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REVIEW

Tumor suppressive pathways in the control of neurogenesis

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Abstract The generation of specialized neural cells in the developing and postnatal central nervous system is a highly regulated process, whereby neural stem cells divide to generate committed neuronal progenitors, which then withdraw from the cell cycle and start to differentiate. Cell cycle checkpoints play a major role in regulating the balance between neural stem cell expansion and differentiation. Loss of tumor suppressors involved in checkpoint control can lead to dramatic alterations of neurogenesis, thus contributing to neoplastic transformation. Here we summarize and critically discuss the existing literature on the role of tumor suppressive pathways and their regulatory networks in the control of neurogenesis and transformation.

Keywords Stem cells · Tumor suppressor · Neurogenesis · Transformation

Introduction

Neurogenesis is the process by which functional neurons are generated from neural stem and progenitor cells (NPCs). Neurogenesis occurs in both developing and adult brains [1–6].

Control of cell division and cell death during neurogenesis is crucial for the generation of new neuronal cells. Neural stem cells (NSCs) have the ability to self-renew (expansion) or generate specialized cells, either directly or via generation of transit-amplifying (or intermediate) progenitors (differentiation) [4, 7]. Significant progress has been made over the last decade in the study of almost all the aspects of mammalian neurogenesis both at embryonic and perinatal stages [5].

Early in nervous system development, NSCs form a polarized epithelium, named the ventricular zone (VZ), whose apical domain delimits the lumen of the neural tube. As development proceeds, an increased proportion of stem cells start to switch from symmetrical division, which generates additional stem cells, to asymmetrical division [4, 7]. In particular, the switch to asymmetrical division in the cerebral cortex leads to the generation of neurons in the cortical plate (CP) and of intermediate progenitors that leave the ventricular zone and form a second germinal region, called the sub-ventricular zone (SVZ) [4, 7–11].

Despite the fact that most precursors are exhausted by the end of the development to generate neurons and glia, a minor proportion of NPCs have also been found within two well-described neurogenic niches: the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) in the dentate gyrus [12–14]. In addition, recent studies suggest that NSCs may also reside in non-canonical neurogenic niche of the adult brain, including the cerebellum [15], substantia nigra [16, 17], and retina [18, 19].

Within the nervous system, cellular and environmental determinants tightly control the expansion and the differentiation of NSCs [7]. In this respect, self-renewal programs rely on complex regulatory networks that balance the function of proto-oncogenes (promoting self-renewal), gate-keeping tumors suppressor (limiting self-renewal), and care-taking tumors suppressors (maintaining genomic integrity) [11, 20, 21]. As a result, proliferation, self-renewal, and genomic stability are tightly controlled in

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both embryonic and adult stem cells [22, 23]. A defect in self-renewal, division, or differentiation of stem cells can lead to developmental defects, premature aging phenotype, failure to repair injured tissue, as well neoplastic transformation [24, 25].

The focus of this review is on the role of tumor suppressive pathways in regulation of neurogenesis in the mammalian brain. Alterations of tumor suppressive control in NSCs can lead to transformation and tumor development in both the embryonic and adult nervous system. It is therefore fundamental to dissect mechanisms underlying tumor suppressive function in the CNS as they may provide insights into its pathophysiology.

We will critically review the existing literature on two main tumor suppressors, retinoblastoma (Rb) and p53, and the stem cell factor Bmi1 (Fig. 1). As shown in Fig. 1, the main point of intersection between the two tumor suppressive pathways is represented by cyclin/cyclin-dependent kinases (CDKs) and their inhibitors (CKIs). p53 positively regulates CKIs, whereas CDK-complexes negatively regulate Rb. The Polycomb protein Bmi1 controls stem cell self-renewal by suppressing expression of CKIs, thus leading to Rb inactivation. Integration of these regulatory modules regulates the balance between expansion and differentiation in the developing CNS and adult neurogenic niches.

G1/S checkpoint: cyclins, cyclin-dependent kinases, and their inhibitors

In mammalian cells, proper progression through the cell cycle is monitored by checkpoints that sense possible defects during DNA duplication and chromosome segregation. Physiological activation of these checkpoints induces cell cycle arrest through modulation of cyclins and cyclin-dependent kinases (CDKs; Fig. 1) [34, 35]. The control of G1/S transition is primarily achieved through the coordinated action of two main cyclin/CDK complexes containing D-type and E-type cyclins. Cyclin D bind CDK4/6 early during the G1/S transition, whereas Cyclin E/Cdk2 complexes are active slightly later. Cyclin/cdk complexes are negatively regulated by CKIs, the main executers of the G1/S checkpoint. These are divided into two families: the Ink4/Arf type ($p16^{Ink4a}$, $p15^{Ink4b}$, $p18^{Ink4c}$ and $p19^{Ink4d}$) and the Cip/Kip type ($p21^{Waf1/Cip1}$, $p27^{Kip1}$ and $p57^{Kip2}$) [36]. For more in-depth analysis of the role of CDK and CKIs in regulation of the cell cycle, the reader can refer to a number of comprehensive review articles by leading laboratories in the field [8, 37, 38].

