Neuronal cell cycle: the neuron itself and its circumstances

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Neurons are usually regarded as postmitotic cells that undergo apoptosis in response to cell cycle reactivation. Nevertheless, recent evidence indicates the existence of a defined developmental program that induces DNA replication in specific populations of neurons, which remain in a tetraploid state for the rest of their adult life. Similarly, *de novo* neuronal tetraploidization has also been described in the adult brain as an early hallmark of neurodegeneration. The aim of this review is to integrate these recent developments in the context of cell cycle regulation and apoptotic cell death in neurons. We conclude that a variety of mechanisms exists in neuronal cells for G1/S and G2/M checkpoint regulation. These mechanisms, which are connected with the apoptotic machinery, can be modulated by environmental signals and the neuronal phenotype itself, thus resulting in a variety of outcomes ranging from cell death at the G1/S checkpoint to full proliferation of differentiated neurons.

The Cell Cycle: A Rapid Overview

Mitosis represents a crucial event by which eukaryotic cells divide and equally segregate their genetic material into 2 daughter cells.[1,2] This process consists of 4 consecutive phases: prophase, when chromatin is condensed, nucleoli and nuclear membrane disappear, and the mitotic spindle is formed; metaphase, when chromosomes are arranged at the equatorial plane of the cell; anaphase, when chromatids separate toward the opposite sides of the mitotic spindle; and telophase, in which chromosomes decondense

into diffuse chromatin, the nuclear membrane becomes generated, 2 new nuclei are formed, and cytokinesis begins to take place. Once the daughter cells have been produced, they go through an interphase period subdivided in 3 different stages: G1, when the proteins responsible for DNA replication are synthesized; S phase, when nuclear DNA is replicated; and G2, when the proteins responsible for cell division are synthesized. Cells can also be found in G0 when they have withdrawn from the cell cycle, as happens with most differentiated cells.[1,2] As shown in **Figure 1**, the transitions between these stages are regulated by cyclins that bind to their specific Cdks, activating their kinase activity.[3] Cyclin D is synthesized at the beginning of G1, and it binds and activates Cdk4/6 when the cell leaves the quiescent state. Cdk4/6 phosphorylates Rb protein, inducing the release of the transcription factor E2F1, which in turn induces the synthesis of the proteins necessary for DNA replication.[4] G1/S progression is regulated by the association between cyclin E and Cdk2, which phosphorylates additional residues of Rb.[5] DNA synthesis is then driven by the association of cyclin A with Cdk2.[6] During late S-phase, the cyclin A/Cdk1 complex activates late replication origins and during late G2 phase, this complex initiates the condensation of chromosomes.[7-9] Finally, G2/M transition is regulated by the formation of the Cdk1/cyclin B complex.[1,3,10-15]

As shown in **Figure 1**, cell cycle progression can also be regulated by CKIs from the Ink and Cip/Kip families, which inhibit the activity of the Cdk/cyclin complexes. In this regard, the members of the Ink family (p15^{Ink4b}, p16^{Ink4a}, p18^{Ink4c}, and p19^{Ink4d}) regulate the quiescent state by their specific binding to Cdk4/6, thus preventing the interaction of the latter with cyclin D.[16] In contrast to the Ink family members, whose inhibitory capacity is restricted to a specific cell cycle stage, the members of the Cip/Kip family (p21^{Cip1}, p27^{Kip1}, and p57^{Kip2}) can bind and modulate the activity of specific complexes formed by Cdks and cyclins.[17] Interestingly, the interaction of p27^{Kip1} and p21^{Cip1} with cyclin D-dependent kinases relieves cyclin E/Cdk2 from Cip/Kip constraint, thereby facilitating cyclin E/Cdk2 activation later in G1 phase.[5]

