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How to keep proliferative neural stem/progenitor cells

A critical role of asymmetric inheritance of cyclin D2

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It has long been argued that cell cycle regulators such as cyclins, cyclin-dependent kinases and their inhibitors affect the fate of neuronal progenitor cells. Recently, we identified that cyclin D2, which localizes at the basal tip of the radial glial cell (i.e., the neural progenitor in the developing neocortex), functions to give differential cell fates to its daughter cells just after cell division. This basally biased localization is due to transportation of *cyclin D2* mRNA via its unique cis-regulatory sequence and local translation into cyclin D2 protein at the basal endfoot. During division of the neural progenitor cells, cyclin D2 protein is inherited by the daughter cell that retain the basal process, resulting in asymmetric distribution of cyclin D2 protein between the two daughter cells. Cyclin D2 is similarly localized in the human fetal cortical primordium, suggesting a common mechanism for the maintenance of neural progenitors and a possible scenario in evolution of primate brains. Here we introduce our recent findings and discuss how cyclin D2 functions in mammalian brain development and evolution.

Keywords: mRNA localization, cyclin D2, asymmetric cell division, radial glia, post-transcriptional regulation

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Introduction

Mammalian brains are characterized by a large neocortex containing numerous neurons and glia generated from neural stem/progenitor cells (NSPCs) situated in the inner wall of the neural tube termed the ventricular zone (VZ). During cortical development, NSPCs are highly polarized stretching to both the ventricular (apical) surface and the pial (basal) surface of the cortical primordium. NSPCs initially divide symmetrically to increase their numbers from embryonic day nine (E9) to E11 in mice (the proliferative period).[1,2] As development proceeds to the neurogenic period (starting around E11 in mice), NSPCs become longer and thinner to form "radial glia (RG)" as they support radial migration of cortical neurons.[3,4] The RG cells divide asymmetrically and produce one apical progenitor cell (AP) and one neuronal cell or intermediate progenitor cell (IP).[3,5] APs continue to divide asymmetrically, thereby increasing the number of neuronal cells while maintaining the number of APs. Newly produced neurons migrate out of the VZ to form the cortical plate (CP), while IPs divide symmetrically in the upper region of the VZ (i.e., the subventricular zone; SVZ) and generate a pair of IPs or neurons[1,6,7] (**Fig. 1**). Asymmetric cell division of NSPCs is critical for establishing the architecture of the mammalian cerebral cortex.[3,8] During the asymmetric division of APs, cell structures such as the basal process and apical membrane are inherited by one of the two daughter cells, and it is proposed that these components may function as cell fate determinants.[4,9,10] Many molecules are localized in the apical region and affect cell fates (e.g., numb, prominin1, Par complex proteins).[10-13] However, relatively little information is available about molecules in the basal side.

Cyclin D2 and Mammalian Brain Development

Mouse *cyclin D2* was first identified in a screen for delayed early response genes

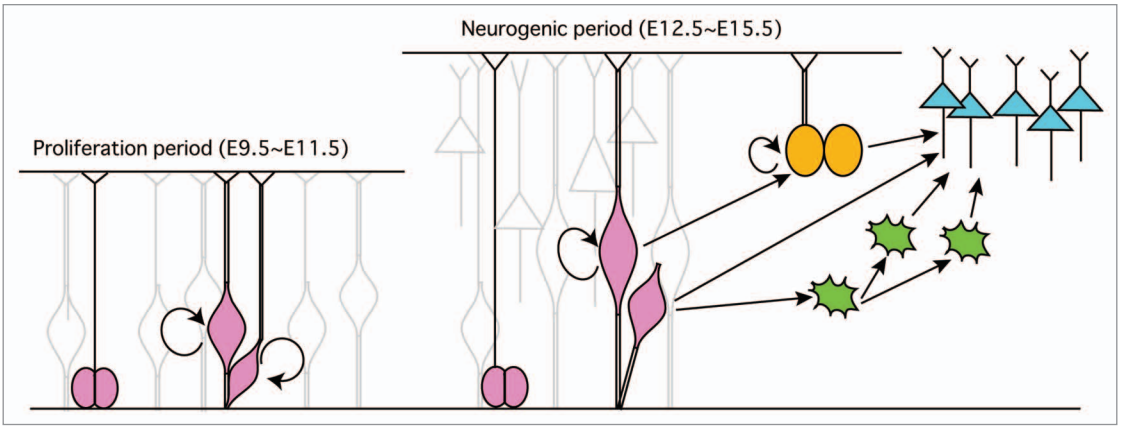

Figure 1. Schematic depiction of cortical development in mammals. At the early stage of corticogenesis (E9.5~11.5), neuroepithelial cells divide symmetrically to yield more progenitors, resulting in a thickened pseudo-stratified sheet where the mitotic cells are concentrated mainly on the apical side of the epithelium (the proliferation period). Later in corticogenesis (E12.5~15.5), neuroepithelial cells become long and thin radial glia (RG) and start to divide asymmetrically (the neurogenic period). Radial glia produce apical progenitors (APs) with self-renewing properties together with a terminally-differentiated neurons (blue) or intermediate progenitors (IPs, green), or outer radial glia (oRGs, yellow).

