Chung. J Ophthalmic Res Ocular Care 2017, 1(1):19-24
DOI: 10.36959/936/562 | Volume 1 | Issue 1

Journal of Ophthalmic Research and Ocular Care

Review Article Open Access

Animal Models of Retinal Degeneration

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Abstract

Retinal degenerations (RDs) are a vast and heterogeneous group of inherited degenerative diseases (dystrophies) of the retina that lead to progressive visual loss. The study of RDs involves animal models of various forms: from those naturally occurring to those genetically engineered, from insects to mammals. In particular, the mouse models from the Jackson Laboratory, with their well characterized phenotype, locus of mutation and corresponding human genetic homolog, have been extensively used in RD research. Knowledge in how abnormal proteomics disrupts the cellular function of photoreceptors provides important guidance in the search for treatment. The potential treatments including transplantation, pharmacological intervention and gene therapy under investigation can also be tested in the animal models at the preclinical stage. This review provides an overview of the various animal models of RDs and their application in clinical research.

Keywords

Retinal degeneration, Retinitis pigmentosa, Animal model, Preclinical drug evaluation, Genetic therapy

Introduction

Retinal degenerations (RDs) are a vast and heterogeneous group of inherited degenerative diseases (dystrophies) of the retina that lead to progressive visual loss. Phenotypically, different types of RDs may be difficult to be distinguished from one another. As the retina only has a limited repertoire of cellular responses to diseases, photoreceptor degeneration is often followed by the proliferation and migration of pigment-laden epithelial cells into the neurosensory retina. Clinically this is observed as pigmentary bony spicules on the retina. Therefore, RDs with characteristic pigmentary changes as such are coined the term "retinitis pigmentosa" (RP). It is estimated that more than fifteen million people worldwide suffer from visual loss due to an inherited RD [1].

The study of RDs involves animal models of various forms: from those naturally occurring to those genetically engineered, from insects to mammals. In particular, mouse models of RDs are among the most frequently studied. The applications of animal models are multifold. First of all, they help to understand the pathophysiology of RDs in humans. Many of the genetic mutations in animal models have been found a correspondence in humans. Knowledge in how a defective protein disrupts the cellular function of photoreceptors provides important guidance in the search for treatment. The potential pharmacological interventions and gene therapy can also be tested in the animal models at the preclinical stage. This review will provide an overview of the various animal models of RDs and their application in clinical research.

Natural Animal Models

A diversity of natural animal models has been used in the study of RDs. A comparison of the advantages of each type of animal model is given in table 1.

Among the most primitive ones is the fruitfly (*Drosophila melanogaster*), frequently employed in studies of the visual system. Their advantages include the large number of mutants available, short life cycle and their

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Received: February 01, 2017: **Accepted:** March 07, 2017: **Published online:** March 09, 2017

Citation: Chung CY (2017) Animal Models of Retinal Degeneration. J Ophthalmic Res Ocular Care 1(1):19-24

Table 1: The advantages of different animal models of retinal degeneration.

Animal model		Advantages
Invertebrates	Fruit fly	Cheap Small Short life cycle Fast breeding
Vertebrates	Zebrafish	Cheap Short life cycle
	Chicken	Large population of cone receptors
	Dogs	Similar mammalian pattern of the retinal cell layers
	Cats	Similar mammalian pattern of the retinal cell layers
	Mice	Ease of care Large variety of disease models Short life span Similarities to human in terms of genetics and physiology
	Pigs	Similar to the human eyes in terms of size, retinal structure and distribution of photoreceptors

fast breeding ability [2]. In fact, many of these advantages are shared by the zebrafish model which allows quick and inexpensive screening [3]. The chicken also makes a good model for RD because it contains a large population of cone photoreceptor cells, similar to the human retina [4].

Various mammals have been used as models of human RDs as they are genetically closer to human. In canine models, many RDs are inherited in an autosomal recessive manner, with the exception of one X-linked model [5]. Among the inherited RDs in feline models, the autosomal recessive progressive retinal atrophy (PRA) in the Abyssian cat is especially well described, although an autosomal dominant form of PRA has also been documented [6].

