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BRAIN RESEARCH

Research Report

Have we achieved a unified model of photoreceptor cell fate specification in vertebrates?

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ARTICLE INFO

Article history:
Accepted 16 March 2007
Available online 20 March 2007

Keywords:
Retinal development
Photoreceptor
Opsin
Cell fate specification

ABSTRACT

How does a retinal progenitor choose to differentiate as a rod or a cone and, if it becomes a cone, which one of their different subtypes? The mechanisms of photoreceptor cell fate specification and differentiation have been extensively investigated in a variety of animal model systems, including human and non-human primates, rodents (mice and rats), chickens, frogs (*Xenopus*) and fish. It appears timely to discuss whether it is possible to synthesize the resulting information into a unified model applicable to all vertebrates. In this review we focus on several widely used experimental animal model systems to highlight differences in photoreceptor properties among species, the diversity of developmental strategies and solutions that vertebrates use to create retinas with photoreceptors that are adapted to the visual needs of their species, and the limitations of the methods currently available for the investigation of photoreceptor cell fate specification. Based on these considerations, we conclude that we are not yet ready to construct a unified model of photoreceptor cell fate specification in the developing vertebrate retina.

1. Introduction

Normal sight depends upon the coordinated activity of specialized retinal cells that are embryonically derived from a simple, apparently homogeneous neuroepithelium. Elucidation of the mechanisms underlying the developmental transition from a sheet of proliferating neuroepithelial cells to the complex, highly specialized and multilaminar array of distinct types of retinal neurons, ranging from sensory receptors (photoreceptors) to projection neurons (retinal ganglion cells), has intrinsic scientific interest as well as clinical relevance. For example, the transplantation of embryonic retinal tissue, neural progenitors or stem cells offers possible therapeutic strategies for diseases such as age-related macular degeneration and retinitis pigmentosa, in which photoreceptor degeneration leads to visual loss, and eventually to blindness. However, experimental approaches using cell transplantation have, so far, achieved limited success, and overcoming these limitations will require better understanding of the molecular mechanisms that regulate the differentiation of retinal cells in general and of photoreceptor cells in particular.

Considerable progress has been made in the investigation of extracellular signaling molecules and intracellular regulatory mechanisms controlling retinal cell fate specification and differentiation in vertebrates, and a number of excellent reviews have been published recently (Adler, 2000; Bailey et

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doi:10.1016/j.brainres.2007.03.044

al., 2004; Boulton and Albon, 2004; Cepko et al., 1996; Fuhrmann et al., 2000; Galli-Resta, 2001; Hatakeyama and Kageyama, 2004; Jean et al., 1998; Livesey and Cepko, 2001; Lupo et al., 2000; Malicki, 2004; Marquardt and Gruss, 2002; Perron and Harris, 2000b; Rapaport et al., 2004; Reh and Levine, 1998; Vetter and Brown, 2001; Zhang et al., 2002). Despite this progress there are still many unanswered questions regarding photoreceptor specification, including (1) is the retinal neuroepithelium a homogeneous collection of multipotent neuroepithelial cells throughout retinal neurogenesis, or does it contain committed retinal progenitors with more restricted cell fate — i.e., cone progenitors and rod progenitors? (2) At what stage in retinal development do neuroepithelial derivatives become "committed" to the photoreceptor fate? (3) Is photoreceptor subtype determination a distinct (and direct) choice among different fates or, instead, do subtypes derive from a 'generic' immature photoreceptor precursor that indiscriminately transcribes low levels of photoreceptor-specific genes (i.e., genes specific for rods and for all subtypes of cones)? (4) Is the time of terminal mitosis/cell birth a determinant of specific photoreceptor cell fates (e.g., cone versus rod), or even of cone subtypes? (5) Does the competence of retinal progenitors/photoreceptor progenitors to produce cones versus rods change as development progresses? (6) Are there specific lineage relationships among different cone photoreceptor cell types? (7) Is the determination of cone subtype identity limited to control of the expression of a specific opsin gene, or is it a much more complex phenomenon? (8) Related to this, is the use of opsin markers sufficient to identify photoreceptor subtypes? (9) Do postmitotic cells retain the plasticity to commit/switch to a photoreceptor versus non-photoreceptor fate, and/or between the rod and the cone fate? (10) Are postmitotic cone precursors committed to a specific cone subtype, or are they plastic? (11) What extrinsic and intrinsic signals determine photoreceptor cell fate, the choice to be a rod or a cone, and/or the choice between cone subtypes? (12) How is photoreceptor cell fate specification regulated in species in which photoreceptors are added to the differentiated retina during normal growth and/or during retinal regeneration?

