Histol Histopathol (2009) 24: 1295-1322

http://www.hh.um.es

Histology and Histopathology

Cellular and Molecular Biology

Review

Animal models and different therapies for treatment of retinitis pigmentosa

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Summary. Retinitis pigmentosa (RP) is a heterogeneous group of retinal degenerative diseases initially affecting the rod photoreceptor. Patients present with night blindness, loss of peripheral vision and finally the loss of central vision, as a consequence of death of cone photoreceptors.

RP is a genetic disease, showing inheritance of autosomal dominant (AD), autosomal recessive (AR) or X-linked (XL) recessive traits, although some patients have no family history of RP (simplex RP).

Many animal models of RP are available and have led to a better understanding of the pathology of the disease, and to the development of therapeutic strategies aimed at curing or slowing down the genetic disorder.

In this review, we describe the selected animal models (natural and transgenic) and their phenotypes and genotypes, as well as the advantages and disadvantages of the use of each animal. Also, we look at different therapeutic strategies being studied worldwide and report the latest results. Nevertheless, many obstacles will have to be overcome before most of these strategies can be applied to humans.

Key words: Retinitis pigmentosa, Leber cogenital amaurosis, Animal model, Therapies, Phototransduction

Introduction

Retinitis pigmentosa (RP) is a heterogeneous group of inherited human retinal diseases that cause degeneration of photoreceptors and the retinal pigment epithelium (Rattner et al., 1999; Phelan and Bok, 2000), together with a group of retinal diseases which also have retinal degeneration as a mayor feature, e.g. Leber Congenital Amaurosis (LCA), Usher syndrome, Bardet Biedle and others. The incidence of RP is 1/4000, making it one of the most common causes of visual impairment in all age groups (Berson, 1993), whereas LCA, a congenital form of RP, is the most prevalent cause of hereditary visual handicap in children (Gu et al., 1997) with an incidence of 1/81000 (Stone, 2007). Some authors have described LCA as an aggressive form of RP (Gu et al., 1997) or juvenile RP (Heckenlively, 1988). Vallespin et al., 2007, established the difference between LCA and the early-onset of RP according to the age of onset. Children presenting congenital symptoms were considered as LCA phenotype, while children whose symptoms were not congenital (but presented it before 10 years old) were classified as early-onset RP (Vallespin et al., 2007).

RP is characterized by initial loss of rod photoreceptors, followed by a decline in other retinal cell classes, particularly cones, inner nuclear layer cells and ganglion cells (Cideciyan et al., 1998; Hicks and Sahel, 1999; Sahel et al., 2001; Leveillard et al., 2004). The first signs of the disease generally occur in the rod photoreceptors, the light-sensing cells of the retina, which mediate vision in conditions of dim light. Once the viability of the rods becomes compromised as a result of a genetic abnormality, patients experience night-vision problems and develop tunnel vision as a consequence of degeneration in the peripheral retina. The death of the rod photoreceptors has a secondary, detrimental effect on the cone photoreceptors, which are responsible for vision in daylight, and these too begin to die, eventually resulting in the loss of central vision. The progressive demise of the photoreceptors also precipitates other pathological symptoms in the retina, including the attenuation of the retinal vasculature and the accumulation of intra-retinal pigment deposits, from which the disease gets its name, "pigmentosa" (Hims et al., 2003; Kalloniatis and Fletcher, 2004). Other symptoms are vitreous degeneration and waxy pallor of

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the optic nerve head (Pruett, 1983).

Several mechanisms have been proposed to explain cone cell degeneration, including toxic products released by dying rods (Bird, 1995; Hicks and Sahel, 1999), lack of contact-mediated interactions with rods, retinal pigment epithelium (RPE) and Müller cells (Hicks et al., 1994; Raymond and Jackson, 1995; Adler et al., 1999), or lack of a rod trophic factor essential for cone cell survival (Hicks and Sahel, 1999).

RP is genetically heterogeneous, showing inheritance as autosomal dominant (AD), autosomal recessive (AR), or X-linked (XL) recessive traits (Dryja, 1992). Although RP is a genetic disease, some patients have no family history of RP and in these cases it is called "simplex" or "isolated" (Newsome, 1988). To date, 40 genes and loci have been implicated in non-syndromic RP (http://www.sph.uth.tmc.edu/RetNet/), yet the genetic bases of more than 50% of the cases remain unknown (Pomares et al., 2007).

The prevalence of the disease presents variations among countries and ethnic groups. For example the highest numbers of ADRP are found in the USA (Bunker et al., 1984) and the lowest in southern Europe (Ayuso et al., 1995).

RP is also a component of over 30 syndromes, most of which show AR inheritance. The best known of these is Usher syndrome, which is the most common form of deaf-blindness (Pagon, 1993). The hearing loss in patients is sensorineural and most severe for high frequencies. Loss of vision is due to RP (Ahmed et al., 2003).

With the exception of vitamin A nutritional supplements (Berson et al., 1993), no treatments have been shown to be effective across the range of these disorders. Regardless of the initial causative genetic defect, the end result is photoreceptor cell death. The multiplicity of mechanisms has stimulated a search for therapeutic agents that are effective in slowing photoreceptor death, although the causative genetic mutation remains.

In the majority of the dystrophies examined in animal models, photoreceptor cell death results from caspase-dependent apoptotic mechanism (Donovan and Cotter, 2002; Azuma et al., 2004, Doonan et al., 2005, Paquet-Durand et al., 2006). However, recent evidence suggests that photoreceptor cell death may involve other death pathways, such as calpain-mediated cell death, autophagy, proteasome activity and complement mediated lysis (Rohrer et al., 2004; Sharma and Rohrer, 2004).

Van Soest and colleagues proposed a subdivision based on the functional mechanism affected by the various mutations distinguished in RP: 1) mutations affecting the renewal and shedding of the photoreceptor outer segment, 2) mutations affecting the visual transduction cascade, and 3) mutations affecting the retinol (vitamin A) metabolism (Van Soest et al., 1999).

In order to simplify this classification we will describe the process of the disease in stages:

Renewal and shedding of the photoreceptor outer segments

In the normal mammalian retina a single type of rod photoreceptor is present, while there are two or three types of different cone photoreceptors (Ahnelt and Kolb, 2000). Rods represent 95% of all photoreceptors in humans (Curcio et al., 1990) and mediate vision in dim light. Cones are the mediators of central vision and color vision, and their density increases toward the center of the retina, the macula (Van Soest et al., 1999).

The photoreceptors consist of an outer segment (OS), an inner segment (IS) comprising mitochondria, ribosomes and membranes where opsin molecules are assembled and transported to be part of the outer segment discs, a cell body and a synaptic terminal where neurotransmission to second order neurons occurs (see Fig. 1). The structure of the OS is characterized by a stack of discs that are formed by invaginations of the plasma membrane at the base of the OS (Matsumoto et al., 1987). The discs are detached and form a stack of discs inside the OS membrane in the case of the rods. In the cones, however, the OS discs remain attached to the OS membrane.

In the curved rim of rod disks, the transmembrane proteins peripherin/retinal degeneration slow (RDS) (Connell and Molday, 1990), retinal outer segment membrane protein 1 (ROM1) (Bascom et al., 1993) and

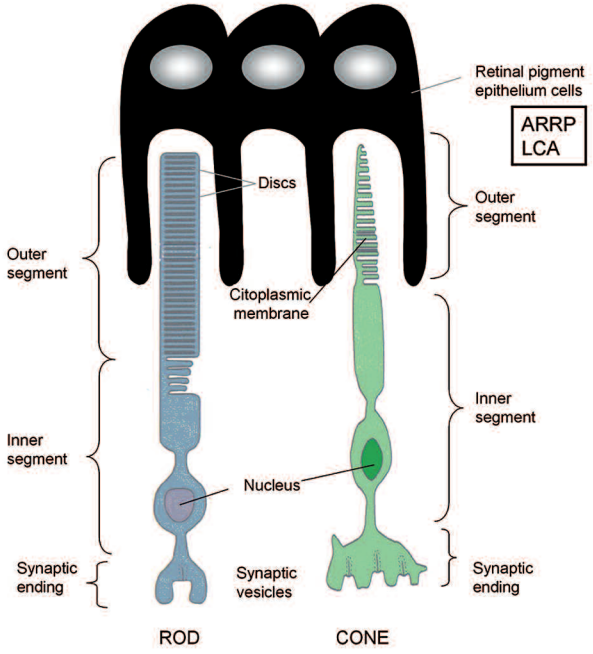

Fig. 1. Schematic representation of rod and cone photoreceptor cells and the retinal pigment epithelium (RPE) cell. The square on the right represents the types of RP heritance in the RPE cells, autosomic recessive (AR) and Leber Congenital Amaurosis (LCA).

rim protein, also known as ABCA4 or ABCR (Illing et al., 1997; Azarian and Travis, 1997), are present. RDS and ROM1 proteins are highly homologous in function and structure, but differ in expression pattern. These proteins are important for the development and structural maintenance of the photoreceptor outer segments (Sanyal et al., 1980). Peripherin/RDS is expressed in both rods and cones, but the ROM1 protein is present only in rods (Bascom et al., 1993). The function of rim protein is to prevent the accumulation of retinoids in the disc membrane (Sun et al., 1999; Weng et al., 1999).

The discs are constantly renewed from the base of the photoreceptor outer segment and the process of renewal requires the active involvement of the RPE. This regeneration is daily and circadian in mammalians. The RPE cells produce pseudopodia that arrive at the OS and separate the distal discs from the remaining discs. The separated discs are internalized into the RPE cell by phagocytosis and are totally degraded, so the photoreceptor outer segment length remains constant (Young and Bok, 1969; Bazan, 2006).

The visual transduction cascade

Vertebrate photoreceptors can respond to light because they contain a visual pigment in the membrane of the OS disc. The visual pigment is a protein called opsin and a cromophore derived from vitamin A, known as retinal. Each OS disc contains several million visual pigment molecules (Wolken, 1966; Palczewski, 2006).

Upon absorption of a photon of light, the retinal isomerizes from the 11-cis form to all-trans form of rhodopsin, with some conformational changes, resulting in bleaching (Hargrave and McDowell, 1992). Rhodopsin, subsequently, catalyzes the activation of the G-protein transducin. This protein, successively, stimulates cyclic guanosine monophosphate phosphodiesterase (cGMP PDE) to hydrolyze cyclic guanosine monophosphate (cGMP). It produces a decrease in the cGMP concentration and therefore cGMP-cation channels (CNCG) are closed in the photoreceptor plasma membrane (Jindrová, 1998).

In the dark cGMP cation channels actively transport sodium and calcium ions into the cell ("dark current") and maintain a continuous efflux of sodium, thereby causing depolarization of the membrane. Under light conditions channels are closed and it disrupts the Na^+ influx, while the efflux of sodium and calcium continues. The decrease in sodium concentration leads to hyperpolarization of the entire cell membrane, which results in decreasing neurotransmitter release to second-order neurons. The decline in calcium concentration intervenes in the recovery of photoreceptors after bleaching (Stryer, 1991).

The concentration of cGMP within the cell is restored by the increased synthesis of cGMP by a retinal guanylate cyclase (RetGC). These pathways are activated by the decrease in the intracellular calcium concentration and mediated by a family of calcium-binding proteins, called recoverin and guanylyl cyclase activating protein (GCAP) (Klenching et al., 1995).

