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Integration of Spatial and Temporal Patterning in the Invertebrate and Vertebrate Nervous System

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The nervous system is one of the most sophisticated animal tissues, consisting of thousands of interconnected cell types. How the nervous system develops its diversity from a few neural stem cells remains a challenging question. Spatial and temporal patterning mechanisms provide an efficient model through which diversity can be generated. The molecular mechanism of spatiotemporal patterning has been studied extensively in *Drosophila melanogaster*, where distinct sets of transcription factors define the spatial domains and temporal windows that give rise to different cell types. Similarly, in vertebrates, spatial domains defined by transcription factors produce different types of neurons in the brain and neural tube. At the same time, different cortical neuronal types are generated within the same cell lineage with a specific birth order. However, we still do not understand how the orthogonal information of spatial and temporal patterning is integrated into the progenitor and post-mitotic cells to combinatorially give rise to different neurons. In this review, after introducing spatial and temporal patterning in *Drosophila* and mice, we discuss possible mechanisms that neural progenitors may use to integrate spatial and temporal information. We finally review the functional implications of spatial and temporal patterning and conclude envisaging how small alterations of these mechanisms can lead to the evolution of new neuronal cell types.

Keywords: neuronal diversity, spatial patterning, temporal patterning, evolution of developmental mechanisms, fate specification, *Drosophila*, vertebrates

SPATIOTEMPORAL PATTERNING AND CELL FATE DETERMINATION

Traditionally, neuronal types were classified by the distinct functions that they perform (Masland, 2004; Zeng and Sanes, 2017). Neurons can be categorized by their arborization and projection pattern, the neurotransmitter they use, and their electrophysiology. Neurons can also be categorized by the genes they express. The recent advent of high-throughput sequencing has demonstrated that molecular cell types and morphological/functional cell types are largely consistent (Shekhar et al., 2016; Li et al., 2017; Konstantinides et al., 2018b; Sathyamurthy et al., 2018;

Delile et al., 2019; Allen et al., 2020; Özel et al., 2020; Yao et al., 2021). How different types of neurons are generated is one of the central questions in developmental neurobiology; the study of spatiotemporal patterning aims to understand the molecular developmental basis of cell type diversity. By deciphering the logic underpinning the patterning process, we can potentially understand how distinct neuronal functions are encoded genetically. Comparing different patterning mechanisms across species could also shed light on how new cell types evolve to generate a more complex nervous system (Holguera and Desplan, 2018; Konstantinides et al., 2018a).

Spatial Patterning

Early in animal development, neural progenitors are partitioned into different domains that express distinct transcription factors (Figure 1A). For example, the nervous system of flies and mammals is patterned along the anteroposterior (A–P) axis by Hox genes (Tümpel et al., 2009; Philippidou and Dasen, 2013; Estacio-Gómez and Díaz-Benjumea, 2014; Jung et al., 2014; Figure 1B). Within each segment along the A–P axis, neural progenitors are further patterned on the A–P and dorsoventral (D–V) axis, forming non-intermingling progenitor populations that will generate distinct neuronal types (Jessell, 2000; Briscoe and Ericson, 2001; Karlsson et al., 2010; Benito-Sipos et al., 2013; Birkholz et al., 2013; Figure 1C).

In each segment of the fly ventral nerve cord, neuroepithelial cells are patterned by the expression of *msh*, *ind*, and *vnd* along the D–V axis (Mellerick and Nirenberg, 1995; D'Alessio and Frasch, 1996; Isshiki et al., 1997; Weiss et al., 1998) and *wg*, *gsb*, *en* along the A–P axis (Doe, 1992; Gutjahr et al., 1993; Skeath et al., 1995; Figure 1C). In the fly optic lobe, neuroepithelial cells of the Outer Proliferation Center form a crescent containing six domains defined by *Vsx1*, *Optix*, and *Rx* along the A–P axis and by *Hedgehog* along the D–V axis (Erclik et al., 2008, 2017; Gold and Brand, 2014; Figure 1D).

