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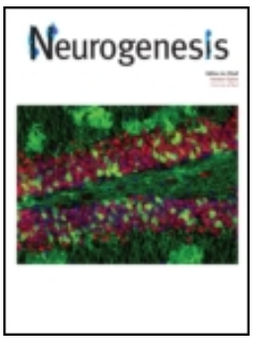

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Neuronal specification exploits the inherent flexibility of cell-cycle gap phases

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Starting from pluripotent stem cells that virtually proliferate indefinitely, the orderly emergence during organogenesis of lineage-restricted cell types exhibiting a decreased proliferative capacity concurrently with an increasing range of differentiation traits implies the occurrence of a stringent spatiotemporal coupling between cell-cycle progression and cell differentiation. A recent computational modeling study has explored in the context of neurogenesis whether and how the peculiar pattern of connections among the proneural Neurog2 factor, the Hes1 Notch effector and antagonistically-acting G1-phase regulators would be instrumental in this event. This study highlighted that the strong opposition to G1/S transit imposed by accumulating Neurog2 and CKI enables a sensitive control of G1-phase lengthening and terminal differentiation to occur concomitantly with late-G1 exit. Contrastingly, Hes1 promotes early-G1 cell-cycle arrest and its cell-autonomous oscillations combined with a lateral inhibition mechanism help maintain a labile proliferation state in dynamic balance with diverse cell-fate outputs, thereby, offering cells the choice to either keep self-renewing or differentiate into distinct cell types. These results, discussed in connection with Ascl1-dependent neural differentiation, suggest that developmental fate decisions exploit the inherent flexibility of cell-cycle gap phases to generate diversity by selecting subtly-differing patterns of connections among components of the cell-cycle machinery and differentiation pathways.

Keywords: cell cycle, computational modeling, fate decision, proneural factor, regulatory network

Abbreviations: Ascl1, Achaete-scute homolog; Cdk, Cyclin-dependent kinase; CKI, Cyckin-dependent kinase inhibitor; Dll1, Delta-like 1; FGF, Fibroblast growth factor; Neurog2, Neurogenin 2; Rb, Retinoblastoma; TGF-β, Transforming growth factor-β

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Development of the mammalian cerebral cortex is characterized by both an enormous increase in cell number and the orderly generation of assorted neural cell types exhibiting a gradual loss of proliferative capacity associated with an increasing number of differentiation traits. Final size, shape and cellular composition of the nervous system therefore relies on a carefully-programmed and tunable balance between self-renewal and differentiation in multipotent neural progenitors, raising the question of the underlying crosstalk mechanisms linking the cell-cycle machinery and differentiation pathways. These mechanisms necessarily integrate the basic requirement that terminal differentiation should coincide with cell-cycle withdrawal in a state that markedly differ from the low metabolic, reversible quiescent/G0 state.[1] Accordingly, proneural factors generally contribute to cell-cycle exit through a variety of means. Notably, the overexpression of proneural factors has been reported to up-regulate the expression of the $p27^{Kip1}$ Cdk inhibitory protein (CKI) in mouse embryonal carcinoma cell lines.[2] Furthermore, the proneural Neurog2 protein not only directly activates the transcription of neuronal differentiation genes but also indirectly represses *cyclins D, E1* and *E2* that participate in G1-phase progression and G1/S transit.[3] In turn, Neurog2 is phosphorylated on multiple sites by cyclins-Cdk2,1 which obstructs its binding to E box DNA and, hence, diminishes both its stability and its ability for activating transcription,[4,5] whereas, conversely, its binding to $p27^{Kip1}$ leads to its stabilization.[6] These data would argue that irreversible cell-cycle arrest occurring in nascent neurons results from a concerted action between the downregulation of G1- and S-phase cyclins and the accumulation of Neurog2 and Cip/Kip

proteins. Nevertheless, the early appearance of differentiation traits and the emergence of lineage-restricted identity in progenitor cells should not definitively block their proliferation and eventual irreversible cell-cycle arrest should not occur before commitment to terminal differentiation. Therefore, the question that springs to mind is: how do the temporal organization of the cell-cycle both contribute to and is determined by cell-type specification?