Deactivation of rhodopsin starts with phosphorylation by rhodopsin kinase, GRK1 (G protein-dependent receptor kinase 1) and is followed by the capture of rhodopsin by the protein arrestin. The arrestin-binding prevents further activation of transducin and releases the 11-trans-retinal from rhodopsin (Sagoo and Lagnado, 1997). Figure 2 shows the visual transduction cascade and the type of RP inheritance which shows the mutation in some proteins.

The Retinol (vitamin A) metabolism

Vitamin A (all-trans-retinol) derivatives have an important role in the visual pathway. The 11-cis isomer of retinal, which is a derivative of retinol, is the light-sensitive component of rhodopsin in both rods and cones. In photoactivation 11-cis-retinal is isomerized to all-trans-retinol, in two steps, and is released by photoreceptors in order to be regenerated by the RPE cells. This is one of the most important functions of the RPE and is essential for the maintenance of photoreceptors (Bok, 1990; Hyatt and Dowling, 1997; Strauss, 2005).

All-trans-retinol leaves the photoreceptor cell, traverses the subretinal space where it encounters interphotoreceptor retinoid-binding protein (IRBP), and enters the RPE, where it is esterified by lecithin-retinol acyltransferase (LRAT). All-*trans* retinyl esters are the substrate for RPE protein 65 (RPE65), recently identified as the retinoid isomerase that generates 11-*cis*-retinol (Redmond et al., 2005). 11-*cis*-retinol can be esterified by LRAT and stored or oxidized to 11-*cis*-retinal by 11-*cis*-retinol dehydrogenase (11-RDH). 11-*cis*-retinal diffuses into the photoreceptor cell where it associates with opsin to regenerate the visual pigment (Edwards and Adler, 1994; Saari, 2000).

Cellular retinaldehyde-binding protein (CRALBP) is bound with its high-affinity ligands, 11-*cis*-retinal or 11-*cis*-retinol. On the other hand, cellular retinol-binding protein (CRBP) is associated with all-*trans*-retinol. Both proteins, CRALBP and CRBP, are localized in the RPE (Saari, 2000).

Alterations in the activity of these processes: renewal and shedding of the photoreceptor outer segments (OS), visual transduction and retinol metabolism are responsible for several types of retinal and RPE degenerations. To date, the cause of much retinal degeneration has been identified as gene defects, leading to reduced or incorrect function of a broad range of proteins involved in these visual reactions (Van Soest et al., 1999; Strauss, 2005). For example, inability of the RPE to phagocytose OS causes an autosomal recessive form of retinitis pigmentosa (Mullen and LaVail, 1976; Thompson et al., 2002; Duncan et al., 2003). This was first described in an animal model for retinitis pigmentosa, the Royal College of Surgeons or RCS rat (Bourne et al., 1938; Mullen and LaVail, 1976).

Animal models of RP

Hereditary retinal degenerations form a diverse spectrum of blinding disorders that affect humans and other mammals. Those diseases recognized in non-human species, either occurring naturally or obtained through transgenic manipulations, provide invaluable model systems for studies of disease pathogenesis and some treatment strategies.

There are a number of animal models available for studying RP. Importantly, many of the genes found to be mutated in animals that result in a retinal degeneration have been found to be similarly abnormal in the human. Thus, in many ways, these animal models are true ''models'' in that they faithfully mimic the human disease genetically and also produce similar phenotypic conditions of vision loss (Chader, 2002).

There are two types of RP animal models, animals with a naturally occurring mutation and those with transgenic manipulations. Naturally occurring retinal dystrophies in laboratory and companion animals represent a wealth of different mutations implicated in RP. All of these offer opportunities to further the understanding of retinal function.

We have decided to include in the classification of RP Leber Congenital Amaurosis (LCA) animal models, because some authors have described LCA as an aggressive form of RP or juvenile RP (Heckenlively, 1988; Gu et al., 1997). However we have not included, in this paper, other rod-cone dystrophies such as stargardt, achromatopsia or macular degeneration, because although animal models of these also exist (Sidjanin et al., 2002; Chang et al., 2006a; McMahon et al., 2007; Guziewicz et al., 2007) they are not homologous to human RP.

We will first present the animal models where the mutation occurs only naturally, e.g. dog, cat and chicken and then we will present the animal models with both natural and induced mutations (mouse, rat and pig).

Canines

Naturally occurring canine hereditary retinal degenerations can facilitate experiments which are currently difficult or impossible in other organisms.

Canine pedigrees have enormous genetic mapping potential, especially when well-characterized canine models are used for the analysis and treatment of corresponding human disorders (Aguirre and Rubin, 1975; Acland et al., 2001; Zangerl et al., 2006). Furthermore, the canine eye is similar in size to the human eye (Tao et al., 2002), and so utilizes the same

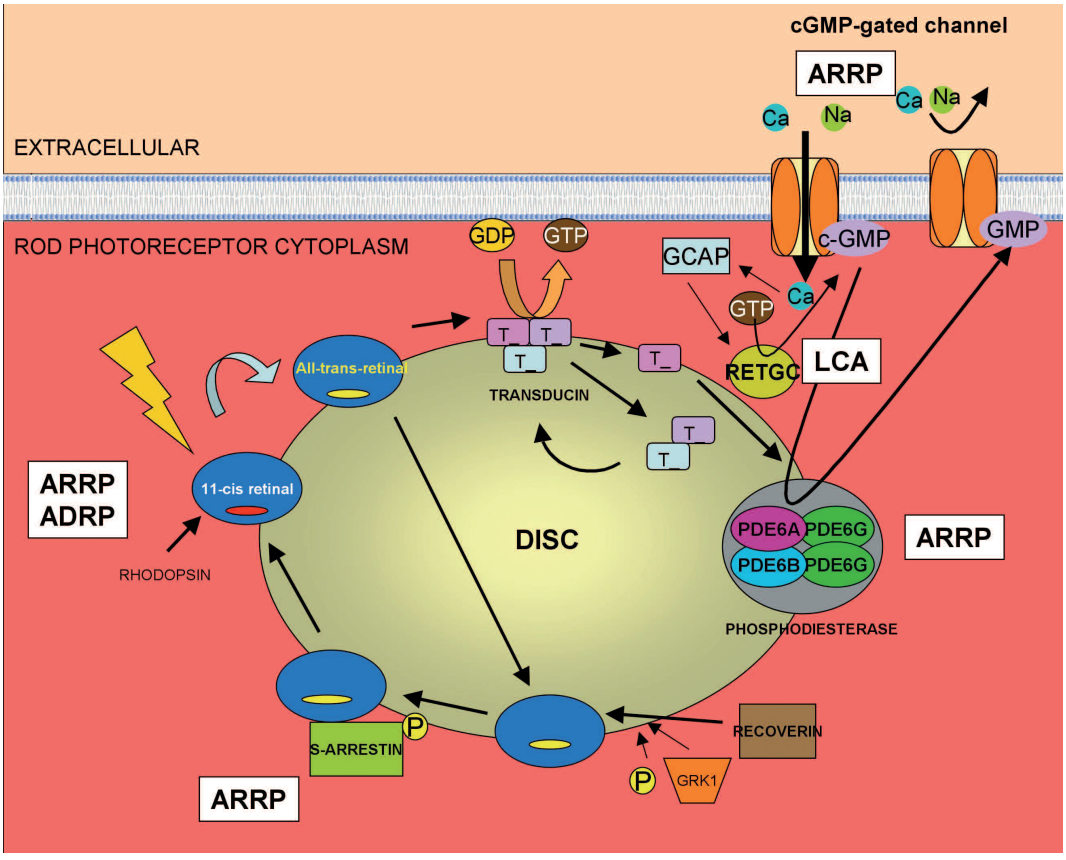

Fig. 2. The signal transduction cascade responsible for sensing light in vertebrates is one of the best studied signal transduction processes, and is initiated by the activation of the chromophore 11-cis-retinal by a photon of light. This event initiates the activation of transducin, which subsequently stimulates cGMP phosphodiesterase to hydrolyse cGMP. Closure of the cGMP-gated cation channels results in a decrease in the calcium and sodium concentration within the cell, which hyperpolarizes the photoreceptor membrane and the recovery of the cell after a bleach of light.

clinical devices as in humans.

Causal mutations for an increasing number of canine hereditary retinal degenerations are being determined. For example, pathogenic mutations have been identified in the canine *PDE6A* and *PDE6B* genes for the α and ß subunits of the cGMP specific phosphodiesterase (autosomal recessive RP) (Suber et al., 1993; Petersen-Jones et al., 1999), the *RPE65* gene (leber congenital amaurosis) (Aguirre et al., 1998), the RP GTPase regulator *RPGR (X*-linked RP) (Zhang et al., 2002) and rhodopsin RHO (autosomal dominant RP) (Kijas et al., 2002). These canine diseases present all rod-cone degenerations in which rod disease, dysfunction, and death precede loss of cones; they are collectively termed Progressive Retinal Atrophy (PRA) and are homologous to human RP (Kijas et al., 2004; Aguirre and Acland, 2006).

erd

Canine Early retinal degeneration (erd) is an early onset form of autosomal recessive retinal disease phenotypically similar to human retinitis pigmentosa. (Acland and Aguirre, 1987; Acland et al., 1989, 1999). Abnormal retinal cells appear during the period of photoreceptor differentiation and maturation. The disease is characterized by abnormal development of rod photoreceptors, particularly their outer segments, as well as the rod and cone synapses, followed by rapid degeneration of both classes of photoreceptors (Acland and Aguirre, 1987). The locus responsible for erd was mapped to canine chromosome 27 in the region corresponding to HSA12p, a region where no human retinal degeneration loci have been mapped. Canine SHARP1 gene has been localized on CFA27 in the erd interval by radiation hybrid (RH) mapping, and considered as a positional candidate gene for erd (Kukekova et al., 2003). More recently, STK38L (also known as NDR2) has also been identified as a potential candidate gene for erd (Goldstein et al., 2008, ARVO E-abstract: 1704).

At 3 months of age, dogs show aberrant development of the retina. It is expressed morphologically as disorganization of the inner and outer segment layer, with intact inner and outer segments and by diminution of the outer plexiform layer. At this age electroretinograms can be recognized by the highly characteristic negative waveform, as well as by reduced amplitudes of responses. Because rod and cone synapses develop abnormally, the ERG b-wave, which represents postsynaptic ionic flow, is essentially absent in responses from *erd*-affected dogs (Acland and Aguirre, 1987).

