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Review

The cell stress machinery and retinal degeneration

Dimitra Athanasiou, Monica Aguilà, Dalila Bevilacqua, Sergey S. Novoselov, David A. Parfitt, Michael E. Cheetham *

UCL Institute of Ophthalmology, 11-43 Bath Street, London EC1V 9EL, UK

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ABSTRACT

Retinal degenerations are a group of clinically and genetically heterogeneous disorders characterised by progressive loss of vision due to neurodegeneration. The retina is a highly specialised tissue with a unique architecture and maintaining homeostasis in all the different retinal cell types is crucial for healthy vision. The retina can be exposed to a variety of environmental insults and stress, including light-induced damage, oxidative stress and inherited mutations that can lead to protein misfolding. Within retinal cells there are different mechanisms to cope with disturbances in proteostasis, such as the heat shock response, the unfolded protein response and autophagy. In this review, we discuss the multiple responses of the retina to different types of stress involved in retinal degenerations, such as retinitis pigmentosa, age-related macular degeneration and glaucoma. Understanding the mechanisms that maintain and re-establish proteostasis in the retina is important for developing new therapeutic approaches to fight blindness.

1. Introduction

The vertebrate eye is one of the most sophisticated organs in biology and initiates our most precious sense, vision. At the back of the eye, the retina captures light and transmits electrical impulses through the optic nerve to the visual cortex in the brain. The mammalian retina is composed of eight different layers that contain a specialised network of approximately 55 neuronal types which process visual information (Fig. 1) [1]. The main light-detecting cells in the retina are the photoreceptors, rods and cones. Rods are approximately 20 times more numerous than cones and are responsible for detecting low levels of light. Cones detect much higher levels of light and are responsible for colour and daytime vision. The outer nuclear layer (ONL) contains the photoreceptor cell bodies, and the photoreceptor visual pigments, rod opsin for rods and cone opsin for cones, are tightly packed into flattened membrane disks in the outer segments (OS). The inner segment (IS) of the photoreceptor contains the main biosynthetic machinery such as the endoplasmic reticulum (ER) and is rich in mitochondria [2]. The biogenesis, post-translational modifications and quality control of many OS proteins, including opsin, take place in the ER. The photoreceptor disks are continually replenished, which leads to a high turnover of proteins, and places a strain on the ER and its quality control machinery. Microvilli from the retinal pigment epithelium (RPE) cells contact the photoreceptor OS tips and phagocytose the shed material, prior to lysosomal degradation within the RPE. The RPE acts as a support for the retina, transporting nutrients and water and is important in for the recycling of 11-*cis*-retinal, known as the visual cycle [3]. The outer plexiform layer (OPL) consists of the processes and synaptic terminals of photoreceptors, where they contact the horizontal cell and bipolar cell dendrites. The inner nuclear layer (INL) contains horizontal, bipolar and amacrine cell bodies. Horizontal cells integrate the signal from the rods and cones by providing an inhibitory feedback to regulate photoreceptor function [4]. Bipolar cells receive the signal from photoreceptors or horizontal cells and contact the retinal ganglion cells (RGCs) [5]. The inner plexiform layer (IPL) is composed of the synapses of bipolar and RGCs and the ganglion cell layer (GCL) contains the nuclei of RGCs and their axons that form the output from the retina to the brain through the optic nerve. In addition to the neuronal cells in the retina, there are retinal glia cells; the Müller cells, microglia and astrocytes. Müller glia surround the neuronal cell bodies within the retina and are crucial for neuronal health and maintenance [6]. Due to this complex architecture and high metabolic demand, the retina needs constant maintenance to en-

* Corresponding author.
E-mail address: michael.cheetham@ucl.ac.uk (M.E. Cheetham).

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sure the proper function of all the cellular components. During evolution retinal cells have developed adaptive responses to a variety of insults, which cooperate to restore cell homeostasis, and increase the resistance of the tissue to further damage. Cell stress can arise in many forms in the retina causing the death of several different neuronal types and leading to blindness. This review will discuss the molecular and cellular mechanisms that are present in the retina to deal with cell stress, in particular protein misfolding problems such as those caused by mutations in rhodopsin.

1.1. Photoreceptor degeneration and retinitis pigmentosa

Photoreceptors are particularly susceptible to cellular stress and loss of photoreceptors due to degeneration is a major cause of blindness. Photoreceptor degenerations are possibly the most heterogeneous inherited disorder known in man, with over 140 different causative genes identified [7]. These inherited disorders can affect either rods or cones primarily, as in retinitis pigmentosa (RP) or cone dystrophy respectively, or both simultaneously, as in Leber congenital amaurosis (LCA). Electroretinogram (ERG) measurements can record the electrical response of the retina, and the measurements can be separated into rod (scotopic) or cone (photopic) responses. In this way ERGs can be used to identify the primary cell type affected in retinal degenerations. For example, RP classically involves the loss of the scotopic response, whereas in LCA, which is an early-onset, extreme retinal degeneration, both the photopic and scotopic responses are lost.