With respect to the role of cyclin/CDK complexes and CKIs in cell-fate regulation during neurogenesis, extensive literature suggests that the latter promote differentiation,

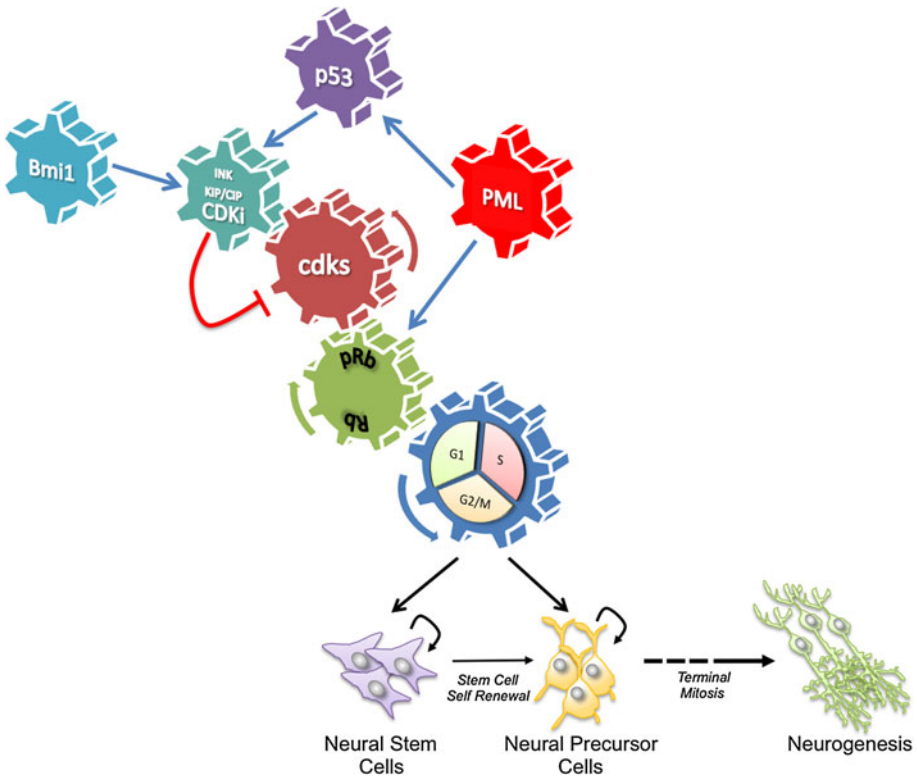

Fig. 1 Tumor suppressive factors and cell cycle control in the developing CNS and adult neurogenic niches. In neural/progenitor stem cells, a complex interplay of different tumor suppressors, downstream effectors, and regulatory networks controls self-renewal and differentiation

whereas the former play an inhibitory role [11, 39, 40]. For example, the anti-proliferative gene p27 has long been proposed to act as part of clock control for oligodendrocyte differentiation by limiting the number of divisions before the onset of differentiation [41]. Other studies have shown that CDK2 is required for S-phase entry and cell progression in NPCs isolated from both embryonic and early postnatal brain [42, 43]. In this contest, CDK2 has also been shown to be dispensable for NPC proliferation, differentiation, and survival of adult-born DG granule neurons in vivo [44]. More recently, work by Calegari and coworkers showed that CDK4/cyclin D1 overexpression inhibited neurogenesis, but at the same time it promoted the generation and expansion of basal progenitors, resulting in thicker SVZ and overall larger cortical surface area [9]. A subsequent study from the same group reported an important role of CDK4/Cyclin D1 also in the control of adult neurogenesis in the hippocampus [45]. Finally, Beukelaers and colleagues implicated CDK6 as a major regulator of adult neurogenesis [46]. Specifically, CDK6 deficiency prevents the expansion of neuronally committed precursors by lengthening duration of the G1 phase, thus reducing concomitantly the number of newborn neurons [46]. Further studies are needed to fully dissect the role and interplay of G1/S checkpoint members in regulation of neurogenesis.

p53 and its family

p53 (also known as tumor protein 53, tp53) was first identified over 30 years ago as a cellular protein associated with the SV40 T-antigen oncoprotein [47–49]. Although it was originally described as an oncogene, p53 is a tumor suppressor inactivated in more than 50 % of human cancers [50–55]. As a "guardian of the genome", p53 induces cell cycle arrest and cell death after DNA damage, thus contributing to the maintenance of genomic stability [56]. p53 is found in both the nucleus and the cytoplasm [57]. Nuclear p53 acts as a sequence-specific transcription factor, which regulates the expression of a vast number of genes involved in many different cellular processes from cell cycle checkpoint control to programmed cell death and metabolism (for extensive review of the literature see [57–61]. In particular, the CKI p21 is a major p53 target and plays an important role in p53-mediated regulation of G1/S transition (Fig. 1). In the cytoplasm, p53 promotes the activation of programmed cell death by directly regulating proapoptotic players such as Puma [57]. In addition, cytoplasmic p53 can repress autophagy, an intracellular degradation pathway involved in regulation of metabolism and survival [62]. In contrast, nuclear p53 has been proposed to induce autophagy via upregulation of the autophagy-associated factor DRAM1 [63]. Thus, p53-dependent regulation of autophagy varies dependent on its subcellular distribution.

In the CNS, p53 plays a key role in regulating programmed cell death in postmitotic neurons [64]. Evidence is emerging that p53 controls neurogenesis in the developing as well as in adult brain [65, 66]. In this respect, the tumor suppressor p53 has been shown to be abundant, both at RNA and protein levels, in regions of active proliferation during development and in adult neurogenic niches such as the SVZ and the SGZ [66–68] (Box 1). While p53 is found in post-mitotic neurons of the cerebral cortex and hippocampus of the developing brain, its expression is enriched in cycling progenitor/stem cells (NPCs) [65, 67, 68]. These data suggested that p53 might play an important role in the control of NPC proliferation and potentially regulation of CNS development. Indeed, p53-deficent mice exhibit high-frequency developmental abnormalities of the nervous system, in particular exencephaly and/or mild to moderate hyperplasia in approximately a quarter of p53-KO embryos [69, 70]. The partial penetrance of these phenotypes may be related to the existence of compensatory mechanisms probably mediated by the other members of the p53 family, p63 and p73 [71–75]. In the postnatal SVZ, p53 loss leads to over-production of NPCs, along with an expansion of neuronal and glial lineages [65, 76]. In accordance with the in vivo phenotypes, NPCs derived from the p53-null mice display enhanced self-renewal capacity, altered differentiation and reduction in apoptosis [65, 76].