The affected dogs show blindness in dim light at 6 weeks of age, and become totally blind between 12 and 18 months (Acland and Aguirre, 1987).

rcd-1 and rcd-2

Rod-cone dysplasia type 1 (rcd-1) in Irish setters, together with rcd-2 in Collies, are forms of early onset of PRA. Both of them represent canine models of retinopathy resulting from abnormal retinal cyclic nucleotide metabolism. rcd-1 and rcd-2 are characterized by increased levels of cGMP in the affected retina and a deficiency in cGMP-phosphodiesterase (PDE) activity in rod photoreceptors (Aguirre et al., 1978; Wolf et al., 1978; Woodford et al., 1982).

rcd-1

Dog carries an autosomal recessive mutation in the cGMP-PDEb gene (Suber et al., 1993). Rod photoreceptor degeneration is evident by 1 month of age; nearly all rod photoreceptors have degenerated by 5 months. The cone photoreceptor degeneration is completed by about 1 year of age (Schmidt, 1985; Voaden, 1990). ERG is altered at 14 weeks after birth in the affected animals (Pearce-Kelling et al., 2001).

rcd-2

In rcd-2 ophthalmoscopic abnormalities can be detected at 3.5 to 4 months of age, including tapetal hyperreflectivity, retinal vascular attenuation, and optic nerve pallor. Retinal dysfunction can be detected by electroretinogram (ERG) as early as 16 days of age. Both rods and cones in the affected retina fail to develop normal outer segments (Santos-Anderson et al., 1980). At 6 weeks of age, when the photoreceptors of normal dogs are fully developed, only a few underdeveloped outer segments are visible in rcd2 dogs. By 2 to 2.5 months of age the outer segments completely disappear in the affected retina. Both types of photoreceptors degenerate but cones more slowly than rods (Kukekova et al., 2006). A recent study demonstrates that canine rcd-2 is the canine ortholog of human and murine RD3 (Kukekova et al., 2008, ARVO E-abstract: 1702).

RHO

Rhodopsin is the visual pigment of rod photoreceptors and it is one of many G-protein coupled receptors that is activated by light and initiates the visual transduction. There are numerous rhodopsin gene (RHO) mutations causing retinitis pigmentosa (Gal et al., 1997; Cideciyan et al., 1998).

Kijas et al., 2002 identified English Mastiff dogs with a naturally occurring dominant retinal degeneration and determined the cause in the *RHO* gene (Thr4Arg). The retinal phenotype of these dogs closely mimics humans with *RHO* mutations. This alteration in phenotype includes, in both humans and dogs, a dramatically slowed time course of recovery of rod photoreceptor function after light exposure and a characteristic topographic pattern to the retinal degeneration (Kijas et al., 2002).

Cideciyan and colleagues reported that the RHO mutant dog shows sensitivity to light, and photoreceptor

degeneration is faster after exposures to light comparable with the normal devices used clinically for eye examinations in humans (Cideciyan et al., 2005). The activation of the activator protein (AP)-1 transcription factor is a critical intermediary identified in retinal damage due to light (Gu et al., 2007).

Normal retinal structure, rhodopsin expression, receptor activation, and post-receptoral signaling in young affected dogs suggest that the pathogenesis does not involve abnormal photoreceptor development (Cideciyan et al., 1998). Photoreceptor degeneration occurs in older animals, with advanced degeneration present at 4.5-11 years of age. In younger affected dogs (11 months old), the disease is expressed with striking topographic variation. Depending on the localization in the retina, photoreceptors can be normal or show different gradation of disease. In general, more severe disease (stages 3-6 months) was present in an area surrounding the optic nerve head but centred in the temporal tapetal region of the fundus. At this stage of the disease most of the retina was comprised of structurally intact photoreceptors, but the severe disease was located centrally (Cideciyan et al., 1998).

ERG rod- and cone-mediated responses were not significantly modifies at 3-6 months of age, although by 13 months of age rod and cone photoresponses are abnormal (Kijas et al., 2002).

This RP canine model offers opportunities to explore the basis of prolonged photoreceptor recovery after light in *RHO* mutations and determine whether there are links between the dysfunction and apoptotic retinal cell death.

RPE65

RPE65 is a 65-KD membrane-associated protein (Redmond and Hamel, 2000; Bavik et al., 1992) involved in retinoid metabolism (Simon et al., 1995; Ma et al., 1998; Saari, 2000).

Molecular genetic studies including candidate gene analysis showed that the visual impairment in these dogs was caused by a homozygous 4-bp deletion in the RPE65 gene (Veske et al., 1999), resulting in a frameshift and a premature stop codon, truncating the protein.

The fundus appearance is normal, at least for the first 3-4 years of age, in affected dogs, but the disease consists of profound visual impairment present at 5-6 weeks of age in this canine model (Aguirre et al., 1998).

The ERG responses, both rod and cone mediated, are abnormal, with only low amplitude responses obtained using strong light stimulation, and the direct current (DC) ERG suggests a defect in the phototransduction process (Nilsson et al., 1992). Histological studies show large RPE lipoidal inclusions. Surprisingly, the photoreceptor cells do not show extensive pathologic abnormalities, at least in the early stages of the disease, which would be expected for animals with such functional deficits (Wrigstad et al., 1992, 1994).

However, some changes have been found in the expression of molecular markers in inner retinas of RPE65 affected dogs (Hernandez et al., 2006, ARVO E-abstract: 1035).

RPGR

Mutations in the retinitis pigmentosa GTPase regulator (*RPGR*) gene account for more than 70% of patients with XLRP, and most of these mutations are found in exon ORF15 (Vervoort et al., 2000).

There are two naturally occurring canine mutations in exon ORF1510 that cause two forms of X-linked progressive retinal atrophy (*XLPRA*).

In *XLPRA1*, a five-nucleotide deletion (del1028-1032) in exon ORF15 causes an immediate premature stop codon that results in a protein truncated of its 230 C-terminal amino acids. This mutation causes a loss of function of *RPGR*. Morphological characterization showed that photoreceptor cells develop and function normally, but then undergo progressive rod-cone degeneration. The earliest histological signs of rod degeneration are detected at 11 months of age, and are followed at later stages by cone death (Zeiss et al., 1999; Zhang et al., 2002). Retinal function remained normal until 6 months of age or later, after which there was a decrease in the amplitude of the dark-adapted rod and cone responses (Zhang et al., 2002).

In *XLPRA2*, preliminary results have shown that the disease is a much more severe and earlier form of retinal degeneration than *XLPRA1*. A two-nucleotide deletion (del 1084-1085) in exon ORF15 results in a frameshift that changes the deduced peptide sequence by the inclusion of 34 additional basic residues and increases the isoelectric point of the truncated protein (Zhang et al., 2002).

It is still unclear how the loss of function of *RPGR* or the expression of a toxic mutant RPGR protein in *XLPRA2* may initiate a cascade of molecular events that ultimately lead to photoreceptor cell death (Beltran et al., 2006). The death of rods occurs in a biphasic manner, beginning as early as 4 weeks of age, and reaching a peak at 6-7weeks. Following this initial burst, the rate of cell death is considerably slowed down, yet persists at an approximately constant rate for at least 9 months (Beltran et al., 2007). ERG abnormalities were evident by 5-6 weeks of age; value of the photo-responses was low in amplitude and abnormal in waveform, this degeneration is bigger with age (Zhang et al., 2002).

RPGRIP1

Mutations in RPGRIP1 (the retinitis pigmentosa GTPase regulator-interacting protein 1) have been shown to cause Leber congenital amaurosis, a recessive condition that occurs naturally in miniature longhaired dachshund dogs (MLHDs) (Mellersh et al., 2006).

Significant histological changes are visible at 10.5 weeks of age, including thinning of the outer nuclear layer, irregularity and attenuation of the rod photoreceptor outer segments, and early disorganization of the rod outer segment disc lamellae. By 25 weeks of age the photoreceptors are grossly degenerate (Curtis and Barnett, 1993).

Recently, Turney and colleagues undertook extensive analyses to characterize further this canine model of retinal degeneration in the MLHD (Turney et al., 2007). Extensive electrophysiological recordings were made. The recordings indicated that at 6 weeks of age, the 30-Hz flicker cone-specific ERG was reduced in amplitude in affected animals, demonstrating loss of cone function. The rod specific ERGs were effectively normal at this stage. By 40 weeks of age the disease had progressed such that no electrophysiological indication of residual photoreceptor function remained, with cone photoreceptors being more severely affected in the first instance, followed by progressive rod involvement, The authors suggest that the retinal degeneration in these animals is a cone-rod dystrophy and not, as previously thought (Curtis and Barnett, 1993), a primary rod degeneration with secondary cone loss (Turney et al., 2007).

Cats

Only two forms of feline progressive retinal atrophy (PRA) have been studied extensively: an autosomal recessive rod-cone degenerative disorder (rdAc model) and autosomal dominant early-onset retinal degenerative disease (Rdy model). Other feline forms of PRA that have been described have a different age of onset or mode of inheritance, suggesting that these diseases represent at least different alleles but not different genes (Wets-Hyde and Buyukmihci, 1982; Narfstrom, 1983, 1985a,b; Barnett and Curtis, 1985; Leon et al., 1991; Chong et al., 1999).

Domestic cats have manageable-sized eyes for examination and surgical and therapeutic manipulations, and present one of the most highly characterized animals for visual neurophysiology, (Chong et al., 1999). They have sufficient genetic resources for efficient genetic studies (O'Brien et al., 1997, 2002; Menotti-Raymond et al., 2003a,b). Cat globes are physiologically and anatomically similar to human globes (Lewis et al., 2002) and cats experience less severe intraocular inflammation after surgery than dogs (Rankin et al., 2002). Combined with the low housing costs of cats, these features suggest these cats could be an efficient model for research investigating transplantation, gene therapy, and drug therapy (Chader, 2002).

rdAc

This important cat model of human RP has been maintained for more than 25 years by Kristina Narfstrom, which segregates for autosomal recessive retinal degeneration. Affected cats have normal vision at birth but develop early funduscopic changes at the age of 1.5-2 years (Narfstrom, 1985a).

By electroretinographic (ERG) studies it has been demonstrated that at the age of 7 months affected cats present reduced a-wave amplitudes (Kang Derwent et al., 2006). Morphological changes have been initially observed in rod photoreceptor outer segments at 5-8 months old (Narfstrom and Nilsson, 1989). Cones degenerate later and complete degeneration and blindness occurs at the age of 3-5 years (Narfstrom, 1985b).

Recently it has been reported that these rdAc (late-onset photoreceptors degeneration) cats have single nucleotide polymorphism (SNP) in an intronic region of the CEP290 gene, which creates a strong canonical splice donor site, resulting in a 4-bp insertion and frameshift in the mRNA transcript, with subsequent premature truncation of the protein (Menotti-Raymond et al., 2007). Mutations in this gene are attributed to Leber's congenital amaurosis (den Hollander et al., 2006).

Rdy

The Rdy model, in Abyssinian cat, presents an autosomal dominant mode of inheritance (Barnett and Curtis, 1985). The gene Rdy has been adopted to the name of this cat model (Curtis et al., 1987).

The first clinical sign, dilatation of the pupils, was usually present by 3 weeks of age and the appearance of secondary nystagmus at 4-5 weeks of age, suggesting severe visual deprivation during the early stages of photoreceptor differentiation. These clinical signs are in accordance with the histological and ultrastructural findings present in the retina of the earliest affected kitten at 22 days of age, and the virtual extinction of the ERG in the same animal at 17 days (Curtis et al., 1987).

Electron microscopy shows that, in the 22-day retina, the photoreceptor inner segments are rudimentary and the outer segments are absent, whereas in the 40-day retina both outer and inner segments are developed, although the outer segments show marked disorganization and degenerative changes (Curtis et al., 1987).