This issue has been formulated and extensively addressed for some time, the chief point of discussion focusing on whether G1-phase lengthening observed during neurogenesis[7] is a result, a cause or a correlate of differentiation.[8-11] The fact that manipulation of G1-phase length by diverse approaches[12-14] has been shown to impact on the differentiation statut tends to suggest that the rate of progression through G1 is limiting for differentiation, though the underlying, direct or indirect, mechanisms remain difficult to disentangle because of the extensive crosstalk between the cellular pathways regulating cell division and cell differentiation. Compounding the problem is that G1-phase duration does not necessarily lengthen during early neurogenic divisions, and other phases of the cell cycle such as S or G2 phases can even be shortened in the course of lineage-restriction of progenitor identity.[15-18] It is of note also that some *bona fide* cell-cycle regulators, such as cyclin D1[19] and Cdc25B,[20] have been shown or postulated to play a direct role in neurogenesis, and reciprocally for proneural factors, such as Ascl1 or Atoh1, that arguably exert a proliferative activity.[21,22]

Deciphering the functional logic of the elaborate network that mutually links the cell-cycle and differentiation pathways challenges our intuitive reasoning based on simple causal chains. Computational modeling approaches provide a set of techniques that have proved well-adapted to decrypt the design and operating principles of biochemical and cellular networks. One particular approach consists in simulating the time courses of protein concentrations and activities by using a set of biochemical reactions translated into mathematical equations. After a careful choice of assumptions and parameter values inferred from prior experimental data and well-supported knowledge, it is possible to simulate not only physiological situations but also pathological or fully virtual ones in which either certain reaction kinetics or network connections or environmental conditions have been modified. These *in silico* experiments allow then to make predictions as well as to clarify the 2-way relationship between the regulatory logic (e.g., the nature or the timescale of interactions, the global feedback architecture) and the functional dynamics (e.g.,, decision switches, oscillations, information processing) of protein networks. In the context of neurogenesis, computational modeling approaches have been harnessed for the purpose of understanding how the dynamics of the neural ultradian oscillator Hes1 is controlled by miR9 inputs[23] or Delta-Notch intercellular signaling.[24] Yet, computational models combining different regulatory modules are still lacking.

A detailed computational model aiming at unravelling the mechanisms underlying the co-ordination between self-renewal and Neurog2-dependent differentiation in neural progenitor cells has been published recently.[25] Extensive model analysis and simulations have allowed to reveal the precise role played by the interactions between the proneural Neurog2 factor and G1-phase cell-cycle regulators. Actually, the delicate balance between the control of Neurog2 stability and activity by cell-cycle regulators[4,6] and the Neurog2-dependent transcriptional control of G1-phase regulators[3] accounts for the occurrence of G1-phase lengthening preceding an irreversible and robust cell-cycle exit in late G1 associated with differentiation. The critical point is that the antagonism between Neurog2 and cell-cycle progression localizes for the most part in late G1 and at the G1/S transition. However, perturbing in the model the interactions between Neurog2 and cell-cycle regulatory elements or altering the intrinsic organization of G1-phase can alter the link between G1-phase lengthening, irreversible cell-cycle exit and differentiation commitment. Thus, disrupting the early G1-phase module (e.g., by knocking down *Rb* or over-expressing *cyclin E*) while providing an excess of differentiation factors may drive irreversible cell-cycle exit and differentiation without prior G1-phase lengthening. This is because the duration of the early-to-mid G1 phase can be gradually tuned through the balanced effect of various activatory and inhibitory signals impacting on the nuclear accumulation of active cyclin D-Cdks. On the opposite, G1-phase lengthening and exit may not culminate into differentiation or may lead to a poorly-stable and reversible differentiation state if the rate of accumulation of the differentiation factors is not boosted due to a concomitant decrease in cyclins-Cdks levels and/or increase in Cip/Kip levels. This could occur for instance if overexpression of the Notch effector Hes1 was inhibiting both proneural factors and cell-cycle activators (e.g., like in adult quiescent neural stem cells) or if the cooperation between Neurog2 and the Cip/Kip proteins was impaired. In all, the mode of coordination between cell-cycle lengthening and withdrawal, and differentiation commitment tightly depends on the way how inhibition of cell-cycle progression and activation of the positive feedback that leads to irreversible differentiation commitment are balanced in strength and coordinated in time, consistently with theoretical data obtained from a detailed model of G1-phase progression[26] and from a minimal model of the coupling between a cell-cycle oscillator and a differentiation switch.[27] In theory, it is then conceivable that, depending on the particular way cell-cycle progression and differentiation pathways intertwine, G1-phase lengthening using a variety of means may fail to induce differentiation, which in fact has been clearly attested in mouse embryonic stem cells.[28] Conceivably too, forced but gradual provisioning of differentiation factors in some specific context might induce differentiation without noticeable cell-cycle elongation, a possibility that still remains to be unambiguously demonstrated.