Analysis of the transcriptome of p53 KO NPCs provided cues on the underlying mechanisms. In this respect, the known p53 targets $p21^{Cip1/Waf1}$ and $p27^{Kip1}$ are down-regulated in p53-null neurospheres [65]. These CKIs are regulated by p53 in a direct [77] as well as indirect manner [27, 78]. Their loss was shown to significantly affect NPC proliferation/differentiation [25]. In the absence of either $p21^{Cip1/Waf1}$ or $p27^{Kip1}$, proliferating NPCs fail to exit the cell cycle, thus eventually leading to their exhaustion [79, 80]. Subsequent studies have suggested that p53-dependent induction of $p21^{Cip1/Waf1}$ results in lengthening of the cell cycle and decreased expansion of NPCs within the developing [81] as well as the adult brain [82, 83]. With respect to $p27^{Kip1}$, Doetsch and coworkers [79] showed that its loss does not affect the number of NPCs in the adult SVZ. Instead, the pool of transient amplifying cells increased, accompanied by a reduction in neuroblast number [79]. Thus, in the adult brain, $p27^{Kip1}$ appears essential for the transition from transit-amplifying cells to neuroblasts. Other studies have confirmed a role for $p27^{Kip1}$ in regulation of neurogenesis in the RMS, olfactory bulb (OB), and cerebellum of the postnatal mouse [84, 85]. In the developing cerebral cortex, $p27^{Kip1}$ is expressed strongly by the post-mitotic neurons of the CP, and in mature granule cells (GCs) of the cerebellum but only weakly in

Box 1 Neurogenic niche

Stem cell niche	References
It is defined as the microenvironment in which stem cells are found. There are two neurogenic niches in the adult brain, where under physiological conditions NPCs give rise to new neurons and macroglia: (1) the subventricular zone (SVZ), a germinal area situated within the walls of the lateral ventricles where NPCs generate cells that migrate into the olfactory bulb (OB); (2) the subgranular zone (SGZ) of the dentate gyrus (DG), where newly generated granule cells become integrated into the local network. These two areas have similar structural organization and tight association with the local vasculature	[29] and [30–32]
Adult progenitors	
A population of multipotent neural cells mainly present in the two specialized niches of the adult mammalian brain (SVZ and SGZ). They maintain neurogenesis throughout adult life. SVZ progenitors derive directly from radial glia (RG) and are called type-B NSCs (astrocyte-like GFAP-positive NSCs). Type-B NSCs are in intimate contact with all the other SVZ cell types, including the rapidly dividing transit-amplifying type-C cells and the lineage-committed migratory neuronal type-A cells. The SGZ contains type-B NSCs (astrocyte-like GFAP-positive NSCs) and GFAP-negative type-D cells. Thus, in both germinal regions of the mammalian postnatal brain, astrocyte-like cells represent the main pool of multipotent progenitors	[29, 33]

proliferating neuroblasts of the SVZ [86] and in granule cell precursors (GCPs) of the cerebellum [85]. The different phenotypes observed in $p27^{Kip1}$ and $p21^{Cip1/Waf1}$ KO animals suggest that they may function at different stages of neurogenesis. Alternatively, they may control cell fate through different mechanisms. In this respect, it is important to note that p27 regulates neuronal migration in the developing cortex in a cyclin-independent manner [87, 88]. Finally, a recent study by Gil-Perotin and coworkers [89] demonstrated a non-redundant role of $p27^{Kip1}$ and p53 in regulation of proliferation of SVZ NPCs and even an antagonistic effect on the generation of adult neuroblasts. Overall, these data suggest that the role of $p27^{Kip1}$ in regulation of neurogenesis may be more complex than previously thought.

Evidence in the literature suggests that p53 cooperates with the phosphatase and tension homolog (PTEN) in regulation of NPC expansion. In particular, proliferation of NPCs lacking p53 is further enhanced by concomitant PTEN inactivation [90]. Phosphatase and tension homolog is a major tumor suppressor antagonizing the oncogenic function of class I phosphoinositide 3-kinase (PI3K). Loss of PTEN results in increased PI3K signaling and augmented proliferation of NPCs [91]. Interestingly, although p53-deficient NPCs are still able to respond to differentiation cues, this property is completely abrogated when both p53 and PTEN are deleted in $GFAP^+$ astrocytic progenitors, thus leading to neoplastic transformation and tumor development [92, 93]. Mechanistically, increased c-Myc expression and activity in double-KO NPCs contributes to the tumorigenic phenotype [92, 93]. Inactivation of the neurofibromatosis gene 1 (NF1) also cooperates with p53 loss in promoting overproliferation, inhibition of differentiation, and ultimately glioma development (Fig. 2) [94]. Notably, a recent study by Zhu and colleagues [95] revealed that loss of p53 transcriptional function via deletion of part of its DNA binding domain induces pleiotropic accumulation of cooperative oncogenic alterations that in turn drive gliomagenesis (Fig. 2). It remains to be determined why a loss of p53-dependent transcription is a stronger tumorigenic signal than its complete genetic loss. One potential explanation would be that cytosolic, transcription-independent function of p53 could contribute to cancer development. Alternatively, the above-mentioned p53 mutant could bear gain-of-function activity and regulate transcription via DNA binding-independent mechanisms.

