing mouse retina**

In mouse eyes, expression of most clock genes has been detected as early as E13 and shows gene-specific and temporal regulated expression throughout development, until adulthood (Bagchi et al., 2020). Interestingly, in line with developmental events in zebrafish (described above), alteration of clock gene expression by knocking out *Bmal1* and *Per1/Per2* in genetically modified mice leads to cell cycle defects in the eye/retina (Bagchi et al., 2020; Sawant et al., 2019). Indeed, double mutation of

*Per1* and *Per2* genes decreases expression of cell cycle genes whereas it increases that of phototransduction genes at P3 (Bagchi et al., 2020). In contrast, retina-specific (driven by a *Chx10-Cre*) loss of *Bmal1* during retinogenesis increased the number of cells entering the S-phase at E15 and reduced the number of cells exiting the cell-cycle (Sawant et al., 2019). This, most likely, underlies the observed reduction in early retinal (ganglion and amacrine) cell types observed in the same study (see below). This aspect was not specifically investigated in the *Per1*<sup>-/-</sup> *Per2*<sup>Brdm1</sup> mutant mice, but it is interesting to speculate that the observed increase of markers of late-born (rod) cells may be associated with a potential reduction in proliferative capacity (Bagchi et al., 2020). Taken together, the aforementioned studies suggest that the clock is important for the timing of cell division during mouse retinal development and, when this is not optimal, cell fate specification is disturbed. It is also noteworthy from these studies that impairment of *Per1/Per2* vs *Bmal1* genes in mouse retina likely exerts opposite effects on precursor proliferation (respectively, decrease vs increase) (Bagchi et al., 2020; Sawant et al., 2019). In the molecular clockwork, *Per1/Per2* and *Bmal1* are involved in opposite regulatory arms and act, respectively, as repressors and activators of E box-containing promoters. Thus, it is possible that the effect on cell division is a result of opposite regulatory effects. Importantly, these data also suggest that a molecular clockwork involving negative feedback between PER1/PER2 and BMAL1:CLOCK (or BMAL1:NPAS2) is already at play early in retinal development (Bagchi et al., 2020; Sawant et al., 2019) (model proposed in Figure 5). We previously hypothesized that extinction of cell cycle genes in the *Per1/Per2* mutant might be due to dysregulation of the Wnt and Hippo pathways (Bagchi et al., 2020). Although this link remains to be demonstrated in the retina, a strong interaction between Wnt signalling and the clock has been repeatedly documented, for instance in adipogenesis or myogenesis (Chatterjee et al., 2013; Chatterjee et al., 2019; Guo et al., 2012).

As mentioned above, clock gene deletion affects cell fate determination in the early developing retina, an effect linked to disturbed precursor proliferation (Sawant et al., 2019). Indeed, Sawant and coworkers found reduced numbers of early-born cells in the *Bmal1* KO, between the mouse E15 and P9 stages, namely *Brn3b*-expressing RGCs and a subset of ACs (Calretinin+ and Choline

acetyltransferase-ChAT+). Conversely, they observed increased numbers of late-born cells, such as (recoverin+) type II cone BCs and (Sox9+) MGCs. In addition, MGCs were partially mislocalized into the ONL, leading to lamination defects in the retina (Sawant et al., 2019). This lack of *Bmal1* also leads to the abnormal presence of stunted dendritic processes of rod BCs already at 1 month, thus suggesting that clock dysfunction also alters rod BCs development (Baba et al., 2018a).

### **3.2. Clock and clock-controlled genes during photoreceptor differentiation**

Lighting conditions are suggested to regulate the dynamics of rod differentiation. For instance, mice pups (P5, P10, P17, P24) raised in constant darkness show alteration of rod development, visual function, and TH-induced-rhodopsin expression. Thus, light exposure and, most likely, circadian regulation, are both important during PR development, as early as P5 (Sawant et al., 2015). Through several well-documented examples described below, we provide an overview of the accumulating evidence that both the central and the secondary regulatory loops of the molecular clock play a role in PR differentiation.

#### **3.2.1. The circadian clock regulates cone spectral identity in rodents**

In mice, several studies have shown that the circadian clock is involved in cone differentiation. For instance, in a PR-specific deletion of *Bmal1* (*Crx-Cre* driven), S-opsin expression was abnormally distributed over the whole retina and the number of M-opsin expressing cones was significantly reduced (Sawant et al., 2017). Approximately the same patterning was seen in *Clock* KO mice (Sawant et al., 2017). Similarly, *Per1*<sup>-/-</sup> *Per2*<sup>Brdm1</sup> mutant mice, that have a global clock defect with arrhythmicity in constant dark conditions (Zheng et al., 2001), are characterized by a number of developmental anatomical/histological eye defects. They display a reduced dorsal territory of blue cones, classically abundant in the ventral part of the retina. This is associated with reduced global mRNA expression of S- and M-opsin measured in whole retinas (Ait-Hmyed et al., 2013). Taken together, these data strongly suggest that the dorso-ventral distribution of cones is indeed regulated by the circadian clock.