Thus, in agreement with certain experimental data,[3] the aforedescribed study supports the notion that cell-cycle lengthening and withdrawal and neuronal differentiation are separable processes which proceed coordinately as developmental programs unfold because of the peculiar connection pattern among components of their respective regulatory network. The

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positive feedback mechanism between Neurog2 and CKI leading to an irreversible cell-cycle exit that coincides with differentiation manifests the existence of bistability between a cell-cycle progression state and a cell cycle-arrested differentiated state, such that a transient signal can trigger an robust switch from one to the other phenotypic state. The very property that G1-phase lengthening precedes an irreversible switch is not only a consequence of the progressive accumulation of Neurog2 and CKI but also implies that the probability of switching from a proliferating to a differentiated state can gradually increase by extending the G1-phase window of sensitivity to differentiation signals and of opportunity to shift toward a differentiated state. In this event, transient signals can be generated for instance by fast temporal changes in Notch-activating extracellular cues.[29,30] The mechanistic and functional link between G1-phase lengthening and exit and Neurog2-dependent differentiation such as that depicted in **Figure 1A**, represents one prevalent mode of coupling between cell-cycle and differentiation, although it is not necessarily the only one.

Although many proneural factors are involved in neurogenesis, Neurog2 and Ascl1 appear to be the master regulators giving rise to glutamatergic (excitatory) pyramidal neurons and GABAergic (inhibitory) neurons, respectively.[31] They not only promote neuronal differentiation cell-autonomously but also ensure the maintenance of a pool of neural progenitors non-cell autonomously by upregulating the expression of Notch ligands such as Delta-like1 (Dll1), whose binding to and activation of Notch receptors on neighboring cells inhibit their differentiation via the Notch effector Hes1 that exhibits a cell-autonomous oscillatory pattern of expression owing to its ability to repress its own transcription. Both Neurog2 and Ascl1 are transcriptionally repressed by Hes1 so that their expression, as well as that of Dll1, oscillates out of phase with Hes1 in proliferating cells.[32,33] They share a further similarity in that they both are phosphorylated on multiple sites by G1- and G1/S-specific cyclins-Cdks whereby their ability to activate pro-differentiaton factors is reduced but not their ability to activate the Notch ligand Delta.[5,34] Yet, Neurog2 and Ascl1 also show important differences in their mode of regulation. Notably, an unexpected distinction between the 2 was uncovered recently by a genome-wide analysis of transcriptional targets of Ascl1 in the embryonic brain and in neural stem cell cultures.[21] At odds with Neurog2 that is well-acknowledged to contribute to cell-cycle exit by indirectly repressing a subset of cyclins and by activating, directly or indirectly, the *Cip/Kip* genes,[2,3] *Ascl1* activates cell-cycle genes that participate in both G1/S transit (e.g., *E2f1, Cdk2* and *Skp2*) and entry into mitosis (e.g., *Cdk1* and *Cdc25b*) as well as cell-cycle genes involved in cell-cycle arrest, but during a later phase of neurogenesis. Thus, Ascl1 seems to function sequentially in promoting, first, cell-cycle progression to facilitate the expansion of ventral telencephalic progenitors when Notch signaling is activated and, then, cell-cycle arrest in differentiating neurons where Notch signaling is disrupted. Interestingly also, Ascl1 is mainly expressed in G2, M and early G1 phase in cycling neural progenitors,[33,35,36] which contrasts with the upregulation of Neurog2 expression in late-G1 phase[35-37] and may reflect certain specificities in the post-translational control of Ascl1 stability and activity by defined signaling pathways.[38-40]