In the mammalian forebrain, morphogen gradients pattern radial glia and induce the expression of two orthogonal gradients of spatial transcription factors (Figure 1E, upper panel) that govern the potency of the neural progenitors to generate specific cell types. Different types of cortical interneurons are also made by spatially distinct progenitors. The medial ganglionic eminence expresses *Nkx2.1* and is the main source of parvalbumin- and somatostatin-expressing interneurons (Xu, 2004; Flames et al., 2007; Fogarty et al., 2007; Xu et al., 2008), the caudal ganglionic eminence expresses *Nr2f2* and generates serotonin-sensing interneurons (Nery et al., 2002; Tripodi et al., 2004; Kanatani et al., 2008; Lee et al., 2010), while the *Pax6*-expressing lateral ganglionic eminence generates interneurons in the olfactory bulb and the striatum (Wichterle et al., 2001; Kohwi et al., 2007; Figure 1E, lower panel). Another classic example of spatial patterning in vertebrates is the developing retina. In zebrafish, neuroepithelial cells in the optic vesicle are patterned along the D–V axis with *foxd1* being expressed in the ventral compartment and *foxg1* in the dorsal (Hatini et al., 1994; Yuasa et al., 1996; Picker and Brand, 2005). During anterior eye rotation when the optic cup forms, the D–V spatial domains become the nasal (projecting to the posterior tectum)

and temporal (projecting to the anterior tectum) hemiretina, respectively (Figure 1F).

Temporal Patterning

The association between time and neural diversity has been known for a long time in mammals. Layers of morphologically distinct neurons in the mammalian cortex are born at specific embryonic days, with each layer projecting to and receiving information from different brain regions (Rakic, 1974; Raedler and Raedler, 1978; Royce, 1983). Two mechanisms could be envisaged to explain how temporal differences result in the generation of distinct neuronal types. First, temporal differences could be intrinsic to each neural progenitor, in which case each progenitor undergoes a cascade of changes to generate different types of neurons at different time points (Figure 2A). Consistent with this model, clonal lineage tracing showed that a single ventricular radial glia cell can generate neurons in all layers (Gao et al., 2014). Alternatively, the neural progenitor pool could be a mixture of different populations that differ in when they start neurogenesis. In this model, progenitors differ both in their potential of generating neurons and the time they commit to neurogenesis (Figure 2A). In support of this model, while the *Olig2*-expressing progenitors give rise to both early-born spinal motor neurons and late-born oligodendrocytes, there are two subtypes of progenitors: the early ones that generate motor neurons and the ones that are recruited later and only generate oligodendrocytes (Ravanelli and Appel, 2015).

In mammals, recent studies have systematically discovered a set of birthdate markers that are shared between different cell types in the hindbrain and spinal cord of human and mouse (Delile et al., 2019; Osseward et al., 2021; Rayon et al., 2021; Figure 2B), and the expression of these markers are consistent with known subtypes within several cardinal classes of spinal neurons (Roy et al., 2012; Bikoff et al., 2016; Hayashi et al., 2018). Some of these birthdate markers are required for early- vs. late-born neuronal fate in neurons (e.g., in the mammalian cortex, *Satb2* is required for later-born callosal neurons from layer 2 to 5, and *Fezf2* and *Ctip2* are necessary for early-born ones in layer 5) (Chen et al., 2005, 2008; Alcamo et al., 2008; Britanova et al., 2008) and in progenitors (e.g., *Nfia* and *Nfib* for the generation of late-born neurons in the retina and ventral spinal interneurons) (Xie et al., 2020; Sagner et al., 2021). Consistent with the idea that neural progenitor temporal factors specify the fate of daughter neurons, cortical neurons inherit the gene modules that are present in radial glia at the stage when the neurons were generated (Telley et al., 2019), and the late-born fate regulators *Nfia/b/x* directly regulate late-born fate associated genes in the mammalian retina (Clark et al., 2019; Xie et al., 2020; Lyu et al., 2021). Whether it is a general rule that these temporal window-specific gene modules specify the neuronal fates of their daughter cells warrants further investigation.

In the nervous system of flies, cascades of transcription factors expressed in the same neural stem cell underlie temporal patterning, and different regions utilize a distinct set of temporal transcription factors (Brody and Odenwald, 2000;

Isshiki et al., 2001; Li et al., 2013; Suzuki et al., 2013; Bertet et al., 2014; Aplitz and Salecker, 2015; Erclik et al., 2017; Mora et al., 2018; Pinto-Teixeira et al., 2018; Konstantinides et al., 2021; Zhu et al., 2021; **Figure 2C**). The temporal cascade in neural stem cells progresses by cross-regulation between temporal factors during neurogenesis, either by a relay of activators (Reviewed in Doe, 2017; Rossi et al., 2017) or by a more robust repressor-decay model (Averbukh et al., 2018). As a result, the expression of each temporal factor in progenitors is responsible for the generation of the neuronal types specific to each temporal window (Isshiki et al., 2001; Mettler et al., 2006; Bayraktar and Doe, 2013; Li et al., 2013; Konstantinides et al., 2021; Tang et al., 2021; Zhu et al., 2021).