Of all mammals, murine models are most extensively employed in RD research. The Jackson Laboratory has developed a collection of sixteen naturally occurring mouse mutants of RDs. Each named mutant has a known genetic mutation as shown in brackets: retinal degeneration (formerly *rd*, identical with rodless retina, *r*, now *Pde6brd1*); Purkinje cell degeneration (*pcd*); nervous (*nr*); retinal degeneration slow (*rds*, now *PrphRd2*); retinal degeneration 3 (*rd3*); motor neuron degeneration (*mnd*); retinal degeneration 4 (*Rd4*); retinal degeneration 5 (*rd5*, now *tub*); vitiligo (*vit*, now *Mitfmi-vit*); retinal degeneration 6 (*rd6*); retinal degeneration 7 (*rd7*, now *Nr2e3rd7*); neuronal ceroid lipofuscinosis (*nclf*); retinal degeneration 8 (*rd8*); retinal degeneration 9 (*Rd9*); retinal degeneration 10 (*rd10*, now *Pde6brd10*); and cone photoreceptor function loss (*cpfl1*) [7].

Transgenic Animal Models

Natural models for RPs are usually limited to the autosomal recessive forms. The animal models for other rarer forms of RP can only be obtained through genetic modification. Among mammals, rodent and pig models are most frequently engineered transgenically.

Many transgenic mice have been produced such that they carry a gene mutation leading to a particular phenotype of RD. For example, Naash, et al. produced a murine model that carries a mutated *opsin* gene, and the resultant phenotype simulates an autosomal dominant form of human RP [8]. Comitato A, et al. developed three murine models of RD with a knocked out *Rhodopsin* gene (*Rho*) or expression of the P23H dominant mutation in *Rho*. Loss of function of *Rho* activates calpains and apoptosis-inducting factor (Aif) in the photoreceptors. The P23H dominant mutation in Rho activates both a stress responses in the endoplasmic reticulum the calpain-Aif apoptosis pathway, resulting in photoreceptor degeneration [9]. Hong, et al. also engineered a mouse model for X-linked RP in which the unidirectional movement of opsin is disrupted through RPGR mutation [10].

Transgenic porcine models make good simulations of human RDs because pig eyes are similar to human eyes in terms of the number and distribution of rod and cone cells. Petters, et al. produced a porcine model that expresses a mutated *opsin* gene (Pro347Leu) leading to early rod degeneration but slow cone loss. This phenotype is similar to human RP and is a desired model for testing treatment efficacy and safety [11].

Application: Understanding Pathophysiology

In RDs, defective genes are associated with loss of function of the protein product by nonsense-mediated mRNA decay (NMD) mechanisms, or translated into abnormal gene products which in turn disrupt the normal physiology of photoreceptors and eventually lead to cell death. Genetic and proteomic information obtained from animal models are invaluable for our understanding of the pathophysiology of RDs [12].

Trophic signalling

Based on the animal models of RDs, it has been known that the survival of photoreceptors is supported by trophic factors, which promote cellular functioning and inhibit apoptosis.

Some trophic factors are derived directly from photoreceptors. This comes from the observation that although the affected gene product in the rd1 mice is the rod-specific cGMP phosphodiesterase-β (PDE-β) subunit, delayed but extensive degeneration of cones is observed in humans, as well as the mouse and pig models [13].

On the other hand, co-culture with photoreceptors from wild-type rats has been found to slow down the rate of degeneration. Thus, the survival of cone photoreceptors may rely on trophic factors that are contributed by rods [14]. This rod-derived cone viability factor was found to exist in two polypeptide isoforms of either 17 kDa or 34 kDa in size [15]. Two isoforms of the rod-derived cone viability factor. The truncated form (RdCVF) is a thioredoxin-like protein produced by rod photoreceptors that promotes the survival of cones, while the full-length isoform (RdCVFL) consisting of a thioredoxin fold that confers protection against oxidative stress [16]. RdCVF binds to the transmembrane protein Basigin-1 (BSG1), which in turn binds to the glucose transporter GLUT1, resulting in increased glucose entry into cones, stimulation of aerobic glycolysis and therefore promotion of cone survival [17].

A number of other trophic factors have been found to be implicated in RDs. It was found that the expression of survival growth factors is enhanced by Dickkopf 3(Dkk3) - involved in the [a]Wnt signaling pathway in mammalian tissues [18]. The importance of the insulin receptor substrate gene (Irs2) was demonstrated in another mouse model, with widespread photoreceptor loss observed after this gene was knocked out [19]. Insulin and insulin-like growth factors are responsible for the activation of phosphoinositide 3-kinase (PI3-kinase), which brings on the Akt (protein kinase B) cascade that inhibits caspase-3 cleavage, rendering the caspase-dependent apoptotic pathway inactive [20]. On the other hand, basic fibroblast growth factor (FGF2) has demonstrated positive effects on rod survival *in vitro,* mediated by the mitogen-activated protein kinase signalling pathway [21]. During stress conditions, the increase in ciliary neurotrophic factor (CNTF) levels may be favourable for neuronal survival. This growth factor binds to the α-subunit of its receptor on the plasma membrane, leading to heterodimerization with two β-subunits and subsequent activation of intracellular signaling pathways that promote survival e.g. Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways [22].