induced by colony-stimulating factor 1, and recognized as a member of a family that include at least two other related genes, *cyclin D1* and *D3*.[14] Cyclin D2 protein forms a complex with cyclin-dependent kinases (Cdk) 4 or 6 and translocates to the nucleus where the tumor suppressor protein Rb is phosphorylated to activate transcriptional factor E2F. This cascade of events progresses the cell cycle from G_1- to S-phase.[15,16]

It is well known that neuronal progenitor cell fate can be affected by cell cycle regulators including cyclins,[17-19] Cdks[20] and their inhibitors.[21-24] In the developing central nervous system (CNS), mRNA of *cyclin D2* shows a unique localization, to the surface of the neural tube, not seen for other cyclins.[25,26] Because of this unique localization pattern, cyclin D2 was initially thought to be expressed in postmitotic neurons[25,26] but recent work identified that the mRNA and protein localized at the tip of the AP (i.e., endfoot).[19,27] As with other cyclins, cyclin D2 is also localized at the nucleus of mitotic cells in the VZ and SVZ, and was assumed to have a function in cell cycle progression.[27] In *cyclin D2*-knockout mice, the brain size is smaller and adult neurogenesis is dramatically impaired.[28-31] Cyclin D2 is essential for expansion of the NSPCs in both embryonic and adult brains, but what is the significance of the biased localization of cyclin D2 in the basal endfoot of the APs?

We have recently shown that overexpression of cyclin D2 increases the population of APs, while the loss of cyclin D2 function increases the neuronal population.[19] This indicates that cyclin D2 being localized to the endfoot of APs is an example of a "basal fate determinant." This is unique in that the mechanism for fate determination of APs is at the subcellular level (**Fig. 2**). *Cyclin D2* mRNA is continuously transferred toward the basal side up to the endfoot via its unique 50-bp cis-element (Step 1), and is locally translated into the protein (Step 2). During asymmetric cell division, one of the daughter cells inherits its basal process, which automatically leads to asymmetrical inheritance of cyclin D2 protein between the daughter cells (Step 3). The daughter cell with cyclin D2 will become an AP, and the other without cyclin D2 will become a neuronal cell or an IP (Step 4).

Although we showed that cyclin D2 affects the fate of APs, the exact molecular mechanism is still unknown. A correlation between G_1-phase lengthening and neurogenesis has been noted[32-37] (data controversial to this has recently been reported, though).[38] If the lengthening of G_1-phase causes neuronal differentiation, the biased localization of cyclin D2 will provide a shorter G_1-phase to the daughter cell that inherits the basal process which in turn biases the fate of that daughter cell to a progenitor. Although this is an interesting scenario, time-lapse studies using slice culture suggest that inheritance of the basal process does not always lengthen the total cell cycle compared with the other daughter cell[39,40] (personal communication with Dr. Matsuzaki). Another model could be that cyclin D2 controls cell fate in a manner other than controlling the cell cycle itself. For example, cyclin D2 is known to have a function in exporting the Cdk inhibitor p27(kip1) out of the nucleus, thereby promoting degradation.[41,42] Since p27(kip1) promotes neurogenesis and radial migration of postmitotic neurons,[21,22] inherited cyclin D2 may inhibit neurogenesis and promote cell proliferation[19] via a p27(kip1)-dependent mechanism. There are many other reports showing that cell cycle regulators may function as cell fate determinants by a role independent of cell cycle regulation.[20,21,43,44] Furthermore, another detailed analysis suggests that not only G_1-phase but also S-phase is correlated with the differentiation state of NSPCs.[38] Thus, the physiological functions of cyclin D2 in aspects of fate determination in vivo still remain to be elucidated.

Cyclin D2 and Brain Evolution

As described above, we have reported a new physiological function of cyclin D2 in the neuronal development of the mouse. The next question we focused on was "Is this mechanism conserved among

