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Tracing the progression of retinitis pigmentosa via photoreceptor interactions

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HIGHLIGHTS

- Retinitis pigmentosa (RP) is modeled via photoreceptor interactions.
- Progression of (RP) is traced/followed through equilibria.
- Steady solutions represent observed states of RP.
- The model's implications to the understanding of RP is discussed.

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ABSTRACT

Retinitis pigmentosa (RP) is a group of inherited degenerative eye diseases characterized by mutations in the genetic structure of the photoreceptors that leads to the premature death of both rod and cone photoreceptors. Defects in particular genes encoding proteins that are involved in either the photoreceptor structure, phototransduction cascades, or visual cycle are expressed in the rods but ultimately affect both types of cells. RP is "typically" manifested by a steady death of rods followed by a period of stability in which cones survive initially and then inevitably die too. In some RP cases, rods and cones die off simultaneously or even cone death precedes rod death (reverse RP). The mechanisms and factors involved in the development of the different types of RP are not well understood nor have researchers been able to provide more than a limited number of short-term therapies. In this work we trace the progression of RP to complete blindness through each subtype via bifurcation theory. We show that the evolution of RP from one stage to another often requires the failure of multiple components. Our results indicate that a delicate balance between the availability of nutrients and the rates of shedding and renewal of photoreceptors is needed at every stage of RP to halt its progression. This work provides a framework for future physiological investigations potentially leading to long-term targeted multi-facet interventions and therapies dependent on the particular stage and subtype of RP under consideration. The results of this mathematical model may also give insight into the progression of many other degenerative eye diseases involving genetic mutations or secondary photoreceptor death and potential ways to circumvent these diseases.

1. Introduction

1.1. Background of retinitis pigmentosa

Retinitis pigmentosa (RP) is a heterogeneous group of inherited disorders that affects approximately 1 in 4000 individuals (nearly 1.5 million) worldwide (Shastry, 2008; Shintani et al., 2009; Mohand-Said et al., 2001). This group of disorders is often classified as *primary* or *syndromic* RP. In the case of syndromic RP, which account for about 20%–30% of all cases, the patients have an associated non-ocular disease with RP with abnormalities in one or more organs (Hartong et al., 2006; Shintani et al., 2009). In contrast, primary RP involves only the eye. RP is primarily genetically programmed with more than 45 genes associated with this disease identified to date. These genes account for only about 60% of all cases. RP may be inherited from one or both parents (autosomal-recessive RP, autosomal-dominant, or X-linked RP, which account for approximately 20%–30%, 15%–20%, and 6%–10% of the cases, respectively) or may be caused by a new mutation even though there may be no family history of the disease

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(Hartong et al., 2006; Shintani et al., 2009; Neidhardt et al., 2008; Bowne et al., 2008; Shastry, 2008; Busskamp et al., 2010). Less common modes of inherited RP include digenic and mitochondrial (Shintani et al., 2009).

RP has been associated with mutations or errant genes encoding for proteins that are essential for rod survival and certain genetic products that are damaging to the rods (Shintani et al., 2009; Hartong et al., 2006; Busskamp et al., 2010; Shen et al., 2005; Chalmel et al., 2007). Even though mutations are normally only expressed in the rods their effects ultimately cascade to the cones. People usually are diagnosed only when they experience serious vision problems making it difficult to decipher the mechanism of development and the channels by which RP develops. Adding to this challenge is the variability of its progression and its time of onset within each individual (Shen et al., 2005; Wong, 1997; Hamel, 2006). The sequences of events (i.e., clinical manifestations) of the various sub-types of RP are well-documented (Shintani et al., 2009; Phelan and Bok, 2000; Hamel, 2006) but this sequential progression varies from individual to individual.

RP is often classified into various sub-types depending on the location of the vision field that is affected. The most common clinical manifestation is rod–cone RP and is characterized by difficulty seeing at night, followed by night blindness (nyctalopia), narrowing of the mid-peripheral field of vision (where the rods are more prevalent), and ultimately a loss of central vision (Chalmel et al., 2007; Hartong et al., 2006; Mohand-Said et al., 2001). Night blindness is the hallmark of rod–cone RP but given that rod function is primarily affected, this is of no surprise since rods contribute solely to night vision. Even though rod–cone RP has a better overall prognosis and slower progression in comparison with other sub-types of RP, the range of the onset of clinical rod–cone RP to its noticeable changes observed by the patient can vary widely in all cases. In this most common form of RP, the causal mutations affect genes exclusively expressed in the rod cells in an overwhelming number of cases and rod death far exceeds and precedes cone death (Shintani et al., 2009). Less common forms of RP see an equal loss of rods and cones or even a cone death exceeding rod death (cone–rod RP or reverse RP) (Hartong et al., 2006; Shintani et al., 2009). Cone–rod dystrophy (reverse RP) is associated with a cone loss preceding rod loss and as a consequence reduction of the central vision, acuity, and color vision are manifested early in the progression of the disease, followed by reduction of the mid-peripheral visual field and night blindness at later stages. However, unlike the rod–cone RP where patients' color vision remains good until the central vision is affected at levels of 20/40 or worse, patients with cone–rod RP experience deterioration of their color vision, ability to adapt to light and day vision very early in the disease as well as the loss of normal cone functioning, which leads to photophobia.