What could be the significance of the differences between Ascl1 and Ngn2 in terms of coordination between cell division and cell differentiation? The mitogenic roles of Ascl1 have been explained by the requirement for a pool of rapidly-proliferating intermediate committed progenitors expressing proneural factors. Indeed, Ascl1 contributes to the relatively rapid proliferation rate of neural

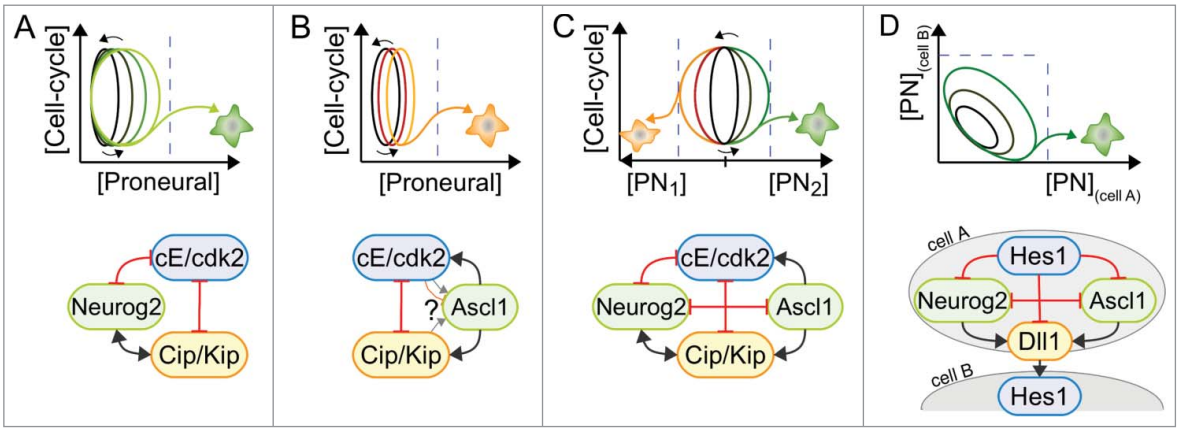

Figure 1. Different aspects of the flexible coupling between proliferation and neural differentiation. (**A-D**) Up: Schematic representation of the correlated dynamics between cell-cycle progression and neuronal specification (lines) in the course of neurogenesis (black to colored). Dashed blue lines represent decision thresholds. Down: Corresponding examples of coupling scheme between proneural factors and cell-cycle regulators (cE/cdk2: cyclin E-Cdk2; PN: Proneural factor). (**A**) Progressive G1-phase lengthening followed by irreversible cell-cycle exit toward a terminal differentiated state. (**B**) Progressive differentiation while keeping active proliferation (e.g.,, transit-amplifying divisions) followed by cell-cycle exit toward a terminal differentiated state. (**C**) Binary differentiation decision associated with distinct mechanism of cell-cycle exit. (**D**) Asymmetric fate decisions through the non-cell autonomous mechanism of lateral inhibition.