MOLECULAR LOGIC OF SPATIOTEMPORAL INTEGRATION

The identity of a neural progenitor is defined by the spatial domain from which it originates; the neural progenitor then undergoes a temporal cascade and generates a specific subset of neuronal types within each temporal window of the cascade. How is spatiotemporal identity in progenitors translated to distinct features that define mature neuronal types? In worms, flies, and mammals, the features that define a type of neuron, including neurotransmitter choices and innervation targets, are regulated by post-mitotic regulators that are required and sufficient for the establishment and/or maintenance of the terminal features. For example, CHE-1 binds to a specific motif and defines ASE neuron fate in worms (Uchida et al., 2003; Etchberger et al., 2007), Bsh is required and sufficient for inducing Mi1 neuron fate in the fly optic lobe (Hasegawa et al., 2013), and Ngn2, Isl1, and Lhx3 specify spinal motor neurons in the mammalian spinal cord (Thaler et al., 2002; Lee and Pfaff, 2003; Son et al., 2011; Mazzoni et al., 2013).

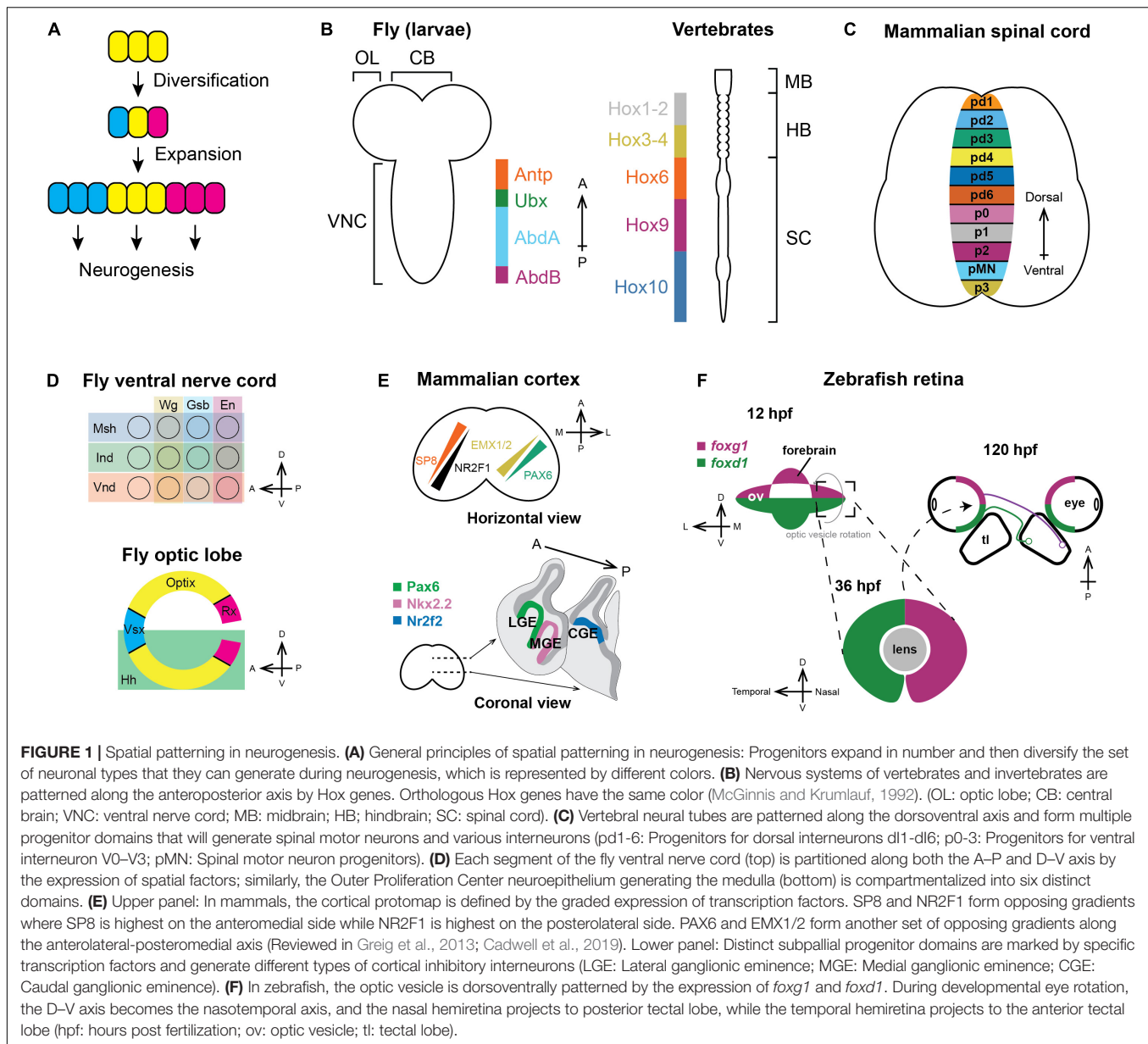
For spatiotemporal patterning to specify neuronal types, each spatial and temporal factor must prime the expression of specific post-mitotic fate regulators. Indeed, the *Drosophila* Mi1 neuron is generated during the Hth-expressing temporal window, and the temporal factor Hth is required and sufficient for downstream Bsh expression (Hasegawa et al., 2011; Li et al., 2013). Similarly, Nkx6.1 and Olig2 define the motor neuron progenitor domain in the neural tube and are required and sufficient for the expression of downstream Isl1 and Lhx3 (Sander et al., 2000; Takebayashi et al., 2002).