Further experimentation, with KO mice and chromatin immunoprecipitation (ChIP), has suggested that *Dio2* (the gene encoding TH-activating enzyme, type 2 iodothyronine deiodinase, which converts T3 to T4 form of TH) is the transcriptional target of BMAL1 during cone differentiation. Partial reversion of the *Bmal1* KO phenotype by T3 supplementation further provided evidence that the clock might regulate the cone-opsin gradient through TH signalling (Sawant et al., 2017). In this hypothesis, the dorso-ventral gradient of T3, the active form of TH, would be further enhanced by the induction of *Dio2* expression. No effect on *Dio2* mRNA was observed in the transcriptome analysis of the *Per1*<sup>-/-</sup> *Per2*<sup>Brdm1</sup> mutants, potentially because the study was performed (E15 to P3) before the induction of M-opsin expression, by P5 (Bagchi et al., 2020). As the level of S-opsin expression appears to also be regulated by the *Per2* gene (Sawant et al., 2017), it confirms the results in the *Per1*<sup>-/-</sup> *Per2*<sup>Brdm1</sup> mutants where retinal S-opsin mRNA levels are decreased (Ait-Hmyed et al., 2013) (model proposed Figure 5).

### **3.2.2. *Rev-Erbs and Rors* are at the interface between circadian clock and PR differentiation**

In mammals, the main TF regulating the expression of PR genes are CRX, NRL, and NR2E3. A complex between NRL, NR2E3, CRX and REV-ERB $\alpha$ /NR1D1 has been shown to activate, *in vitro*, the expression of rod phototransduction genes, namely those coding for Rhodopsin (*Opn2*) and the alpha subunit of rod transducin *Gnat1* (Cheng et al., 2004). Another example based on ChIP analysis from P2 and P21 C57BL/6J mouse eyes provided evidence that *Rev-Erba/Nr1d1* is itself a direct target of NR2E3, suggesting that *Rev-Erba/Nr1d1* and *Nr2e3* function in the same transcriptional network during PR development (Haider et al., 2009). Interestingly, in the degenerating retina of the *Nr2e3*-deficient *rd7* mouse, *in vivo* rescue experiments pointed to *Rev-Erba/Nr1d1* as a candidate modifier gene for *Nr2e3* (Cruz et al., 2014). Furthermore, during retinal development NR2E3 and REV-ERB $\alpha$ /NR1D1 co-target phototransduction genes, such as Recoverin (*Rcvn*), whose expression is rhythmic in LD and under constant dark conditions (Mollema et al., 2011; Storch et al., 2007). Knock down of *Rev-Erba/Nr1d1* induces pan-retinal spotting of the fundus associated with reduced light response as measured by electroretinography, but no obvious alteration of PR (Mollema et al., 2011). Neither did *Rev-*

*Erba/Nr1d1* KO mice show morphological PR defects, whereas they displayed altered light responses (Ait-Hmyed Hakkari et al., 2016). Another standing question is whether the *Nr2e3/Rev-Erba* common signalling pathway has a link with a circadian clock controlling PR development. It is worth noting in this respect, that in fruit flies the orthologs of *Nr2e3* and of *Rev-Erba/Nr1d1* together contribute to circadian clock function in the neuronal pacemaker, as shown in relevant fly mutants (Jaumouille et al., 2015).

During retinal development, the ROR clock factors have also been described as early actors (described above). Loss of *Rora* and *Rorb* in mice leads to, respectively, defective cone differentiation and complete depletion of rods (Fujieda et al., 2009; Jia et al., 2009). Interestingly, *Rorc* gene is over-expressed in the developing eyes of *Per1<sup>-/-</sup>Per2<sup>Brdm1</sup>* mutants (Bagchi et al., 2020).

Although precise mechanisms still need to be identified, the data described above suggest that clock genes control PR differentiation in mice. The clock might be involved in modulation of the balance between rod and S-cone genesis and the ratio of M-opsin vs S-opsin expression in cones. It has not been established whether these effects correlate with rhythmic expression of involved clock factors.

### **3.3. Is transcriptional regulation of retinal development more generally under clock control ?**

It is possible that the circadian clock has a more widespread link with development of retinal cell types. This is suggested by a number of studies summarized below. Using *Nr1d1* KO mice, Chavan and coworkers (Chavan et al., 2017) found that REV-ERB $\alpha$ /NR1D1 (that is abundantly expressed in the inner retina in addition to PR) can regulate transcription through interaction with other binding partners such as *Hnf6/Oc1* that also controls HC fate (Wu et al., 2013). Other clock-related factors, such as the BHLHE40 and BHLHE41 TF, compete with BMAL1/CLOCK for binding to the E-box. Both *Bhlhe40* and *Bhlhe41* genes have been associated with the generation of RPE lineage cells derived from human iPSC and *Bhlhe40* is an early marker of the presumptive RPE in zebrafish (Cechmanek and McFarlane, 2017; Chuang et al., 2018). A microarray analysis of the daily and circadian transcriptome conducted in larval

zebrafish at 5dpf allowed the identification of GRNs underlying developmental effects of the clock (Li et al., 2013). This study pointed to a series of phase-specific oscillating TF genes controlling retinal fate. A number of first examples are genes involved in the developing retina, such as *Mitfa* and its downstream targets *Vsx1* and *Six3* (Li et al., 2013). Regarding the regulation of PR development, TF genes with oscillating expression include *Crx*, *Nr1d1*, and *Rorab*, the orthologue of mammalian *Rorb*. Interestingly in the ONL of 3dpf and more mature zebrafish larvae, several TF regulating retinal development (*Neurod* followed by *Nr2e3*, and then *Rx1* and *Crx*) are rhythmically expressed (Laranjeiro and Whitmore, 2014). This suggests that TF which regulate developmental PR differentiation are later re-activated by the circadian clock to control phototransduction over the 24 h cycle.