Progression through the different phases of the cell cycle is regulated by checkpoints that ensure that the cell has completed a phase before entering the next one.[15] These checkpoints result
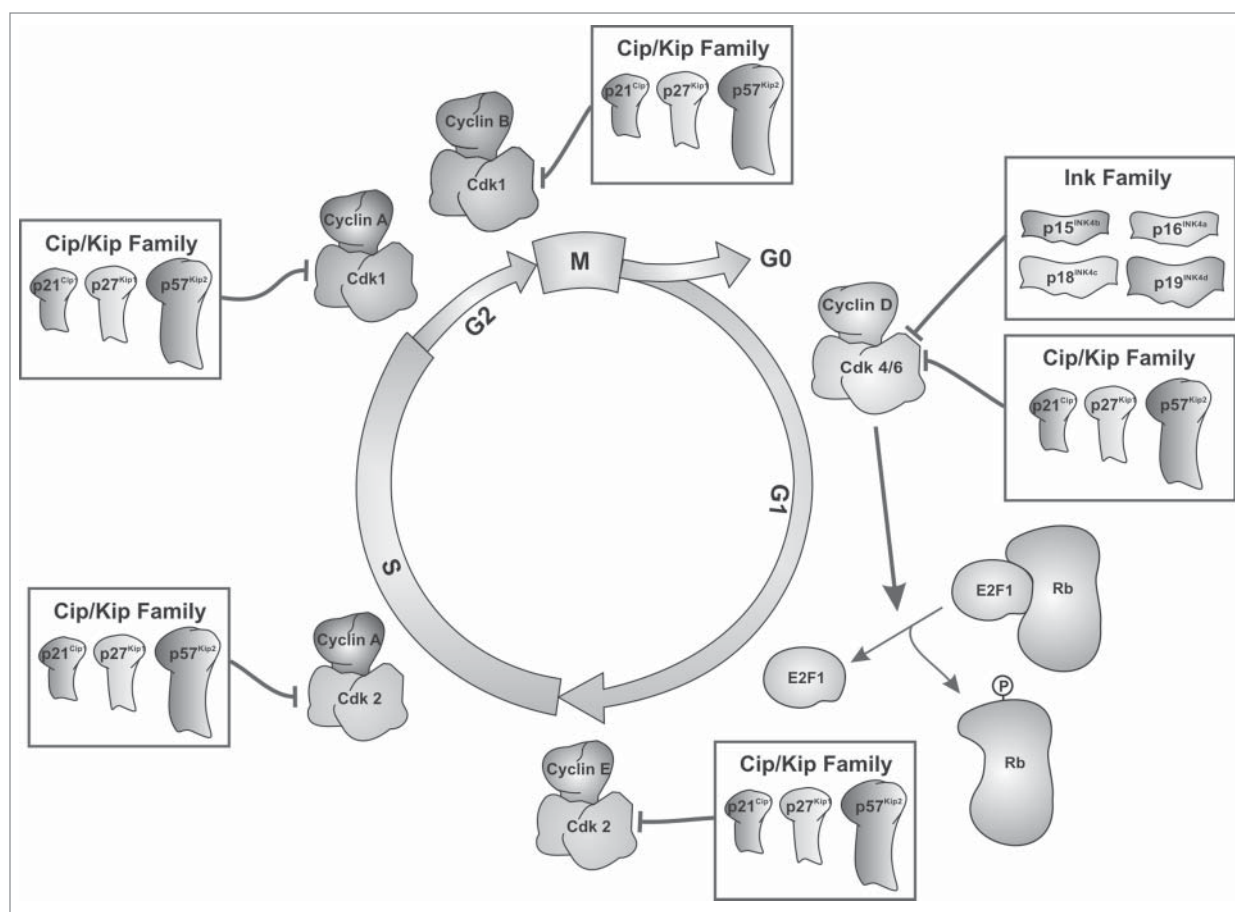
Figure 1. A scheme showing the canonical cell cycle and its main regulatory mechanisms.

from the activation of different signaling pathways leading to the inhibition of Cdk/cyclin complexes.[18] If a defect is detected, these checkpoints induce the blockade of cell cycle until it has been repaired, thus impeding its transmission to the resulting daughter cells or inducing apoptosis if the defect cannot be corrected.[12,19] Different kinds of checkpoints are distributed along the cell cycle, especially in the transitions between the different cell cycle stages.[1,2,15] Two different checkpoints regulate G1: the first one at the beginning of this phase, when the cell senses the accessibility of growth factors responsible for the suppression of the quiescent signaling, and the other one during late G1, when the cell checks the availability of nutrients and also if the cell has reached the appropriate size to undergo DNA replication.[20] The intra-S-phase checkpoint is activated by DNA damage produced during DNA synthesis or by unrepaired DNA damage that has not been detected by the G1/S checkpoint.[18] Before undergoing mitosis, the cell must verify that the DNA is not damaged to avoid transmission of mutations to the daughter cells. In both of the latter cases, the tumor suppressor gene p53 is activated if DNA has been damaged, blocking the cell cycle until the damage has been repaired or inducing apoptosis if this damage is unrepairable.

