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Editorial

Time, space, and diversity

ARTICLE INFO

Our brain generates billions of neurons and glial cells of diverse types, which assemble to form a functional nervous system. One of the most fascinating and exciting frontiers in neuroscience is to understand the conserved principles regulating the generation of diverse cell types from a small pool of neural progenitors known as neural stem cells (NSCs). During development, NSCs located at different spatial domains generate different neural types, and this process is called spatial patterning. Additionally, individual NSCs sequentially generate distinct neural types over time in a process known as temporal patterning. The phenomenon of temporal patterning is observed in both vertebrate and invertebrate nervous system development. Decades of work has identified conserved principles of temporal patterning mechanisms from invertebrates to humans.

In *Drosophila*, classical studies in the ventral nerve cord (VNC), equivalent to the vertebrae spinal cord, demonstrated that NSCs called neuroblasts sequentially express a series of Temporal Transcription Factors (TTFs), and these TTFs control the sequential generation of specific temporal fates and the final cell cycle exit [1,2]. The TTF sequence is largely the same in different neuroblasts of the VNC, but they direct the generation of different neural types due to integration with spatial patterning [3,4]. Subsequently, TTF cascades using different sets of TFs were identified in the *Drosophila* medulla neuroblasts and central brain type II neuroblast lineages [5–11]. In parallel to these TTF cascades, another critical temporal patterning mechanism was identified in *Drosophila* central brain neuroblasts, that relies on the opposing gradients of two RNA-binding proteins [12–14]. These gradients of RNA-binding proteins and dynamic expression of TTFs work together to regulate temporal patterning of *Drosophila* neuroblasts. Extrinsic signals including the steroid hormone Ecdysone and other signaling pathways regulate these temporal patterning mechanisms [12–14]. In vertebrates, although NSCs also generate different neural types is a birth-order dependent manner, there is much more plasticity is response to environmental signals [15–18]. In contrast to the deterministic role TTFs plays in *Drosophila* neuroblasts, often only modest phenotypes were observed when candidate temporal factors were knocked down. Recently, there have been great advances in the study of temporal patterning, partly due to the development of single cell multi-omics technologies especially single-cell RNA-seq (ScRNA-seq). Conserved transcriptional changes were observed in the young NSCs versus late NSCs that are transmitted to the progeny [19–21]. Temporal patterning is regulated by a combination of mechanisms including transcriptional and epigenetic changes, extrinsic cues, voltage differences, and post-transcriptional mechanisms [22–28]. After neural fate specification, temporal patterning, on a broader sense, continues in the postmitotic neurons and in the neural circuit assembly. Extrinsic cues, especially hormonal signals, heterochronic pathways and neural activity play critical roles in the postmitotic temporal patterning process [29,30].

We are very grateful to our colleagues who contribute thought-provoking reviews for this special issue, covering the most recent advances in the study of temporal patterning of the nervous system, and provide important perspectives to the knowledge gaps and further development of this field. Studies in *Drosophila* have provided very valuable information and has contributed tremendously towards understating the mechanisms regulating temporal patterning. The review article by **Pollington et al.** [31] focuses on the *Drosophila* type I neuroblasts including those in the VNC and in the optic lobe medulla, and covers recent advances in the essential roles TTFs play in controlling proper connectivity and neural circuit assembly, and also touches on the conservation of these mechanisms in vertebrates. With the advent of ScRNA-Seq which enables the identification of many new temporal genes and cell types, **El-Danaf et al.** [32] provide a timely overview of recent advances in transcriptomic and epigenomic analyses of temporal patterning. They discuss conserved or convergent mechanisms in the intrinsic and extrinsic control of temporal patterning and neuronal specification in flies and vertebrates. While Drosophila embryonic neuroblasts have provided valuable information on temporal patterning mechanisms, recent studies on post-embryonic neuroblasts have identified new RNA-binding protein gradients and extrinsic cues regulating temporal patterning. **Hamid et al.** focus on the Drosophila type II neuroblast, which give rise to a much larger lineage through proliferating intermediate progenitors and covers recent advances on how

Abbreviations: NSCs, neural stem cells; TTFs, Temporal Transcription Factors.

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cell-intrinsic and extrinsic hormonal cues regulate temporal transitions, and neural fate specification. The authors discuss the possible ways to link type II neural stem cells with the central complex neural cell types and behavior.

In vertebrates, the specification of different neural types from NSCs relies on a combination of internal competence and extrinsic cues. The piece by **Santos-França et al.** [33] describes the temporal patterning of mammalian retina progenitors, and discusses the various mechanisms through which a number of Temporal Identity Factors, including transcription factors and post-transcriptional regulators, function in the regulation of the competence of retinal progenitors. Recent studies have identified epigenetic and epitranscriptomic mechanisms regulating temporal expression of genes, and the review by **Koo et al.** [34] highlights the importance of these epigenetic and epitranscriptomic regulatory mechanisms in controlling the temporal competence of Radial glial cells. They also discuss how biochemical reaction speed, local environmental changes, and subcellular organelle remodeling contribute to temporal patterning and the interspecies developmental tempo differences.

The correct specification of neural fates requires integration of temporal patterning with spatial identity factors in neural progenitors. The review by **Sen** [35] highlights possible mechanisms by which spatial patterning is integrated with temporal patterning in fly and vertebrate neural progenitors, and also addresses gaps in this field.

After neurons are generated by neural progenitors in embryonic stage, they continue to undergo temporal changes until they reach a mature state in adulthood. The review by **Sun and Hobert** [36] discusses such temporal changes in post-mitotic neurons in the nervous system of the nematode C. elegans, highlighting the importance of neuronal activity, heterochronic pathway genes, and neuron extrinsic cues including hormonal signals in the neuron maturation process. Continuing on this theme, the piece by **Jain and Zipursky** [37] discusses how temporal regulators control the dynamic expression of wiring genes to enable neural circuit assembly, with a focus on how cell-extrinsic cues and neural activity act on cell-type specific transcriptional landscapes to control formation of neural circuits.

In sum, the review articles in this special issue highlight the progress that has been made in recent years towards understanding the molecular mechanisms regulating neural diversity of the CNS. With the new tools including single cell multi-omics technologies and connectomics available, understanding how genes, hormones, time and space orchestrate in patterning brain development is becoming achievable.

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