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Retinal Glia

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Ion channels as therapeutic targets, part B

Jonathan P. Giblin, ... Xavier Gasull, in Advances in Protein Chemistry and Structural Biology, 2016

6.8 The Role of $P2X_7$ in Retinal Pathophysiology

The death of retinal neurons (and glia) is a major contributor to the visual impairments, which can eventually lead to blindness, in a range of pathological conditions. For example, photoreceptors die in RP and age-related macular degeneration (AMD), while retinal ganglion cells are lost in glaucoma and diabetic retinopathy (Doonan, Groeger, & Cotter, 2012).

Although numerous signaling pathways mediate retinal cell death, a key upstream event is the elevation of the cytosolic calcium concentration (Donovan, Carmody, & Cotter, 2001; Doonan, Donovan, & Cotter, 2005; Fox, Poblenz, & He, 1999). It is well established that inherited retinal degenerative diseases such as RP are associated with an increased cation permeability of photoreceptors (Doonan et al., 2005). At least in part, retinal cell death is mediated by the stimulation of the ATP-gated nonspecific cation channel, $P2X_7$. $P2X_7$ expression has been observed in photoreceptors, horizontal cells, retinal ganglion cells, and Müller glial cells (Ishii, Kaneda, Li, Rockland, & Hashikawa, 2003; Pannicke et al., 2000; Puthussery & Fletcher, 2004; Wheeler-Schilling, Marquordt, Kohler, Guenther, & Jabs, 2001). Under physiological conditions, $P2X_7$ is thought to play a role in the modulation of retinal neurotransmission. ATP is released in large amounts by cells in response to stressful stimuli such as inflammation, osmotic stress, oxidative stress, ischemia,

hypoxia, mechanical stimulation, and injury (Franke, Krügel, & Illes, 2006). Evidence is accumulating that extracellular ATP can contribute to retinal cell death via $P2X_7$ activation (Fletcher, 2010). Increases in cytosolic calcium concentration caused by activation of $P2X_7$ channels have been shown to mediate death of retinal ganglion and amacrine cells under hypoxic conditions and after optic nerve crush (Kakurai, Sugiyama, Kurimoto, Oku, & Ikeda, 2013; Niyadurupola et al., 2013; Sugiyama et al., 2010). Indeed, preventing activation of these channels using the specific antagonist PPADS slowed rod photoreceptor death in a mouse model of RP (the *rd1* mouse) and application of the $P2X_7$ antagonist brilliant blue G increases survival of retinal ganglion cells after optic nerve crush injury (Kakurai et al., 2013; Puthussery & Fletcher, 2009).

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Neural Stem Cells: Ocular

T.A. Reh, in Encyclopedia of Neuroscience, 2009

Retinal Stem Cells in the Ciliary Marginal Zone

In the mammalian retina, the neurons and glia are generated in a continuous period of time from fetal to neonatal stages. In the mouse, for example, retinal neurons and glia become postmitotic starting at embryonic day 12.5 and ending approximately 1 week after birth. In all vertebrates, there is a central-to-peripheral pattern to histogenesis and differentiation in the retina. The first neurons are produced in the central retina and the last are produced at the periphery.

In contrast to the mammalian retina, in the amphibian, fish, or avian retina, histogenesis continues after the embryonic or neonatal period. In these animals, the retina continues to add new neurons into adulthood and, in some, throughout life. Teleost fish, for example, have a dramatic growth of the eye during their lifetime of up to 100-fold. The growth of the retina is accomplished by the continued production of new retinal neurons from a zone of cells at the peripheral margin, adjacent to the nonneuronal ciliary body, called the ciliary marginal zone (CMZ; **Figure 1(b)**). This zone is similar to neural stem cell zones in other regions of the CNS, such as the hippocampal progenitor zone or the subventricular zone. However, in contrast to these other zones, which typically generate only one type of neuron, the CMZ cells generate all types of retinal neurons and Müller glia. In fact, most of cells in the retina of the mature frog or fish are generated by the cells of the CMZ. Lineage tracing studies of CMZ cells have shown that these cells can give rise to clones that contain all types of retinal neurons. The CMZ is thought to be organized with the

most primitive cells (true stem cells (?)) in the most peripheral part (possibly mixed with the cells of the ciliary epithelium) and progressively more mature progenitor cells (transit amplifying cells (?)) closer to the differentiated retina.