1.2. Interactions of photoreceptors

Research that might shed light on improving the photoreceptors longevity has been paramount to physiological, anatomical, and medical research in the last 2 decades due to the prominent role that these cells play in the vision process (Stone et al., 1999). The photoreceptors are the rods and cones, located in the retina, that convert light energy into nerve impulses through the process of visual transduction (Keener and Sneyd, 2008). The rods and cones are specialized for different aspects of vision: the rods and cones are different in shape (cylindrical vs. conical), contain different types of photopigment, and are distributed differently throughout the retina (Oyster, 1999). The reduction of normal light vision, visual acuity, detail perception, night vision, and narrowing of the peripheral fields can be caused by a depletion of cones and rods, respectively (Mohand-Said et al., 2001). The photoreceptors undergo tremendous oxidative stress over the course of a day and undergo a continuous cellular renewal and periodic shedding process of their outer segments (OS) in order to minimize depletion and help to ensure proper functioning of these cells (Oyster, 1999; Kolb et al., 2008; Kevany and Palczewski, 2010; Jonnal et al., 2010). Photoreceptors shed approximately the same amount of material that is renewed over the course of a day so that the length roughly remains constant, with complete renewal in rods and cones occurring from 11 days up to 3 weeks depending on the photoreceptor and its location within the retina (Oyster, 1999; Fisher et al., 1983; Tassi et al., 2000; LaVail, 1973; Young, 1971, 1967; Anderson et al., 1980; Anderson and Fisher, 1975; Guérin et al., 1993). The shedding and renewal of photoreceptors, their interactions, and circadian rhythms were previously examined and discussed in greater detail (Colón Vélez et al., 2003; Camacho et al., 2010).

Much research has examined the processes of renewal and shedding within the photoreceptors and suggests the photoreceptors together with the adjacent retinal pigment epithelium (RPE) operate as a functional unit (Tassi et al., 2000; Bhatt et al., 2010; O'Day and Young, 1978; Fisher et al., 1983; Hogan et al., 1974; Bok, 1985; Papermaster, 2002; Jonnal et al., 2010; Young and Bok, 1969; Young, 1967, 1971; Besharse and Spratt, 1988; Mukherjee et al., 2007; LaVail, 1973; Li et al., 2010; Strauss, 2005). The rod and cone cells undergo a daily rhythmic shedding in which their photoreceptor outer segments (POSs) are phagocytized by the RPE. The RPE recycles parts of the shed POS for future use by the photoreceptors and contributes additional trophic and growth factors utilized in the renewal process of these cells (Bhatt et al., 2010; Mohand-Said et al., 2001; Mohand-Saïd et al., 1998; Mukherjee et al., 2007). The RPE transports, secretes, and redelivers essential growth factors such as PEDF, CNTF, bFGF, Gas6, PDGF, and ATP, metabolites (including glucose, retinal, and omega-3 fatty acids), ions, and water to and from the photoreceptors (Strauss, 2005; Murakami et al., 2008; Longbottom et al., 2009; LaVail et al., 1998; Li et al., 2010; Wenzel et al., 2005; Frasson et al., 1999). It is unclear if other essential proteins are linked to the interactions of these two retinal tissues but the interdependency of the RPE and photoreceptors is key to the proper functionality of the eye.

Pivotal to the vision is also the connection and interplay between the rods and cones. These cells have long been suspected of communicating directly or indirectly with each other (Mohand-Saïd et al., 1998). It has been recently shown that the rods produce a protein referred to as the Rod-derived Cone Viability Factor (RdCVF) that is essential for the functionality and survival of the cones (Léveillard et al., 2004; Mohand-Said et al., 2001; Yang et al., 2009; Léveillard and Sahel, 2010; Sahel, 2005; Hanein et al., 2006). While the neural degeneration of the photoreceptors that typically results from genetic defects and mutations (such as RP) may disrupt and break the balanced shedding and renewal processes leading to shorter OS and, in some cases, the complete disappearance of the rods and cones (Mohand-Said et al., 2001; Pallikaris et al., 2003), the amount of RdCVF appeared to be the same in both normal and mutated rods prior to their degeneration. Additionally, a subsequent decrease in RdCVF was reported to be strongly correlated with the decrease in the number of rods during their degenerative process (Yang et al., 2009). The effect of RdCVF appears to be independent of the casual mutation leading to rod degeneration (Léveillard et al., 2004; Yang et al., 2009; Sahel, 2005). Experiments have revealed that RdCVF had a significant cone rescuing effect, that its protective effects did not extend to degenerating rods, and that the presence of the rod cells is not necessary for cone survival as long as RdCVF is present (Sahel, 2005; Léveillard et al., 2004; Yang et al., 2009; Léveillard and Sahel, 2010; Hanein et al., 2006; Camacho et al., 2010). Moreover,