Taken together, these data suggest a link between regulators of retinal development and the circadian clock. Furthermore, the clock might control retinal rhythmic physiology through these factors in the mature tissue. However, the exact relationship between circadian clock mechanisms, the LD cycle and retinal differentiation remains to be determined. A few data about light perception during differentiation provide some clues.

### **3.4. Ontogeny of circadian rhythms in the retina**

#### **3.4.1. Light perception and ontogeny of rhythms**

In rats, light responses in the retina are observed immediately after birth (Mateju et al., 2010) while only at P4 in mice (Munoz Llamosas et al., 2000). In parallel, it was observed that melanopsin is already light-sensitive during fetal development in the mouse and has significant impact on the development of eye vasculature (Rao et al., 2013). It is also worth noting that in chicken, mRNAs for different circadian markers (*Bmal1*, *Clock*, *Per2*, *Cry1*), for the AA-NAT enzyme involved in melatonin synthesis, as well as for melanopsin (*Opn4*), were found expressed in inner retinal cells as early as E8, when the distinct retinal layers are forming (Diaz et al., 2014). Furthermore, chick retinal cell cultures from E8

embryos are able to express 24 h rhythms in clock gene mRNAs, provided they have been exposed to daily LD cycle (Chaurasia et al., 2006; Lima et al., 2011). Taken together, these data suggest that cells are likely to acquire rather early the capacity to sense ambient lighting conditions and measure time. How this genetic effect gets harmonised with the synchronising effect of the LD cycle is presently unknown. However, data obtained in chicken with photoreceptor-enriched embryonic retina cultures or with cultures of embryonic RGC suggest that light sensitive oscillations of cAMP, interconnected with light affected  $Ca^{2+}$  levels might be the initial circadian regulators in the retina, that might prime the retina for clock-controlled gene regulations. Such model has been especially proposed for the regulation of rhythmic melatonin synthesis, that has been used since decades as a marker of rhythms in the circadian field.

#### **3.4.2. Development of the rhythm in melatonin synthesis**

Rhythmic synthesis of melatonin is one of the major functional outputs of the circadian clock in the vertebrate retina, especially in PR. In the PR, melatonin is primarily synthesized during darkness in most species (Cahill and Besharse, 1992; Tosini et al., 2007a; Zawilska and Iuvone, 1992). In addition to its role in controlling dark-adaptive retinal physiology, melatonin regulates cone viability (Gianesini et al., 2016). This rhythm mainly involves cyclic activity of AA-NAT. *Aanat* expression is regulated by the LD cycle but also by the circadian clock (Fukuhara et al., 2004; Tosini and Fukuhara, 2002). In *Xenopus*, rhythmic production of melatonin was greatly altered when a dominant-negative CLOCK protein was expressed specifically in PR (Hayasaka et al., 2002).

The onset of circadian rhythms in melatonin levels was first reported in chick retinas. Significant day/night differences in NAT activity emerged around E20, regulated by the LD cycle, to reach a maximum amplitude at post-hatch day 3 (3dph). A circadian rhythm in NAT activity also appeared around hatching, indicating its regulation by the clock developed in ovo (Iuvone, 1990). In *Xenopus* embryos, a functional, photo-responsive circadian clock was shown to develop in the eye within the first days of life (Green et al., 1999). Optic vesicles of young *Xenopus laevis* embryos cultured *in vitro*

slowly start releasing melatonin at developmental stage 26. The latter secretion becomes rhythmic in 2-3 days if optic vesicles are exposed to LD cycle but stays at constitutively high levels under constant darkness. In older *Xenopus* embryos (stage 47), melatonin is rhythmically released *in vitro* in the cultured mature eye/retina and shows similar amplitude when maintained in cyclic light or under continuous dark conditions (Green et al., 1999). In embryonic zebrafish, it is suggested that the first circadian melatonin rhythms are not of retinal but of pineal gland origin (Kazimi and Cahill, 1999). Indeed, a functional and light-responsive circadian oscillator regulating melatonin synthesis in zebrafish becomes apparent just after 20-26 h post-fertilization, before retinal PR maturation (Kazimi and Cahill, 1999). More recently, the developmental rat retina expression pattern of *Aanat* mRNA was examined using Northern blot analysis (Sakamoto et al., 2002). The daily LD cycle-induced rhythmic changes in the *Aanat* mRNA levels began as early as P2. In contrast to LD, *Aanat* rhythms persisted for 1 day in constant darkness only after P14 (Sakamoto et al., 2002). Another study in rats, showed that maternal entrainment of circadian rhythms in pups persists during the first postnatal week (Duncan et al., 1986). However, the required signals from the mother were not sufficient to induce rhythmic expression of retinal AA-NAT during this period (Duncan et al., 1986). This indicates that the rhythm observed at P2 was essentially driven by the LD cycle and that the latter was required for later maturation of the circadian retinal system. Whether rhythmic melatonin release itself played a role in this maturation remains to be established.