The CMZ is highly productive in fish and some amphibians, but in birds it is greatly reduced. In birds, most of the retina is generated during embryonic development and only a small number of retinal neurons are generated by the CMZ. It is not known whether this zone persists throughout the lifetime of the bird, but new retinal neurons are generated at the peripheral edge of the retina in chickens up to 1 month of age and in the quail eye for up to 1 year. Like those of fish and amphibians, the CMZ cells of birds resemble the early progenitor cells of the retina, in terms of both their gene expression and their response to mitogenic factors.

The CMZ is greatly reduced or absent in the eyes of mammals that have been examined to date, including rodents and nonhuman primates. However, there is evidence that a CMZ-like zone can form in rodents under certain conditions. For example, mice with a single functional allele of the patched gene, a negative regulator of Shh signaling, retain a small number of proliferating, nestin-expressing cells at the retinal margin into adulthood. Moreover, when these mice are bred onto a background in which photoreceptors degenerate, the proliferation increases, reminiscent of the response to retinal damage observed in the CMZ cells of lower vertebrates. Studies have found that the normal period of proliferation of retinal progenitors can be extended by the injection of specific growth factors, but no study has successfully 'resuscitated' cells at the retinal margin of an adult mammal *in vivo*.

The CMZ in fish, amphibians, and birds can provide a source of regeneration following damage to the retina. In fish and amphibians, destruction of retinal neurons with neurotoxins or by surgery causes an increase in the proliferation of the CMZ cells. The cells produced by the CMZ then differentiate into neurons and in some cases migrate considerable distances to replace the cells lost by the experimental injury. In birds, neurotoxin damage does not by itself stimulate the proliferation of the CMZ cells, but destruction of retinal ganglion cells, followed by insulin-like growth factor and FGF injections, causes the CMZ cells to produce new ganglion cells, replacing the lost ganglion cells in the peripheral retina.

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Sensory Epithelium of the Eye and Ear

Constance Cepko, Donna M. Fekete, in Essentials of Stem Cell Biology (Third Edition), 2014

14.2 Introduction to Progenitor and Stem Cells in the Retina

The retina has served as a model of central nervous system (CNS) anatomy, physiology, and development. Most studies aimed at understanding its development have concerned the production of the retinal neurons and glia from retinal progenitor cells. These cells were originally shown by lineage analysis to be multipotent throughout development, capable of generating both neurons and glia, even in a single, terminal cell division. Retinal progenitor cells do not appear to be totipotent except for the earliest progenitor cells, when clones can comprise all retinal cell types. Moreover, retinal progenitor cells do not appear to be able to proliferate extensively *in vivo* or following explantation and exposure to different culture conditions. More recent studies have been aimed at finding retinal stem cells. These studies have been conducted along the two lines established in the search for stem cells elsewhere in the CNS. One approach has been to search for mitotic cells capable of generating retinal neurons in the adult *in vivo*. The other approach has been to culture cells in growth factors. Both types of experiments have begun to yield promising answers, but much more needs to be done.

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Invertebrate and Vertebrate Eye Development

Denise M. Davis, Michael A. Dyer, in Current Topics in Developmental Biology, 2010

Abstract

Neurogenesis in the retina occurs via the coordination of proliferation, cell cycle exit and differentiation of retinal progenitor cells. Until recently, it was widely assumed that once a retinal progenitor cell produced a postmitotic neuron, there was no possibility for cell-cycle re-entry. However, recent studies have shown that mature differentiated horizontal neurons with reduced Rb pathway function can re-enter the cell cycle and proliferate while maintaining their differentiated features. This chapter will explore the molecular and cellular mechanisms that help to keep differentiated retinal neurons and glia postmitotic. We propose that there are cell-type specific barriers to cell-cycle re-entry by differentiated neurons and these may include apoptosis, chromatin/epigenetics mechanisms, cellular morphology and/or metabolic demands that are distinct across cell populations. Our data suggest that differentiated neurons span a continuum of cellular properties related to their ability to re-enter the cell cycle and undergo cytokinesis while maintaining their differentiated

features. A deeper understanding of these processes may allow us to begin to explain the cell type specificity of neuronal cell death and tumor susceptibility. For example, neurons that have more barriers to cell-cycle re-entry may be less likely to form tumors but more likely to undergo degeneration. Conversely, neurons that have fewer barriers to cell-cycle re-entry may be more likely to form tumors but less likely to undergo degeneration.