But how do spatial and temporal factors cooperate? Several strategies could be employed:

- (1) Spatial and temporal factors could directly cooperate by forming a complex and regulating downstream genes including the post-mitotic regulators (**Figure 3A**). This strategy is utilized to generate Ap-expressing neurons in the fly embryonic nervous system. Ap⁺ neurons are only present in thoracic segments while the neural stem cells, NB5-6, that generate them are present in every segment. During neurogenesis, Antp, the spatial factor defining the thoracic segments (**Figure 1B**) and the temporal factors,

Cas and Grh (**Figure 2C**), bind together in a feed-forward loop to activate Col, the post-mitotic regulator for Ap⁺ neurons. The abdominal spatial factors Ubx, Abd-A, and Abd-B together terminate the neurogenesis before the Cas and Grh temporal window to prevent the generation of Ap⁺ neurons in the abdominal segment (Karlsson et al., 2010). Cis-regulatory modules targeted by spatiotemporal factors underlie the integration: The *col* cis-regulatory module requires binding by both Antp and Cas to activate, while Antp and Col are required to bind together for Ap and Eya to express and in turn drive the expression of Nplp1, a neuropeptide used by Ap⁺ neurons (Stratmann and Thor, 2017). Extrinsic signals could also introduce regulators to participate in cooperative regulation. For example, in *C. elegans*, AIY neurons are specified by the expression of TTX-3 and CEH-10 (Altun-Gultekin et al., 2001), which depends on iterative integration of the asymmetric Wnt/ β -catenin signaling that is only active in the posterior daughter cell (Lin et al., 1998): In a REF-2-expressing progenitor that will generate four types of neurons including an AIY neuron, REF-2 activates *ttx-3* in the anterior daughter cell that is not sensing Wnt (Murgan et al., 2015). When the TTX-3-expressing progenitor divides again, TTX-3 cooperates with β -catenin to activate *ceh-10* and specify AIY neuron (Bertrand and Hobert, 2009).

- (2) However, spatial and temporal factors are not always expressed at the same time, which requires regulators that are expressed at different points to integrate across time. One possibility for an earlier factor to interact with a later factor is by epigenetic memory (**Figure 3B**). In worms, ASER and ASEL neurons both express the same post-mitotic regulator, CHE-1, but only ASEL expresses LSY-6. The lineages giving rise to ASER/ASEL differ in their early transient expression of TBX-37/38 and become molecularly equivalent after 4 divisions. However, the seemingly equivalent lineages remember their lineage history. Early expression of TBX-37/38 in the ASEL lineage results in transient transcription of *lsy-6*, which is required and sufficient for keeping the locus accessible in the ASEL but not in the ASER lineage, and the difference of accessibility allows CHE-1 to activate *lsy-6* in ASEL but not ASER (Charest et al., 2020). In flies, spatial factors in the ventral nerve cord and optic lobe are expressed in the neuroepithelium and disappear in the neuroblasts, while temporal factors are expressed only in neuroblasts when they commit to neurogenesis. In the ventral nerve cord neuroblasts, chromatin accessibility is regulated differently between spatial domains through the action of a spatial factor, Gsb. Reminiscent to how ASE asymmetry is regulated, the binding pattern of a temporal factor Hb, which is expressed later, is dependent on the pre-existing chromatin landscape and can only bind to the accessible regions (Sen et al., 2019). While chromatin accessibility is determined by multiple factors including histone modifications, DNA methylation (Cusack et al., 2020), pioneer factors (Voss and Hager, 2014), etc., and

