The International Journal of Biochemistry & Cell Biology 61 (2015) 115–119

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

journal homepage: www.elsevier.com/locate/biocel

Medicine in focus

Inherited Retinal Dystrophies: The role of gene expression regulators

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ARTICLE INFO

Article history:
Received 22 January 2015
Received in revised form 6 February 2015
Accepted 7 February 2015
Available online 16 February 2015

Keywords:
Inherited Retinal Dystrophies
Transcription factors
OTX2
CRX
NRL

ABSTRACT

Inherited Retinal Dystrophies (IRDs) are a clinically and genetically heterogeneous group of rare disorders characterized by a significant impairment in retinal function and vision. More than 150 genes have been associated with retinal dystrophies and the genetic overlap among different IRDs renders diagnosis and prognosis challenging. In this In Focus article, we give a summary on the pathogenic role of gene expression regulators in IRDs. Emphasis is given on key transcription factors that participate to regulatory gene networks controlling photoreceptor specification and maintenance, and their possible relevance as therapeutic targets. The increasing knowledge on the composition and function of these transcriptional regulatory networks indicates that intervening on transcription factors may be instrumental for a more effective treatment of some forms of IRDs, although the development of appropriate molecular tools to target them remains a formidable challenge.

1. Introduction

Inherited Retinal Dystrophies (IRDs) are a heterogeneous group of genetic disorders collectively characterized by a progressive degeneration of the retina and by a significant impairment or loss of vision. These retinopathies represent one of the main causes of low vision and blindness at young ages, affecting more than two million people worldwide (Sohocki et al., 2001). IRDs can be subdivided in isolated forms, such as Retinitis Pigmentosa (RP) and Leber Congenital Amaurosis (LCA), and syndromic forms that involve non–ocular features, such as Bardet–Biedl and Usher syndromes among others. The age of onset and severity of progression are also variable and difficult to predict. IRDs are characterized by a remarkable genetic heterogeneity with more than 150 genes being implicated (Retina Information Network; http://www.sph.uth.tmc.edu/RetNet/). Mutations in a specific gene can give rise to distinct IRD phenotypes of variable severity, progression and mode of inheritance. As a consequence, establishing a reliable genotype-phenotype relationship is rarely possible. Depending on the photoreceptor cell type that is primarily targeted by the disease, IRDs are clinically classified as rod-cone dystrophies (RCD) and cone-rod dystrophies (CRD).

Rod-cone dystrophies (RCD) are characterized by primary rod dysfunction followed by secondary cone degeneration. RP is the most common form of rod-cone dystrophy, with a prevalence of 1:3500 (Wright and Chakarova, 2010). RP is characterized by night blindness, progressive loss of peripheral and, subsequently, central vision (due to secondary cone involvement). The pathology affects primarily the mid-peripheral retina with loss of rod photoreceptor function, followed by degeneration of cones. RP is almost exclusively a monogenic disease that can be inherited in an autosomal dominant (ad), autosomal recessive (ar), or X-linked manner. To date, mutations in over 60 genes have been implicated in RP (http://www.sph.uth.tmc.edu/RetNet/); however, a significant proportion of RP cases remain genetically unresolved. LCA is a less frequent (1:30,000–81,000), yet more severe, RCD of early onset (i.e. within the first year of life). It is characterized by vision loss, nystagmus and non-recordable electroretinogram (ERG). Inheritance is typically recessive but some forms of adLCA due to mutations in the *CRX* and *IMPDH1* genes were also documented (Wright and Chakarova, 2010). To date, at least 19 genes are associated with LCA (Wright and Chakarova, 2010). Mutations in some of these genes have been shown to cause also RP (Wright and Chakarova, 2010). This illustrates the genetic overlap between different IRDs and the complexity of high-confidence diagnosis and patient counseling.

Cone-rod (CRD) and cone dystrophies are forms of IRDs in which cones are primarily affected and rod degeneration occurs at a subsequent stage. CRDs have an estimated prevalence of 1:40,000 and are characterized by central scotoma and a prominent decrease in

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http://dx.doi.org/10.1016/j.biocel.2015.02.007
1357-2725/