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Gliotransmitters

Jacqueline A. Hubbard, Devin K. Binder, in Astrocytes and Epilepsy, 2016

Reversal of Glutamate Transporters

Astrocytes play an important role in removing glutamate from the extracellular space through specific sodium-dependent glutamate transporters found near synapses. The two major astrocytic transporters are glutamate transporter-1 (GLT1) and glutamate/aspartate transporter (GLAST). Under homeostatic conditions, glutamate is driven into astrocytes through its concentration gradient. During pathophysiological events, however, perturbed extracellular ionic concentrations may favor the reversal of these transporters. This was initially demonstrated with whole-cell clamp of Müller cells from salamander retina by Szatkowski et al. [76]. They found that raising extracellular K^+ concentrations around glial cells evoked an outward current produced by the reversal of glutamate uptake [76]. This current was inhibited by extracellular glutamate and sodium and was increased by membrane depolarization.

Many studies used primary rat or mouse astrocyte cultures to study gliotransmitter release through glutamate transporter reversal. Massive excitatory amino acid efflux was seen under conditions of energy failure, including blockade of glycolytic and oxidative metabolism and ATP production [77,78]. Prolonged exposure to high extracellular K^+ concentrations (60 mM for 15–20 min), however, did not increase extracellular glutamate concentrations [78]. Similar results were seen in pure cultures of retinal neurons and glia preloaded with [^{3}H]-acetate (preferentially metabolized by astrocytes) and [U-^{14}C]-glucose (preferentially metabolized by neurons). After total metabolic blockade with iodoacetate and KCN, release of [^{3}H]-glutamate was significantly increased within 15 minutes whereas [U-^{14}C]-glutamate remained unchanged [79]. Pretreatment with a glutamate transporter blocker inhibited about 57% of the glutamate release after 30 minutes of metabolic block, suggesting that sodium-dependent glutamate transporter reversal is a major contributor, but not the sole component, to increased extracellular glutamate levels during energy depri-

vation [79]. Similarly, inhibition of sodium-dependent glutamate transport with the astrocytic GLT1 blocker dihydrokainate (DHK) was protective against anoxia-induced glutamate release [80].

Ischemia has been associated with increased extracellular glutamate levels. Forebrain ischemia was induced in anesthetized rats and microdialysate concentrations of glutamate were measured in the presence or absence of various blockers [81]. Inhibition of the astrocytic GLT1 with DHK or anion channel blockers diminished ischemia-induced glutamate release in rat striatum, suggesting that both cell swelling and the reversal of glutamate transporters might contribute to elevated extracellular glutamate levels [81]. A separate study induced ischemia in hippocampal slices from 12-day-old rats and bathed slices with various blockers of different glutamate release mechanisms. They found that reversal of neuronal glutamate transporters was the primary contributor to ischemia-induced glutamate release [82].

Reversal of glutamate transporters has excitotoxic consequences including lipoxygenase pathway-mediated cell death [83]. Exposure of co-cultures of rat cortical neurons and glia to the excitatory amino acid transporter inhibitor l-*trans*-pyrrolidine-2,4-dicarboxylate (PDC) led to a rapid elevation in extracellular glutamate and NMDA receptor-mediated excitotoxicity [84]. The glutamate increase was insensitive to tetrodotoxin, independent of extracellular calcium levels, present in astrocyte-pure cultures, and was suppressed in sodium-free medium. To confirm these findings, Volterra et al. [84] used glutamate transporters functionally reconstituted in liposomes to show that PDC activated carrier-mediated release of glutamate via transporter reversal. Taken together, these data suggest that the net efflux of glutamate may occur in the unhealthy brain, but the contribution to the healthy brain has yet to be determined.

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Animal Models of Human Disease

Erica L. Fletcher, ... Paul N. Baird, in Progress in Molecular Biology and Translational Science, 2011

II Overview of Retinal Structure and Function

The retina is a multilayered outpouching of the central nervous system that consists of alternating layers of neurons and synapses (Fig. 1A). Light passes through all layers of the retina prior to being absorbed by photopigments located within the outer segments of photoreceptors.[1] Photoreceptors convert light into a neurochemical signal that is passed to second order neurons, called bipolar cells. Bipolar cells

communicate in turn with the temporally acting amacrine cells and ganglion cells, with the latter being the main output neurons of the retina. Thus, the retinal "through" pathway consisting of photoreceptors, bipolar cells, and ganglion cells plays a central part in visual processing within the retina. Diseases of the retina are associated with the loss of function or death of one or more classes of neurons in the retinal through pathway. Visual impairment can arise from loss of photoreceptors, defects in synaptic transmission between photoreceptors and bipolar cells, or loss of ganglion cells.