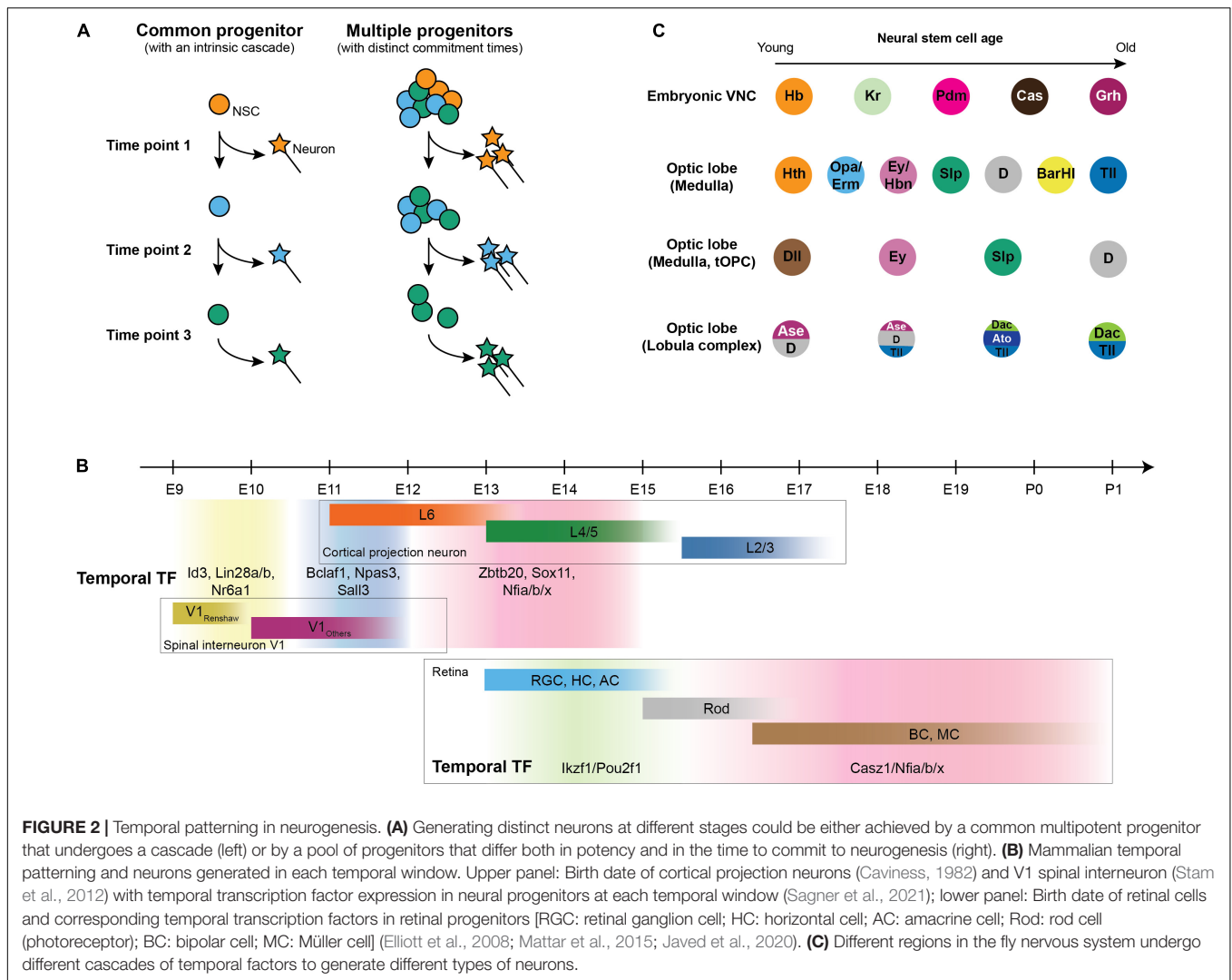


is used as a proxy of inheritable chromatin modifications, the molecular nature of epigenetic memory remains to be investigated.