Glutamate homeostasis

In the rd1 mice with PDE-β mutation, continuous depolarization of rods leads to opening of voltage-gated calcium channels and excessive glutamate release. To protect against excitotoxicity, L-glutamate/L-aspartate and glutamine synthetase may be upregulated by Muller cells. When this protective mechanism is overwhelmed, cone degeneration ensues as a result of excitotoxicity [23].

Oxygen homeostasis

The loss of rod cell population leads to a lower oxygen demand. The constant supply of oxygen from the choroidal circulation may then cause oxidative stress to the remaining photoreceptors. In the *rd1* model, proteins that protect against oxidative stress were found to be actively expressed during the peak of cone degeneration and immediately after the loss of rods, on 50 days post-natal life. These proteins include antioxidant protein-2 and glutathione peroxidase 2. When the maximal adaptive capacity of cone photoreceptors is reached, uncontrolled oxidative stress may contribute to cell death [24].

Phototoxicity

Mutation of the ABCA4 gene has been implicated in Stargardt's disease. In the ABCA4-deficient mice, deposition of the lipofuscin fluophore A2E is observed in the RPE layer, which results in the subsequent loss of RPE cells and photoreceptors. However, if these mice are raised in the dark, A2E formation is largely reduced. Thus, phototoxicity may be implicated in the pathogenesis of certain RDs [25,26].

Application: Preclinical Testing

Animal models are useful in preclinical testing of potential treatment. Different sizes of animal models are used in different phases of trials. In general, small and inexpensive animals are chosen for earlier phases with particular interest in efficacy, while large and more costly animals are used later to address issues of dosage, safety and route of delivery. The preliminary results from animal models allow further clinical trials in human subjects [27].

Transplantation

Various tissues have been explored for transplantation for the treatment of RDs. In a murine model of congenital stationary night blindness (*Gnat1*$^{-/-}$ mice), Ali RR, et al. observed that the transplanted rod precursors were able to form synaptic connections with second-order bipolar and horizontal cells in the recipient, projecting visual signals to higher visual areas in the cerebral cortex [28].

Retinal pigment epithelial cell (RPE) transplantation was performed on an RCS rat model, with results showing efficacy and safety [29]. Selective transplantation of rods was found to promote cone survival in the RD mouse [30]. Light-driven ganglion cell responses were detected in the rd mice after transplantation of neural retinal tissue isolated from newborn normal C57/BL6J mice on

[a]Wnt signaling pathway: The name Wnt is a portmanteau of Int (meaning Integration) and Wg (meaning "wingless-related integration site). It is a group of signal transduction pathways consisting of the canonical Wnt pathway, the noncanonical planar cell polarity pathway, and the noncanonical Wnt/calcium pathway. All three pathways are activated by binding a Wnt-protein ligand to a Frizzled family receptor, which passes the biological signal to the Dishevelled protein inside the cell.

day 13 postnatal life [31]. Recent studies also explored the efficacy of stem cell transplantation in photoreceptor replacement. Hippocampal progenitor cell transplant in the RCS rat was found to demonstrate neuronal differentiation and morphological integration [32].

Pharmaceutical therapy

Knowledge in the pathophysiology of RDs provides guidance for the search for possible pharmaceutical therapy.

Various growth factors have been involved in therapeutic trials. In the study by LaVail, et al. fibroblast growth factor beta (bFGF) was demonstrated to slow down disease progression in the RCS rat [33]. Ciliary neurotrophic factor (CNTF) was also shown to be capable of morphological rescue in several animal models of RD [34]. Other trophic factors shown to be neuroprotective in RD animal models include brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) [35].

In the RPE65-deficient mice, oral retinoid supplement was found to be useful in bypassing the block in visual cycle attributable to the mutation [36]. Similarly, vitamin A supplement was shown to significantly reduce the decline of a-wave and b-wave amplitudes in the T17M opsin mutant mouse [37].