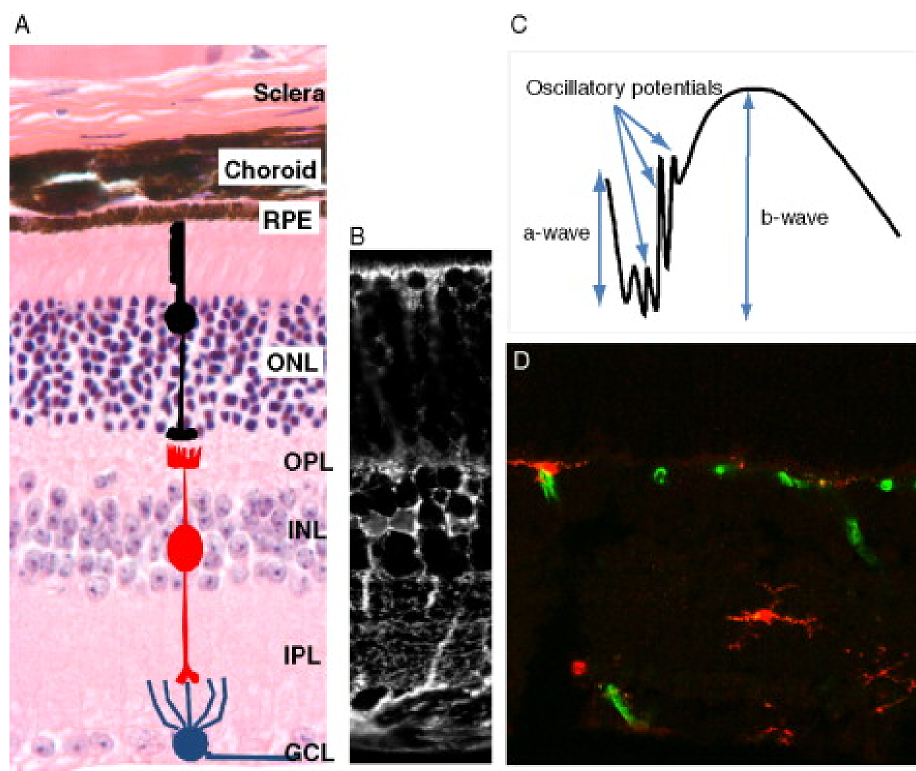

Fig. 1. Summary of the cellular structure and function of the retina. (A) A vertical section of the adult rat retina showing the retinal layers and major neuronal subclasses. The neuronal layers of the retina include the outer nuclear layer (ONL) corresponding to the location of photoreceptor nuclei (black cell), the inner nuclear layer (INL), where horizontal, bipolar and amacrine cells are located, and the ganglion cell layer (GCL), where nuclei of ganglion and displaced amacrine cells are located. The two synaptic layers include the outer plexiform layer (OPL) and the inner plexiform layer (IPL). Beneath the retina, are located the retinal pigment epithelium (RPE), choroid, and sclera. The major neuronal circuit that carries visual information through the retina is the retinal through pathway which comprises photoreceptors (indicated as a black cell), bipolar cells (indicated as a red cell), and ganglion cells (indicated as a blue cell). (B) Vertical section of rat retina immunolabeled for the glial cell marker, glutamine synthetase. Müller cells span the entire thickness of the retina and have their somata located in the middle of the inner nuclear layer. (C) Schematic diagram of the major wavelet components of the flash ERG, including the a-wave (derived from the activity of photoreceptors), b-wave (attributed to postreceptoral neurons

especially ON Bipolar cells) and oscillatory potentials (attributed to the function of amacrine cells). (D) Vertical section of the rat retina immunolabeled for the microglial marker, IBA-1 (red) and a marker of blood vessels (green). Microglia, the main resident immune cell of the retina, are stellate cells located within the two plexiform layers. (See Color Insert.)