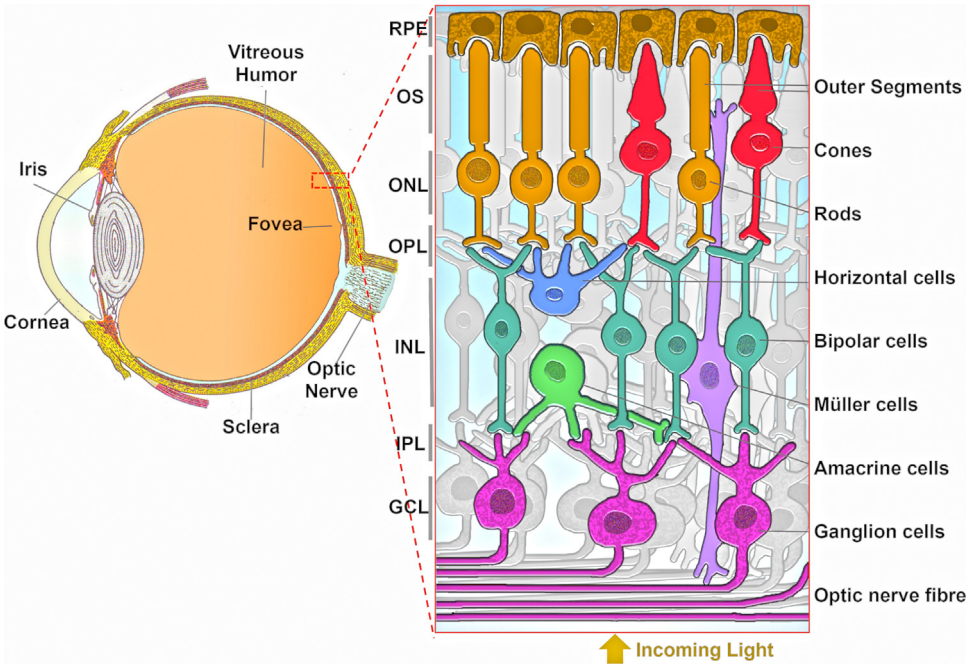

Fig. 1. Structure of the human eye and retina. Diagram illustrating the main structures of the human eye (left). The incoming light passes through the transparent cornea, lens and vitreous body and reaches the retina. A schematic representation of the neural retina and the Retinal Pigment Epithelium (RPE) is shown on the right panel. The retina lies at the innermost part of the eye bulb and comprises neurons, interneurons and ganglion cells. The retina is a highly stratified tissue organized in five distinct layers of cells (GCL, Ganglion Cell Layer; INL, Inner Nuclear Layer; ONL, Outer Nuclear Layer) and neuronal synapses (IPL, Inner Plexiform Layer; OPL, Outer Plexiform Layer). The light-sensitive rod and cone photoreceptors convert incoming light into electrical signals. Phototransduction takes place at the photoreceptor outer segments (OS) that are in contact with the apical microvilli of RPE cells. Bipolar and amacrine cells transmit signals from the photoreceptors to the ganglion cells, which in turn convey visual information to the brain via the optic nerve.

visual acuity. Rod-related symptoms, such as night blindness and loss of peripheral vision, appear only at a later stage. The clinical course of CRDs is fast, leading to legal blindness and disability within few years from the onset of symptoms. Similar to RCD, they are genetically heterogeneous with approximately 30 genes involved (Wright and Chakarova, 2010).

2. Pathogenesis

The main pathogenic event that underlies IRDs is photoreceptor (PR) dysfunction or death. Rod and cone PRs (Fig. 1), which represent more than 70% of retinal cells, are specialized light-sensitive neurons able to convert incoming light into electrical signals. Phototransduction takes place at the PR outer segments (OS) that are in contact with the apical microvilli of the Retinal Pigment Epithelium (RPE) cells (Fig. 1). Photoreceptor function and viability depends upon integrity of the adjacent RPE as demonstrated by the fact that primary RPE defects can elicit PR degeneration. Therefore IRDs can arise from defects occurring primarily in either PRs or RPE cells.

Rods and cones develop from a common pool of retinal progenitors and their specification is controlled by an intricate gene regulatory network (GRN) of transcription factors (TFs) and signaling pathways (Fig. 2) (Swaroop et al., 2010). Several functional pathways are essential for PR and RPE integrity and function, and mutations in any of their members can ultimately lead to PR cell death (Wright and Chakarova, 2010). Among IRD-associated genes, TFs and, more generally, gene expression regulators represent one of the first sub-groups to be identified (Wright and Chakarova, 2010). However, due to their lower frequency of involvement compared to other functional classes, such as phototransduction and retinoid cycle components, their role in IRDs has not been extensively addressed. Out of the TFs responsible for IRDs (Table 1), the ones that are most frequently mutated are *OTX2*, *CRX*, *NRL* and *NR2E3* that play a prominent role in controlling critical steps of PR differentiation, as outlined below. Interestingly, mutations in these TFs are implicated not only in congenital or early-onset IRDs (e.g. LCA), but also in the pathogenesis of late-onset forms (e.g. RP and CRDs). In this review, we highlight the concept that gene expression regulators are important elements for a better understanding and management of IRDs and could represent potential therapeutic targets for intervention even in late-onset conditions.

2.1. Photoreceptor specification

OTX2 and CRX are the key TFs that regulate the initial specification of the PR lineage.

2.1.1. OTX2

OTX2 (orthodenticle homeobox 2 protein) belongs to the paired homeobox family. Mutations in this gene have been mainly associated with major malformation of the eyes of variable expressivity and penetrance (Ragge et al., 2005). *OTX2* mutations also cause IRDs, accounting for less than 1% of infantile retinal disorders such as early-onset retinal dystrophy or LCA (Ragge et al., 2005) and were recently implicated in an autosomal dominant pattern dystrophy of the RPE (Vincent et al., 2014). In the context pertinent to IRD pathogenesis, Otx2 is a master upstream effector that controls (a) the specification of the RPE (Martinez-Morales et al., 2003) and (b) the differentiation and maintenance of PRs via the transactivation of Crx, a closely related homeobox TF (Nishida et al., 2003; Roger et al., 2014). Otx2 also acts in concert with the TF Onecut1 to regulate the expression of early cone markers (e.g. TRβ2) and promote cone photoreceptor cell fate (Emerson et al., 2013). Conditional Otx2 ablation in the mouse retina impairs the conversion of progenitors to PR cells, causing a complete loss of photoreceptors and a marked increase in amacrine-like cells (Nishida et al., 2003). The inducible inactivation of *Otx2* in the adult retina and RPE, leads to rapid RPE dystrophy and progressive PR cell death by