G2/M transition is the last step before mitosis, so it is tightly controlled to avoid that either incomplete DNA synthesis or aberrant distribution of chromosomes could eventually lead to cancer.[2,12] Therefore, this transition is subjected to a number of checkpoints to control that the previous steps have been correctly completed.[15,21] Although the detailed sequence of events that lead to the activation of G2/M transition is not fully understood, it includes the activatory phosphorylation of the Thr160/Thr161 motif of Cdk1, catalyzed by the Cdk-activating kinase complex.[22-26] In addition, Cdk1 is also subjected to inhibitory phosphorylation, catalyzed by both Wee1, which phosphorylates this kinase in Tyr15,[27-30] and Myt1, which phosphorylates Cdk1 in Thr14.[31] Both phosphorylation events can be reverted by the phosphatase Cdc25, thus fully activating the Cdk1 complex.[32,33] The regulation of the subcellular location of every protein and their regulators, as well as the absence or inactivation of the cyclin kinase inhibitors also plays a role in the activation of the Cdk1/Cyclin B complex.[34] Finally, other checkpoints monitor the correct position of the mitotic spindle, separation of the chromosomes and cell cycle exit.[1,2,15]

Cell Cycle in Neurons

Cell cycle re-entry in neurons and apoptosis

Unlike most cell types, neurons are believed to have permanently blocked their capacity to proliferate once they are

differentiated, being typically found in a quiescent state in the adult nervous system. However, a number of genes that encode for regulators of G1/S transition, including cyclin D1, Cdk4, Rb proteins, E2Fs, and CKIs, can be detected in different structures of the normal adult brain (see **Table 1**). Most of these transcripts are actually translated, as evidenced by the detection of the proteins they encode in normal adult neurons.[35-40] Traditionally, the presence of core cell cycle regulators in adult neurons has been explained as these molecules may fulfill differentiative functions, including neuronal migration, neuronal maturation, and synaptic plasticity.[41,42] Nevertheless, it remains plausible that, potentially, these proteins could also lead to cell cycle re-entry provided that specific conditions are met. In this regard, there are examples in which specific neuronal types, including sympathetic and cortical neurons, upregulate the expression of cell cycle markers and try to reactivate the cell cycle when subjected to acute insults such as neurotrophic factor deprivation, activity withdrawal, DNA damage, oxidative stress, and excitotoxicity. Under these conditions, they usually die at the G1/S checkpoint before any sign of DNA synthesis can be observed (for a review see refs. 43,44). This process, classically referred to as "abortive cell cycle re-entry," is characterized by upregulation of cyclin D-Cdk4/6 activity and deregulation of E2F transcription factors,[45-51] followed by cell death. In this regard, E2F1 can be a trigger of neuronal apoptosis,[52,53] and 2 proapoptotic signaling pathways have been shown to be activated by this transcription factor in cerebellar granule cells and cortical neurons. These pathways include the activation of Bax/caspase-3 in a p53-independent manner[54,55] and the induction of the Cdk1/FOXO1/Bad pathway.[56-58] In addition, deregulation of p130/E2F4, a repressive complex that maintains the postmitotic state of neurons, has also been shown to participate in the induction of neuronal apoptosis through the upregulation of B-myb and C-myb.[59,60] Overall, these observations indicate that a number of signaling pathways triggered by different environmental conditions can elicit cell cycle reactivation and cell death in specific neuronal phenotypes.