Maintenance of retinal integrity depends on support cells, including macroglia such as Müller cells and astrocytes,[2,3] or the retinal pigment epithelium (RPE), a monolayer of epithelial cells that sits below the retina and is integral to photoreceptor function[4] (Fig. 1). Retinal glia, including Müller cells take up and recycle the neurotransmitters, glutamate and GABA, siphon potassium from the extracellular space, shuttle energy metabolites between the vasculature and neurons, and also play a role in maintaining the blood retinal barrier.[2,3] If any of these functions is disrupted, deleterious effects on retinal neurons ensues.[2]

The RPE is an epithelial monolayer of cells that forms a barrier between the underlying choroidal vasculature and the neural retina[4] (Fig. 1). Photoreceptor outer segments sit within the microvillus projections of the apical surface of RPE cells. The RPE has an enormous range of functions but four of the most crucial are absorption of stray light by virtue of the melanin granules found with the cells, transport of retinoids between the choroidal vasculature and photoreceptor outer segments, phagocytoses photoreceptor outer segments and detoxification of photoreceptor outer segment debris.[4] Secondary loss of photoreceptors can occur if any of these functions of the RPE are disrupted.

Microglia are generally considered the resident immune cells of the retina.[5] However, owing to their rapid activation following retinal injury and their contribution to the development of inflammation they have been implicated in a variety of retinal diseases. They lie dormant within the inner retina, and in their quiescent state have a distinct stellate morphology (Fig. 1). Several studies suggest that microglia in this resident state extend and retract their fine processes so as to constantly survey their local environment.[6–8] Following injury they change morphology by retracting their processes and take on a more amoeboid morphology that is also associated with the release of a range of cytokines.[6,7]

A common method used to test the functional status of the retina is with electroretinogram (ERG) recording.[9] The flash ERG is an extracellular recording that derives from the activity of different cohorts of retinal neurons, that is often used in animal studies to gain an understanding of the onset and severity of disease.[9] Following a brief flash of light, recording electrodes placed on the cornea signal a serial waveform[9] (Fig. 1). As shown in Fig. 1C, the first negative deflection of the waveform is called the a-wave and reflects photoreceptor activity. The second positive going waveform is the b-wave and is attributed to the activity of ON bipolar cells.

On the leading edge of the b-wave are small oscillations, called oscillatory potentials that reflect inner retinal processing, especially from amacrine cells. By examining the amplitude and timing of each of these waveforms it is possible to determine the retinal locus of disease.

In summary, visual impairment is caused by the loss or dysfunction of neurons that form the retinal through pathway, including photoreceptors, bipolar cells, and ganglion cells. Deficits can be caused by direct loss of these cells, or by secondary affects via loss of function affecting the range of support cells that retinal neurons rely on.

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Growth of the retina and tectum: Implications for the retinotectal map

John T. Schmidt, in Self-Organizing Neural Maps: The Retinotectal Map and Mechanisms of Neural Development, 2020

5.2 Histogenesis of retina

5.2.1 Radiolabeled thymidine technique

Most studies of neurohistogenesis have depended on the use of ^{3}H thymidine, a specific precursor for DNA, followed by radioautography to date the time of final cell division. Cells incorporating ^{3}H thymidine are identified by the presence of silver grains over their nuclei, and the number of grains indicates the level of radioactivity. If the animal is killed shortly after exposure to the ^{3}H thymidine, then dividing cells synthesizing DNA are heavily labeled. With longer survivals, some of the initially labeled cells may have divided again after the tracer dissipated, so that those daughters become less heavily labeled. After several divisions, the label in the progeny would be undetectable. In contrast, labeled cells that never divided again would be most heavily labeled, since their label had not been diluted. Thus, a short survival (relative to the cell cycle time) reveals the proliferative cells, whereas a long survival shows what has become of the cells that divided for the last time while the tracer was present or just after the tracer was exhausted.

In the early optic cup, all cells in the retinal primordium are proliferative (Fig. 5.2 Top). Later, some of the cells in central retina withdraw from the mitotic cycle and begin to differentiate into retinal neurons and glia. The presumptive ganglion cells are the first postmitotic cells to appear, and the alternating nuclear and plexiform layers

develop shortly thereafter, the inner layers first. The synaptic organization of the inner retina is ready to function before the photoreceptors have developed the ability to transduce light signals. This initial histogenesis has been observed, using 3H thymidine radioautography, in amphibians (Hollyfield, 1968, 1971; Jacobson, 1968a; Straznicky and Gaze, 1971), fish (Hollyfield, 1972; Sharma and Ungar, 1980), birds (Dutting et al., 1983; Fujita and Horii, 1963; Kahn, 1973), and mammals (Sidman, 1960).