RP is one of the most common forms of inherited retinal degeneration comprising a group of retinal disorders that typically involve progressive degeneration of rod photoreceptor cells followed by secondary cone photoreceptor death. The first symptom is night blindness, due to the dysfunction of rod cells, which later advances to the loss of peripheral vision (tunnel vision). RP progresses towards the macula at the centre of the retina with the death of cone cells resulting in loss of central vision and partial or complete blindness by middle age [8]. Clinical examinations of the retinae of RP patients show abnormal fundi with pigmented bone-spicule deposits, attenuated retinal vessels and pallor of the optic nerve. The prevalence of RP is 1 in 4000 people worldwide, resulting in over 1.5 million visually impaired patients. The inheritance patterns of RP are varied; 15–25% are autosomal dominant (adRP), 5–25% are autosomal recessive (arRP), 5–15% are X-linked (XLRP), while the remaining 35–50% cannot be easily classified genetically [9]. To date, 27 adRP, 36 arRP and six XLRP genetic loci have been identified, often with overlap [10]. RP can also be syndromic, where other organs are also affected, such in Usher's syndrome which is associated with hearing impairment and RP symptoms [11].

1.1.1. Rhodopsin RP

Rhodopsin, the light-absorbing photopigment of rod cells, is the archetypal G-protein coupled receptor (GPCR) and therefore one of the best characterised. Rhodopsin is composed of the 348 amino acid apoprotein rod opsin, which is covalently linked with the chromophore 11-*cis*-retinal, an analogue of vitamin A. Rhodopsin undergoes multiple post-translational modifications such as N-linked glycosylation, disulphide bond formation, acetylation, palmitoylation, phosphorylation and ubiquitylation. Each of these post-translational modifications is either essential for the maintenance of rod OS structure or the fine-tuning of rhodopsin function [12]. Rod opsin is synthesised on the rough ER membranes before transit to the Golgi and traffic to the OS disks in rod cells or to the plasma membrane (PM) in heterologous expression systems.

Rhodopsin was the first RP gene identified [13]. To date, over 200 rhodopsin point mutations have been described which account for approximately 25% of all adRP cases. Six classes of rhodopsin mutants have been proposed, based on their cellular and biochemical characteristics [14]. Class I mutants fold normally but are not trafficked to the OS correctly, while class II mutants are misfolded and retained in the ER. The remaining mutations are classified according to their effects on endocytosis, opsin stability, increased transducin activation and constitutive activation [14]. The class II P23H mutation is the most common mutation found in North America and is the best studied. The role of the proteostasis machinery in rhodopsin biogenesis and quality control of mutant rhodopsin will be discussed in detail below.

1.2. Light-induced damage

The retina is a transparent tissue, since visible light needs to penetrate the inner retina, where the RGCs and bipolar cells reside, to reach the outer retina and the photoreceptors. While an appropriate amount of visible light is needed to initiate phototransduction, too much light entering the retina can also induce damage; therefore, the eye has developed natural mechanisms to restrict

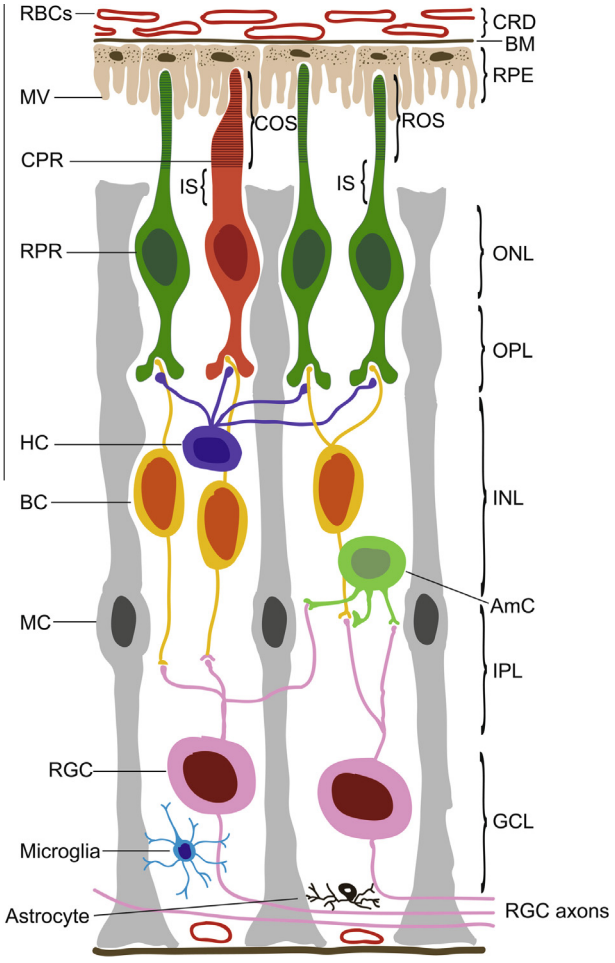

Fig. 1. Structure of the mammalian retina. Schematic cross section representing the different cell types and layers of the retina. The choroid (CRD) containing red blood cells (RBCs) is found at the very back of the eye and is separated from the retinal pigmented epithelia (RPE) by the Bruch's membrane (BM). The RPE extends microvilli (MV) that facilitate the interaction between the RPE and photoreceptors (PRs). Cone (CPR) and rod (RPR) photoreceptors contain the cone and rod outer and inner segments (COS, ROS and IS respectively), the outer nuclear layer (ONL) and outer plexiform layer (OPL), which contains the synapses of the photoreceptors, horizontal cells (HCs) and bipolar cells (BCs). The inner nuclear layer (INL) contains the cell bodies of the horizontal, bipolar and amacrine cells (AmCs). The inner plexiform layer (IPL) is formed of the connections between bipolar and amacrine cells to the retinal ganglion cells (RGCs), in the ganglion cell layer (GCL).

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