Chicken

The chicken eye differs from that of a human in a number of ways. Unlike the rod-dominated human retina, avian retinas are generally cone-dominated. (Meyer, 1986). Approximately 82% of the inner segment area of the chicken retina consists of double-cones, a species of photoreceptor found in all vertebrate groups except placental mammals (Walls, 1942; Matsusaka, 1963). However the chicken eye can be compared in size to that of a human, which facilitates pathological

examination and should simplify the testing of experimental therapies. The level of conservation of gene order between the chicken and human genomes is similar to that between humans and mice, in spite of the much greater evolutionary separation (Burt et al., 1999). Therefore the study of spontaneously occurring inherited blindness in chickens as a model for human retinal dystrophies has the potential to make a valuable contribution, both to understanding these conditions and to the search for therapies.

rd

The research efforts have focused on a retinal degeneration (rd) chicken strain carrying an autosomal recessive mutation that produces blindness at hatching (Cheng, 1980). Pathology appears 7-10 days after hatching and is limited to the photoreceptor cells located in the central retina, and proceeds from central to peripheral regions (Ulshafer et al., 1984; Ulshafer and Allen, 1985a). At 115 days of age, very few cone photoreceptors remain in the central retina, and by 6-8 months, the photoreceptor cell layer is mostly degenerated (Ulshafer and Allen, 1985b). Degenerative changes in the retinal pigment epithelium and inner retina become apparent only after photoreceptor degeneration is underway (Ulshafer and Allen, 1985).

The low level of cGMP in rd chicken retina is a consequence of a null mutation in the photoreceptor *guanylate cyclase* (GC1) gene. Thus, the rd chicken is a model for human Leber congenital amaurosis. The absence of GC1 in rd retina prevents phototransduction and the survival of cones and rods is affected. However, it does not interfere with normal photoreceptor development (Semple-Rowland et al., 1998).

The feature of Leber congenital amaurosis disease that distinguishes it from other animal models of recessive retinitis pigmentosa is that light fails to elicit measurable ERGs before any signs of rod or cone photoreceptor degeneration are detected (Ulshafer et al., 1984).

rdd

The rdd (retinal dysplasia and degeneration) phenotype in chickens was first reported in 1979 in Scottish commercial stocks imported from the USA (Randall and McLachlan, 1979). The chicken rdd trait is a sex-linked recessive form of inherited retinal degeneration with many similarities to severe early-onset retinitis pigmentosa in humans. Linkage mapping places rdd in a region homologous to human chromosomes 9p and 5q. The strongest candidate gene in these regions as judged by phenotype is *PDE6A*, mutations in which cause recessive retinitis pigmentosa in humans (Burt et al., 2003).

Chicks at hatching had only limited vision and were noticeably less active than normal birds. Signs of defective vision became more apparent by 8-10 weeks when head nodding and small circling movements developed. Vision deteriorated progressively and by sexual maturity at 15 weeks, most chickens were blind. A marked reduction in photoreceptors compared to normal controls was evident by day 18 of incubation and continued after hatching. The retina continued to thin due to cell loss of photoreceptor and inner nuclear layers (Wilson et al., 1982).

At three weeks of age, rdd chickens have a flat ERG indicating severe loss of visual function (Burt et al., 2003).

Genetically modified animal models have been produced, including transgenic mice, rats and pigs. Recently, Kondo et al., has generated a rabbit that expresses a mutant rhodopsin gene, Pro347Leu. ERGs indicated a progressive retinal dysfunction with age. Histology demonstrated a progressive loss of photoreceptors and a shortening of the outer segments (Kondo et al., 2008, ARVO E-abstract: 2200).

In the case of mice and rats naturally occurring inherited retinal degeneration exists as well, but in pigs there is only a transgenic model.

In the next part of the review, first, we show retinitis pigmentosa animal models which have natural mutations, and then we explain the transgenic mutations of each animal model. The genetically modified animals can be created by means of transgenesis or producing knock-out animals.

Mice

The rodless mouse was the first animal where retinal degeneration (rd) was described (1920s), and it was later shown to be identical to the rd mouse, which is now a widely researched model of recessive RP (Pittler et al., 1993). The rds model was described in the late 1970s and extensively characterized in the 80s by Sanyal (Sanyal and Jansen, 1981). The mouse has distinct advantages over other animal models for studying age-related human conditions. The average life span of the mouse is two years, and it is possible to see the ERG changes or histological findings of aging by five months in some mouse strains. Protocols for genetic studies in mice are well established. Because defined breeding experiments can be used for linkage analysis, a single gene disease typically can be mapped in less than six months. Mouse and human genomes have at least a 90% homology of functional genes and correlation maps between the two species allow gene locations to be precisely determined once they are found in either species (Rakoczy et al., 2006).

Peripherin-rds

A naturally occurring rds-peripherin null mutation in the mouse causes a retinal degeneration termed ‘retinal degeneration slow’, or rds (Sanyal et al., 1980; Sanyal

and Jansen, 1981; Travis et al., 1989; Connell et al., 1991). Several pathogenic mutations in P/rds are associated with autosomal dominant retinitis pigmentosa.

In this degeneration, a tetraspanning membrane protein, peripherin, is involved in photoreceptor outer segment disc morphogenesis and maintenance (Molday et al., 1987; Connell, et al., 1990, 1991; Arikawa et al., 1992).

rds is an inherited retinal degeneration that has been identified in an inbred strain of mice (Van Nie et al., 1978). Mice that are homozygous for the rds gene fail to develop the outer segment of photoreceptor cells (Sanyal and Jansen, 1981; Cohen, 1983; Jansen and Sanyal, 1984). Other retinal cells and other parts of the photoreceptor cells, including the inner segment, cell body, synaptic region, and cilium, develop normally during the 3-week postnatal period. After this time, however, the photoreceptor cells lacking the outer segments begin to undergo a slow progressive degeneration, and after 12 months few photoreceptor cells remain (Démant et al., 1979). At P21 rod-mediated ERG presents severely impaired responses (Cayouette et al., 1998).

rd

The first retinal degeneration, and one of major importance, is rd1 (formerly rd, identical with Keeler rodless retina, r) (Keeler, 1966; Pittler et al., 1993).

This model has a deficiency in the rod photoreceptor-specific cGMP phosphodiesterase subunit (PDE), a mutation homologue to autosomal recessive retinitis pigmentosa (McLaughlin et al., 1993; Frasson et al., 1999b). The rd1 photoreceptor cell death is both early and rapid, starting at approximately P10 and almost reaching completion at P21 (Sanyal and Bal, 1973; Bowes et al., 1990; Jiménez et al., 1996). Several other studies have also noted morphologic changes in other areas of the inner retina (Carter-Dawson et al., 1978). In this model ERGs were never normal, but rod and cone ERG a- and b-waves were measured at P18 and steadily declined over 90% by two months of age (Chang et al., 2007).

rd4

This autosomal dominant retinal degeneration was found in a stock carrying the chromosomal inversion In(4)56Rk, which was induced in a DBA/2J male. The inversion is homozygous lethal and in heterozygotes is always associated with retinal degeneration. In affected mice, the retinal outer nuclear layer thickness begins to decrease at 10 days of age, showing total loss at 6 weeks. Retinal vessel attenuation, pigment spots, and optic atrophy appear in the fundus at 4 weeks of age (Roderick et al., 1997). The recordable electroretinograms are poor between 3 and 6 weeks and are barely detected thereafter (Roderick et al., 1997; Kitamura et al., 2006).

The phenotype is always associated with an inversion encompassing nearly all of chromosome (Chr)4 (Roderick et al., 1997). Recently, it has been demonstrated that the distal breakpoint of the inverted rd4 Chr 4 is localized in the second intron of the Gnb1 gene. Gnb1, coding for the transducin ß-1-subunit (Tß1) protein that is directly involved in the response to light of rod photoreceptors. Before the beginning of retinal degeneration in Rd4 retina, the levels of Gnb1 mRNA and T,1 protein are 50% of those in wild-type retina (Kitamura et al., 2006).

rd8

Mutations within the CRB1 gene have been shown to cause human retinal diseases, including retinitis pigmentosa and Leber congenital amaurosis (Den Hollander et al., 2001; Bernal et al., 2003; Hanein et al., 2004). Retinal degeneration 8 (rd8) mouse model has a single base deletion in the *Crb1* gene. This mutation is predicted to cause a frame shift and premature stop codon which truncates the transmembrane and cytoplasmic domain of CRB1. Shortened photoreceptor inner and outer segments are observed at 2 weeks of age, suggesting a developmental defect in these structures rather than a degenerative process. Photoreceptor degeneration is observed only within regions of retinal spotting, which is seen predominantly in the inferior nasal quadrant of the eye, and is caused by retinal folds and pseudorosettes (Mehalow et al., 2003). ERGs demonstrate initial attenuation of the a- and b waves compared to normal controls and remain relatively stable for one year, at which time further progressive amplitude loss is noted (Chang et al., 1999).

The Crb1 rd8 mouse model will facilitate the analysis of Crb1 function in the neural retina and the identification of interacting factors like candidate retinal disease genes (Mehalow et al., 2003).

rd10

Mutant mice homozygous for the rd10 mutation show retinal degeneration with sclerotic retinal vessels at 4 weeks of age. Histology at 3 weeks of age shows retinal degeneration. Electroretinograms of rd10 mice were never normal. The maximal response occurred at 3 weeks of age and was non-detectable at 2 months of age. Genetic analysis showed that this disorder was caused by an autosomal recessive mutation that occurred in the beta subunit of the rod phosphodiesterase gene. Therefore, the gene symbol for the rd10 mutation is now Pde6brd10. Rd10 mice may provide a good model for studying the pathogenesis of autosomal recessive retinitis pigmentosa (ARRP) in humans. It may also provide a better model than rd1 for experimental pharmaceutical-based therapy for its later onset and

milder retinal degeneration (Chang et al., 2007).

rd12

A naturally occurring rodent model of RPE65 LCA, is the *rd12* mouse, which has been recently reported (Pang et al., 2005). In this animal, a recessive nonsense mutation in the Rpe65 gene leads to the absence of RPE65 protein and blockage of the retinoid cycle. Despite undetectable RPE65, 11-cis-retinal, no obvious structural change in the retina was observed until 3 weeks after birth, when small lipid-like droplets in RPE cells were first detected. These increases in the frequency and size with age were accompanied by progressive retinal photoreceptor degeneration. The rod ERG response was profoundly diminished at 3 weeks of age (Pang et al., 2005).

CEP290: rd16

Rd16 mutant mouse exhibits early-onset retinal degeneration with autosomal recessive inheritance. This mouse carries an in-frame deletion in a novel centrosomal protein, CEP290. The CEP290 protein is localized to the connecting cilium of photoreceptors and associates with several ciliary and centrosomal proteins, including RPGR. In the rd16 retina an altered interaction of RPGR and mutant CEP290 and a redistribution of RPGR and phototransduction proteins occurs (Chang et al., 2006b).The phenotype of homozygote rd16 mice can be distinguished from wild-type (WT) animals by the appearance of white retinal spots at 1 month and large pigment patches at 2 months of age. Electroretinograms under dark- and light-adapted conditions indicate a considerable deterioration of rod and cone functions in the rd16 homozygotes compared with the WT as early as postnatal P18. Light microscopy of the rd16 retina shows degeneration of outer segments and reduction in the thickness of the outer nuclear layer as early as P19 and progresses with age (Chang et al., 2006).