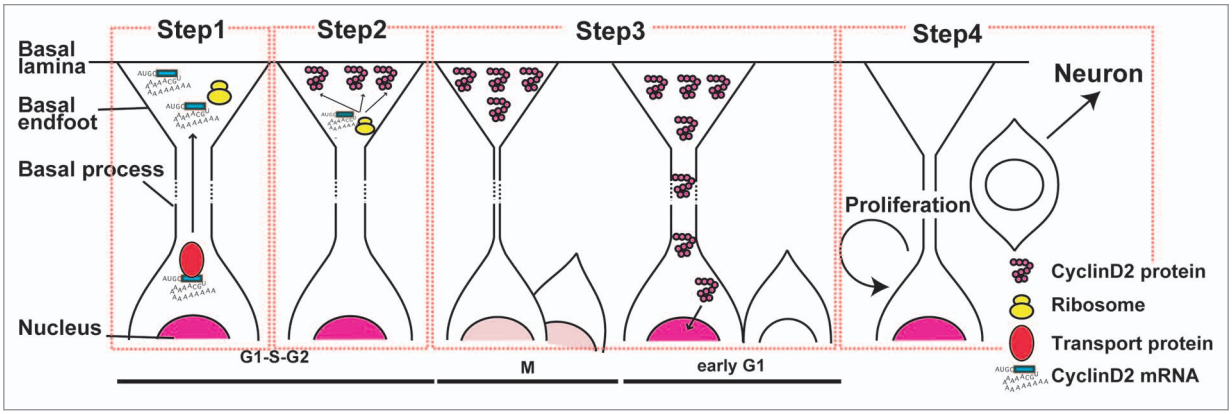

Figure 2. Schematic depiction of *cyclin D2* mRNA and protein dynamics during the cell cycle and its putative role as a fate determinant. Pink in the nucleus indicates cyclin D2 protein. (Step 1) *Cyclin D2* mRNA is transported to the basal endfoot during G_1, S- to G_2-phase due to the cis-transport element that resides in the 3'UTR region of *cyclin D2* mRNA (blue box in mRNA) together with the transportation machinery that recognizes the cis-element (red circle). (Step 2) Transported mRNA is locally translated into protein via ribosomes localized at the basal endfoot. (Step 3) During mitosis, cyclin D2 protein is inherited by one of the daughter cells with its basal process. In early G_1-phase inherited cyclin D2 creates clear asymmetry of the cyclin D2 protein level between two daughter cells. (Step 4) The daughter cell that has inherited cyclin D2 with the basal process remains as a progenitor, whereas the other daughter without the basal process proceeds differentiation.

species?". In humans, we found an accumulation of cyclin D2 protein at the basal side of the cortical primordium at gestation week 16.[19] We also noted that the cis-acting element we identified in mice for basal transportation is highly conserved in human (74% match in NCBI database). Therefore, it is probable in the human cortical primordium that *cyclin D2* mRNA transported within the basal process toward the basal endfoot and locally translated into protein in a similar manner. It is of note that the basal transport cis-element we have identified appears to be unique to mammals, as similar sequences are not found in avians nor amphibians (NCBI database). Indeed, accumulation of *cyclin D2* mRNA in the basal side of the chick forebrain is not observed (unpublished results). Acquisition of the genomic DNA sequences corresponding to the basal transportation regulatory element in the 3'UTR of *cyclin D2* mRNA might be a critical diversification point in vertebrate brain evolution.

Recent progress in live imaging studies has revealed a new population of proliferative progenitors that have basal processes but no apical processes. These neural progenitor cells locate in the outer subventricular zone (OSVZ) of the fetal cortex of human and ferret, and are thus called OSVZ radial glia-like cells (oRG).[45-47] Originally, oRG is believed to exist only in primates or gyrencephalic mammals, several groups have recently reported that there is a population of oRGs also in non-gyrencephalic mammals, including mice and marmosets.[39,40,48] In the human fetal cortex, oRGs show a clear correlation between Hes1 expression and basal process inheritance.[46,47] This indicates that the basal process may be required for receiving the Notch signal, a pivotal mechanism in maintaining the progenitor state. Furthermore, the basal process is reported to receive from the meninges a retinoic acid signal that controls the proliferation of the progenitor cells.[49] Even though it is obvious that there is a clear relationship between brain size and percentage of oRGs out of all proliferating progenitors,[50] more studies are required to understand the physiological significance of oRGs. Interestingly, cyclin D2-positive cells are observed in the OSVZ, and the dotted staining of cyclin D2 is frequently seen in the basal side but not in the apical side[19] making it likely that these cells are oRGs.

In the mouse, cyclin D2 is also expressed in IPs and is shown to be required for their proliferation.[27] This is further confirmed by our group; gain or loss of cyclin D2 function experiments drastically increased or decreased, respectively, the population of Tbr2-positive IPs in SVZ.[19] Therefore, cyclin D2 is very important for proliferation not only of APs, but also of IPs. Taken together, it is reasonable to assume that cyclin D2 has proliferative activity also in oRGs.

In sum, cyclin D2 function is generally required for proliferation of various neural progenitors, i.e., APs, IPs and probably oRGs. There is little doubt that prolonged maintenance and the massive proliferation of NSPCs are essential in brain evolution, and that cyclin D2 is a key player.

Concluding Remarks

Asymmetric inheritance of cyclin D2 in dividing daughter cells of APs is the first description of a post-transcriptional, regulatory mechanism in the developing vertebrate CNS. This unique mechanism comes from the shape of the AP, which is highly polarized and has a long basal process. Although cell cycle regulators such as cyclins are one of the most well-studied molecules, there is still little information about the molecular dynamics in vivo. There are many questions that remain to be elucidated about the physiological functions of cyclin D2 in the developing CNS. This is a first step toward the next cycle of research in cortical development and evolution.

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