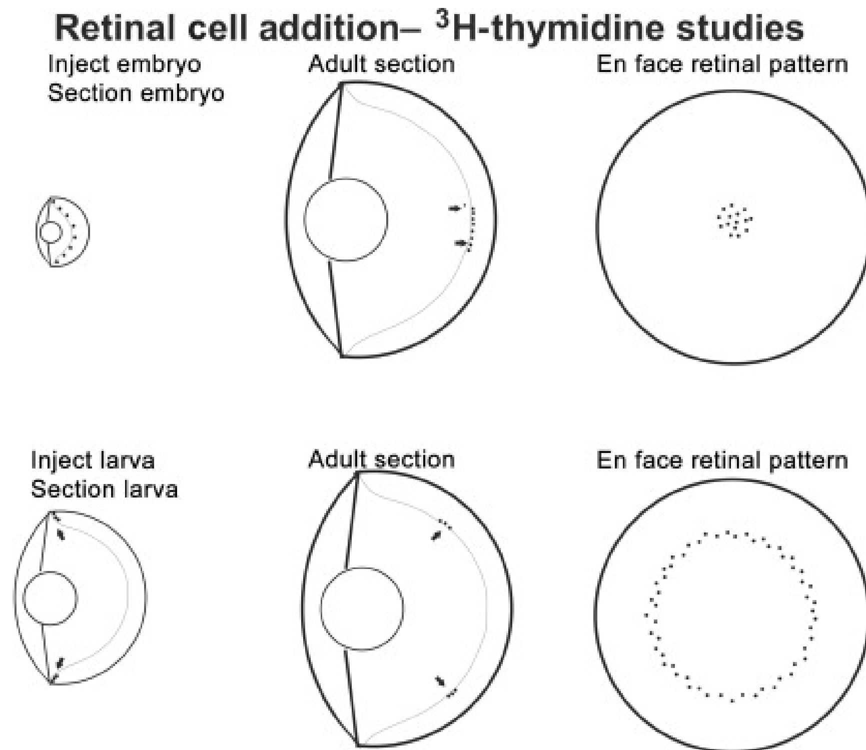

Fig. 5.2. **Growth pattern of the retina in fish and frog, determined by labeling with 3H-thymidine.***Top left:* Labeling in the embryo and fixing hours later shows mitotic ganglion cells all over presumptive retina *(black dots). Middle and Right:* After growing to adulthood, sections show these labeled mitotic cells are now located at the center of the retina, displaced inward by later generated cells. *Bottom left:* Labeling at larval/juvenile age with immediate examination shows mitotic cells restricted to the retinal margin *(arrows). Middle and Right:* After growing to adulthood, the labeled cells are displaced to two sites *(arrows)* centered on the optic nerve, and forming an annulus across retina (right), verifying the continued addition of annuli of cells with time.

During a second phase, postmitotic cells continue to differentiate in central retina as proliferation stops or slows considerably there, and new cells are added preferentially at the margins. This pattern, which is clearest in fish and amphibians, has been inferred from short survivals following later injections of 3H-thymidine. The great majority of labeled nuclei are found on the edge of the retina, adjacent to the boundary of the iris (Fig. 5.2, bottom). Following longer survivals, the labeled cells still lie in a ring, but are displaced from the edge of the retina (Fig. 5.2, bottom).

This ring identifies the cells that made their terminal divisions at, or soon after, the time when the thymidine was available. The longer the survival, the greater is the distance between the labeled cells and the edge of the retina. These results imply that the peripheral retinal cells stay in place after their terminal divisions, and differentiate at that site. Meanwhile, some of their sibling cells remain proliferative and the retinal margin gradually grows away from the labeled post mitotic cells. Unlabeled cells central to the ring made their terminal divisions prior to the time that the ^{3}H-thymidine was available. Unlabeled cells peripheral to the ring divided enough times since the initial injection that they have lost their label by dilution. Within the labeled annulus, the labeled ganglion cell bodies are situated slightly more peripherally than the other labeled cells, suggesting that they were the first to withdraw from the mitotic cycle, as they were in central retina during the initial phase. Thus, the retina grows appositionally, and a cell's distance from the edge correlates directly with its age, the older cells central, the younger, more peripheral. This annular addition is not always symmetric, as one side may grow faster by adding more cells on that side, a pattern seen in some frogs and fish (Easter, 1992).