It is worth noting that accumulation of mutant p53 within the SVZ gives rise to uncontrolled proliferation of $Olig2^+$ transient-amplifying progenitor-like cells, thus suggesting that this subpopulation, rather than more truly stem cells, may drive brain cancer development (Fig. 2) [95]. A recent study using a mouse genetic mosaic system showed that indeed $Olig2^+$ *Nf1/p53* DKO progenitors act as cell of origin for the proneural subtype of glioma (Fig. 2) [96]. It is therefore possible that acquisition of an oligodendrocytic precursors fate is required for development of this glioma subtype. Overall, these data implicate the tumor suppressor p53 in the control of NPC expansion, differentiation, and transformation. One of the remaining outstanding questions is whether p53 could control neurogenesis also via mechanisms not related to its role in cell cycle regulation. In particular, it would be important to study the impact of p53 metabolic function on neural stem cell fate and transformation. This could extend beyond regulation of survival. In this respect, it is conceivable that p53-mediated regulation of metabolism and cellular redox could contribute to the control of self-renewal, which has been shown to be sensitive to changes in ROS levels.

However, p53 is not the whole story. In the late 1990s, two novel p53 family members were identified, termed respectively p63 [97, 98] and p73 [99]. The full-length isoforms of these proteins, called TAp63 and TAp73, respectively, function as pro-apoptotic proteins [98, 100–104], whereas naturally occurring N-terminal truncated variants of p63 (ΔNp63) and p73 (ΔNp73) act as pro-survival proteins, at least partially by antagonizing the full-length family members [105–109]. Could the TA

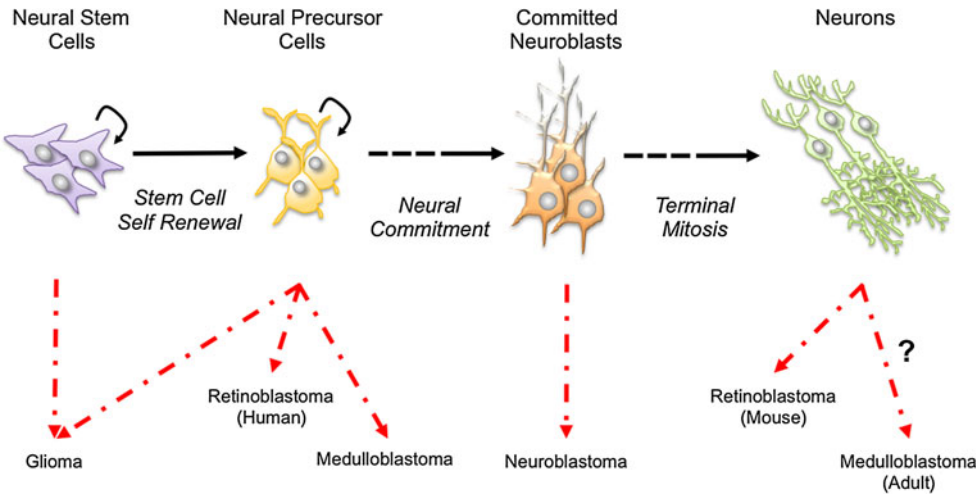

Fig. 2 Neurogenesis and transformation. Nervous system neoplasms are believed to originate from different stages of the neurogenesis process. The figure summarizes the current knowledge. Please refer to the text for more details information and references

isoforms bear tumor-suppressive properties like p53? Research in this area has been in part disappointing, as only a small percentage of human cancers display mutations in *p63* and *p73* [110]. However, Tyler Jack's laboratory proposed that p63 and p73, rather than being redundant, contribute to p53 activation and tumor suppressive function [111]. A subsequent study showed that dual inactivation of p63 and p73 results in increased tumor susceptibility, which is further enhanced upon inactivation of p53 [112]. Although p53 family members appear to act synergistically in controlling tumor suppression, their inactivation leads to distinct developmental phenotypes [106, 113, 114]. In this respect, mice lacking all p73 isoforms display severe defects in CNS development [114], including congenital hydrocephalus and hippocampal dysgenesis, but fail to show exencephalic outgrowth. Loss of p73 results in decreased NPC self-renewal during both embryonic and adult neurogenesis, thus suggesting that p73 is a novel regulator of NPC function [102, 115–117]. One of these studies [102] also demonstrates a correlation between the reduced proliferation capacity of $p73^{-/-}$ NPCs and expression levels of the transcription factor Sox2, an essential player in the maintenance of NSC self-renewal property. It is currently unclear what is the effect of p73 loss on p53 activation in NPCs. Finally, isoform-specific inactivation of either TA- or ΔN-p73 fails to fully recapitulate the CNS phenotypes observed in $p73^{-/-}$, thus suggesting a degree of redundancy between the two isoforms [118].

The third member of the family, p63, is a known regulator of self-renewal during development/homeostasis of epithelial tissues. With respect to its role in neurogenesis, p63 shorter isoform, ΔN-p63 has been implicated in regeneration of the olfactory bulb (OB) epithelium [119]. In particular, it regulates quiescence in horizontal basal (stem) cells (HBC), thus inhibiting their differentiation to fully mature olfactory neurons and/or other cell types [120]. These observations suggest that ΔN-p63 acts as a molecular switch controlling self-renewal and differentiation of OB stem cells. ΔN-p63 may also regulate survival in embryonic cortical NPCs by antagonizing p53 pro-apoptotic function [121]. Thus, tuning the balance between ΔN-p63 and p53 may dictate the survival of embryonic NPCs. However, a separate study failed to report abnormal development of either brain or spinal cord in $p63^{-/-}$ mouse embryos [117]. Further work is needed to address these discrepancies between the abovementioned studies and fully dissect the role and interplay of p53 family members in regulation of neurogenesis.