Growth factors specific to the eye were also tested in animal models. Intravitreal injection of pigment epithelium-derived factor (PEDF) and the associated peptides in the signalling pathyway in the *rd1* model was found to promote photoreceptor survival [38].

Knowledge in the apoptotic pathway of photoreceptors has provided new directions for neuroprotection. Paquet-Durand F, et al. found that pharmacological inhibition of calpain for short periods of time (16 hours) conferred neuroprotective activity in the *rd1* model [39]. In a mouse model of primary cone degeneration (*cpfl1*), pharmacological inhibition of histone deacetylase was found to protect *cpfl1* cones *in vitro* in retinal explant cultures, and the abnormal cone migration pattern in the *cpfl1* retina was significantly improved [40].

Gene therapy

Local administration of therapeutic agents has its limitations. Intraocular penetration is unpredictable when the drug is administered topically on the cornea or systemically. Intravitreal injection can bypass the blood-retina barrier (BRB), but repeated injection is associated with cumulative risk. This leads to the clinical trials with gene therapy in animal models of RDs.

The vehicle of gene delivery may be viral or non-viral. Non-viral vehicles include specially designed liposomes packed with transgenes. These liposomes are uptaken into cells by endocytosis [41]. Viral vectors commonly manipulated include herpes simplex virus, adenovirus, adeno-associated virus (AAV) and retroviruses such as lentivirus.

There are limitations associated with using viral vectors for gene transfer. For example, the location of genetic transduction by lentivirus is unpredictable. Although both actively dividing and senescent cells are transduced, the integration of viral genome into the host genome is random and thus associated with unknown risks [12]. For adenovirus, gene transfer is efficient but the subsequent expression of transgene is usually not sustained. Immune reaction against adenovirus is another shortcoming that limits its application [42].

Adeno-associated virus serves as a promising viral vector for gene transfer. The transfer of genes coding for neurotrophic factors using recombinant adeno-associated virus serotype 2 (rAAV2) has been shown to promote survival of photoreceptors in many mouse models of RD [43]. In a canine model of Leber's congenital amaurosis with a mull mutation in RPE65, AAV transfer of this deficient gene was found to restore vision with minimal side effects [44].

Following on their work, Bainbridge JWB, et al. performed gene therapy in 12 patients with Leber's congenital amaurosis using a rAAV2 vector delivering the RPE65 complementary DNA. Improvement in retinal sensitivity was observed in 50% of the patients for up to 3 years [45]. In another study, the AAV vector was used to deliver an artificial protein known as ZF6-DB which binds to the regulatory element of the *Rhodopsin* gene, switch off the expression of the defective copy of *Rhodopsin* gene and insert a normal copy of the *Rhodopsin* gene into living pig cells [46].

However, the use of AAV as a viral vector of gene transfer still needs further investigations for fine adjustment. The kinetics of transgene expression is affected by the serotype of AAV, of which AAV2/5 was found to be faster in terms of action [47]. The mechanisms of genomic transduction, either as episomal or integrated genetic materials, also require further control in future clinical trials.

Choice of Animal Models

Albeit being useful tools for studies in RD, the application of animal models is associated with limitations. In general, primitive animals such as fruitflies are used to study the genetics and pathophysiological mechanisms of RDs owing to their low cost, short life cycles and fast breeding property. As the extent of validity of extrapolating the results from animal experiments depends on the resemblance of the animal model to the human condi-

tion under investigation, large mammals such as pigs are used for therapeutic trials especially gene therapy [48]. In particular, mouse models are extensively used in RD researches due to easy breeding and maintenance, and the availability of a large spectrum of well-defined genetic defects.

Conclusion

Various animal models, from those naturally occurring to those genetically engineered, from insects to mammals, have enhanced our understanding on retinal degenerations. In particular, the mouse models from the Jackson Laboratory, with their well characterized phenotype, locus of mutation and corresponding human genetic homolog, have been extensively used in RD research. Knowledge in how genetic defects affect the pathophysiology of photoreceptors has shed light on developing potential treatment for RDs. Preclinical trials of cellular transplantation, pharmaceutical treatment and gene therapy involving animal models of RDs are under way. The preliminary efficacy and safety data from animal models are invaluable for the guidance of clinical trials in human patients of RDs.

Acknowledgements

The authors did not receive any sponsorship or financial support from any academic or commercial organization.

Conflict of Interest

The authors declare that there are no competing financial interests in relation to the work described.

Financial Support

None.

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