An important question concerns the clonal relations between the ganglion cells and the other cells generated. At the one extreme, a progenitor cell might be prespecified to produce only ganglion cells, while others were specialized to produce only amacrines, only bipolars, etc. At the other extreme, each progenitor might produce serially a ganglion cell and all the other cells within a vertical column of retina that feed onto it. An in-between hypothesis would be the production of multiple cell types by each progenitor under the influence of factors in the environment. The experiments of Wetts and Fraser (1988) rule out the first possibility, as individual progenitors in *Xenopus* retina, injected with fluorescent dextran, gave rise to a wide variety of cell types including nonneuronal cells, such as Mueller cells and pigmented epithelium. The number of progeny cells varied greatly suggesting that there may be two types of progenitors: those set to undergo a limited number of divisions and those set to divide indefinitely with one daughter remaining a neuroblast and the other differentiating. Studies in mouse using retroviral tracers of clones also show production of several neuronal types and glia from the same clone (Turner and Cepko, 1987). Generally the lack of any repeatable pattern in cell types produced versus number of progeny suggests that the environment or position may determine the differentiation pathway after the final division.

This pattern of annular growth presented above, with postmitotic cells remaining in place, is generally accurate, but some significant exceptions and qualifications should be noted. First, neurogenesis continues in central retina, too, in fish, but only new rods are produced (Johns and Fernald, 1981). All new ganglion cells are produced at the annular margin. Second, the discontinuity between postmitotic central retina and the proliferative marginal retina is variable, depending on the

species in question. The addition of new ganglion cells exclusively at the margin has been demonstrated very clearly in amphibians (Beach and Jacobson, 1979; Hollyfield, 1968, 1971; Jacobson, 1968a, 1976) and fish (Hollyfield, 1972; Johns, 1977; Meyer, 1978; Muller, 1952). In the chick, the transition is not so sharp (Dutting et al., 1983; Kahn, 1973, 1974). In cats, the centroperipheral gradient is evident, but the pattern of proliferation is quite complex. At any retinal locus, the various subtypes of ganglion cells are born in waves at slightly different (but still overlapping) times, and each wave of proliferation traces out a spiral, rather than an expanding annulus (Walsh and Polley, 1985; Walsh et al., 1983). In general, the medium-sized □ cells begin to be generated earlier than the larger □ cells, and the smallest □ cells are the last to be generated. These correspond to the physiological types X, Y, and W. In other mammals, the pattern of generation of cells may vary in order to produce high density areas in retina, called either the area centralis or the fovea. In rodents, proliferation may not vary centroperipherally (Sidman, 1960), but differentiation does (Morest, 1970). Third, the idea that all postmitotic cells remain where they were born has been questioned. In *Rana pipiens*, there is some evidence that cells migrate from the retinal margin to occupy locations in the inner nuclear layer among older cells (Hollyfield, 1968). But no such migration occurs in another anuran, *Xenopus laevis* (Straznicky and Gaze, 1971).

The retina also increases in area by “stretching”; that is, by the movement of differentiated cells apart, resulting in a lower planimetric density (number per square millimeter of retinal surface) (Ali, 1964; Beach and Jacobson, 1979; Coulombre, 1955; Johns and Easter, 1977; Lyall, 1957a,b). This is analogous to what would occur during the inflation of a balloon; imagine that the retinal cells are represented by dots on a balloon, and the balloon is inflated. There are no more dots than before, but they are farther apart, spread over a larger area. The analogy is supported by the finding that when the intraocular pressure of an embryonic chick eye was lowered, the retinal area did not increase (Coulombre, 1956). Stretching does not seem to begin until fairly late in retinal development (Fernald, 1991), and when it occurs, it is usually accompanied by the concurrent addition of new cells at the margin. Harman and Beazley (1987a,b) have suggested that the selective addition of other cells without ganglion cells in the peripheral areas causes differential stretch there, with a resulting low density of ganglion cells. In contrast, the lack of both addition and stretch in central retina allows the maintenance of a high density of ganglion cells, an area centralis (Kelling et al., 1989). In juvenile goldfish which has no high density area of retina, stretch has been quantified. Stretching accounts for most of the retinal growth after 1 year: 80% of the increase in the surface area of the retina was a result of stretch, and only 20% due to marginal cell proliferation (Johns and Fernald, 1981).

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