- (3) Finally, spatiotemporal factors that seem not to be co-expressed could also integrate fate information if the regulator that is expressed earlier turns on a downstream factor that continues to be expressed before eventually cooperating with a later-expressing regulator (Figure 3C).

The models for spatiotemporal integration are not mutually exclusive. On the contrary, spatiotemporal factors are likely to regulate their targets in a hybrid mode. In the fly ventral nerve cord, temporal factors not only regulate their targets directly but could also cooperate with Polycomb complexes to set the epigenetic landscape to restrict the generation of motor neurons

to certain temporal windows (Touma et al., 2012). Additionally, genes that are known to be spatiotemporal factors could also play multiple roles in fate specification. For example, in Ap^+ neurons in the ventral nerve cord, Antp is not only required for the activation of a post-mitotic regulator, Col, but also directly regulates Ap and Eya together with Col, effectively making Antp not only a spatial factor but also a neuronal regulator of post-mitotic features. Finally, while we only used activators as examples in this section, a regulator could serve simultaneously as an activator and a repressor for different sets of targets (Clovis et al., 2016). Therefore, repressors can have a role in all three models: a repressor can suppress the expression of some of the regulators in the complex and change the composition and target genes in the direct cooperation model; a repressive chromatin modifier could silence a locus and prevent later regulators from



accessing it in the epigenetic memory model; finally, regulator relay could not only be achieved by an activator cascade but also a sequential decay of repressors (Averbukh et al., 2018).

Our current knowledge of how spatial and temporal patterning are integrated and define cell fates comes from studies of a few genes in a few cell types and is rather limited. The integration of spatial and temporal patterning is more than spatial and temporal factors functioning independently and regulating their own targets. Instead, we know that there are genes that are not activated by either a spatial or a temporal factor alone but only expressed when a specific combination of spatial and temporal factors is present. For example, in the fly optic lobe, *Svp* is only expressed in neurons generated from the early *Hth* window from the *Vsx* and *Rx* domains but neither *Hth* nor *Vsx* or *Rx* alone is sufficient for the expression of *Svp* (Erclik et al., 2017). In the ventral nerve cord, *Ap* neurons are only generated in the *Cas* window in the thoracic segment defined by *Antp* (Karlsson et al., 2010). Similarly in vertebrates, *Calbindin* is only expressed in the early-born V1 interneurons from the p1 progenitor domain but not in early-born neurons from other

spatial domains of the spinal cord (Stam et al., 2012). To have a more comprehensive understanding of the molecular logic of spatiotemporal integration, models with known spatial and temporal regulators will be a great entry point, like the fly central nervous system and the mammalian retina and neural tube. To understand the origin of molecular spatiotemporal integration, we need to identify more spatiotemporal factors in various nervous tissues in different species to investigate how these mechanisms have evolved; the advent of high-throughput profiling of gene expression and chromatin landscape specific for each spatiotemporal identity holds the promise to decipher both the rules and exceptions of spatiotemporal integration.

HOW DOES SPATIOTEMPORAL PATTERNING CONTRIBUTE TO FUNCTION?

Spatiotemporal patterning provides an elegant way to generate a wide array of neuronal types that provide the basis for nervous

