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Mechanisms of temporal identity regulation in mouse retinal progenitor cells

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While much progress has been made in recent years toward elucidating the transcription factor codes controlling how neural progenitor cells generate the various glial and neuronal cell types in a particular spatial domain, much less is known about how these progenitors alter their output over time. In the past years, work in the developing mouse retina has provided evidence that a transcriptional cascade similar to the one used in *Drosophila* neuroblasts might control progenitor temporal identity in vertebrates. The zinc finger transcription factor *Ikzf1* (*Ikaros*), an ortholog of *Drosophila hunchback*, was reported to confer early temporal identity in retinal progenitors and, more recently, the ortholog of *Drosophila castor*, *Casz1*, was found to function as a mid/late temporal identity factor that is negatively regulated by Ikzf1. The molecular mechanisms by which these temporal identity factors function in retinal progenitors, however, remain unknown. Here we briefly review previous work on the vertebrate temporal identity factors in the retina, and propose a model by which they might operate.

Keywords: Casz1, differentiation, development, fate, Ikzf1, neurogenesis, neuroblast, neuron, progenitor, retina

Abbreviations: CNS, central nervous system; TF, transcription factor

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A prevailing model explaining cell fate specification during central nervous system (CNS) development is the 'combinatorial code', in which cell identity is determined by the expression of specific combinations of transcription factors (TFs). TF codes controlling cell fate during neurogenesis are indeed well established in many CNS regions, such as the *Drosophila* ventral nerve cord or vertebrate spinal cord. In these systems, neural progenitors interpret morphogen gradients to acquire distinct TF signatures based on their position in space.[1,2] These TF combinations act as a code to endow progenitors with the potential to give rise to the appropriate neuronal subtypes. A wide variety of TFs participate in these codes. Particularly prominent are homeodomain TFs from the Hox and extended Hox families, as well as bHLH TFs of the proneural Hes and Olig families.

While TF combinations represent a powerful and elegant framework for explaining cell fate decisions during CNS development, it has proven to be difficult to 'decode' the most complicated neural lineages. In regions such as the vertebrate neocortex and retina, multipotent progenitors of a given spatial domain alter their output over time to generate sequences of different types of neuronal and glial cells. In the retina, this sequence begins with the production of retinal ganglion cells, followed closely by the overlapping generation of cone photoreceptors, horizontal, and amacrine neurons. As the generation of these cell types peaks, rod photoreceptors begin to be produced. At birth, production of most of the early-born neuronal subtypes ceases, rod production continues, and bipolar neurons and latest-born Müller glia begin to be generated in an overlapping fashion.[3–7]

In the neocortex and hindbrain, evidence suggests that both extrinsic factors,[8–14] and cell-intrinsic processes[15,16] are important to control the temporal identity of progenitors. In the developing retina, however, even though extrinsic signaling has been shown to alter progenitor output,[17–19] these factors are thought to mostly control proliferation and act as negative feedback inhibition signals to refine the size of a specific neuronal

population, rather than regulate temporal identity in retinal progenitors.[20,21] Instead, cell-intrinsic processes appear to play a dominant role to control progenitor fate output, both when retinal progenitors were cultured in heterochronic transplants or cell pellets,[22–25] or when cultured individually.[4,26]

Retinal progenitors cannot maintain the same combinatorial TF code during retinogenesis, or their output would be static. Yet, identification of the key TFs that define the competence state of retinal progenitors at specific phases of development has remained largely elusive. While a great deal of progress has been made in identifying TFs that contribute to the generation of particular cell fates during retinal development, many of these factors, such as Lhx2, Pax6, Rx, and Vsx2 are expressed in retinal progenitors throughout development and therefore cannot explain on their own the sequential order of cell birth.[27–33] Conversely, fate determinants such as Ascl1, Atoh7, Olig2, Onecut1/2, Otx2, Prdm1 (Blimp-1), and Sox4/11 exhibit dynamic patterns temporally, but in each case, data suggests that these factors act at the last or penultimate cell division rather than in bona fide multipotent progenitors.[32,34-43] Thus, although the collective efforts of a large number of laboratories have identified many TFs that contribute to the combinatorial coding of each retinal cell type, we have little understanding of how multipotent vertebrate retinal progenitors select between them to generate lineages of the appropriate size and complexity.

