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Review

The developing and evolving retina: Using time to organize form

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ABSTRACT

Evolutionary and other functional accounts of the retina and its normal development highlight different aspects of control of its growth and form than genomic and mechanistic accounts. Discussing examples from opsin expression, developmental regulation of the eye's size and optical quality, regulation of eye size with respect to brain and body size, and the development of the fovea, these different aspects of control are contrasted. Contributions of mouse models, particularly with regard to relative timing of events in different species are reviewed, introducing a Web-based utility for exploration of timing issues (www.translatingtime.net). Variation at the individual level, in early experience, and also across species is an essential source of information to understand normal development and its pathologies.

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1. Introduction

Any collection of titles of articles on retinal development and the genome, or neural development generally will typically show that the word "control" is the most common word elected to describe the relationship between a gene and a process or product. What the word "control" means in research on the genome varies enormously, however, from the direct sense of the activation of a gene that produces a protein immediately involved in function (such as an opsin) to the coordination of genes which regulate the size and placement of whole organ systems. Comparative and evolutionary studies typically consider and describe levels of control at more organismal levels than do mechanistic studies of gene expression in studies of single animals, typically the mouse. Both levels are important, and the issue to be discussed here is their coordination, rather than the choice of one or another.

This review will have two sections. In the first section, three cases will be described in which evolutionary approaches versus genetic–mechanistic approaches contrast relationships between the two types of analysis. Those cases are first, color vision and opsin expression; second, control of retinal and eye size as it relates to optics and visual niche; and finally, control of retinal neuron number with regard to total neuron number in the brain. In the second section, we will consider the particular case of the relative timing and duration of events as a source of order in the developing retina, and how timing might be modified in evolution to produce eyes of different functional classes. The virtues and the limitations of the mouse model for understanding the construction of eyes will be considered in the particular context of developmental timing, from the immediate production of structural proteins, to the coordination of cell specification, to the emerging morphology of the entire organ. Finally, using the concept of "control" we will come back to consider a few ways evolutionary, individual and pathological variation could be linked.

2. Three control problems in retinal development

2.1. *Background: Overall patterns of conservation and variation*

Vertebrate eyes are quite conservative in their cell types, neurotransmitters, neuromodulators and general structure (Rodieck, 1973; Arendt, 2003; Fernald, 2004). It is a remarkable, though rarely noted feature of retinas that the eye of a 20 mm fish may be used quite confidently to explore the fundamental deployment and physiology of the photoreceptor–bipolar–retinal ganglion cell processing unit of the retina, as well as its modulation by horizontal processes, in any other vertebrate, including ourselves (Schmitt and Dowling, 1999). The fundamental cellular morphology and resulting receptive field structure of vertebrate eyes, including both its diurnal and nocturnal variations, apparently represent deep solutions for image analysis for both aquatic and terrestrial life.

Vertebrate eyes vary in the size and arrangement of their basic retinal processing units in typical ways. Eyes can have clearly different rules for scaling with respect to the body and brain, with eye size, photoreceptor number and retinal ganglion cell number scaling differently depending on the animal's niche and taxon (Hughes, 1977). For example, in nocturnal rodents, the number of retinal ganglion cells scales up steeply with brain size, though their eyes are on average relatively small compared to all mammals, while in anthropoid primates (monkeys and great apes), retinal ganglion cell number scales at a very low slope with respect to brain size, while on average their eyes are fairly large (Franco et al., 2000; Heesy and Ross, 2001). Within the eye, vertebrates differ in the conformation of non-neural elements, in the ratio of the numbers of types of cells in the retina and in the "topography" of the arrangement of these cells (Stone, 1983). With the exception of photopigments, the observation that vertebrate eyes appear to be principally "topological" permutations of an essentially conserved structure suggest that timing, duration, or number of genes expressed, rather than the nature of structural proteins produced, are the principal sources of variation in eyes in evolutionary time.

Why should those interested in the mechanistic and medical aspects of retinogenesis, and not evolution per se, have any interest in patterns of evolutionary variability? If your interest is congenital abnormalities, refractive errors, defects of color vision, disorders of cell cycle control leading to cancers, or other disease processes, the unusual features of the color vision of the cichlid fish of Lake Malawi (Kocher, 2004) might at first seem an interesting bit of arcanery at best. The long answer to this question involves a very fundamental change in our understanding of the genome and its control processes that has occurred in biology since the growth of the field of evolution and development, "evo–devo". Callaerts et al. (1997) produced one of the initial observations of conserved developmental sequences across taxa, and Kirschner et al. (2006) offers an accessible and comprehensive account of this enterprise. Essentially, the classes of mechanisms that organize fundamental systems are extremely conserved. Certain classes of genomic variation are permissible and occur very commonly (like gene and partial-gene duplication), while others are not, resulting in highly non-random patterns of individual variation. Finally, multiple and redundant mechanisms cooperate in the construction of adult phenotypes, such that any genetic change will encounter a variety of epigenetic mechanisms in place to assure that the components of any organ scale gracefully, integrated with other organ systems. All of these directly impact the kinds of disorders that can occur. The following examples all illustrate genetic change nested epigenetic mechanisms in various ways.