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Retinal Cell Fate Specification

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Abstract

How are different neural cell types generated from progenitor cells? In 1990, Turner et al. used new lineage tracing techniques to show that different cells in the mammalian retina share their progenitor origin. The findings established a key step towards our understanding of how multipotent progenitor cells give rise to complex circuitry in the retina.

Keywords

Lineage-independent; Retinal cell development; differentiation

Main text

Vision is one of our richest senses and the dedication of our central nervous system to visual processing is astounding. In mammals, vision originates with sensory processing in the retina, which demonstrates remarkable evolutionary conservation. Shared molecular and cellular features in development and adulthood from rodent to human have allowed many basic questions to be modeled across species. One of the key questions relating to the formation of the visual system is, how are different retinal cell types generated during development? Three decades ago, there were generally two hypotheses regarding the origin of retinal cells. According to one hypothesis, different cell-type classes – for instance retinal ganglion cells (RGCs), rods and cones – originate each from separate precursor cells, with each precursor restricted to produce only one or a few cell types. According to the second hypothesis, different retinal cell types could be differentiated from the same precursor cell. The question at the core of these competing hypotheses is relevant not only for retinal development, but also for other parts of the nervous system, and even other body organs. To track cell lineages, scientists had come up with methods for labeling precursor cells, and then determining what cell types differentiated from labeled precursor or stem cells. In the

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1980s, a retrovirus-mediated gene transfer technique was developed for labeling individual precursor cell in the vertebrate central nervous system (CNS) by expression of β-galactosidase and tissue staining [1; 2]. In 1987, Turner and Cepko reported a study in a postnatal rat retina showing that retrovirus-marked progeny clones differentiated into four different cell types with various overlapping combinations [1]. The study represented an important milestone in clarifying retinal cell lineages. However, since only 4 of the 7 major retinal cell-type classes were labeled, the study did not fully differentiate between the two hypotheses outlined above, and particularly when it comes to the earlier origin of retinal cell-types, both theories remained plausible. Differentiating between the two accounts required taking the challenging step of going into earlier stages of development, i.e., the embryonic retina.

To label retinal precursor cells in the embryonic retina, Turner, Snyder and Cepko conducted ex-utero surgery, which had not been applied much in retina studies by that time, to perform subretinal viral injections into embryos at embryonic days 13–14 (E13–14) [3] (gestation in rodent lasts approximately 3 weeks). They now observed all 7 retinal cell-type classes (retinal ganglion cells, cones, horizontal cells, amacrine cells, bipolar cells, rods and Muller glial cells) in labeled clones of the precursor progeny. Their data suggested that ganglion and horizontal cells, as well as cones, differentiated at early stages. The 4 other cell-types seemed to differentiate at later stages. Moreover, most multi-cell clones encompassed two or more cell types, and clone sizes were larger in retinas infected at E13 than in those infected at E14. Given those findings, the authors suggested that the different cell-types observed in the adult retina originated from common progenitors [3].

Over the years, this common progenitor theory was also supported by studies in other species and in other parts of the CNS. For instance, the two very different classes of neurons in the mature precerebellar system, one projecting mossy fiber axons to cerebellar granule cells and one projecting climbing fiber axons to cerebellar Purkinje cells, may be derived from a shared progenitor pool [4]. One of the implications of the lineage-independent theory relates to the question of environmental influences. Turner et al. proposed that given the common progenitor origin of retinal cell types, environmental factors might also alter retinal cell fate determination. Indeed, shortly after, numerous studies began to place focus on cell-extrinsic factors and their role in regulating cell fate specification in the retina, as well as in other parts of nervous system. Cell-cell interactions were shown to determine certain retinal cell phenotypes [5]; and on the molecular level, secreted growth factors such as CNTF and TGF-α/EGF [6; 7] were found to influence RGC specification (to name one example) [8].

Following the observations on retinal cell progeny using retrovirally marked clones, researchers turned to another key question: how is retinal cell fate regulated? Two opposing models were proposed. One model suggested that the environment is completely responsible for dictating the choice of cell fate. The second model, in contrast, hypothesized that all information concerning cell fate is derived from intrinsic information, and that retinal progenitors were ‘programmed’ to progress in a linear fashion, from one state of competence to the next, and in only one direction. Consistently with one of the tenets of the latter view, early progenitor cells appear to be unable to jump ahead to later stages of competence [9]. Based on the foundation of the lineage-independent cell fate determination,

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a later study indicated that Muller glial cells shared a lineage and a precursor with retinal neurons, and further research demonstrated the potential of Muller glia to become neurogenic retinal progenitor cells [10]. Together these studies pointed towards a strong contribution of intrinsic regulation of lineage restriction.

The studies by Turner et al., and the work that followed them received attention and appreciation from audiences beyond the retinal-development field – partly, in view of the emergence of stem-cell-based approaches in the past two decades. Given the potential of progenitors to generate all types of retinal cells, studies into stem cell-based regenerative approaches have flourished. Protocols have been developed to harvest certain types of retinal cells, e.g. RGCs and photoreceptors, differentiated directly from stem cells rather than from progenitor cells in shorter duration [11]. It is interesting to note that most protocols demand that cells go through a progenitor phase, expressing progenitor cell markers, before differentiating into mature progeny, but without clear markers to distinguish stem cells from committed progenitors, it is hard to distinguish self-renewing pluripotent versus restricted divisions of the multipotent cells [12].

Elucidating the molecular pathways that regulate retinal cell fate determination remains an important area for study. Cell subtype determination may be regulated by extrinsic or intrinsic factors. SoxC transcription factors, for example, seem necessary and sufficient for RGC fate specification [13] and may specify subtype-specific crossing at the optic chiasm [14]. Whether such factors involved in rodent progenitor cell differentiation can also regulate human stem cell differentiation remains an important question. Another critical area of study that follows from the foundational work outlined above is the link between cell type specification and retinal circuit integration. During retinal differentiation, nascent neurons integrate with each other into circuits—to what degree is this process specified by differentiation processes during development? Understanding the regulatory mechanism of circuit integration during development is important also in the context of neuronal cell replacement strategies based on stem cell-derived progeny in the adult, as circuit-integration mechanisms (or at least some of them) may be shared between this scenario and normal development.

Clarifying the processes governing neuronal differentiation during development remains critical for unmasking the basis of complex circuit- and system-properties in the retina and throughout the nervous system. The findings by Turner, Snyder and Cepko continue to be acknowledged as a major step forward in understanding principles of CNS neuron differentiation, and continue to drive follow-up research, new technique development, and novel approaches to understanding the development of the nervous system and exploring new strategies for repairing it.

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