I-255/256

Transgenic mice express a mutant opsin gene with a 3-bp deletion of isoleucine at codon 255/256. This highly conserved amino acid is located in the sixth transmembrane domain of the rhodopsin protein. Phenotypic changes are similar to those observed in ADRP patients carrying the same mutations (Penn et al., 2000). This model is characterized by early onset of a rapidly progressing retinal degeneration. At P5 to P10, the photoreceptors appear to be developing normally but at P15 half of these cells have disappeared. By P20, only one row of photoreceptor nuclei remained in the outer nuclear layer, indicating that both rods and cone are affected by this mutation (Penn et al., 2000).

The mutant phenotype shows rapid progression of rod photoreceptor cell death that leads to complete absence of a dark-adapted ERG b-wave by P20 (Gryczan et al., 1995).

Knockout RPE65

A transgenic knockout RPE65 mouse ($RPE65^{-/-}$) has been produced (Redmond et al., 1998) that over accumulates retinyl esters in the RPE and lacks 11-cis-retinal. This mouse also exhibits congenital blindness with severely attenuated ERGs (Dejneka et al., 2004). Rod photoreceptors appear to develop normally, with no apparent loss of cells until approximately 6 months of age (Van Hooser et al., 2000; Rohrer et al., 2003). In contrast, cones degenerate quickly in this model (Lai et al., 2004; Znoiko et al., 2005), and so it is particularly interesting to note that in the $RPE65^{-/-}$ mouse model, cones seem to be more vulnerable (Rohrer et al., 2005). $RPE65^{-/-}$ mice showed significant cone loss in both the central and ventral retina between 2 and 3 weeks of age (Znoiko et al., 2005). The remaining photoresponse, in this model, is due to a rod response, based on their failure to elicit a response from a 4- to 5-week-old using normal ERG protocols (Seeliger et al., 2001).

P347S

To explore the pathogenic mechanism of dominant mutations affecting the carboxyl terminus of rhodopsin that cause retinitis pigmentosa five lines of transgenic mice have been generated carrying the proline-347 to serine (P347S) mutation. The severity of photoreceptor degeneration correlated with the levels of transgene expression in these lines (Li et al., 1996). This transgenic mouse has been developed expressing a human rhodopsin with the P347S mutation (Li et al., 1996), and another group has done it with a pig rhodopsin (Weiss et al., 1995).

The P347S mutation appears to cause aberrant transport of rhodopsin, possibly by disrupting a signal sequence that normally directs the vectorial transport of rhodopsin to the outer segments (Deretic et al., 1996; Li et al., 1996).

In lines with an intermediate level of expression, approximately four to five rows of photoreceptor nuclei remained at 20-30 days of age. By 4 months of age, only one to two rows of nuclei remained. In lines with the lowest expression, photoreceptor cell loss was not apparent at 20-30 days, but the outer segments appeared slightly shorter and disorganized. ERG amplitudes appeared to correlate with the extent of photoreceptor cell loss, thus at 20-30 days of age in some lines amplitudes were diminished (Li et al., 1996).

Peripherin-rds 307

Mice heterozygous for the codon 307 mutation showed a marked reduction in rod photoreceptor cell numbers. Nine or ten rows of photoreceptor nuclei were

present in the central retina at 2 months, four or five rows at 6 months, three or four rows at 10 months and two or three rows at 12 months.

Mice homozygous for the codon 307 mutation exhibited severe loss of rod photoreceptors with the ONL being reduced to three or four nuclei in thickness at 5 weeks and essentially a single row at 4 months.

No convincing rod-isolated responses could be elicited from homozygous rds-307 mice even at 1 month of age, although relatively normal rod responses persist up to 6 months in heterozygotes, but diminish significantly by 10 months (McNally et al., 2002).

Q344ter

Transgenic mice that express a truncated rhodopsin due to a mutation resulting in a stop codon at position 344, referred to as Q344ter mice, develop degeneration of rod photoreceptors starting at about P10 and completed by about P21 (Sung et al., 1994). This same mutation has been identified in patients with dominant RP (Sung et al., 1991). Therefore, Q344ter mice provide a model of rapidly progressive dominant RP. Three independent lines were obtained that carry the Q344ter transgene (Sung et al., 1994).

In humans, a diagnosis of RP is often based upon the finding of abnormalities in the dark-adapted electroretinogram (ERG) (Heckenlively, 1988). Over time, the amplitude of the ERG response shows a decline that is parallel to the degeneration of the retina. This transgenic mouse model shows slowing of transduction in rods, at 3-4 weeks of age. It may represent the lengthened in ERG implicit time (the time interval between the light stimulus and the peak of the b-wave) in RP patients (Sung et al., 1994).

rho

Animal models of retinal degeneration provide useful systems in which to undertake such explorations. Mice carrying a targeted disruption of the rhodopsin gene lose their photoreceptors over a period of ~3 months, although the severity of degeneration was influenced by the nature of the genetic background upon which the mutation was expressed (Kennan et al 2002).

$Rho^{-/-}$ mice have no functional rhodopsin gene and the rod function is completely absent (Heckenlively, 1988; Humphries et al., 1997), because of the impaired phototransduction and the failing morphogenesis of rod outer segments (Morrow et al., 1998). Because the $Rho^{-/-}$ mice have no rod visual pigment rhodopsin, they have no rod function, and their photopic and scotopic ERG signals are entirely generated by cones (Jaissle et al., 2001).

Cone degeneration begins at about post weeks 6 age and leads to an almost complete loss of outer segments by week 13. The sequence of changes can be observed histologically, begining with normal-looking cones at P14. At P58, the degeneration of cones was clearly visible, and in advanced stages at P77 no clear cone outer segments were detectable (Jaissle et al., 2001).

VPP

VPP mice express a mouse opsin gene containing three points mutation within a seven aminoacid sequence near the N-terminus of the molecule (Naash et al., 1993). One is the P23H mutation, whereas the other two mutations result in the substitution of glycine for valine at position 20 (V20G), and leucine for proline at position 27 (P27L). These mice are called "VPP" to identify the aminoacid substitutions. Neither V20G nor P27L mutations has been associated with ADRP in humans (Sung et al., 1991; Berson et al., 1993; Gal et al., 1997) but VPP mice exhibit a slowly progressive retinal degeneration, as in patients with ADRP (Wu et al., 1998).

During early postnatal development, these animals appear to develop normal photoreceptors but their light sensitive outer segments never reach normal length, this decrease in average length of outer segments was accompanied by a decrease in the number of photoreceptors (Naash et al., 1993).

Reduced light-evoked responses (ERGs) are present in mutant mice at P30, when no structural damage of photoreceptor cells except a shortening of outer segments is evident (Naash et al., 1993).

Mouse models of retinal degeneration have been investigated for many years in the hope of understanding the causes of photoreceptor cell death. In this review, as we said before, we studied the RP animal models and Leber congenital amaurosis, like a type of early onset-RP, but there exist an enormous variety of retinal degeneration diseases in mice: for example models in usher syndrome (rd3) (Danciger et al., 1999), Bardet-Biedl syndrome (rd5 or TULP1) (Noben-Trauth et al., 1996), stargardt disease (rd6) (Hawes et al., 2000), s-cone syndrome (rd7) (Sharon et al., 2003), achromatopsia (cpfl1) (Chang et al., 2001), etc.

Rats

Rats exhibit retinal disease remarkably similar to that observed in humans. Rat photoreceptors have been well studied, and there is extensive knowledge of basic biological mechanisms. The rat eye is several times larger than the mouse, which simplifies surgical manipulations and electroretinographic evaluation. In addition, rats breed as rapidly as mice, generating large litters in a short gestational time (Flannery, 1999).

RCS

The Royal College of Surgeon (RCS) rat is a naturally occurring animal model of recessively inherited retinal degeneration, in which cooperation

between the photoreceptor cell and the RPE has gone wrong, and there is postnatal loss of photoreceptor cells (Dowling and Sidman, 1962; Herron et al., 1969).

RCS rat has a recessive mutation occurring as a deletion, which disrupts the gene encoding for the receptor tyrosine kinase, Mertk (D'Cruz et al., 2000; Nandrot et al., 2000). The site of major expression of Mertk in the rat retina is the RPE (D'Cruz et al., 2000). The deletion results in production of an aberrant mRNA leading to a frameshift and premature stop signal 20 codons after the start of the ORF. This severe disruption of a gene that normally encodes a 994-aa protein is almost certainly a null mutation (Vollrath et al., 2001).

Histological examination of the RCS retina reveals an abnormal build-up of outer segment debris between the photoreceptor outer segments and the RPE (Dowling and Sidman, 1962; Herron et al., 1969; Bok and Hall, 1971). The retinal ONL cell degeneration begins early in postnatal life (20-30 days) leading to complete loss of the ONL layer, and this degeneration steadily proceeds until about 70 days of life (Strauss et al., 1998; Amendola and Aloe, 2002). The RCS rat mutation leads to the progressive death of rods followed by cones (Dowling and Sidman, 1962; Cicerone et al., 1979). The RCS rat has been used widely to study retinal degeneration and to develop experimental therapies directed at limiting the progress of photoreceptor loss (La Vail, 2001; Lund et al., 2001; Vollrath et al., 2001).

At P21, both scotopic mixed a-waves and b-waves were reduced in amplitude compared with age-matched nondystrophic RCS rats. Photopic intensity responses at P21 also showed smaller maximal b-wave amplitudes (Cuenca et al., 2005).

P23H

One of the most common rhodopsin mutations is the P23H (Dryja et al., 1990b), it is a model of autosomal dominant "gain of function" retinitis pigmentosa Steinberg et al., 1996). The P23H transgenic rat carries a mutant mouse opsin gene in addition to the endogenous native opsin genes (Lewin et al., 1998). The opsin transgene contains a histidine substitution at the proline 23 position (Machida et al., 2000) and undergoes a gradual photoreceptor loss that is generally characteristic of human ADRP (Berson et al., 1991a). Three lines of P23H transgenic rats carrying a mouse transgen have been created. They differ in their rates of degeneration as measured by ERG and histological analysis (Machida et al., 2000; Organisciak et al., 2003). Lines 1 and 3 provide information about late severe and early mild degeneration, respectively (Machida et al., 2000).

The P23H rat shows a progressive loss of rod photoreceptors over several months. Abnormal rod ERG function was detected as early as 4 weeks of age. Some authors have shown that the a-wave is more sensitive than the b-wave for tracking the histopathologic status across a wide range of photoreceptor cell loss in this rat RP model (Machida et al., 2000). By 21 days of age in the P23H rat retina, there is already substantial loss of rods. The cone pathway is relatively unaffected. By 150 days, when rods are absent from much of the retina, some rod bipolars remain and dendrites of rod and cone bipolar cells form synaptic complexes associated with cones and horizontal cell processes (Cuenca et al., 2004).

S334ter

The S334ter transgenic rat is a model of autosomal dominant "gain of function" and it expresses a mutated rhodopsin gene (Steinberg et al., 1996). The opsin transgene contains a termination codon at residue 334, resulting in the expression of a rhodopsin protein lacking the 15 C-terminal amino acids. The C terminus is involved in rhodopsin localization to the outer segments, and its absence contributes to photoreceptor degeneration by a caspase-3-dependent mechanism (Liu et al., 1999; Green et al., 2000).