In conclusion, circadian clock genes most likely fine tune retinal development at distinct steps, from very early progenitors to cell type-specific differentiation. These effects involve control of cell cycle, as well as direct control of target genes acting as regulators of patterning/differentiation, most of which have not yet been identified. It also remains to be determined when and how, within these processes, the retinal circadian clock starts ticking. Answering this long-standing question is hindered by the difficulty to track clock gene oscillations at the cellular level. Another question is how the clock in the developing retina gets synchronized by the LD cycle. In lower vertebrates such as zebrafish and

*Xenopus*, these events are likely to occur rather early, facilitated by the embryo transparency. The data presently available indicate that they take place later in mammals. Moreover, the phenotypes of clock mutants in mice support the notion that the circadian clock only modestly contributes to retinal development. However, examination of the more general effects of clock disturbance on retinal and ocular health in adulthood provide a more comprehensive idea of the importance of clock regulation in the retina.

#### **4. Circadian clocks and ocular health**

Visual perception and light have a profound influence on human physiology, well-being and quality of life. According to the World Health Organization (WHO), an estimated 36 million people worldwide had blindness in 2015, a scale-up of 217 million individuals with moderate to severe visual impairments (Bourne et al., 2017). The role of the circadian clock in retinal development has been discussed in chapter 3 and a number of target developmental genes were listed. Interestingly, some of these genes are also involved in early-onset retinal diseases; however, a potential link between these diseases and the circadian clock has not been documented yet. Conversely, due to their pervasive control of gene expression and to their role in homeostasis and long-term health, circadian clocks can possibly also modulate detrimental pathological effects of the aging retina. This can be illustrated by a number of examples from the literature: accelerated degeneration of (cone) photoreceptors has been reported upon aging in mice carrying *Bmal1* deletion (Baba et al., 2018a; Baba et al., 2018b). Also, a rhythmic component in retinal sensitivity to phototoxicity has been reported in rats and, of note, retinas were much more vulnerable at night (Organisciak et al., 2000). Thus, clock dysfunction might constitute a risk factor for blinding diseases. However, besides a few examples, the (long term) effects of circadian misalignment on human retinal disease remain essentially to be explored.

Below, we describe in more depth a few examples of a possible relationship between a disturbed circadian clock in the developing or aging eye and ocular defects, starting with the retina and extending to distinct eye compartments.

#### **4.1. Clock dysfunction and retinal pathophysiology**

##### **4.1.1. Glaucoma**

Glaucoma is a leading cause of irreversible blindness characterized by RGC degeneration resulting in visual field defects and optic nerve deterioration. Abnormal, high intraocular pressure (IOP) physically damaging the RGC is considered the main risk factor for glaucoma. The variation of IOP across the circadian cycle have been long recognized (Aihara et al., 2003; Lozano et al., 2015; Nickla et al., 1998; Read et al., 2008). IOP rhythm depends, at least in part, on the integrity of a circadian clock (Maeda et al., 2006). This rhythm derives notably from changes in the aqueous humor production by the ciliary body. Indeed, rhythmic expression of clock genes have been reported in the iris-ciliary body complex (Dalvin and Fautsch, 2015; Tsuchiya et al., 2017), and depends on signals from the SCN, likely through glucocorticoids and the sympathetic pathway activation (Ikegami et al., 2020). In humans, IOP is highest during the night (Liu et al., 1998).

It has been proposed that not the IOP alone, but the translaminar pressure over the optic nerve head determines RGC damage. This would explain the proportion of patients with a so-called normal-tension glaucoma. The translaminar pressure can then be defined as the difference of pressure between the IOP and the intracerebral pressure (ICP) (Janssen et al., 2013). Interestingly, not only IOP, but also ICP has been reported to be highest at night in rodents (Starcevic et al., 1988). Also, the choroid plexus, responsible for cerebrospinal fluid generation in the brain harbors a circadian clock (Myung et al., 2018). Finally, unlike the IOP and ICP, systemic blood pressure is minimal during the night [reviewed in (Bowe et al., 2015)]. This might increase the risk for reduced perfusion of eye or brain tissues at night-time and potentially contribute to the progression of glaucoma [reviewed in (Ciulla et al., 2020)]. Clearly, the relationship between circadian controlled fluid pressure in the relevant body compartments in the context of glaucoma development is complex and warrants further investigation.

##### **4.1.2. Diabetic retinopathy**

Diabetic retinopathy (DR) is a complication of diabetes and considered a microvascular disease of the retina. Due to hyperglycemia, retinal vessels are damaged, leading to formation of ischemic zones and exudation from capillaries that contributes to macular edema. A strong link between DR and the circadian clock has been proposed in several studies. First, DR was associated with the reduction of clock gene expression in the rat retina (Busik et al., 2009). In 2013, Bhatwadekar and co-workers conversely showed in mice that circadian disruption by mutation of *Per2* induced DR, likely through a retinal microvasculature phenotype (Bhatwadekar et al., 2013; Jadhav et al., 2016). Later, the same authors corroborated these findings: conditional deletion of *Bmal1* in endothelial cells induces pathologic vascular and neuronal hallmarks of DR (Bhatwadekar et al., 2017). Finally, Vancura and coworkers found that, in mouse retina, disturbances in circadian and dopamine-directed regulation of fatty acid oxidation enzymes required for daily adaptation of energy metabolism, lead to DR pathology (Vancura et al., 2016). Unexpectedly, more recent data suggested that *Bmal1* KO does not pose a risk, but rather protects against DR (Vancura et al., 2021). Thus, the link between the clock and DR remains to be clarified.

