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DEVELOPMENT AT A GLANCE

Retinal neurogenesis

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ABSTRACT

A unique feature of humans is the complexity of our central nervous system. A fully functional brain requires that billions of neurons make specific contacts in a highly coordinated way, an issue that is still not well understood. The neural retina constitutes an excellent system with which to analyze key aspects of neurogenesis and circuit formation in the central nervous system. Here, we provide an overview of retinal neurogenesis in vertebrates and discuss implications of the developmental mechanisms involved for regenerative therapy approaches.

KEY WORDS: Neural progenitor cell, Neurogenesis, Retina

Introduction

As the most accessible part of the vertebrate central nervous system (CNS), the neural retina (NR) is an excellent system in which to analyze key aspects of neurogenesis, particularly since both the retinal architecture and the mechanisms underlying retinal development are highly conserved across vertebrates. The vertebrate NR contains seven major cell types (six types of neuron and one glial cell type), which are distributed in three nuclear layers separated by two plexiform layers (Livesey and Cepko, 2001). Photoreceptors (cones and rods) constitute the most external nuclear layer [the outer nuclear layer (ONL)], where they convert the incoming photons into a chemical signal. Retinal ganglion cells (RGCs) occupy the innermost nuclear layer [the ganglion cell layer (GCL)] and are the only neurons with axons that exit the eye, projecting in a retinotopic manner (maintaining a topographic map) to the brain: the optic tectum in amphibia, fish and chicken and the superior colliculus in mammals. The remaining four cell types [the bipolar, horizontal and amacrine cells, as well as Müller glia cells (MGs)] form the inner nuclear layer (INL), which is located between the ONL and the GCL, although a particular subgroup of so-called displaced amacrine cells is found in the GCL. Bipolar cells contact both photoreceptors and RGCs, transferring the information from one layer to the other. Horizontal cells face the outer plexiform layer and contact photoreceptor cells, whereas amacrine cells face the

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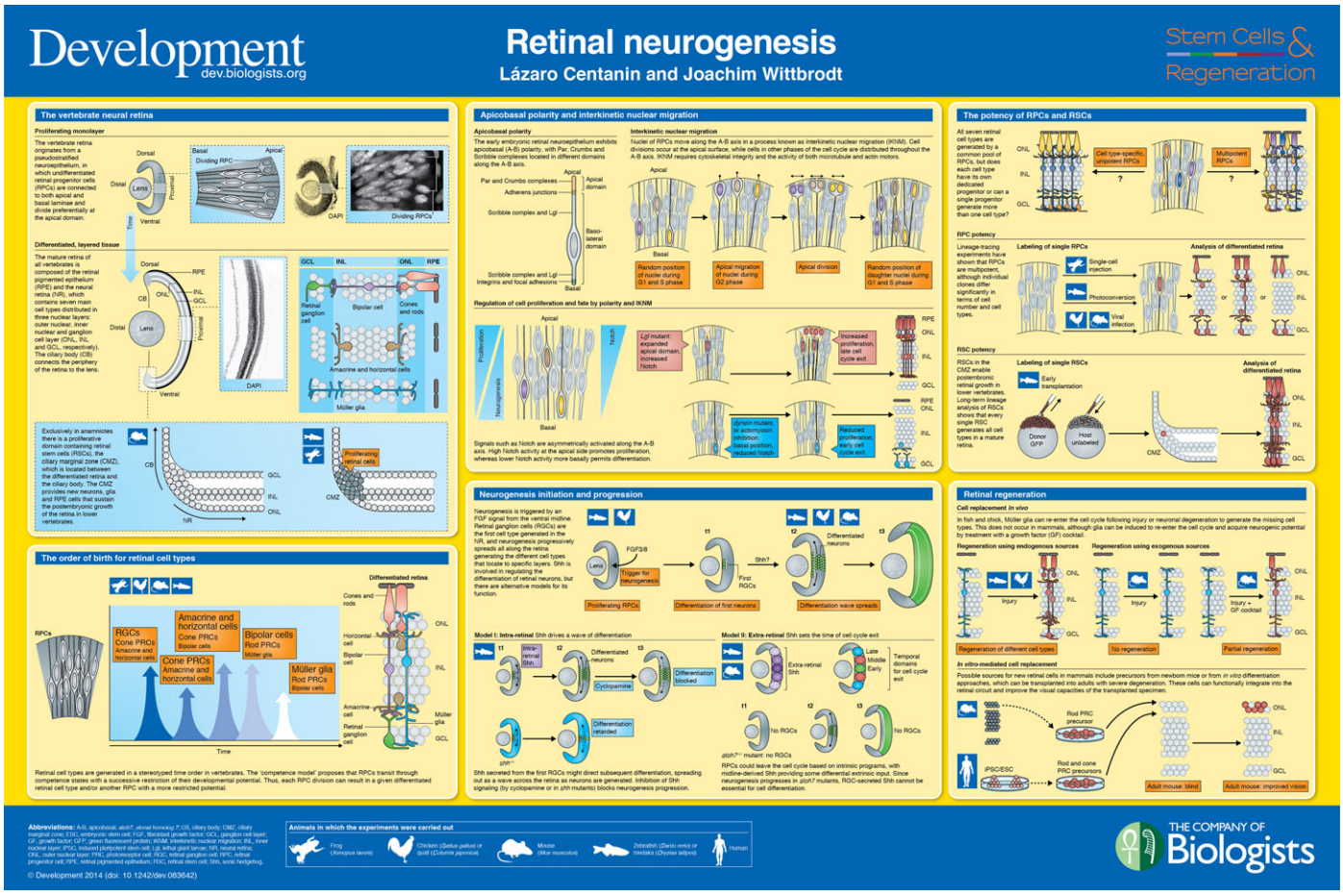

