also reduced, suggesting that the role of PML in neural progenitor proliferation and differentiation is not specific to neurogenesis but affects gliogenesis as well. The authors used an *in vitro* differentiation paradigm to corroborate their *in vivo* findings, and showed that reintroduction of PML into PML mutant cells *in vitro* reversed the decrease in neuronal and glial cell differentiation.

To probe PML function in neocortical progenitors on a molecular level, the authors examined interactions between PML and pRb, as these proteins are known to interact in other settings[8] and pRb has been shown to play an essential role during neocortical development[9–11]. pRb is expressed at high levels in the developing neocortex where it is involved in cell cycle regulation, differentiation, apoptosis and even migration[9]. The primary mechanism by which pRb regulates cell cycle progression is inhibition of EF2 transcription factors. When phosphorylated, pRb is unable to bind E2F proteins, allowing them to promote the transition from G1 to S phase[1].

Investigation of the putative interactions between PML and pRb in neocortical progenitors led Regad *et al.* to examine pRb expression and subcellular localization in PML mutants[3]. As part of this analysis, they also considered the expression of protein phosphatase 1α (PP1α), which dephosphorylates pRb, thereby permitting it to inhibit E2F. Normally, pRb and PP1α are expressed in nuclear granules whose expression partially overlaps with those of each other and PML-NBs; however, in $Pml^{-/-}$ neocortical progenitors, both pRb and PP1α were dispersed throughout the nucleoplasm and cytoplasm. In addition, pRb was hyperphosphorylated in PML mutants, consistent with previous work showing that PML overexpression led to pRb hypophosphorylation[12]. Re-introduction of PML into $Pml^{-/-}$ neocortical progenitors rescued the subcellular localization of both PP1α and pRb and the phosphorylation state of pRb. Consistent with the idea that pRb and PP1α functionally interact with PML, immunoprecipitation studies showed that both physically interact with PML. All told, the work of Regad *et al.* suggests that PML regulates pRb in neocortical progenitors, through direct protein-protein interaction and in a PP1α-dependent fashion (**Fig. 1**).

This work raises many interesting questions about the role of PML, also a tumor suppressor, in normal neural development. For example, is PML function temporally regulated and, if so, how? The balance between RGCs and IPCs in the neocortex is fundamental to proper development, and the temporal regulation of PML could promote a gradual shift from RGC to IPC identity. As the work by Regad *et al.*[3] focused primarily on neurogenesis at embryonic day 15, future studies should consider how PML functions at other time points. Another interesting question raised by Regad *et al.* is, how does PML, and how do cell cycle regulators in general, interact with the many pathways and genes known to control neocortical progenitors? For example, several recent reports showed that disruption of Tbr2 greatly reduced the number of IPCs in the neocortex[13,14], producing a phenotype similar to that observed with PML disruption. This similarity suggests that it would be worthwhile, and potentially very interesting, to determine whether overexpression of Tbr2 in PML mutants promotes IPC character. The mechanistic connection of cell cycle regulators to transcription factors such as Tbr2 is likely to create new avenues of pursuit for the field. It will be especially interesting to determine the extent to which cell cycle regulators influence neural development not only through the direct control of cell division, but also through novel interactions with other pertinent signaling cascades and regulatory molecules[1].

That $Pml^{-/-}$ mice survive to maturity without any gross neurological defects[5], and that a limited number of IPCs are still generated in these impaired animals, suggests that some functional redundancy, on the molecular and/or cellular levels, exists during neocortical development. However, by showing that the PML plays an important role in IPC generation and pRb regulation during neocortical development, Regad *et al.*[3] have identified a new avenue connecting the somewhat disparate fields of cell cycle control and neural progenitor regulation. In addition, this work is pertinent to the biology of brain tumors, in which the balance between cancer stem cells and more restricted proliferative cell types[15] may be regulated by mechanisms similar to those controlling the balance between RGCs and IPCs during development. Determining how PML works in concert or in parallel with other signaling pathways will contribute to a comprehensive understanding of neural progenitor regulation and brain development, and it may add to our understanding of the causes and potential treatment of brain cancer.

1. McClellan, K.A. & Slack, R.S. *Cell Cycle* **5**, 1506–1513 (2006).
2. Dehay, C. & Kennedy, H. *Nat. Rev. Neurosci.* **8**, 438–450 (2007).
3. Regad, T., Bellodi, C., Nicotera, P. & Salomoni, P. *Nat. Neurosci.* **12**, 132–140 (2009).
4. Bernardi, R., Papa, A. & Pandolfi, P.P. *Oncogene* **27**, 6299–6312 (2008).
5. Wang, Z.G. *et al. Science* **279**, 1547–1551 (1998).
6. Dellaire, G. & Bazett-Jones, D.P. *Bioessays* **26**, 963–977 (2004).
7. Pontious, A., Kowalczyk, T., Englund, C. & Hevner, R.F. *Dev. Neurosci.* **30**, 24–32 (2008).
8. Labbaye, C. *et al. Oncogene* **18**, 3529–3540 (1999).
9. Ferguson, K.L. & Slack, R.S. *Neuroreport* **12**, A55–A62 (2001).
10. Ferguson, K.L. *et al. EMBO J.* **21**, 3337–3346 (2002).
11. MacPherson, D. *et al. Mol. Cell. Biol.* **23**, 1044–1053 (2003).
12. Mu, Z.M., Le, X.F., Vallian, S., Glassman, A.B. & Chang, K.S. *Carcinogenesis* **18**, 2063–2069 (1997).
13. Arnold, S.J. *et al. Genes Dev.* **22**, 2479–2484 (2008).
14. Sessa, A., Mao, C.A., Hadjantonakis, A.K., Klein, W.H. & Broccoli, V. *Neuron* **60**, 56–69 (2008).
15. Stiles, C.D. & Rowitch, D.H. *Neuron* **58**, 832–846 (2008).

Sleep on it

A period of sleep is known to benefit performance in memory tasks, but a study on page 122 of this issue suggests that it is not just the amount, but the kind, of sleep that is important.

This study recorded electroencephalograms from people as they slept and set off a beeping sound when the electroencephalograms were consistent with a sleep stage known as slow-wave sleep. Slow-wave sleep is a state of deeper sleep, so although the beep did not awaken the subjects, they slid out of slow-wave sleep into a different, shallower sleep stage.

Although the total amount of sleep that subjects got was unchanged, these people did worse on a later test of scene recall than subjects who had slept normally. Moreover, when the subjects were later scanned in a functional magnetic resonance imaging scanner, they also showed reduced hippocampal activation while they were encoding the to-be-remembered scenes. These results suggest that hippocampus-dependent memory is particularly affected by shallow sleep. ***Charvy Narain***