Rb and the pocket protein family

The retinoblastoma gene (Rb or Rb1) was the first tumor suppressor to be identified on the basis of its involvement in tumorigenesis [122–125]. In this respect, germline mutations in the *Rb* gene (chromosomal location 13q14) predispose to the ocular tumor retinoblastoma (Fig. 2), a rare childhood cancer of the retina that initiates during development [126–128]. Subsequent studies led to the demonstration that affected individuals develop retinal tumors as a consequence of the loss of the second *Rb* allele [125]. Additional evidence for a tumor suppressive role of the *Rb* gene came from the discovery of the absence of functional Rb in virtually all retinoblastoma tumors examined and its frequent inactivation in other human cancers, such as brain tumors, small-cell lung carcinoma, and osteosarcoma [129–131].

Studies examining the transformation mechanisms of DNA tumor viruses started to shed new light on the role of Rb as a major regulator of cell proliferation. Rb is a target of several viral oncoproteins, such as adenovirus E1A [129, 132], simian virus 40 (SV40) large T antigen (Tag) [133, 134], and the E7 proteins of human papillomavirus

(HPV-16) [135]. Importantly, mutation of the Rb binding region of any of these viral oncoproteins abrogated viral transformation [136]. Subsequent studies revealed a key role played by Rb in regulation of the G1/S transition (Fig. 1). In particular, Rb encodes a 110-kDa nuclear phosphoprotein (Rb) that is able to bind and inhibit members of the E2F transcription factor family, thus repressing transcription of genes important for S-phase entry and progression [128, 137, 138]. Retinoblastoma phosphorylation by CDKs relieves repression of E2F transcriptional activity, thus promoting cell cycle progression [139, 140]. Retinoblastoma can actively repress transcription [141] of E2F target genes through recruitment of histone deacetylase (HDAC), thus directly affecting their epigenetic status [141].

More recently, in addition to its role in regulating the G1-to-S-phase transition, Rb has been shown to mediate both accurateness and timing of DNA replication and to control proper segregation of chromosomes in mitosis [142–144]. Using gene targeting, Coschi and coworkers demonstrated that Rb facilitates chromosome condensation, independently to its role in DNA replication [142]. Further studies reported that Rb is also required for regulation of centromeres. In this respect, Rb mediates the proper condensation and orientation of centromeres on duplicated chromosomes and thus their attachment to the spindle [143]. When Rb function is compromised, the level of chromosome mis-segregation increases dramatically and becomes comparable to tumor cells [143]. Finally, mouse embryo fibroblasts (MEFs) lacking functional Rb and its related proteins p107 and p130 (see also below) have been shown to be more prone to chromosome breakage [144]. Together, these data suggest that the chromosome instability (CIN) resulting from the inability of Rb to maintain sister chromatid cohesion represents another important function of Rb as tumor suppressor [143, 145].

Insights into the importance of Rb as a regulator of cell cycle and differentiation in vivo and in particular in the central nervous system came from the analysis of *Rb* knockout animals. Rb is necessary for embryo development, as $Rb^{-/-}$ embryos die by embryonic day 15 (E15), exhibiting dramatic neural tube defects and skeletal muscle defects [146–149]. In particular, these abnormalities were accompanied by a partial failure of differentiation, increased apoptosis, as well as ectopic cell cycle [146–148, 150]. Further studies showed that part of the described neural phenotypes, including increased apoptosis, were due to a non-cell autonomous effect of *Rb* inactivation [151]. Conditional inactivation of *Rb* in the CNS confirmed the increased ectopic mitosis in the developing cortex. However, $Rb^{-/-}$ NPCs were able to survive and differentiate, thus leading to increased brain cellularity [152]. Conditional inactivation of *Rb* in the cerebellum and the retina revealed its key role in regulation of development also in these CNS structures [153, 154]. Finally, Rb was shown to regulate migration of newborn interneurons in the embryonic cortex in a cell-autonomous fashion, thus suggesting a role of Rb beyond cell cycle control [155]. Interestingly, this phenotype is observed also in $p27^{-/-}$ embryos, although it is still unclear whether [87] $p27^{Kip1}$ function in this context appears independent of cell cycle regulation [87]. It is presently unclear whether $p27^{Kip1}$ and Rb regulate neuronal migration through similar mechanisms.

The Rb protein is a member of a family of three closely related mammalian proteins that includes p107 (also known as retinoblastoma-like 1) and p130 (retinoblastoma-like 2). Together they are known as "pocket proteins" due to shared sequence homology in the pocket A/B domain, which mediates interactions with transcription factors and oncoproteins [138, 156–160]. Although the three "pocket protein" family members have been shown to bear distinct binding properties for the various E2Fs [161], overexpression experiments have indicated functional similarities in the regulation of the cell cycle as well as development [127, 162]. For example when overexpressed, all three family members cause G1 phase arrest via repression of E2F-mediated gene transcription. Moreover, all Rb proteins are phosphorylated by CDKs [127, 163]. $p130^{-/-}$ and $p107^{-/-}$ mice survive to adulthood without overt phenotypes, unlike those observed in Rb-deficient animals [164, 165]. The lack of severe phenotype in the $p107^{-/-}$ and $p130^{-/-}$ mice may be due to the compensatory activity of Rb. Vice versa, Rb loss was accompanied by compensatory upregulation of p107 [166, 167]. Additional evidence for redundancy within the pocket family came from the observation that inactivation of *Rb* only is not sufficient to cause retinoblastoma in mice. In contrast, loss of all three members is sufficient to transform retinal cells and lead to metastatic retinoblastoma [168]. As human retinoblastoma is predominantly associated with loss of *Rb* only, it is possible that mouse retinoblastoma pathogenesis differs from human retinoblastoma (Fig. 2). In this respect, human retinoblastoma is believed to originate from cone cell precursors (Fig. 2), whereas postmitotic neurons act as cell of origin of retinoblastoma in pocket family knockout mice [128, 169]. Interestingly, in human retinoblastoma, Rb deficiency is associated with Mdm2 amplification, which in turn impairs p53 activation downstream Rb loss, thus providing an additional oncogenic signal for full transformation [169]. Notably, *Rb* loss cooperates with *p53* loss in promoting glioma as well as medulloblastoma development in NPCs [170, 171], two tumors displaying genetic and/or functional inactivation of both tumor suppressive pathways in humans (Fig. 2). Finally, glioma can be induced by inactivation of pocket family members via overexpression of SV40 [172]. Overall, these studies suggest that redundancy among pocket family members act as