In contrast, in *Drosophila*, the mechanism controlling temporal competence during development has been well characterized. In neuroblasts of the ventral nerve cord or medulla, additional TF cascades operate in time, acting to diversify the TF code established spatially by the actions of morphogens.[44,45] In the fly ventral nerve cord, landmark work had shown that most neuroblasts express a sequence of TFs as development proceeds: hunchback, Krüppel, nub/pdm2 (collectively pdm), and castor[46,47] (**Fig. 1A**). These TFs are necessary and sufficient to confer temporal identity to neuroblasts, such that they produce daughter cell types in the correct sequence.

Previously, we had shown that the zinc finger TF *Ikzf1* (*Ikaros*), an ortholog of *Drosophila hunchback*, was sufficient to impart late retinal progenitors with the competence to generate early-born neuronal subtypes, as well as being required for the generation of normal numbers of early-born fates during development.[48] Because Ikzf1 had no effect on retinal progenitor proliferation, these results indicated that Ikzf1 does not control the timing of cell cycle exit, but instead directly confers early temporal identity in retinal progenitors, which are biased to give rise to early-born neurons when they express Ikzf1 (**Fig. 1B**). Interestingly, recent work showed that Ikzf1 misexpression in cortical progenitors resulted in prolonged period of production of early-born neurons well into the late temporal identity window.[49] Although Ikzf1 was not absolutely required for early-born neuronal cell type production in the developing cortex, these results suggest that Ikzf1 could be a general factor regulating early temporal identity in vertebrates, much like hunchback is essential to control early temporal identity in multiple fly neuroblast lineages. While Ikzf1 and hunchback appear to function analogously, it remained unclear how Ikzf1 achieved these effects in the retina. Whereas *Drosophila* hunchback operates within the context of a TF cascade that changes over time, no such cascade had been described in the mouse. Yet other members of the *Drosophila* TF sequence are conserved and expressed during mouse retinogenesis. Indeed, a single homolog of the *Drosophila* zinc finger TF castor, called *Casz1*, was previously shown to be expressed in later phases of retinogenesis, as well as in differentiated photoreceptors.[50,51] We therefore hypothesized that an Ikzf1 → Casz1 sequence might represent conservation of the *Drosophila* temporal code.

To test this hypothesis, we recently used mouse genetics and retroviral lineage tracing to study *Casz1* function during retinogenesis.[52] We showed that Casz1 is not expressed at significant levels at early stages, but is upregulated in retinal progenitors during mid/late stages of retinal development, suggesting a role in controlling temporal identity at these later stages (**Fig. 1B**). Consistently, we found that precocious misexpression of Casz1 in retinal progenitors was sufficient to increase the production of mid/late fates like bipolar cells and rod photoreceptors, at the expense of early fates such as cone photoreceptors, horizontal cells, and amacrine cells. Conversely, analysis of retinal progenitor cell lineages in conditional *Casz1* knockout retinas showed increased production of early-born fates at the expense of rod photoreceptors within a lineage. Importantly, similar to what was observed with Ikzf1, the cell fate changes observed following Casz1 manipulations were independent of an effect on proliferation or cell death, indicating that Casz1 directly controls temporal identity in retinal progenitors and not cell cycle exit. Interestingly, we also found that Ikzf1 normally represses Casz1 expression in retinal progenitors, and identified the cis-regulatory modules in *Casz1* that can mediate the transcriptional effects of Ikzf1. Together these results suggest that, much like in *Drosophila* neuroblasts, a cross-regulatory mechanism of TF expression operate to control temporal identity progression in mouse retinal progenitor cells.