Several lines of S334ter rats have been made with different rates of retinal degeneration, proportional to the transgene copy number and the resultant level of expression of the mutant mouse opsin. The S334ter-line four (S334ter-4) rats have a relatively low mutant opsin expression and a correspondingly slow, progressive retinal degeneration, and this permits more time to see a therapeutic effect (Green et al., 2000).

At P15 when degeneration begins, these animals have 8 to 10 rows of photoreceptor nuclei in the outer nuclear layer (ONL). The degeneration rate is biphasic, with a faster initial rate between P15 and P60 and a slower one afterward. The ONL degenerates to 2 to 4 rows of nuclei by P60 and to 1 to 2 rows by P120 (Green et al., 2000). At P60 electroretinogram shows a decrease in a and b wave amplitudes compared with control animals (Lau et al., 2000).

Pigs

Genetic engineering in a larger animal model has produced an excellent model for RP in the pig. The pig eye is not only similar in size to the human but has a fairly similar number and distribution of rod and cone cells, and many authors have reported the similarities between the pig eye/retina with that of the human (Prince et al., 1960; Peichl et al., 1987; De Schaepdrijver et al., 1990; McMenamin and Steptoe, 1991; Olsen et al., 2002; Ruiz-Ederra et al., 2003, 2004; Garcia et al., 2005). The porcine retina is even more similar to the human retina than that of other large mammals, such as the dog, goat, cow or ox (Prince et al., 1960).

Additionally, tools employed for diagnostics in ophthalmology, such as optical coherence tomography, corneal topography imaging or multi-focal electro-retinography can be applied to the pig eye, without requiring adaptation supporting the use of this animal as a good model for ophthalmological studies (Ruiz-Ederra et al., 2003, 2004; Maverick et al., 2004; Van Velthoven et al., 2004).

Mutant rhodopsin transgenic pigs have been created

as models for RP research; the mutations are P347L and P347S, which cause autosomal dominant retinitis pigmentosa (ADRP) in humans (Kraft et al., 2005).

P347L

Petters et al. produced a porcine model in which the degeneration was quite similar to human RP (Petters et al., 1997). The transgenic animals expressing a mutated opsin gene (Pro347Leu) have early rod loss with slower cone cell degeneration, making the pig a very attractive model for preclinical efficacy drugs and safety trials.

Similar to retinitis pigmentosa in patients with the similar mutation (Berson et al., 1991b; Dryja et al., 1990a; Gal et al., 1997), these pigs have early, severe rod degeneration. At birth, rod numbers were normal in the transgenic retinas, but their outer segments were short and disorganized and their inner segments contained stacks of rhodopsin-positive membranes. Rod cell death was apparent by 2 weeks and was pronounced in the mid periphery and central regions by 6 weeks. Far peripheral rods were initially better preserved, but by 9 months virtually all rods had degenerated. Cones degenerated more slowly than rods (Li et al., 1998).

Rod maximum amplitude in P347L pig was 12% of value mean normal at 4 weeks, 5% at 47 weeks, and not detectable by 80 weeks (Banin et al., 1999). These results would be consistent with reduced rod outer segment membrane area through cell loss or decreased outer segment length (Hood and Birch, 1994).

Parallel to severe rod degeneration, ectopic synapses form early between cone photoreceptors and rod bipolar cells and this introduces a complicating factor into the design of therapy (Peng et al., 2000). A P347S transgenic pig model has also been produced that showed a much more gradual rate of rod degeneration. It was produced under the supervision of Dr. Petters (Kraft et al., 2005). This model affords a more extended time period for therapeutic intervention (Shaw et al., 2001) but really, there is very little information about P347S pigs, as there are no inmunohistochemical or electrophysiological studies.

In Table 1 we show the different RP animal models, the natural and transgenic mutations and a summary of their genotypes and phenotypes. Furthermore Fig. 3 represents the different times of degeneration in each animal model according to studies undertaken. It is important to decide which model is more relevant for the specific study.

Different therapies in the study of RP

There is a critical need to achieve a better understanding of the disease mechanism in RP in order to design rational therapies. To this end, a major research effort is under way to identify the cellular, molecular, and systemic factors involved in the pathophysiology of this disease. Investigations are using many different approaches, including epidemiology, morphology, cell and molecular biology, and genetics.

Animal studies have not proceeded in isolation; there has been a great deal of interaction between basic researchers and clinical studies involving patients. In fact, animal models of inherited retinal diseases have played a vital role in uncovering the genetic and biochemical defects in some human retinal diseases.

The goals of preclinical safety evaluation for retinal therapies will be to recommend initial safe starting doses in humans, to identify potential target organ(s) of toxicity, to identify appropriate parameters for clinical monitoring, and to identify "at risk" patient populations for exclusion from a clinical trial (Flannery, 1999).

Different therapeutic strategies have been developed, aimed at curing the specific genetic disorder (i.e. gene therapy) (Bainbridge et al., 2008; Maguire et al., 2008) slowing down or even stopping the process of photoreceptor degeneration (growth factors) (Sieving et al., 2006), vitamin A (Holopigian et al., 1996; Berson, 1998) and DHA supplementation (Mukherjee et al., 2007), preserving the cones implicated in the central visual function (identification of endogenous cone viability factors (Fintz et al., 2003) or even replacing the lost cells by means of transplantation (Lund et al., 2003), use of stem or precursor cells (Delyfer et al., 2004)) and the use of retinal prosthesis (Gekeler et al., 2006). Still, many obstacles will need to be overcome before most of these strategies can be applied to humans.

In this review, we describe the different therapeutic strategies under study worldwide and report the latest results in this field.

Gene therapy

Mutations in every identified gene whose expression is restricted to rod photoreceptor outer segments have been found associated with RP phenotypes (Hims et al., 2003). These include mutations in the visual pigment rhodopsin (Berson et al., 1991b; Rosenfeld et al., 1992; Li et al., 1994); enzymes of the phototransduction cascade, like transducin a-subunit (Dryja et al., 1996); guanylate cyclase (Perrault et al., 1996); cGMP-dependent phosphodiesterase (McLaughlin et al., 1993) and arrestin (Fuchs et al., 1995). Other structural or trafficking proteins like mutations in peripherin/RDS (Dryja et al., 1997) or ABCA4 (Allikmets, 2000). More rarely, mutations affect genes expressed in the adjacent retinal pigment epithelium (RPE) cells and coding proteins involved in vitamin-A metabolism as is the case of CRALBP (Maw et al., 1997) and RPE65 (Marlhens et al., 1997) or in phagocytosis of photoreceptor outer segments, Mertk (D'Cruz et al., 2000). Different gene-mediated therapeutic strategies have been developed for the treatment of inherited retinal degenerations using either viral or non-viral vectors.

In mutations leading to change of function (autosomal recessive or X-linked recessive retinal degenerations) the principle of gene therapy is to correct the genetic defect by the introduction of a wild-type version of the mutated gene into the cells in which normal functioning of this gene is required

(photoreceptors or RPE cells).

The animal models of autosomal recessive retinal degeneration most commonly studied are the rd mouse, the rds mouse and the Royal College of Surgeons (RCS) rat. In these models of retinal degeneration, gene therapy has been performed using several different vectors and has resulted in the slowing down of the photoreceptor degeneration process in the rd mouse (Bennett et al., 1996; Jomary et al., 1997; Kumar-Singh and Farber, 1998; Takahashi et al., 1999), in the rds mouse (Ali et al., 2000), and in the RCS rat (Vollrath et al., 2001). The most conclusive results were observed in the RPE65$^{-/-}$ dog. This canine model of an early severe inherited retinal degeneration, called Leber congenital amaurosis, lacks the RPE65 protein involved in retinoid metabolism. By injecting a recombinant AAV carrying the missing wild-type RPE65 cDNA into the subretinal space, definitive recovery of visual function occurred that was assessed by electrophysiological and behavioural tests (Acland et al., 2001). Recently, it has

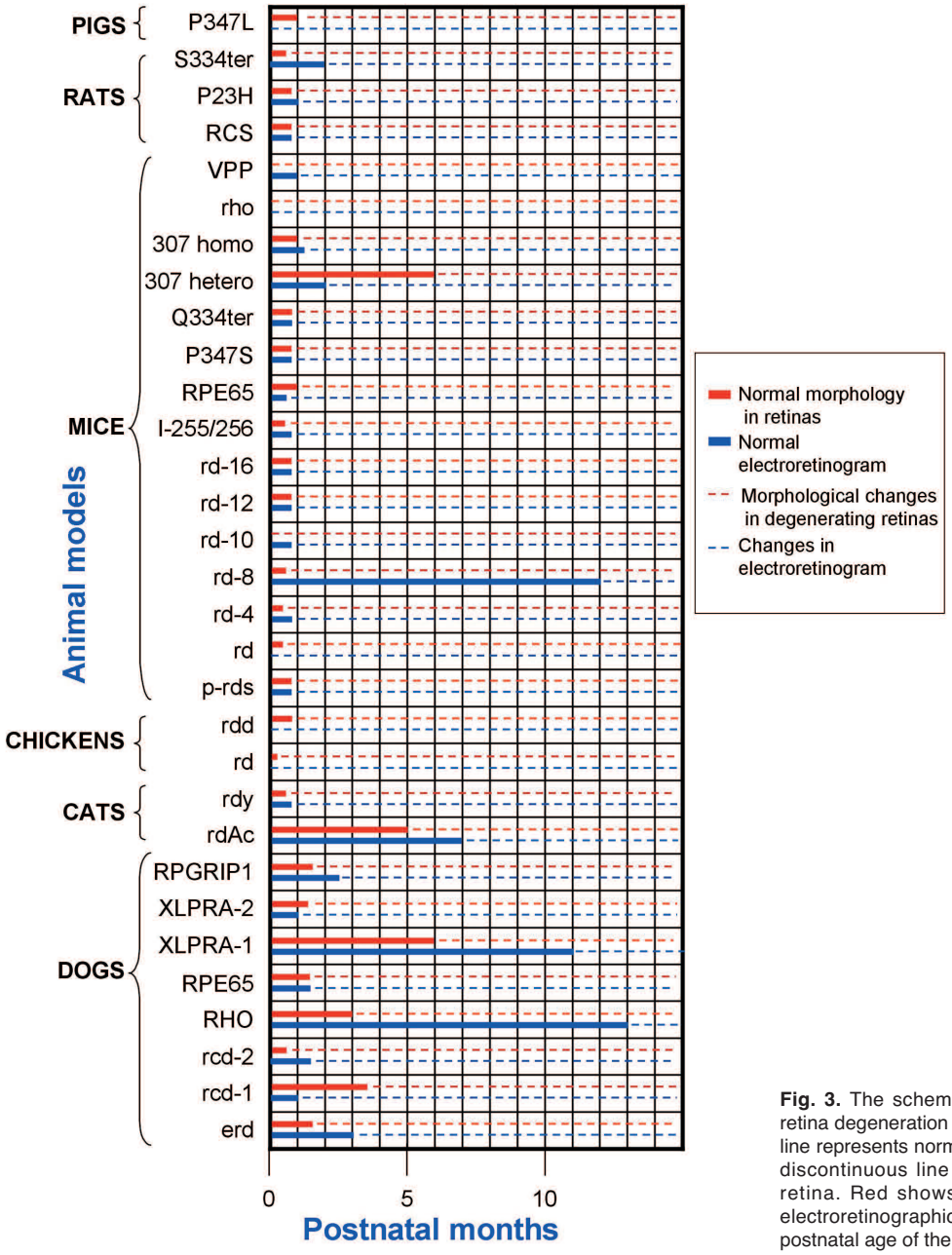

Fig. 3. The schema represents the initiation of the retina degeneration in each animal model. Continuous line represents normal retina (non degenerating) while discontinuous line represents degeneration of the retina. Red shows morphological state and blue electroretinographic state. The squares indicate the postnatal age of the animal, in months.