tumor suppressive barrier, unless the p53 pathway is inactivated. Mechanisms underlying this phenomenon remain unexplored.

Despite the observed redundancy, pocket family members may have specialized function. In this respect, expression of p107, unlikely Rb and p130, appears restricted to cycling NPCs in the SVZ, and is downregulated as NPCs differentiate into neurons [173]. p107 may regulate the decision of NPCs to exit the cell cycle and commit to neuronal fate [174]. Accordingly, p107-deficent cortices display increased proliferation associated with augmented *Hes1* expression and impaired neurogenesis [173, 174]. p107 may also be acting through the FGF growth factor signaling pathway. Like *Hes1*, the expression of *Fgf2* is increased in neural progenitor of p107-deficent mice to promote proliferation of NPCs [175].

Regulators of the Rb and p53 in the CNS

PML

Tumor suppressors appear to work in a complex network of functional interactions, which finely tune their activities in regulation of cell fate and transformation. Among them, the promyelocytic leukemia protein (PML) and the Polycomb group protein Bmi1 have been shown to play important roles in regulation of the p53 and Rb pathways.

The *PML* gene was originally identified at the t(15;17) chromosomal translocation breakpoint of acute promyelocytic leukemia (APL), a subtype of acute myeloid leukemia [176–181]. This translocation generates the oncogenic fusion gene PML/retinoic acid receptor-α (PML/RARα), which drives APL in humans and mice [177, 178, 182, 183]. Promyelocytic leukemia protein/retinoic acid receptor-α exerts its oncogenic effects in part by blocking normal PML function [184, 185]. Promyelocytic leukemia protein is localized within discrete nuclear structures referred to as PML-nuclear bodies (PML-NBs), of which it is the essential component [184, 186–188].

To date, PML has been shown to influence and/or regulate several cellular processes, including transcription, cell cycle and cellular senescence. In this respect, we will largely refer to the many comprehensive review articles by our laboratory and others. Several studies have implicated PML in the regulation of Rb and p53 through multiple mechanisms (Fig. 1) [184, 189–194].

Our more recent work has described a functional interaction between Rb and PML in NPCs during neocortex development. We proposed that PML-mediated regulation of Rb occurs at least in part via its direct targeting, along with the protein phosphatase 1 alpha (PP1α), to the PML-NBs, thus favoring Rb dephosphorylation [195]. As a result, loss of PML leads to Rb hyperphosphorylation and inactivation of G1–S checkpoint. In vivo, PML loss promotes increased cycling in cortical NPCs, thus leading to the expansion of the VZ. This effect appears restricted to a specific NPC subtype, radial glial cells (RGCs). Expansion of RGCs is accompanied by a reduced number of more committed intermediate progenitor cells (IPCs), thus suggesting that PML via Rb regulates transition from RGCs to IPCs. This is particularly interesting as little is known abut the molecular mechanisms regulating the generation of IPCs from RGCs. Promyelocytic leukemia protein-deficient embryos show smaller brains with a prominent reduction in neocortical wall thickness, although the overall layered structure of the cortex remains unaffected. Thus, PML plays an important role in regulation of cell fate and corticogenesis.

It remains to be investigated whether PML works solely through Rb or if other Rb family members are involved. In this respect, the phenotype of PML-deficient brains resembles the one observed in $p107^{-/-}$ mice [173, 174], thus suggesting that PML could affect the function of other pocket proteins. In addition, it is currently unclear whether PML regulates p53 in NPCs. Finally, our recent work has shown that the PML-interacting protein, DAXX, acts as chaperone for the histone variant H3.3 in neurons, thus regulating chromatin remodeling and transcription upon neuronal activation [196]. As both H3.3 and DAXX are found in PML-NBs in cycling cells [197], these new findings raise the exciting possibility that PML may control cell fate in neural stem cells via regulation of DAXX-mediated H3.3 loading [196]. Interestingly, PML also colocalizes with ATRX, which is part of the DAXX chaperone complex [198]. ATRX has been shown to regulate transition through mitosis in the developing brain. Mutations of ATRX cause the ATR-X syndrome, which is characterized by brain retardation and thalassemia. Furthermore, a number of disease-associated mutants of ATRX are impaired in their ability to localize to PML-NBs [199].

A number of recent studies have also highlighted a more general role of PML in the control of stem cell function. For instance, recent work from Pandolfi's group has implicated PML in the regulation of stem cell quiescence in the hematopoietic system [200]. As a result, PML loss affects self-renewal of hematopoietic stem cells (HSCs) potentially through its action on the mTOR pathway. Interestingly, the tumor suppressor p53 and its target gene p21 have recently been shown to control the cell fate in HSCs [201]. Another recent study has shown that PML loss skews the balance between different progenitor subtypes in the mammary gland and affects its development, although the underlying mechanisms have not been investigated [202].