Although the biochemical activities underlying Casz1 function have been studied to some extent in the developing heart, muscle and vascular systems, where Casz1 is thought to control progenitor proliferation and differentiation,[53–57] the mechanism by which Casz1 confers temporal identity in neural progenitors remains unknown. In *Drosophila* neuroblasts, *cas* was initially suggested to function as a transcriptional repressor,[47] but a mechanistic understanding of its activities remains incomplete. In an effort to provide some clues about Casz1 mechanism of action, we recently carried out a gene expression profiling experiment using RNA-Seq on *Casz1* knockout retinal progenitors. However, this approach failed to identify strong effects on cell fate determinants that could explain Casz1 function (Mattar and Cayouette, unpublished data). Although changes were observed in the levels of transcripts for genes that are known to control the production of cell types affected by *Casz1* conditional deletion, the changes

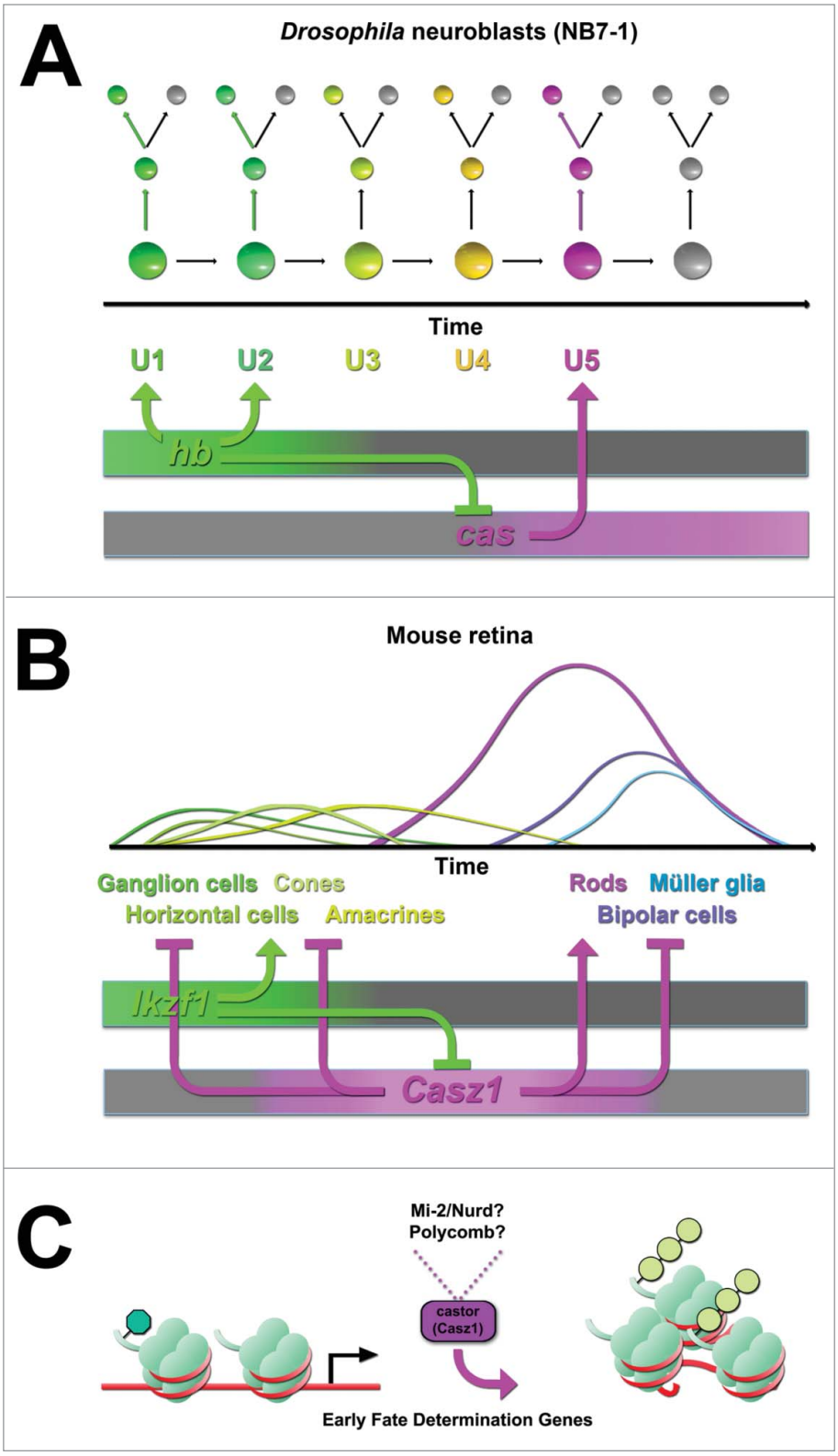

Figure 1. Control of temporal competence in neural progenitors. (**A**) Roles of the temporal TFs hunchback (hb) and castor (cas) in the sequential generation of cell fates during development of the *Drosophila* neuroblast NB7–1 motoneuron lineage. (**B**) Analogous roles of the murine *hb* and *cas* orthologues *Ikzf1* and *Casz1* in regulating the temporal competence of retinal progenitors. (**C**) Proposed model for the molecular mechanism underlying Casz1 functions. Casz1 might function by suppressing the competence of genes to be expressed rather than by directly controlling target gene levels. Elucidation of the co-factor complexes utilized by Casz1 should allow this hypothesis to be addressed. Possible complexes include Mi-2/Nurd and polycomb repressive complexes. This model is not meant to be exclusive, and alternative factors not shown here could be involved.

observed were no larger than ~5-fold for any of them. These results suggest that Casz1 might not directly modify the combinatorial TF code, but instead could function by mediating more subtle epigenetic changes. Indeed, castor proteins have recently been shown to associate with a variety of transcriptional regulators, including the Mi-2/Nurd and polycomb repressor complexes.[58–61] Intriguingly, previous work has shown that Mi-2/Nurd is required for Ikzf1-mediated fate determination functions in lymphocytic development.[28,62] Similarly, in fly neuroblasts and mouse cortical or retinal progenitors, polycomb repressive complexes have been shown to regulate temporal identity,[63–68] suggesting that temporal TFs might regulate competence via common epigenetic pathways. In such a model, Casz1 could act by altering the probability and/or competence of specific fate determination genes to be transcribed, rather than acting as a straightforward modifier of TF expression levels (**Fig. 1C**). Consistent with this hypothesis, changes in the temporal competence of *Drosophila* neuroblasts are controlled by alterations in the competence of fate determinant genes to be expressed.