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inner plexiform layer and contact RGCs. Both cell types integrate and refine the visual output from the retina. Horizontal cells are involved in contrast enhancement, whereas amacrine cells contribute to a precomputation of visual stimuli via feedback between ganglion and bipolar cells. MGs are the only non-neuronal cell type in the vertebrate NR and play a support role during homeostasis. They can also re-enter the cell cycle after injury (Dyer and Cepko, 2000), as discussed below. They have also been suggested to operate as optic fibers, mediating photon transfer to photoreceptors (Franze et al., 2007).

Although there are only seven major cell types in the retina, there is actually considerable diversity within each neuronal type. For example, a subgroup of RGCs has been shown to set circadian rhythm in mammals, using melanopsin as a photoreceptor (Freedman et al., 1999). Morphological diversity of subtypes is extreme among inhibitory cells. There are up to 28 different types of horizontal cells and multiple types of amacrine cells, and both intrinsic and extrinsic cues are necessary to generate the proper numbers of each subtype (Jusuf et al., 2012; Jusuf et al., 2011).

Notably, all these cell types are generated from a population of retinal progenitor cells (RPCs) in a rather narrow window of time. Several questions arise from this. How is neurogenesis initiated? Are different cell types born in a particular order and what are the mechanisms that ensure a balanced distribution of cell types? Does each cell type derive from a predetermined unipotent precursor or are there multipotent RPCs common to all? Although considerable progress has been made in answering these questions, we are still far from a complete understanding of the mechanisms underlying retinal neurogenesis.

The early neural retina and apicobasal polarity

Prior to neurogenesis, the NR consists of a pool of proliferating RPCs that form a pseudostratified neuroepithelium, in which each RPC contacts both apical and basal laminae. Large-scale mutagenesis screens for defects in retinal development, primarily in fish, led to the identification of factors involved in the establishment and maintenance of apicobasal (A-B) polarity (Malicki, 2004), including Par, Crumbs and Scribble complexes. Disruption of A-B polarity during early embryogenesis in various animal models affects RPC proliferation and retinal organization (Herder et al., 2013; Wei and Malicki, 2002), and mutations in A-B polarity genes are associated with various retinopathies in human patients (Richard et al., 2006).

One key manifestation of the A-B polarity of RPCs is a process known as interkinetic nuclear migration (IKNM) (Baye and Link, 2008). In various neuroepithelia, proliferating cells preferentially divide at the apical surface. It was thought that the cells (and in particular their nuclei) undergo stereotyped migrations through the cell cycle: towards the basal domain during G1, such that basally located nuclei would be in S phase, and then moving apically in G2 to divide again (Baye and Link, 2008). However, this view changed drastically when 4D imaging techniques allowed IKNM dynamics to be followed in the fish retina (Baye and Link, 2007; Norden et al., 2009). These analyses showed that, with the exception of a fast migration to the apical side just before mitosis, nuclei progress through the cell cycle anywhere along the A-B axis. Microtubule-associated motor proteins control the movements of nuclei along the A-B axis, although the fast migration to the apical side is mainly mediated by actomyosin activity (Del Bene et al., 2008; Norden et al., 2009; Xie et al., 2007; Yu et al., 2011).