The role of PML in the regulation of NPC expansion and differentiation could have obvious implications for cancer

research, as alterations of these processes can lead to the development of brain tumors [203]. In this respect, PML expression is substantially decreased in human cancers of multiple histologic origins, including a small subset of tumor medulloblastoma [204]. However, a comprehensive study of PML expression in brain cancer is still missing. PML inactivation is not sufficient to cause cancer [11, 95, 193], but it can promote tumor progression in the context of other oncogenic lesions, such as loss of PTEN. It is therefore conceivable that also in brain cancer PML downregulation could act in concert with loss of other tumor suppressor and/or oncogenic activation. One could hypothesize that decreased PML expression could affect tumors where the p53 or Rb pathways are not genetically inactivated. In this respect, a number of medulloblastomas and gliomas do not present genetic loss of either tumor suppressive pathway [205]. In these tumors, PML could contribute to p53 and/or Rb functional inactivation potentially in conjunction with other regulators, such as Mdm2 or G1/S cyclins.

Finally, modulation of PML expression could be used to modulate expansion and differentiation of neural stem cells for regenerative medicine-related applications. In this respect, regulation of PML stability can be achieved also via pharmacological means using arsenic trioxide, which targets PML for proteasomal degradation either directly or indirectly via increased PML oxidation [206, 207]. However, it is important to note that arsenic trioxide has rather pleiotropic effects in the cell, thus suggesting that PML could be only one of its targets.

The Polycomb group protein Bmi1

The embryonic and postnatal development of the CNS requires a fine balance between cell proliferation and differentiation. This is in part achieved by maintenance of an active or repressed state at discrete loci through epigenetic regulation. The family of Polycomb group (PcG) proteins regulate gene expression by forming large complexes at specific chromosomal sites called Polycomb response elements (PREs) and inducing chromatin remodeling. There are two main PcG complexes, Polycomb regulatory complex 1 and 2 (PRC1 and PRC2). The B cell-specific Moloney murine leukemia virus integration 1 (Bmi1) Polycomb ring finger oncogene is the first functional PcG member identified [208]. The B cell-specific Moloney murine leukemia virus integration 1 is part of PRC1, which mediates histone ubiquitylation. The activity of PRC1 is regulated by interaction with H3K27me3, which is catalyzed by PRC2. However, recent findings suggest that the PRC1 can also work in an H3K27me3-independent manner [209]. In mammals, the main targets of PcG proteins during embryogenesis are homeobox (Hox) genes, which regulate key developmental processes including self-renewal and maintenance of developmental potential of neural stem/progenitor cells [210]. Polycomb-group proteins generally act as repressors, but based on a recent study, they can also promote transcriptional activation of genes involved in metabolism through association with a specific RNA polymerase II variant [211].

Bmi1 is ubiquitously expressed in mammalian tissues, but higher levels are detected in thymus, heart, testis, embryonic stem cells (ES), and embryonic and postnatal neural stem cells [212, 213]. The first evidence of a possible role of Bmi1 in the CNS was revealed by the study of *Bmi1* knockout mice, which showed, in addition to hematopoietic and skeletal abnormalities, neurological symptoms manifested by an ataxic gait and sporadic seizures within a month after birth [213]. In this respect, histopathological analysis of the $Bmi1^{-/-}$ brain revealed an overall reduced size, in particular a reduced cellularity of the granular and molecular layer of the cerebellum [73]. Despite these changes in brain size, the overall brain architecture was not affected [73]. To gain insight into the molecular mechanism underlying this phenotype, Jacobs and colleagues [73] used primary mouse embryonic fibroblasts (MEFs) derived from $Bmi1^{-/-}$ embryos and found that expression of the tumor suppressors $p16^{Ink4a}$ and $p19^{Ink4d}$ ($p14^{Arf}$ in human), which are encoded by the *ink4a* locus [214], was markedly raised in Bmi1-deficient cells (Fig. 1). As discussed above, $p16^{Arf4a}$ directly inhibits the cyclin D1 and cyclin-dependent kinase 4/6 (Cdk4/6) complex, thus leading to Rb activation and inhibition of G1/S progression [215]. In contrast, $p19^{Ink4d}$ expression leads to p53-mediated cell cycle arrest and apoptosis [216, 217]. $p19^{Ink4d}$ attenuates mouse double minute 2 (Mdm2)-mediated degradation of p53, which then activates the transcription of several growth suppressive and apoptotic genes such as Bax, Puma, and another CDKi, $p21^{Waf1/Cip1}$ [216, 218]. Conversely, increased expression of Bmi1 leads to fibroblast immortalization and down-regulation of $p16^{Ink4a}$ and $p19^{Ink4d}$ [219]. *ink4a* loss dramatically reduced the neurological defects observed in Bmi1-deficient mice, indicating that *ink4a* was a critical in vivo target of Bmi1 [73]. The B cell-specific Moloney murine leukemia virus integration 1 also represses the expression of $p21^{Waf1/Cip1}$ through direct binding to its promoter [220, 221] or via cooperation with Forkhead box protein G1 (FoxG1; [222]—see also below). In agreement with its role downstream Shh [223, 224], Bmi1 is essential for cerebellar development and contributes to medulloblastoma genesis [223, 224] (see below). In conclusion, these in vitro and in vivo studies identify the CKIs $p16^{Ink4a}$, $p19^{Ink4d}$, and $p21^{Waf1/Cip1}$ as critical

downstream targets of the PcG protein Bmi1 for regulation of development and tumorigenesis.