#### **4.1.3. Age-Related Macular Degeneration (AMD)**

AMD is a progressive chronic disease of the central retina. The disease affects 4% of the elderly, and no effective or patient-friendly cure exists. Subretinal drusen formation and neovascularisation are clinical hallmarks of the disease (Bergen et al., 2019). AMD is caused by environmental and genetic factors. Mechanistically, the oxidative stress, the complement system, lipid metabolism and local extracellular matrix changes have been implicated in the disease. So far, the potential role of the clock in AMD development has received little attention. However, because of the major importance of oxidative stress in AMD, and the fact that circadian clocks are major regulators of metabolism and cellular redox state, led to the hypothesis that clock dysfunction may contribute to AMD phenotypic variability (Fanjul-Moles and Lopez-Riquelme, 2016; Ruan et al., 2021). Also, biosynthesis and turnover

of the oxidative stress-protective melanin pigment in the RPE (the primary retinal layer implicated in the pathology of AMD) is under circadian control (Bergen; personal communication). Genetic linkage, association and expression studies suggested the influence of genetic variation in the *Rora* clock gene on neovascular AMD (Jun et al., 2011; Silveira et al., 2010). Finally, it has been proposed that aberrant upregulation of the WNT/ $\beta$ -catenin signalling controlled by clock genes and involved in exudative AMD, might be due to a disrupted circadian clock (Guo et al., 2012) [reviewed in (Vallee et al., 2020)].

#### **4.2. Effects of clock dysfunction on the anterior eye segment: lens and cornea**

Initial studies with *Bmal1* and *Clock* KO mice reported development of cataract, an abnormally cloudy lens. This phenotype has been linked to accelerated aging in the case of *Bmal1* KO (Dubrovsky et al., 2010; Kondratov et al., 2006). More recently, it was shown that *Bmal1* depletion induces a progressive decline of antioxidant-defence pathways in primary human lens epithelial cells and derived cell lines, making them vulnerable to reactive oxygen species (ROS) accumulation and apoptosis (Chhunchha et al., 2020). These processes might underlie the lens premature aging effect induced by *Bmal1* KO. Whether alteration of the circadian clock might also affect lens development was investigated in a genetic study of congenital cataract families. However, no genetic variation in *BMAL1* could be linked to the disease (Bagchi, 2019).

The renewal and repair of the corneal epithelium are (also) influenced by the circadian clock (Lavker et al., 1991; Sandvig et al., 1994; Scheving and Pauly, 1967). Initial studies in mice showed that the ocular abnormalities induced by *Bmal1* or *Clock* deficiency also include corneal inflammation (Dubrovsky et al., 2010; Kondratov et al., 2006; Yang et al., 2016). Indeed, the whole cornea expresses clock genes that invoke circadian rhythms (Xue et al., 2017; Yoo et al., 2004). These rhythms, measured in whole corneas, are entrained by signals from the retina. For example, melatonin (most likely secreted by the retinal PR) is able to entrain the PER2-luciferase circadian rhythms in the mouse cornea (Baba et al., 2015). When normal environmental lighting cycles are replaced with altered light

schedules (constant light, constant dark, reversed LD and jet-lag conditions), the homeostasis of the corneal epithelium, namely mitosis and wound healing, gets disturbed (Xue et al., 2017). Interestingly, analysis of the daily transcriptome in the mouse cornea showed significant enrichment in metabolic pathways and DNA replication during the day, consistent with the finding that corneal epithelial mitosis also peaks during the light phase (Jiao et al., 2019).

### ***4.3. The retinal clock in refractive development and myopia***

Myopia or near-sightedness is a prevalent vision disorder projected to affect 50% of the global population by 2050 (Holden et al., 2016). It is a complex disease caused by genetic and environmental factors. Myopia itself predisposes the eye to many other blinding conditions in adulthood. In the 19<sup>th</sup> century, inadequate lighting or insufficient exposure to the outdoors was suggested for the aetiology of myopia (Hobday, 2016). Indeed, outdoor or natural light exposure partially protected children to develop myopia in the early years of life (French et al., 2013). Today, it has become clear that light-induced retinal (dopamergic) signalling is an important driver for refractive error in myopia (Tedja et al., 2018; Wallman and Winawer, 2004; Zhou et al., 2017). A recent meta-GWAS analysis confirmed that refractive errors are associated with the two Gene Ontology Terms “circadian rhythms” and “circadian regulation of gene expression” (Hysi et al., 2020). Indeed, artificial lightning during dark hours, prolonged computer use (indoors) and irregular lifestyle contribute to the development and progression of the disease (Chakraborty et al., 2018).

Interestingly, eye dimensions undergo diurnal fluctuations both in humans (Burfield et al., 2018; Chakraborty et al., 2011; Stone et al., 2013) and in animal models [reviewed in (Nickla, 2013)]. The fluctuating ocular dimensions include axial length, vitreous chamber depth, and choroidal thickness (Chakraborty et al., 2018). Eye dimensions, and even their daily fluctuations, vary in response to imposed optical defocus (ie: artificially induced myopia or hyperopia) (Chakraborty et al., 2012; Nickla, 2013). At the same time, imposed optical defocus also disrupts rhythmic expression patterns of some

clock genes in the retina/RPE and in the choroid (Stone et al., 2020). These data corroborate the potential link between refraction, circadian clock mechanisms, and the retina.