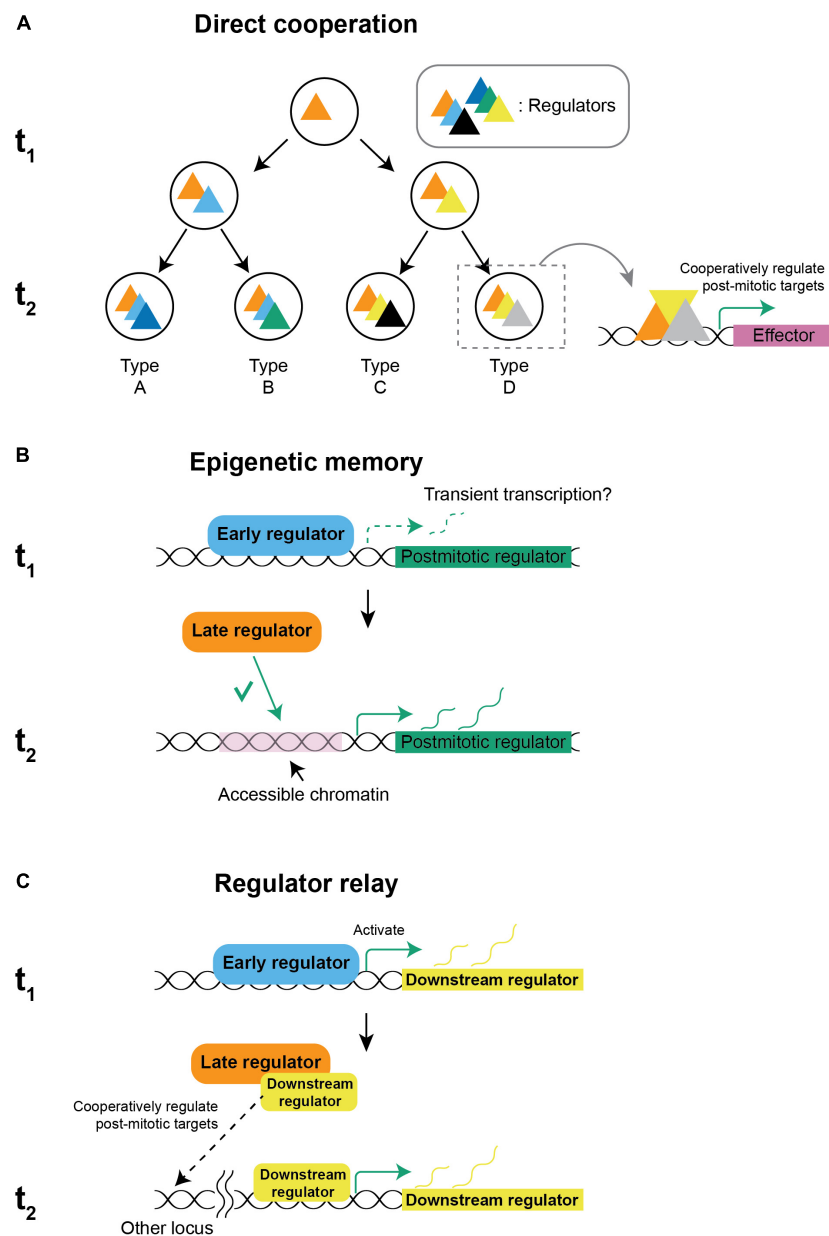


FIGURE 3 | Possible mechanisms of spatiotemporal integration. **(A)** Direct cooperation: New regulators are introduced by an intrinsic cascade or by extrinsic signals and regulate target genes cooperatively with early regulators that are already present to establish distinct gene signatures for different neuronal types. **(B)** Epigenetic memory: Spatial and temporal factors might cooperate by early regulators establishing the chromatin landscape and defining a permissive subset of targets to be regulated by other regulators that are expressed later. The restriction of targets defines a specific set of post-mitotic regulators to be expressed after cell cycle exit. In ASE neurons, transient transcription in early development is sufficient to establish accessibility (Charest et al., 2020). **(C)** Regulator relay: When spatiotemporal factors are not co-expressed, the regulator that is expressed earlier might activate a downstream factor that is persistently expressed. When the later regulator is set to express, it directly cooperates with the downstream factor of the early regulator and activates a specific set of post-mitotic regulators. (t_1 : first time-point, e.g., neural stem cell, t_2 : second time-point, e.g., neuron).

system function. For example, spatial patterning of the neural tube in vertebrates changed concordantly with the emergence of walking in tetrapods and new subtypes of spinal motor neurons were specified to innervate the limbs (Jung et al., 2014, 2018).

Besides providing a gene regulatory framework to enable neurons to acquire their molecular identity, temporal

synchronization in neurogenesis helps limit the number of possible targets each neuron encounters and make neural wiring robust and precise during development. Alternatively, temporal patterning allows different types of daughter neurons to be generated next to each other, and this adjacency between daughter neurons could help them to preferentially connect

to each other and reduce the number of possible partners by excluding neurons that are farther away. Consistent with this, neurons generated from the same neural progenitor tend to form a circuit, and when each circuit is activated, specific movements, like walking or wing waving, are generated in the fly ventral nerve cord (Harris et al., 2015).