IKNM has been proposed as a mechanism for balancing neurogenic and proliferative signals acting on RPCs (Del Bene et al., 2008; Murciano et al., 2002). Notch signaling, which is a well-known regulator of neurogenesis, is asymmetrically activated along the A-B axis. Preventing nuclei from undergoing apical migration, such that progenitors are less exposed to apical Notch signaling, leads to premature cell cycle exit and differentiation, disrupting the normal distribution of cell types (Del Bene et al., 2008). Conversely, expanding the apical domain of RPCs increases exposure to Notch signaling and prevents neurogenesis (Clark et al., 2012).

How is neurogenesis initiated and coordinated?

At a certain time point in development, RPCs start to differentiate. Experiments in fish and chicken showed that fibroblast growth factor (FGF) signaling (specifically FGF8 and FGF3, expressed at the ventral midline) is necessary for the initial neurogenic switch in the retina (Martinez-Morales et al., 2005), triggering the differentiation of RGCs as the first cell type to be specified. Once neurogenesis has been triggered by FGFs, further differentiation is initiated and eventually propagates through the entire retina. Sonic hedgehog (Shh) secreted by differentiated RGCs has been implicated in propagation of the differentiation wave in zebrafish (Neumann and Nuesslein-Volhard, 2000). However, since neurogenesis and layering still proceed in the absence of RGCs (Kay et al., 2001), alternative models have to be considered. Extra-retinal factors (such as Shh and FGF) could influence the cell-intrinsic decisions of RPCs to exit the cell cycle (Kay et al., 2005). FGF signaling has also been implicated in triggering neurogenesis in the mouse retina (Cai et al., 2010), but the role of Shh in mammalian retinal neurogenesis is still obscure.

In all vertebrates analyzed, the generation of neuronal and the non-neural retinal cell types follows a stereotyped birth order (Cepko et al., 1996; Livesey and Cepko, 2001). RGCs are generated first, whereas bipolar cells and MGs are the last cell types to be born. These studies led to the so-called ‘competence model’ (Cepko et al., 1996), according to which RPCs pass through successive competence states in a fixed temporal order. In each state they can either generate particular differentiated cell types or transit to the next stage with a further restricted potential. Notably, recent clonal studies in fish showed that the birth order of individual RPCs, although biased, is not as strictly determined as expected from the model (He et al., 2012). Similar experiments have yet to be performed in other species, and so further analysis is required to determine whether the strict order of histogenesis observed for the entire organ still holds true at the level of the individual clone.

Potency of retinal progenitors

The competence model implies that RPCs pass through a series of competence states in which different neurons are generated. But is this true for all RPCs, and are individual RPCs unipotent or multipotent? This question has been addressed in various animal models using diverse experimental approaches. In all cases, the aim was to label a single RPC and analyze the postmitotic progeny generated from it. The techniques used ranged from clonal virus infection in rodents and chicken (Fekete et al., 1994; Turner et al., 1990) and micro-injection of dye/enzymes/DNA into single *Xenopus* RPCs (Holt et al., 1988; Wetts and Fraser, 1988; Wong and Rapaport, 2009) to modern recombinant approaches in fish involving fluorescent proteins that can change color and allow the entire process to be followed *in vivo* (He et al., 2012). Every study reported a recurring scenario: individual RPCs can generate two or more postmitotic retinal cell types, i.e. are multipotent. Interestingly, different RPCs within the same retina can, and indeed do, generate clones that differ in both cell number and cell type composition *in vivo* (He et al., 2012; Holt et al., 1988; Turner et al., 1990; Wetts and

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Fraser, 1988) and *in vitro* (Gomes et al., 2011). Whether the reported differences are genetically encoded (deterministic) or are stochastically decided *in situ* is still an open issue, although stochastic models seem to better represent the observed behavior.

In anamniotes, and to a lesser degree also in birds, the retina continues to grow during postembryonic stages. In fish there is life-long generation of all neural cell types, which originate from retinal stem cells (RSCs) at the periphery of the NR – a region known as the ciliary marginal zone (CMZ) (Perron and Harris, 2000). As a neural stem cell niche, the CMZ has been extensively characterized in recent decades (Centanin et al., 2011; Perron and Harris, 2000; Raymond et al., 2006). Notably, the heterogeneity reported for the potency of early embryonic RPCs changes dramatically within the CMZ. Every single neural stem cell in the CMZ, unlike individual RPCs, produces all the main types of retinal neurons and MGs (Centanin et al., 2011).