This link may also be important for eye development. In the retina-specific *Bmal1* KO mouse, the eyes developed longer axial length and an elongated vitreous chamber (Stone et al., 2019). Consequently, KO mice were significantly more myopic than control mice. Noteworthingly, similar anatomical changes were reported in chicks when reared under constant light, suggesting the need of a proper day/night rhythm for optimal eye growth (Stone et al., 1995). Interestingly, it was also reported that brief bright light inhibits the growth of myopic eyes in the chick, when exposure takes place at a specific time of day-in the evening (Sarfare et al., 2020). Taken together, these investigations support the idea that the effects of lighting on refractive development are linked to the circadian clock.

## 5. Summary

The studies presented above suggest that vertebrate eye development is, in part, under circadian control. Indeed, the circadian clock (or at least clock genes) affects a number of steps of eye development, from the anterior neural tube to the optic cup and PR differentiation. Interestingly, in the same developmental timeframe, expression of cell cycle genes and S phase entry are also controlled by (mouse) clock genes. Moreover, in fish, where embryonic development occurs in transparent eggs (thus exposed to light), experimental results indicate that eye formation and circadian rhythms are settled synchronously and could influence each other. However, in higher vertebrates, besides proliferation of early precursors, solely PR differentiation appears to be regulated by the circadian clock, especially in mammalian cones (summarized in Figure 5). We also report evidence that the clock, integrating environmental cues, modulates a number of pathological processes, not only in the retina, but also in other ocular compartments, suggesting that proper clock function may positively influence eye pathology.

## 6. Conclusions and perspectives

During retina embryonic and postnatal development, the circadian clock acts as a modulator of both precursor proliferation and differentiation, likely by defining the appropriate timing for these processes to occur. The results presented in this review suggest that the clock plays an important role in (24 hr) eye physiology and homeostasis. Disruption of the clock most likely enhances eye pathology. These data also designate the eye as a perfect clock model to study these processes, both at the cellular, tissue and functional level.

Further research in understanding the role of circadian clocks in retinal development, disease and therapeutics may include (1) a better understanding of the contribution of individual cell-specific clocks to retinal differentiation (2) a more thorough analysis of the clock in models for retinal disease, and (3) better understanding of a potential role of the clock in therapies for retinal disease. These therapeutic studies may include natural history studies in patients, time restricted application of drugs, and, more fundamentally, the role of the clock in stem cell development and cell replacement therapy.

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## FIGURE LEGENDS

### Figure 1. The circadian clock machinery.

The endogenous molecular mechanism generating circadian rhythms is based on two main transcriptional–translational feedback loops involving clock genes. The CLOCK/BMAL1 heterodimer binds to an enhancer box (E-box) and drives the transcription of the clock genes *Period (Per1-2)*, *Cryptochrome (Cry1-2)*, *Rora-c*, and *Rev-Erb $\alpha$ - $\beta$* . PER and CRY (phosphorylated) proteins in turn inhibit CLOCK/BMAL1 transcriptional activity. By competitive binding to retinoid-related orphan receptors response elements (RORE) sites, the REVERB and ROR proteins repress and activate *Bmal1* transcription, respectively. The clock machinery modulates cell-specific gene expression via two transcriptional processes (direct and indirect), thus leading to 24 h rhythms in tissues [adapted from (Felder-Schmittbuhl et al., 2017)].

### Figure 2. Rhythmic functions in the distinct retinal layers

A schematic transversal section through retinal layers and cell types is shown with the three main oscillators previously identified (Jaeger et al., 2015). Examples of mostly documented rhythmic, clock-controlled processes are listed on the right in RGC, INL, ONL and RPE [references in (Besharse and McMahon, 2016; Felder-Schmittbuhl et al., 2017; Felder-Schmittbuhl et al., 2018)]. R, RGC; A, AC; B, BC; H, HC; M, MGC, R, rods; C, cones.

### Figure 3. The genetic signalling in the optic vesicle and optic cup.

**A)** Diagram depicting the optic vesicle (OV) and the optic cup (left) with their corresponding Gene Regulatory Networks. **B)** Genes which alteration has dramatic consequences in early development of the vertebrate eye [adapted from (Garita-Hernandez et al., 2016; Harding and Moosajee, 2019)]. KO: Knock Out; LP: Lens Placode; NR: Neural retina; OV: Optic Vesicle; RPE: Retinal Pigmented Epithelium.

**Figure 4. A network of genes essential for the development of retinal cell types in the mouse retina.**

Among photoreceptors, cones and rods GRN are described in separate colored hemispheres: grey for rods and multicolored (blue, green) for cones. Proportion of the seven retinal cell types are indicated [adapted from (Harada et al., 2007; Hughes et al., 2017)].

Dotted lines indicate indirect or poorly characterized gene relationships. Large colored arrows indicate that the TF directly activates generation of the cell type. AC: amacrine cells; BC: bipolar cells; HC: horizontal cells; MGC: Müller glial cells; RGC: retinal ganglion cells [adapted from (Boije et al., 2015; Brzezinski and Reh, 2015; Ivanov, 2019; Zagozewski et al., 2014a; Zhang et al., 2011)]. Prepared with elements from Servier Medical Art <https://smart.servier.com/>.