In this review, we will limit our focus to vertebrate photoreceptors and consider cell fate specification and differentiation with special attention to what we know about how the different types of photoreceptors are generated, the methods used to identify photoreceptor subtypes, and their life history. Limitations of space and knowledge prevent us from addressing individually each one of the questions posed above. While it is clear that these questions are applicable to all vertebrates, mechanisms of photoreceptor cell fate specification and differentiation have only been investigated in a limited number of animal model systems, including human and non-human primates, rodents (mice and rats), chickens, frogs (*Xenopus*) and teleost fish (several species).

To build a truly unified model of photoreceptor cell fate specification in the developing vertebrate retina requires a comparative analysis that takes into account very substantial differences in photoreceptor subtypes, development and specializations that are found in vertebrates. In this review we have attempted to highlight fundamental questions that remain unanswered, or have only been partially answered, or even have different and sometimes contradictory answers in different animal model systems. We also point out that the many very powerful methods currently available for the study of photoreceptor cell fate specification are not free of limitations, which in some cases are quite significant, and we suggest that new experimental approaches will be needed before we can construct a unified model.

2. Vertebrate visual pigments and the evolutionary origins of rods and cones

The duplex theory of vision is based on the idea that rod photoreceptors mediate scotopic vision and cone photoreceptors are responsible for photopic vision. In brief, the characteristics of rod-mediated visual function include response to low light intensity, black and white vision, low acuity and high sensitivity, with slow kinetics (rate of pigment regeneration and dark adaptation). In contrast, cone-mediated vision functions at high light intensity, allows color discrimination, has high acuity and low sensitivity, and rapid kinetics.[2] Ebrey and Koutalos (2001) suggest four complementary criteria for classifying vertebrate photoreceptors as rods or cones: (i) their visual pigment, (ii) the components of their phototransduction cascade, (iii) their morphology, and (iv) their electrophysiological properties. Many studies of photoreceptor cell fate determination rely largely or exclusively on the first criterion, so we will first review what is known about the vertebrate visual pigments. It will quickly become clear to the reader that reliance on opsin expression as a proxy for photoreceptor identity (and lineage) is inadequate because of notable exceptions to the standard 'rule' that rhodopsin is found in rods and all the remaining opsins are in cones. The various components of the visual transduction cascade appear to be distinct in rods and cones (and correspond to separate but related genes), and the biochemical properties of rod and cone isoforms account for some of the differences in physiological properties (Ebrey and Koutalos, 2001). Expression of rod or cone components of the transduction cascade may provide a more robust measure of photoreceptor identity, but to date only a few developmental studies have examined this question (Cheng et al., 2006; Nikonov et al., 2005).

Vertebrate visual pigments are grouped by molecular phylogeny into five evolutionarily distinct opsin gene families (Fig. 1): *RH1*, *RH2*, *SWS1*, *SWS2* and *LWS/MWS* (Yokoyama, 2000).[3] The *RH1* (rhodopsin) gene is generally associated with rods and the other four opsin genes are usually expressed in

[2] A detailed discussion of the numerous biochemical, morphological, and functional differences between rods and cones is beyond the scope of this review. We refer the interested reader to excellent classic and recent reviews on this topic (Ahnelt and Kolb, 2000; Cohen, 1972; Ebrey and Koutalos, 2001; Walls, 1942).

[3] We use a terminology based on opsin gene families (Yokoyama, 2000) because this designation is unambiguous and accurate across all vertebrate species. Opsins are commonly referred to by their color name, corresponding to the λ_{max} of the visual pigment (e.g., red, green, blue, etc.), but spectral sensitivity is subject to rapid and large evolutionary fluctuations within a group of genes that share a common ancestor, so experts recommend avoiding the use of color names (Ebrey and Koutalos, 2001).