The presence of an active CMZ in lower vertebrates encouraged researchers to search for homologous structures in mammals. Although absent from the peripheral mouse retina, persistent proliferative progenitors were observed when the activity of the Shh pathway – a well-known regulator of the CMZ in fish, amphibians and chicken – was enhanced (Moshiri and Reh, 2004). The restoration of a CMZ-like structure in mammals by weak perturbation of a key signaling pathway supports the hypothesis of a progressive loss of active RSCs in the course of vertebrate evolution, and illustrates how the knowledge acquired in anamniotes can be readily translated into the mammalian RSC field, with obvious clinical relevance.

Retinal regeneration

In addition to RSCs in the CMZ, there is another group of proliferating cells in postembryonic fish, frog and chicken retinae: the MGs. MGs are distributed all over the differentiated retina and, at least in fish, produce new rod photoreceptors under homeostatic conditions (Bernardos et al., 2007; Johns and Fernald, 1981). They can also react to injuries to generate other retinal neuron types (Bernardos et al., 2007; Fimbel et al., 2007; Ramachandran et al., 2012). Their regenerative potential in fish and chicken retinae makes MGs an attractive target for treatment of mammalian retinopathies. Although MGs do not react spontaneously after retinal injuries in mammals, they can be induced to do so by activation paradigms such as addition of growth factor cocktails (Lamba et al., 2008) in an approach similar to that used to activate radial glia in the rodent brain.

Pigmented cells in the rodent ciliary body [the pigmented ciliary margin (PCM)] were postulated as an alternative source for RSCs due to their ability to form neurospheres and express markers of retinal neurons *in vitro* (Tropepe et al., 2000). However, it is still under debate whether PCM cells constitute genuine RSCs or are differentiated pigmented cells that can proliferate under certain culture conditions (Cicero et al., 2009).

In mice, a more efficient way to achieve regeneration of retinal neurons, such as rod photoreceptors, with a view to eventually restoring vision, is the transplantation of donor cells. Donor cells that can be used range from photoreceptor precursors of newborn mice (MacLaren et al., 2006; Pearson et al., 2012) to precursors derived *in vitro* from mouse embryonic stem cells (ESCs) (Gonzalez-Cordero et al., 2013) or human induced pluripotent stem cells (iPSCs) (Lamba et al., 2009). Furthermore, researchers have managed to form an entire 3D optic cup *in vitro* (Eiraku et al., 2011; Nakano et al., 2012) starting from ESCs. Retinogenesis in a dish could be used to gain insight into molecular aspects and visualize dynamic traits of human retinal development *in vitro*. Retinae generated from patient-derived iPSCs could contribute to a better understanding of the disease and be used to identify personalized therapies.

Perspectives

The NR, as an experimentally highly accessible part of the vertebrate CNS, has been the organ of choice to tackle key aspects of neurogenesis, and studies performed in the retina have significantly contributed to our understanding of vertebrate neurogenesis. The rapid development of new tools will certainly enable the many exciting open questions in the field to be addressed directly. We have highlighted how establishing a proper A-B polarity in RPCs is fundamental during early stages of retinogenesis, but it is still not known if and how the very same factors affect the remarkable A-B morphological asymmetries observed among mature retinal neurons. Inducible tools could be used to disrupt A-B polarity just after neurogenesis has started, and the entire process of axonogenesis, layering and retinal interconnection could be followed in the entire organ either *in vivo* or in 3D organoids growing in culture. Live imaging combined with cell type-specific fluorescent reporter lines paves the way toward an understanding of whether position within the retina determines the fate of a newly born neuron or, conversely, if the predetermined neuronal fate specifies the position within the retina that a newborn cell will take.

As discussed above, we still lack a complete understanding of the differentiation potential of individual RPCs and how this might be controlled intrinsically or extrinsically. Life-long neurogenesis in the retina of anamniotes opens an additional field beyond developmental neurogenesis, and there is much still to be learned about how postembryonic neurogenesis is regulated under homeostatic and regenerative conditions. This is particularly important since growth and regeneration are not just relevant for understanding basic principles of neurogenesis but have crucial implications for regenerative therapies. It is striking that the presence of a functional CMZ in lower vertebrates is tightly correlated with their higher efficiency in regenerating all retinal cell types after injury; whether efficient regeneration will be possible in species lacking a CMZ remains to be seen. Although we are still far from stem cell-based therapies for patients suffering from retinal degeneration or other retinal diseases, we are beginning to translate our understanding of developmental and regenerative neurogenesis into approaches for generating retinal cells and tissues that should prove therapeutically valuable.

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Competing interests

The authors declare no competing financial interests.

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