**Figure 5. Schematic of the retinal developmental processes regulated by circadian clock (genes)**

The model proposes that the circadian clock, or at least the action of BMAL1 (transcriptional activator) or PER1, 2 (transcriptional inhibitors), regulates the balance between proliferation and cell cycle exit in early retinal progenitors (around E15), the expression of S-opsin (effect specifically observed in the absence of *Per2* or of both *Per1* and *Per2*) and the dorso-ventral patterning of M/S-opsin expression, by enhancing conversion of T4 (inactive) to T3 (active) versions of TH. After the data from (Ait-Hmyed et al., 2013; Bagchi et al., 2020; Sawant et al., 2017; Sawant et al., 2019).

Fig 1

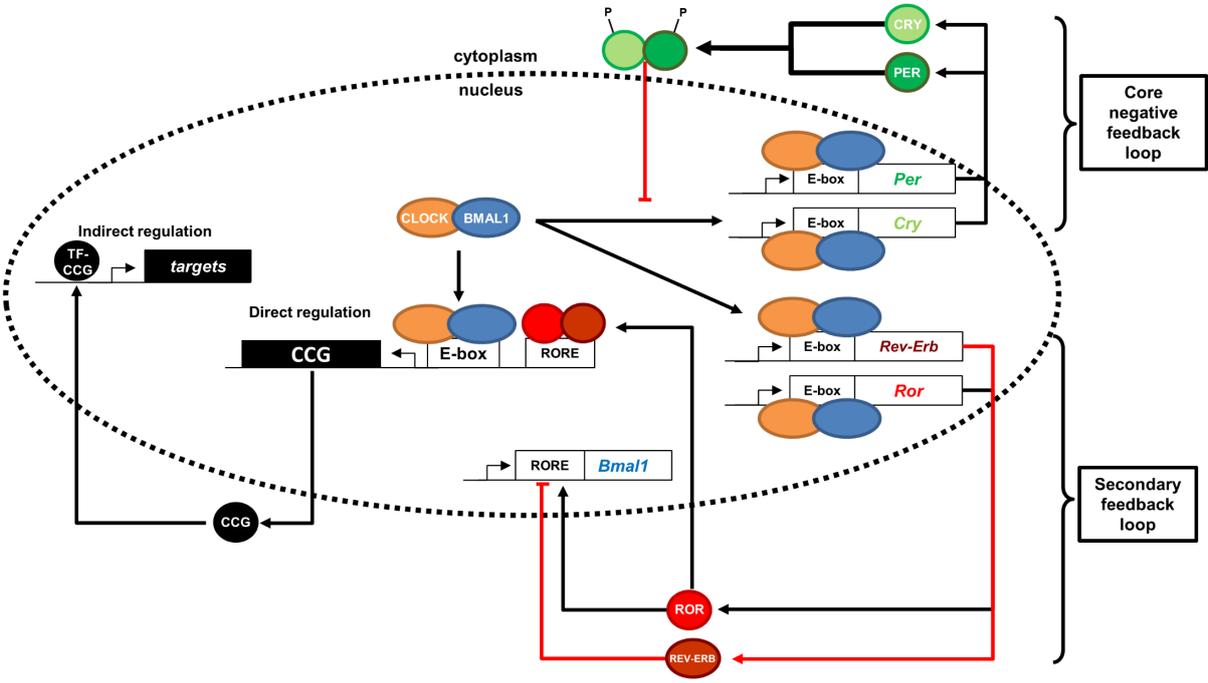
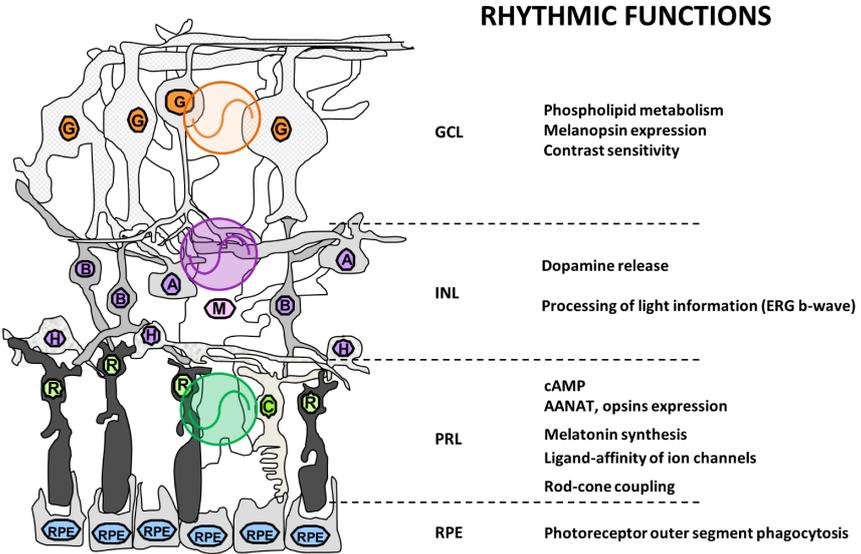