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precursors in the developing retina,[41] in the olfactory epithelium,[42] in the adult hippocampus[43] and in cultured conditions.[36] Although the cell-cycle promoting activities of Ascl1 appear to challenge the notion that the expression of differentiation factors should reduce the proliferative capacity of expresser cells by lengthening the cell cycle and promoting cell-cycle exit, an abrupt transition from a proliferative state to a differentiated state is an alternative possibility[27] (**Fig. 1B**) that would nevertheless require a stringent cell cycle-dependent control of Ascl1 activity and stability, for instance through Notch signaling.[21,38] Moreover, because Neurog2 and Ascl1 are co-expressed in cycling progenitors during early neurogenesis within opposite cell-cycle windows (namely in late G1 and in G2/M/early G1, respectively) and are prone to antagonize each other (discussed in Wilkinson et al,[31]), selection between Neurog2+/glutamatergic or Ascl1+/GABAergic (or Ascl1+/oligodendrocyte) lineages can be efficiently achieved in a dynamic cell cycle-dependent manner and with little interference (**Fig. 1C**). The hypothesis of a cell cycle window-dependent gating of differentiation gains support from the observation that cell-fate choice is biased by the cell position in the cell-cycle in several developmental systems. For instance, the initial choice made by starving amoeba cells to differentiate into a spore or a stalk cell depends on whether the cells reside in early- or late-G2 phase at the time of starvation, because their intrinsic sensitivity to developmental signals depends on the cell-cycle machinery.[44,45] A similar phenomenon has been uncovered in human pluripotent stem cells: cells in early-G1 phase are responsive to TGF-β-dependent endoderm differentiation whereas those in late-G1 phase undergo neuroectoderm differentiation because cyclin D restricts the activity of Smad2/3 in late G1.[46] A previous theoretical study suggests that fate decisions biased by the state of a cell-autonomous (cell-cycle) oscillator at the time of signal reception allow for a more tunable and reliable control of decision timing and probabilities.[47]

The various modes of coupling between progression through the cell-division cycle and the accumulation of differentiation factors that are discussed above stem from the interplay between cell-autonomous mechanisms and slow spatiotemporal changes in the signaling environment and pathways (e.g., FGF, Wnt, Shh or TGF-β) that influence the fate of neural progenitors.[48] However, neural progenitors also communicate with each other through Delta-Notch signaling, which affects fate decisions of neighboring cells in a highly dynamic and integrated fashion. It needs be reminded that the Notch effector Hes1 exhibits 2 utmost important features: (i) it indiscriminately represses activators and inhibitors of the cell cycle, differentiation factors and the Notch ligand Dll1, and (ii) its expression level oscillates cell-autonomously whereby the levels of expression of its various targets are forced to fluctuate.[32,33] Accordingly, Notch signaling mediates a lateral inhibition mechanism by which Hes1 and proneural gene expression display a heterogeneous (salt-and-pepper) pattern that dynamically changes at the typical timescale of the Hes1 oscillation.[29] Such a dynamic coupling between adjacent cells is naturally inclined, with the help of cellular noise, to desynchronize their respective expression levels of Hes1 or proneural factors, but also their relative position in the cell cycle.[25] Hence, neighboring cells will have different inclination for arresting their division cycle and differentiating in response to transient and global extracellular signals. Lateral inhibition thus needs to be supplemented by dynamic cell-autonomous mechanisms promoting cellular heterogeneity and asynchrony to produce robust asymmetric fate decisions (**Fig. 1D**).

Neural progenitors are confronted with critical decisions regarding not simply whether to divide or to differentiate, but also the rate at which they should proliferate and the subtype specification they should acquire.

However, their repertoire of choice and decisional probabilities tightly depends on cell type-specific determinants and context-dependent signals. This commentary aimed at emphasizing that neurogenesis involves a mechanism of coordination between cell-cycle progression and cell differentiation in which both flexibility and robustness have to combine to produce such an extraordinarily complex organ that is brain. In my opinion, the success of developmental strategies in general primarily relies on the unique organization in metazoa of the G1-phase regulatory network that comprises 2 temporally separable but flexibly coupled modules separated by the restriction point,[49,50] which allows for a differential control of early and late G1 events and the generation of binary cell-fate outputs. Finely-tuned temporal control of cell-cycle progression provides cells with adjustable gate mechanisms that bias the sensitivity to multitudinous mitogenic and differentiation signals, enabling cell-fate decisions to simultaneously match cell-autonomous requirements and the extracellular context.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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