In mammals, the projection pattern of excitatory cortical neurons has long been known to associate with their birthdate (Rakic, 1974; Raedler and Raedler, 1978; Royce, 1983), and clonally related excitatory neurons preferentially connect with each other (Yu et al., 2009, 2012; Li et al., 2012; Ohtsuki et al., 2012). Recently, the organization and projections of spinal neurons were also found to be dependent on their birthdate: Early-born spinal neurons are positioned laterally and enriched in neurons that project a long range, while late-born ones are positioned medially and enriched in neurons that project locally (Osseward et al., 2021). Spatial patterning is also shown to influence multiple neuronal features: Spatial origin is associated with electrophysiological properties of cortical interneurons (Butt et al., 2005) and defines a wide variety of interneurons and motor neurons in the spinal cord (Jessell, 2000; Sagner and Briscoe, 2019). It remains an open question if neurons born at similar stages in different regions of the mammalian nervous system, e.g., the cerebellum and spinal cord, also take advantage of the synchronicity of neurogenesis and preferentially connect and form a circuit among neurons born at similar time windows.

Little is known about the consequences of spatiotemporal patterning dysregulation. In flies, perturbation of temporal patterning by knocking down *eyeless*, an early temporal factor in the central complex, results in impairment of navigation (Sullivan et al., 2019). Similar disruption of navigation is observed when neurons generated during the Eyeless window are silenced (Giraldo et al., 2018; Green et al., 2018; Sullivan et al., 2019). In mice, overproduction of late-born layer 2/3 cortical neurons by prolonging the proliferation of intermediate progenitors results in compulsive behavior and deficits in social behavior reminiscent of autism spectrum disorder (Fang et al., 2013, 2014). Autism spectrum disorder (ASD), a disease involving neocortical function, has been long hypothesized to be associated with miswiring of neural circuitry, and it is tempting to speculate that patterning failure in the cortex results in autistic features if spatiotemporal patterning makes neurogenesis and wiring less error prone. Consistent with this hypothesis, mutations of mammalian cortical layer markers are often associated with ASD (Kwan, 2013). Recently, disorganized cortical lamina and changes in cortical layer thickness were also reported in ASD patients, which indicates that temporal patterning might malfunction during neurogenesis in patients with autism (Wegiel et al., 2010; Stoner et al., 2014; Trutzer et al., 2019).

SPATIOTEMPORAL PATTERNING AND EVOLUTION OF NEW CELL TYPES

It has long been hypothesized that cell type duplication and diversification underlie nervous system evolution. In this

model, the number of neurons expands and then diversifies to serve novel roles to form a more complicated nervous system. Indeed, brain volume and layer thickness differ substantially among vertebrates (Tosches and Laurent, 2019). The gain or loss of spatiotemporal factors is among the plausible mechanisms to diversify an expanded population of neurons. Consistent with this model, recent comparative studies in vertebrates have shown that evolutionary novel subtypes often share the gene expression profile with a conserved cardinal type. For example, birds have only two cerebellar nuclei, medial and interposed, while mammals have three: medial, interposed, and lateral. Neurons from each of the three nuclei in chicken, mice, and humans can be categorized into two molecular classes, while the neurons of the same class from different nuclei still differ from each other (Kebschull et al., 2020). While it remains to be determined if changes in spatiotemporal patterning are responsible for the emergence of new subtypes during evolution, it provides a feasible molecular infrastructure for duplication and diversification to occur.

The recent advent of high-throughput profiling techniques not only made possible the discovery of a shared set of temporal regulators across different vertebrate neuronal tissues (Lu et al., 2020; Sagner et al., 2021) but also opened the opportunity to understand the gene regulatory networks governed by these temporal factors (Telley et al., 2019; Lyu et al., 2021) and other birthdate-specific post-mitotic regulators (Di Bella et al., 2021). Our rapidly expanding knowledge of the molecular logic of spatiotemporal integration and fate specification in various species will set the stage for more comparative studies, such as the investigation of how the targets of conserved spatiotemporal regulators differ between species, how novel spatial domains or temporal windows emerge, and, ultimately, how new cell types are generated during development and evolution.

AUTHOR CONTRIBUTIONS

Both authors contributed equally in the conception and writing of the manuscript.

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