[27] Whether Casz1 could function together with Mi-2/Nurd and/or polycomb to provide target gene specificity for chromatin modifications remains unknown, but this is certainly an interesting possibility.

Other potential explanations for the effects of Ikzf1/Casz1 on progenitor competence are of course possible, based on the identification of factors that have also been shown to regulate progenitor temporal identity or progression. In *Xenopus laevis*, dicer, a key determinant of microRNA biosynthesis and function, was shown to control the correct onset of markers of late-born cell types, and several microRNAs were implicated in this effect.[69,70] Subsequently, a role for dicer and the microRNAs *let7*, *mir9*, and *mir125* in the progression of retinal progenitor temporal identity from early- to late-phase was uncovered.[71,72] These effects may be mediated in part by protogenin and lin28, which were shown to be targets of the microRNAs. Thus, dicer/microRNAs apparently also participate in several aspects of temporal identity. Moreover, the requirement for dicer/microRNAs in the progression of temporal competence states is very similar to that of Lhx2, which when mutated, stalls retinal progenitors in the earliest phase of neurogenesis.[29] Whether there are mechanistic connections between Ikzf1/Casz1, dicer/microRNAs, and Lhx2 remains unclear, but in *C. elegans*, the *hunchback* ortholog *hbl-1* and the *let-7* microRNA cross-regulate each other, with hbl-1 repressing *let-7* expression, and *let-7* binding and inhibiting the *hbl-1* 3' UTR.[73–75] If conservation of this negative feedback loop is maintained in the retina, this might suggest a possible point of convergence for these pathways. Alternatively, these pathways might act independently, providing redundancy and robustness to the system.

Elucidating how temporal identity factors function in vertebrate neural progenitors to control the production of specific cell types associated with a given developmental window will be important, as this knowledge could provide novel ways of manipulating stem cell differentiation for cell replacement therapies. A recent study, for example, reported that Tgfß functions as a regulator of temporal identity in hindbrain progenitors and provided proof of concept that manipulating Tgfß can be applied to control temporal specification of specific neuronal types from stem cells.[9]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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