Table 1. Different RP animal models and differences between their genotypes and phenotypes.

Animal models	Genotype	Retinal phenotype	Reference
Canines (Natural)	erd	Affected dogs show night blindness at 6 weeks of age. The disease is characterized by abnormal outer segments and rod and cone synapses, followed by degeneration of both photoreceptors. It has been observed that amplitudes of ERG are reduced at 3 months of age.	Acland and Aguirre, 1987
	Rcd-1	Photoreceptor degeneration commences by about a month of age and culminates at about 1 year when the population of rods and cones are depleted. Electroretinogram (ERG) is altered at 16 weeks after birth.	Schmidt, 1985; Voaden, 1990; Pearce-kelling et al., 2001
	Rcd-2	Retinal dysfunction can be detected by ERG as early as 16 days of age. At 6 weeks of age only a few underdeveloped outer segments are visible in rcd2 dogs. By 2 to 2.5 months age, the outer segments completely disappear in the affected retina.	Santos-Anderson et al., 1980; Kukekova et al., 2006
	RHO	Photoreceptor degeneration occurs in older animals but at 3-6 months of age there exist some variations in an area surrounding the optic nerve. By 13 months of age rod and cone photoresponses are abnormal.	Cideciyan et al., 1998; Kijas et al., 2002
	RPE65	Rod outer segments were distorted and disoriented in dogs as early as the age of 5 weeks, the earliest stage studied. ERG in affected dogs is diagnostic at the age of 5 weeks.	Veske et al., 1999
	RPGR XLPRA1	The earliest histologic signs of rod degeneration are detected at 11 months of age, and are followed by cone death at later stages. Retinal function remained normal until 6 months of age, measured with ERG.	Zeiss et al., 1999; Zhang et al., 2002
	RPGR XLPRA2	Death of rods reaches a peak at 6-7weeks, then the rate of cell death is considerably slowed and remains constant for at least 9 months. ERG abnormalities were evident by 5-6 weeks of age.	Zhang et al., 2002; Beltran et al., 2007
	RPGRIP1	At 10,5 weeks of age ROS are irregular and attenuated, ONL is obviously thinner and disorganization of the ROS lamellae. ERG is reduced in amplitude at 6 weeks of age.	Curtis and Barnett, 1993; Turney et al., 2007
Cats (Natural)	rdAc	By ERG at the age of seven months cats present reduced amplitudes. Changes in rod photoreceptor outer segments are present at 5-8 months old, cones degenerate later and total blindness results at 3-5years old.	Kang Derwent et al., 2006; Narfstrom and Nilsson, 1989; Narfstrom, 1985
	Rdy	The disease begins at or before 3 weeks of age and progresses rapidly until there is almost complete loss of photoreceptors by 16 to 17 weeks of age. The first changes in the ERG are present at 17 days of age.	Curtis et al., 1987; Rah et al., 2005
Chickens (Natural)	Rd	Pathology appears 7-10 days after hatching and proceeds from central to peripheral photoreceptors. By 6-8 months, the photoreceptor cell layer is degenerated. ERG is altered at hatch the avians.	Ulshafer et al., 1984; Ulshafer and Allen, 1985
	Rdd	Signs of defective vision became more apparent by 8-10 weeks. Vision deteriorated progressively and by sexual maturity at 15 weeks most birds were blind. At 3 weeks of age, chickens have a flat ERG indicating visual loss.	Wilson et al., 1982; Burt et al., 2003
Mice (Natural and transgenic)	Peripherin-rds (N)	After 3 weeks postnatal period the photoreceptor cells lacking the OS begin to undergo a slow progressive degeneration, and after 12 months few cells remain. At P21 rod-mediated ERG presents severely impaired responses	Démant et al., 1979; Cayouette et al., 1998
	Rd (N)	Photoreceptor cell death starting at approximately P10 and almost reaching completion at P21. ERG was never normal.	Jiménez et al., 1996; Chang et al., 2007
	Rd-4 (N)	In affected mice, the outer nuclear layer is decreased at 10 days old and present total loss at 6 weeks. ERG is poorly detected between 3 and 6 weeks.	Roderick et al., 1997
	Rd-8 (N)	Shortened photoreceptor inner and outer segments are observed at 2 weeks of age, predominantly in the inferior nasal quadrant of the eye. ERGs are stable for one year, at which time amplitude loss is noted.	Chang et al., 1999; Mehalow et al., 2003
	Rd-10 (N)	Histology at 3 weeks of age shows retinal degeneration. ERGs are never normal, the maximal response occurs at 3 weeks of age and is non detectable at 2 months of age.	Chang et al., 2007
	Rd-12 (N)	Structural changes in the retina are observed 3 weeks after birth with small lipids in RPE cells. These alterations, with age are accompanied by progressive retinal degeneration. ERG responses are diminished at 3 weeks old.	Pang et al., 2005
	Rd-16 (N)	ERGs indicate a considerable deterioration of rod and cone functions as early as P18. Light microscopy of the retina shows degeneration of OS and reduction in the thickness of the ONL as early as P19 and progresses with age.	Chang et al., 2006
	I-255/256 (T)	At P15 half of photoreceptors have disappeared, by P20, only one row of photoreceptor nuclei remained in the outer nuclear layer, indicating that both rods and cones are affected by this mutation. At 20 days of age the ERG b-wave is absent.	Gryczan et al., 1995; Penn et al., 2000
	Knockout RPE65 (T)	There is no apparent loss of rod photoreceptor until 6 months of age but, in contrast, cones degenerate quickly in this model, between 2-3 weeks after birth. At 4 weeks-old ERG is abnormal.	Van Hooser et al., 2000; Rohrer et al., 2003; Znoiko et al., 2005; Seeliger et al., 2001
	P347S (T)	In lines with an intermediate level of transgene expression, approximately four to five rows of photoreceptor nuclei remained at 20-30 days of age. By 4 months of age, only one to two rows of nuclei remained. At 20-30 days amplitudes of ERG are diminished.	Li et al., 1996
	Q344ter	The amplitude of the ERG response shows a decline that is parallel to the degeneration of the retina. This transgenic mouse model shows slowing of transduction in single rods, at 3-4 weeks of age	Sung et al., 1994
	Peripherin-rds (T)	Heterozygous rds-307 mice show a marked reduction in rod photoreceptor cell number from 2 months of age. Normal rod responses persist up to 6 months. Homozygous rds-307 mice exhibit severe loss of rod photoreceptor at 5 weeks after birth. Rod responses are not normal even at 1 month of age.	Mc Nally et al., 2002
	Rho (T)	Rho-/- mouse has no functional rhodopsin gene, there is no doubt that rod function is completely absent, both because of the impaired phototransduction and the failing morphogenesis of rod OSs.	Heckenlively, 1988; Humphries et al., 1997; Morrow et al., 1998
	VPP (T)	Reduced light -evoked responses (ERGs) are present in mutant mice at P30, when no structural damage of photoreceptor cells except a shortening of outer segments is evident. Outer segments never reach normal.	Naash et al., 1993
Rats (Natural and transgenic)	RCS (N)	The retinal ONL cell degeneration begins early in P20-30 and then this degeneration steadily proceeds reaching at about 70 days of life almost the complete loss of ONL layer). ERGs, both scotopic and photopic are reduced in amplitude at 21 days of age.	Strauss et al., 1998; Amendola and Aloe, 2002; Cuenca et al., 2005
	P23H (T)	Abnormal rod ERG function is detected as early as 4 weeks of age. By 21 days of age in the P23H rat retina, there is already substantial loss of rods. It shows a progressive loss of rod photoreceptors over several months	Machida et al., 2000; Cuenca et al., 2004
	S334ter (T)	The degeneration begins at P15, at this age animals have 8-10 rows of photoreceptors in the outer nuclear layer. By P120, only 1-2 rows are present. At 60 days of age ERG shows a decrease in a and b waves amplitudes.	Green et al., 2000; Lau et al., 2000
Pigs (Transgenic)	P347L	At birth, rod numbers were normal in the transgenic retinas, but their outer segments were short and disorganized Rod cell death was apparent by 2 weeks. ERG results reduced at 4 weeks of age.	Li et al., 1998; Banin et al., 1999

been used in clinical trials with LCA patients and it seems to produce visual improvement in two out of six patients (Bainbridge et al., 2008; Hauswirth et al., 2008; Maguire et al., 2008).

In mutations leading to a toxic gain of function (autosomal dominant retinal degenerations), the principle of gene therapy is to inhibit the expression of the gene responsible for deleterious effects. Gene silencing can be obtained by the use of single-stranded antisense oligonucleotides or the use of ribozymes (Farrar et al., 2002). Some groups examined the potential effects of ribozyme therapy in the P23H transgenic rat (LaVail et al., 2000; Gorbatyuk et al., 2007b). They demonstrated that in vivo expression of either a hammerhead or hairpin ribozyme specific to the mutant transcript significantly delays the degeneration of the photoreceptors in transgenic rats for at least 8 months (Lewin et al., 1998; LaVail et al., 2000).

Recently, gene silencing has also been obtained through the use of RNA interference (RNAi). Codon-modifed RHO replacement genes express functional wild-type protein has been explored transgenically, together with in vivo expression of AAV-delivered RHO-replacement genes in the presence of targeting RNAi molecules. Observation of potential therapeutic benefit from AAV-delivered suppression and replacement therapies has been obtained in Pro23His mice (Gorbatyuk et al., 2007a; O'Reilly et al., 2007). This is the first "in vivo" indication that suppression and replacement can provide a therapeutic solution for dominantly inherited disorders such as RHO-linked RP, and can be employed to get around mutational heterogeneity.

Development of therapies for each individual mutation would be technically difficult to achieve and not economically viable; thus, a therapeutic approach that circumvents mutational diversity would be of great value.

Pharmacological neuroprotection of photoreceptors

Besides the therapies aimed at curing the genetic anomaly per se (gene therapy), several labs have demonstrated the ability of protective pharmacological molecules to slow down the progression of photoreceptor degeneration in different models. By modulating the microenvironment of photoreceptors, certain neuroprotective molecules can stabilize the disease before loss of cones occurs.

Vitamin A supplementation

Based on a study where patients happen to have been taking vitamin A, vitamin E, or both, they were shown to have slower declines in ERG amplitudes than those not taking such supplements (Berson et al., 1993a).