Cell cycle re-entry in neurons and tetraploidy

There are cases in which neuronal injury results in G1/S transition and DNA synthesis. Examples of this situation are cerebellar granule neurons subjected to excitotoxic stimuli[61] and cortical and hippocampal neurons subjected to hypoxia/reperfusion.[62] Although terminally differentiated neurons that replicate their DNA are typically fated to die,[63,64] this is not always the case,[65] and these neurons may remain alive with double amount of DNA content. For instance, sensory and sympathetic neurons are able to replicate their DNA without any apoptotic response,[66,67] and Rb-deficient brain neurons have been shown to undergo cell cycle re-entry and remain alive with 4C DNA content.[68] These observations are consistent with the capacity for DNA replication of a population of differentiating RGCs in the developing chick retina.[69] Evidence from our laboratory indicates that these newly formed neurons, defined by the expression of specific differentiation markers,[69] re-enter into the cell cycle during their migration to the ganglion cell layer in response to the activation of the receptor p75[NTR] by nerve growth factor, and then they remain with 4C DNA content during adulthood.[69] This process, which participates in the normal development of the nervous system, is not generalized. Instead, tetraploid neurons in the chick retina constitute a specific population of large RGCs that innervate defined layers of their target tissue.[69] Therefore, duplication of the DNA content in neurons during development constitutes a mechanism for neuronal diversification in vertebrates. As these neurons cannot proliferate it is not possible to determine the number of chromosomes they contain, therefore they are referred to as somatic tetraploid neurons in a broad sense. Heteroploidy in the retina does not seem to be exclusive of the RGCs. Indeed, a recent study suggests that other newly formed retinal neurons, constituting a subpopulation of horizontal cells, may also become tetraploid.[70] This observation fits with the increase in ploidy observed in horizontal cells from mice with retina-specific knockout of the *Rb1* gene.[71] Like in the chick, the mouse retina also contains tetraploid RGCs,[69] an observation consistent with the maintenance of proteins involved in cell cycle progression in

Table 1. Expression of cell cycle genes in the adult mouse brain. *In situ* hybridization raw expression values as defined by Allen Brain Atlas (http://mouse.brain-map.org). Average values above 1.00 from all described experiments are shown. CX: isocortex, OL: olfactory areas, HP: Hippocampal formation, CS: cortical subplate, ST: Striatum, PA: Pallidum, TH: Thalamus, HY: Hypothalamus, MB: Midbrain, PO: Pons, ME: Medulla, CB: Cerebellum.

Protein	Gene	CX	OL	HP	CS	ST	PA	TH	HY	MB	PO	ME	CB
E2f1	*E2f1*	20.14	18.88	19.72	23.47	21.05	19.75	19.45	20.57	18.45	15.03	14.42	18.15
E2f2	*E2f2*	—	—	1.02	1.58	—	—	—	—	—	—	—	—
E2f3	*E2f3*	6.13	3.53	3.91	8.04	5.35	3.36	2.34	3.28	2.43	2.18	2.34	4.30
E2f4	*E2f4*	3.87	4.08	4.28	4.47	2.48	2.04	2.32	1.59	2.14	2.10	2.50	2.30
E2f6	*E2f6*	12.42	8.23	12.95	14.91	11.35	9.61	10.59	8.09	9.65	10.04	10.48	6.77
E2f8	*E2f8*	1.37	1.15	1.21	1.16	—	—	—	—	—	—	—	—
Rb	*Rb1*	4.55	3.17	4.52	2.27	1.34	—	2.25	—	1.59	—	—	1.94
p130	*Rbl2*	1.70	2.00	2.26	—	—	—	—	—	1.61	1.03	1.36	3.09
Cdk4	*Cdk4*	2.24	2.86	2.72	2.52	2.65	2.19	1.97	2.14	1.65	1.47	1.54	—
Cyclin D1	*Ccnd1*	12.78	10.21	12.06	15.62	9.22	6.34	5.14	4.65	5.47	2.79	3.05	11.00
p18[Ink4c]	*Cdkn2c*	6.48	7.75	8.63	14.63	6.18	8.06	3.81	10.73	6.33	4.54	4.79	1.32
p27[Kip1]	*Cdkn1b*	1.57	1.84	1.36	—	1.11	—	1.25	—	1.48	1.57	2.16	5.55
Cdc25b	*Cdc25b*	1.07	—	1.33	—	—	—	—	—	—	—	—	—
Wee1	*Wee1*	5.44	2.53	4.03	2.94	2.05	1.93	2.43	1.37	2.87	2.47	2.14	1.76

differentiated mouse RGCs.[72] The presence of neuronal markers in 6–7% of the Ki67^{+} cells located in the proliferating layer of the mouse retina[72] suggests that, like in the chick, a population of migrating RGCs undergo cell cycle re-entry and tetraploidization in this species.