Fig 2



**Fig 3**

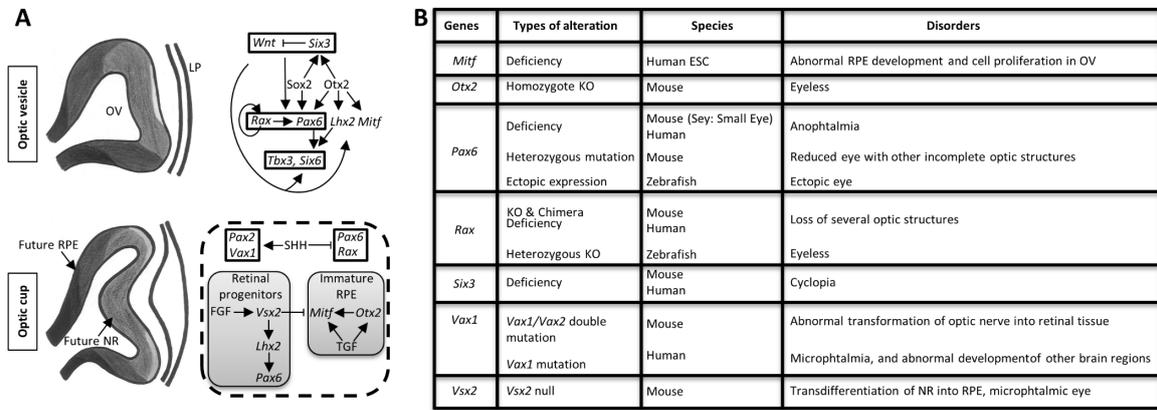


Fig 4

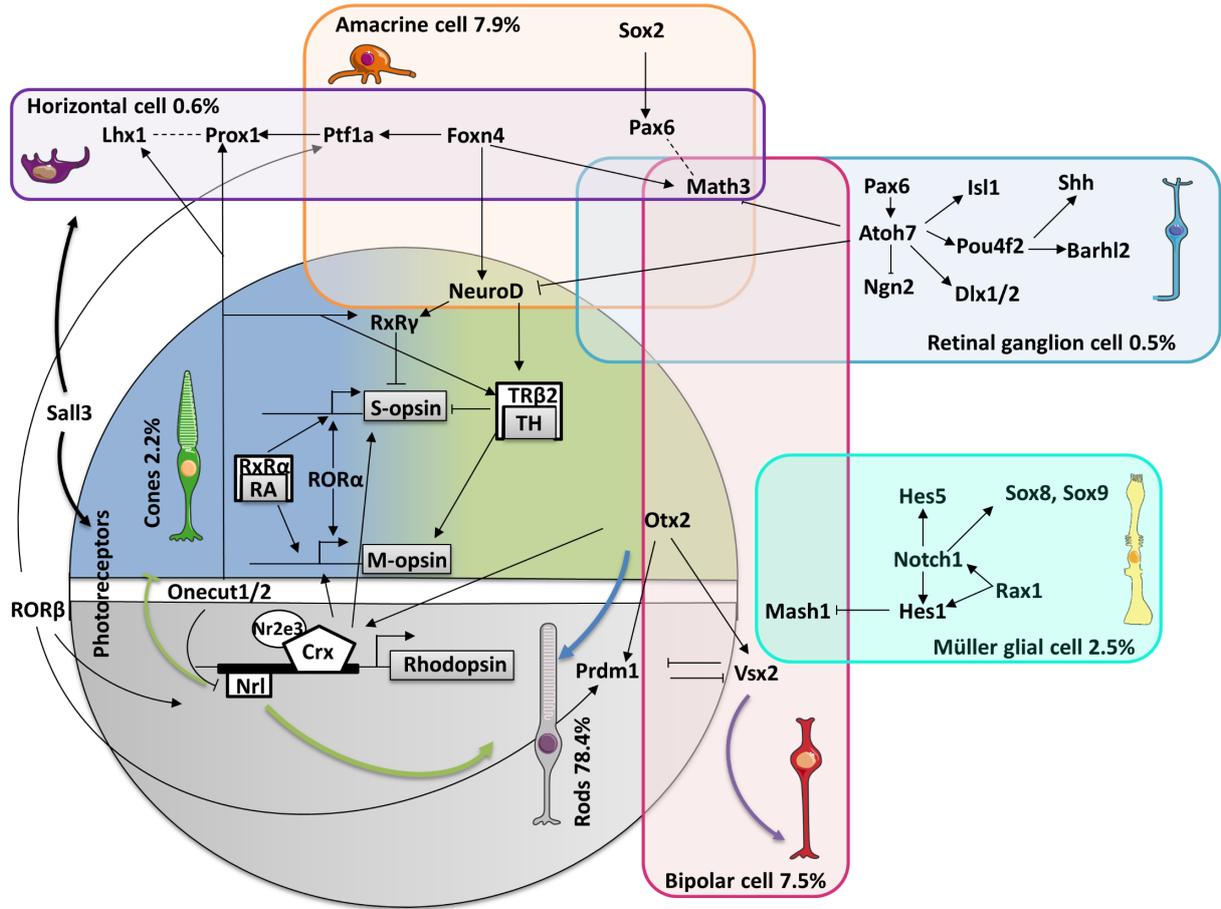


Fig 5