This observation prompted a randomised clinical trial of oral vitamin A and E supplements in 601 patients with dominant, recessive, and X-linked non-syndromic retinitis pigmentosa and Usher's syndrome type II. Participants were randomly assigned either daily vitamin A, vitamin E, the combination, or trace amounts of both vitamins. Follow-up was for 4-6 years. Patients assigned high-dose vitamin A showed a significantly ($p=0.01$) slower decline in flicker cone ERG amplitudes than did those in the other groups. Differences were more pronounced ($p<0.001$) in a subgroup of 354 individuals with higher initial cone ERG amplitudes. In these people, a significant ($p=0.04$) negative effect of vitamin E was also recorded (Berson et al., 1993b).

Critics of the trial point out that the measure of retinal function (other than cone ERG) such as visual-field area and visual acuity did not differ significantly between groups (Massof and Finkelstein, 1993). In a subsequent analysis of 125 participants who did visual-field tests, those assigned vitamin A showed a significantly slower loss of field than those not taking vitamin A (Berson et al., 1993a,b; Berson, 1998). In most patients, however visual acuity declines slowly or not at all in earlier stages (Holopigian et al., 1996), and suggests that a therapeutic effect would need a larger or longer study than was undertaken.

Supplementation with DHA

Another nutritional treatment assessed for patients with retinitis pigmentosa is docosahexaenoic acid (DHA), an omega-3 fatty acid. DHA is apparently important for photoreceptor function, since membranes containing rhodopsin and cone opsins in photoreceptor cells have very high concentrations of this fatty acid (Fliesler and Anderson, 1983). DHA is the precursor of neuroprotectin D1 (NPD1), which acts against apoptosis mediated by A2E, a byproduct of phototransduction that becomes toxic when it accumulates in pigment epithelial cells in some retinal pathology (Mukherjee et al., 2007). Amounts of DHA in red-blood cells are on average lower in patients with retinitis pigmentosa than in unaffected people, but whether the difference is attributable to a metabolic variation or to changes in diet or other factors is unknown. Results from two independent studies of oral DHA supplements for individuals with retinitis pigmentosa, one consisting of 44 males with X-linked disease and the other of 208 patients with various inheritance patterns, did not show a clear benefit (Berson et al., 2004; Hoffman et al., 2004). The same findings were observed by Aguirre's group in a canine model of RP (Aguirre et al., 1997).

Trophic factors

The demonstration of the neuroprotective effect of basic Fibroblast Growth Factor (bFGF or FGF-2) on degenerating photoreceptors in a rat model of inherited retinal dystrophy (Faktorovich et al., 1990) was at the origin of growth factor-based therapeutic strategy. Yet, it was soon observed that while FGF-2 exerts both histologic and functional rescue on degenerating

photoreceptors (Faktorovich et al., 1990; Akimoto et al., 1999; Uteza et al., 1999; Ali et al., 2000; Lau et al., 2000), it also triggers pathological retinal neovascularization (Perry et al., 1995), which makes it unacceptable for human therapy.

Since then, several trophic factors have been shown to protect photoreceptors from degeneration (LaVail et al., 1998; Liang et al., 2001; Tao et al., 2002; Dykens et al., 2004; Leveillard et al 2004; Otani et al., 2004 and Sahel, 2005). The most commonly reported trophic factor is the Ciliary Neurotrophic Factor (CNTF). CNTF was shown to delay photoreceptor degeneration in different mouse models of retinal degeneration (Cayouette and Gravel, 1997; LaVail et al., 1998; Liang et al., 2001; Bok et al., 2002). Tao et al, demostrated that CNTF delivered through encapsulated cells directly into the vitreous of the eye protects photoreceptors in the PDE6B-deficient rcd1 canine model. In each animal, the number of rows of photoreceptor nuclei in the outer nuclear layer (ONL) was significantly higher in the eye that received a CNTF-secreting implant than in the untreated contra lateral eye. No adverse effects were observed on the retina in the treated eyes (Tao et al., 2002).

Results of a human phase I study of an intravitreal capsule containing cells that release CNTF, have been reported. One patient in the study had a decline in ERG amplitudes; however, the same individual and some others had improvements in visual acuity over the 6-month duration of the study (Sieving et al., 2006).

Calcium blockers

An increase in intracellular calcium level represents one possible mechanism of activation of the apoptotic cascade. As cGMP gates cationic channels that are normally responsible for the light-sensitive current in photoreceptors, intracellular calcium level is linked to cGMP level. An increase in cGMP level is observed in numerous forms of RP, both in those following a mutation on the gene PDE6 encoding the cGMP dependant phosphodiesterase cGMP-PDE, (Farber and Lolley, 1974), which results in a non functional cGMP-PDE, and in those where no mutation on PDE6 is found (Kommonen et al., 1996).

In a study of a calcium-channel blocker (diltiazem), researchers claimed a beneficial effect in a mouse model of a form of recessive retinitis pigmentosa due to recessive mutations in the subunit of rod phosphodiesterase (Frasson et al., 1999a). However, three subsequent trials of this drug in mice and other RP animal models by independent groups failed to confirm a benefit (Bush et al., 2000; Pearce-Kelling et al., 2001; Pawlyk et al., 2002).

Transplantation

The last decade has seen numerous animal studies concerning retinal transplantation. Two different strategies have been developed: RPE transplantation, on the one hand, attempts to obtain beneficial effects upon the adjacent photoreceptors, and retinal neuronal transplantation, on the other hand, hopes to replace the degenerate tissue altogether.

RPE transplantation

In the RCS rat, RPE fails to phagocytose shed outer segments, and the photoreceptor cells subsequently die. Using this model, various studies showed that fresh RPE cell transplants considerably delayed the loss of photoreceptors (Li and Turner, 1988; Sheedlo et al., 1989; Gouras and Lopez, 1989), restored normal metabolism (LaVail et al., 1992) and improved visual function (Jiang and Hamasaki, 1994; Whiteley et al., 1996). Since the extent of photoreceptor survival exceeded the site of transplanted RPE, the effects provided by these transplantations in the RCS rat retina could possibly be due to the release of trophic factors by the grafted cells, and in particular FGF-2 (Sahel et al., 2001).

Neuronal transplantation

Neuronal transplantation hopes to replace lost photoreceptor cells. Transplantation of either embryonic dissociated cells or retinal sheets into the subretinal space of rodent models of retinal degeneration demonstrate that transplants survive and differentiate and that neuronal fibers originating from the transplant develop synapses with the remaining host retina (Aramant and Seiler, 1995; Kwan et al., 1999; MacLaren et al., 2006). It has been demonstrated that transplantation of rod-rich photoreceptor sheets into the subretinal space of 5-week-old *rd1* mice, which at this age contain few remaining rods but numerous surviving cones, induced a significant increase in host cone survival (Mohand-Saïd et al., 2000). Rod transplants promoted survival effects not only on the cones facing the transplant but also on cones distant from the graft. Rods release some diffusible trophic factors and these factors promote cone survival in the rd mouse (Mohand-Saïd et al., 1998). One of these factors had been named Rod-dependent Cone Viability Factors (RdCVFs) (Fintz et al., 2003).

Ghosh et al. has carried out a transplantation of fetal full-thickness neuroretinal sheet in the subretinal space in 6-month-old rhodopsin transgenic pigs. The transplants develop a normal laminated morphology and survive for at least 6 months. Graft and host retinal neurons do not form connections. Retinal function in the host is reduced initially by the surgical trauma, but the presence of a well-laminated graft counteracts this effect and rescues rods from degeneration (Ghosh et al., 2007).

Still, numerous obstacles remain before RPE or retinal transplantations may be used in clinical therapy (see reviews by Berson and Jakobiec, 1999; Lund et al., 2003). A greater knowledge of the immune and

inflammatory components that accompany the degenerative events and the introduction of specific transplants represent a major area for further investigation (Lund et al., 2003).

Stem cells transplantation

Research in the last decade has demonstrated that new neurons are generated continuously from stem cells in different regions of the adult mammalian brain (McKay, 1997; Gage, 2000; Momma et al., 2000; Zhao et al., 2003).

Cellular transplantation has been proposed as a potential treatment of these retinal-degenerative diseases (Delyfer et al., 2004). The donor cells and the host recipient are two key aspects of the procedure. Various injection studies have been undertaken with different cellular types to replace lost cells. Hippocampal (Nishida et al., 2000; Young et al., 2000), embryonic (ES) (Meyer et al., 2004), and bone marrow (Kicic et al., 2003) stem cells have been tested in models of retinal degenerative disorders. These cells show high migratory and differentiation capacity, as they can differentiate into neurons, astrocytes and oligodendrocytes. It is worth mentioning that cells derived from ES cells can form retinal neurons (Banin et al., 2006; Meyer et al., 2006).

Conversely, the use of retinal stem/progenitor cells in suspension or as neurospheres exhibit poor migration, but are successful in expressing retina-specific markers after transplantation (Chacko et al., 2000; Klassen et al., 2004; Qiu et al., 2005). It has been shown that adult human retinal stem cells (RSC) can generate retinal cells when grafted into a developing retina (Coles et al., 2004).

Another possibility is to couple the injection of the cell suspension with growth or proneural factors, or to engineer the cells genetically to commit them to the desired aim (Lawrence et al., 2004).

Furthermore, it has been shown that in transplantation model, RSCs can incorporate into a diseased retina when subretinally transplanted, but exhibit a migration and a differentiation preference (Canola et al., 2007).

The extrapolation of these successes to humans is still to be demonstrated, but progress is being made to this end.

Retinal prostheses

Devices to electrically stimulate the retina, optic nerve, or visual cortex are being developed and tested in animal models and patients (Lee et al., 2000; Chow et al., 2004; Brelen et al., 2005; Jensen et al., 2005; Gekeler et al., 2006). The few people tested with the first versions of these devices have reported seeing phosphenes (flashes of light) in response to direct retinal stimulation.

However, some of the subjects have reported increased visual fields away from the implant site, suggesting that the presence of the implant alone, or coupled with low-level electrical stimulation, induced a "neurotrophic effect" that improves the health of the retina and the visual function (Yanai et al., 2007).

Conclusion

The search for RP animal models has been long but exceedingly successful.

There are a lot of different natural and transgenic RP animal models, although natural models represent the real disease, transgenic animals permit the study of new mutations which mimic the process in RP.

The election of a RP animal model depends on the work that we need to carry out and of other factors. A variety of studies regarding RP have opened the door to hope, although it will take time before this can be achieved in humans. At any rate, it will not be applicable to all patients suffering from RP, considering the tremendous genetic heterogeneity associated with the RP phenotype. Mutation-independent therapies would be applicable to most patients regardless of the genetic defects.

In view of the growing research effort on therapeutic approaches for retinitis pigmentosa, new treatments for some forms of the disease will probably be amendable to patients within the next 5-10 years. Strategies to save or restore vision in all individuals might need many decades of research.

Acknowledgements: We would like to acknowledge for grants that were received from Spanish Ministry of Science and Education (SAF2007-62060), Grupos consolidados Gobierno Vasco, Ayudas investigación enfermedades raras (BIOEF), Jesús Gangoiti Barrera Foundation, Red patologia Ocular Inst. Carlos III and Fellowship of University of the Basque Country

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Accepted April 1, 2009