Stem cells persist throughout life in numerous tissues including the central nervous system (CNS) [6, 225–227] and peripheral nervous system (PNS) [228]. Interestingly, reduction of self-renewal in Bmi1-deficient neural stem cells leads to their postnatal depletion via up-regulation of the $p16^{Ink4a}$ and $p19^{Ink4d}$ CKIs [212]. *Arf* deficiency, but not *Ink4a* deficiency, partially rescued cerebellum development, thus demonstrating regional differences in the sensitivity to loss of $p16^{Ink4a}$ or $p19^{Ink4d}$ [229].

Loss of Bmi1 in hematopoietic stem cells (HSCs) and thymocytes results in a marked increase of the intracellular levels of reactive oxygen species (ROS) and subsequent engagement of the DNA damage response pathway [230]. The increased levels of ROS occur through de-repression of targets genes (other than the Ink4a/Arf locus or p21) involved in ROS generation and via impaired mitochondrial function. Similarly, it has been shown that in Bmi1-deficient neurons increased $p19^{Ink4d}$/p53 levels and co-repressors at promoter regions of antioxidant genes results in a repressed chromatin state and antioxidant gene down-regulation, which in turn leads to increased ROS levels and cell death [231]. Interestingly, NPCs and HSCs seem to differ with respect of dependence on ROS levels. In this respect, HSCs appear to require low ROS to self-renew [232]. In contrast, NPCs seem to thrive in higher ROS levels [233]. It would be important to determine whether the Bmi1-mediated regulation of genes involved in redox control is as pronounced in NPCs as in HSCs. Interestingly, a context-specific role of Bmi1 has been reported in the nervous system. In particular, the dramatic increase in NPC self-renewal seen in CNS NPCs upon Bmi1 overexpression is not observed in spinal cord progenitors, which do not express FoxG1, thus suggesting that the Bmi1/FoxG1/p21 axis is critical for Bmi1 function [222]. In addition, one could hypothesize that Bmi1-mediated suppression of Ink4a/Arf locus is more important for postnatal NPCs as opposed to inhibition of $p21^{Waf1/Cip1}$ and/or cooperation with FoxG1 during development.

As mentioned above, Bmi1 can contribute to CNS cancer development. In addition to medulloblastoma [224], Bmi1 is highly expressed in human glioma [234, 235], where its copy numbers are increased [236]. In particular, Bmi1 accumulates in glioma stem cells and promotes their self-renewal [237]. While no studies have reported that Bmi1 overexpression is sufficient to induce tumor initiation in the CNS, Bmi1 genetic loss impairs Shh-driven medulloblastoma initiation [238]. Furthermore, Bmi1 downregulation in primary medulloblastoma [239] and glioma cells [240, 241] limits their tumorigenic capacity in vivo. Interestingly, Bmi1 appears to regulate glioma stem cell-induced tumorigenesis also in an Ink4a/Arf-independent manner, thus suggesting that other Bmi1 targets are important for glioma progression [240]. In this respect, the role of Bmi1 in regulation of ROS levels in glioma has not been investigated. Overall, these studies suggest that Bmi1 may contribute to tumor development, but it remains to be established why Bmi1 overexpression is not sufficient to promote transformation. One possibility is that higher levels of Bmi1 may activate tumor suppressive checkpoints, which can in turn lead to differentiation and/or death instead of self-renewal. Furthermore, there is an urgent need to produce genome-wide studies analyzing Bmi1 target genes in normal and neoplastic stem cells and their association with selected epigenetic traits. This fundamental work will shed light on the role of Bmi1 in normal development/tissue homeostasis and cancer pathogenesis in the CNS.

Conclusions

Several lines of evidence indicate that the p53 and Rb tumor suppressive pathways are key regulators of neural stem cell function. Importantly, their regulatory networks (Bmi1, PML, and others) have several points of intersection, thus further strengthening the concept that a complex integration of intracellular (and extracellular) cues is what dictates the final outcome, i.e., expansion, death, or differentiation. Among the many outstanding questions, we believe it will be crucial to determine the role of the p53 and Rb pathways and their regulatory networks at the different stages of neurogenesis. This could have implications for our understanding of the transformation process in the central nervous system. For instance, inactivation of a growth suppressive checkpoint could have completely different effects on self-renewal and differentiation in a stem cell versus a committed progenitor. Another important question is to define the effect of defective tumor suppressive control on genomic stability and its consequences on cell fate decisions, particularly in view of the differentiation-inducing effect of DNA damage in non-neural stem cells. Future research aimed at addressing these questions will have to rely more and more on an integrated approach to tackle the complexity of cell fate regulation in neural stem cells as well as other stem cell types.

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Glossary

Neural stem cells (NSCs)	Neural stem cells are the self-renewing, multi-potent stem cells of the nervous system. Neural stem cells have the potential to give rise to offspring cells that grow and differentiate in neurons and glia cells.
Transit amplifying cells	Transit amplifying cells are mitotic cells of the neural lineage with a fast dividing cell cycle that retain the ability to proliferate and to give rise to terminally differentiated cells but are not capable of indefinite self-renewal.
Neural precursor cells (NPCs)	Neural precursor cells (NPCs) general term to identify any neural stem or progenitor cells.
Note	Controversy about the exact definition remains and the concept is still evolving [1, 26–28].
Self-renewal	The process by which a stem cell divides asymmetrically or symmetrically over an extended period of time (for example, during the life-span of an animal) to generate one or two daughter stem cells that have a developmental potential similar to the mother cell. Self-renewal is used by neural stem cells to expand during development, within niche of the adult brain, and upon brain injury.
Quiescent cell	A cell whose cell cycle has been temporary arrested, although, strictly speaking, it might still be cycling but with a particular long cell cycle. *Note!* Adult neural stem cells can be quiescent.
Post-mitotic cells	A cell that is incapable of proliferation, such as a neuron, in which cell cycle is irreversibly blocked.

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