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The pros and cons of vertebrate animal models for functional and therapeutic research on inherited retinal dystrophies

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ABSTRACT

Over the last decade, huge progress has been made in the understanding of the molecular mechanisms underlying inherited retinal dystrophy (IRD), as well as in the development and implementation of novel therapies, especially in the field of gene therapy. The use of mutant animal models, either naturally occurring or generated by genetic modification, have contributed greatly to our knowledge on IRD. Yet, these mutant animal models do not always mimic the retinal phenotype that is observed in humans with mutations in the orthologous gene, often due to species-specific characteristics of the retina, and/or diverse functions of the gene products in different species. In this manuscript, we compare general and ocular characteristics of a series of widely used vertebrate animal models, i.e. zebrafish, chicken, rodents, cats, dogs, sheep, pigs and monkeys, in terms of genetic architecture and sequence homology, methods to modify genomes, anatomy of the eye, and structural details of the retina. Furthermore, we present an overview of mutant vertebrate animal models that have been used to study or develop treatments for the various genetic subtypes of IRD, and correlate the suitability of these models to the specific characteristics of each animal. Herewith, we provide tools that will help to select the most suitable animal model for specific research questions on IRDs in the future, and thereby assist in an optimal use of animals and resources to further increase our understanding of inherited retinal dystrophies, and develop novel treatments for these disorders.

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1. Introduction

Inherited retinal dystrophies (IRDs) are a group of heterogeneous disorders characterized by a progressive loss of visual function due to degeneration of the light-sensing photoreceptor cells in the retina, often resulting in complete blindness. Over the past two decades, the molecular and phenotypic characterization of mutant animal models resembling IRD has contributed greatly to our understanding of the physiological processes that regulate vision and of the pathophysiological mechanisms that underlie IRD. In addition, several of these models have shown to be instrumental for the development of novel treatments, such as gene augmentation therapies that are now in clinical trials (Bainbridge et al., 2008; Hauswirth et al., 2008; MacLaren et al., 2014; Maguire et al., 2008). On many occasions however, animal models that carry mutations in genes underlying IRD in humans do not, or only partially, mimic the human phenotype. Why is that? Do the gene products have diverse functions in different species? Is this due to structural differences in the retinal cells of the various animals? In this manuscript, we will describe the general and ocular characteristics of a series of vertebrate species commonly used in functional and/or therapeutic research on IRDs. In addition, we provide a comprehensive overview of currently existing IRD models, and assess whether they resemble the human phenotype. With this, we aim to provide insight in the utility of the various different animal models for IRD, and why some species may be particularly suited for certain types of functional or therapeutic research in the future.

1.1. The retina

Vision is a complex and highly regulated biological process. When light enters the eye through the cornea and the lens, it is refracted and focused onto the retina that lines the inner surface of the eye. In the retina, light is converted into an electrical signal that is transmitted via the optic nerve to the visual cortex in the brain where the actual images are formed. The retina is a thin, multilayered and highly structured tissue composed of several different cell types that each play a crucial role in the conversion and amplification of light to electrical signals (Marc, 2008). The light-sensing photoreceptor cells are arranged in a defined layer, that at one end contacts the retinal pigment epithelium (RPE) and at the other end feeds into the outer plexiform layer (OPL). Here, the photoreceptor terminals form synapses with the second order neurons (bipolar cells, horizontal cells and amacrine cells), the nuclei of which together with the nuclei of the Müller cells define the inner nuclear layer (INL). These neurons again form synapses in the inner plexiform layer (IPL) with the ganglion cells, whose nuclei are situated within the ganglion cell layer (GCL). The axons of the ganglion cells define the retinal nerve fiber layer (RNFL) and exit the retina through the optic nerve head (ONH) or papilla. The borders of the Müller cells delineate the internal (ILM) and external limiting membrane (ELM). A cartoon describing the layered structure of the human retina is provided in Fig. 1A.

When light reaches the retina, it first passes through the ganglion and inner nuclear cell layer to reach the photoreceptor cells. In the photoreceptor cells, photons are captured by the photopigment molecules after which the phototransduction cascade is initiated, a complex chain of events that results in the closing of voltage-gated ion channels producing a change in membrane potential. Subsequently, this electrical signal is structured and specifically amplified by the different cell types in the inner retina to be ultimately transported to the brain via the retinal ganglion cells for the generation of images. Oxygen and nutrients for the outer retina (i.e. the photoreceptors) are provided through diffusion from the