The mechanism used by p75[NTR] to induce cell cycle re-entry in newly formed chick RGCs is not dependent on the activity of Cdk4/6,[73,74] an observation consistent with the absence of cyclin D1 in a subpopulation of Ki67^{+}/BrdU^{+} cells located in the developing mouse retina,[72] as well as the lack of Rb in differentiating chick tetraploid neurons.[69] Therefore, cell cycle re-entry in these neurons seems to differ from the canonic mechanism used by quiescent cells when they reactivate the cell cycle, based on Cdk4/6-dependent phosphorylation of Rb and subsequent release of E2F1.[4] In newly formed RGCs, p75[NTR] induces a novel signaling pathway for cell cycle re-entry, mediated by p38[MAPK], which leads to the phosphorylation of E2F4 in a conserved Thr-containing motif.[73] The capacity of phospho-E2F4 to lead to cell cycle progression in differentiating retinal neurons contrasts with the role of E2F4 as a cell cycle repressor that participate in neuronal differentiation.[75] E2F1, which is also expressed in newly formed RGCs that become tetraploid,[69] might cooperate with phospho-E2F4 in the production of tetraploid RGCs.

The presence of tetraploid neurons in the vertebrate nervous system is not restricted to the neural retina. In fact, around 10% of human cortical neurons have DNA content higher than 2C, and 2% of them are tetraploid.[76] Tetraploid neurons have also been found in the mouse cerebral cortex, where most of them constitute a subpopulation of long-projection neurons,[77] as well as in different regions from the chick nervous system, including the optic lobes, cerebellum, spinal cord and dorsal root ganglia.[78] Cortical tetraploid neurons in the mouse are generated through a p75[NTR]-dependent mechanism that differs from that observed in the chick retina, since these neurons do actually express Rb as they migrate through the neuroepithelium to the differentiated layers.[77] Therefore, different mechanisms for regulating G1/S during neuronal tetraploidization seem to exist, depending on the neuronal phenotype.

The reason why the E2F1-dependent mechanisms that induce apoptosis when neurons trespass the G1/S checkpoint are not active in the examples described above remains unknown, but this may be related to their specific phenotype and/or environmental conditions they are subjected to.

Neuronal cell cycle re-entry in neurodegenerative diseases and other injuries of the nervous system

Cell cycle reactivation in adult neurons is an early hallmark of neurodegeneration[79] and CNS injury.[80-82] Although cell cycle reactivation has been classically linked to apoptosis (see above), cumulative evidence indicates that neurons can actively re-enter cell cycle, replicate its DNA, and survive as tetraploid neurons during the course of different neurodegenerative diseases. Nevertheless, these neurons seem to be much more vulnerable to die than diploid neurons, and therefore they may directly participate in the etiology of the disease.[83,84] In the next lines, we will summarize what is currently known about cell cycle re-entry and *de novo* tetraploidization of neurons in different diseases and injuries affecting the nervous system.

AD is likely the best documented example of a neurodegenerative disease where affected neurons may undergo DNA replication, as evidenced by Mcm2 phosporylation,[85] and *de novo* tetraploidization.[76,83,84,86-88] DNA replication in AD neurons is consistent with the presence in these cells of proliferation markers such as PCNA and the Ki-67 antigen, as well as a number of regulators of G1/S transition, including Cyclin D, Cdk4, hyperphosphorylated Rb, E2F1, and cyclin E.[89-94] Importantly, the presence of cell cycle events in the affected neurons is likely to be involved in the development of the disease. In this regard, transgenic mice expressing oncogenes in postmitotic cortical neurons to force these cells to re-enter the cell cycle show a phenotype that is reminiscent of AD, which includes intracellular tau hyperphosphorylation[64,94] and extracellular accumulation of β-amyloid peptide.[64] In contrast to the idea that cell cycle re-entry causes rapid neuronal death by apoptosis,[92] tetraploid neurons observed in the AD brain survive for years, as expected from the slow progression of this neurodegenerative condition. In this regard, the percentage of hyperploid neurons (i.e. those with a more than diploid content) is doubled in brains from AD patients as compared to that from non-affected individuals,[76] being these neurons much more susceptible to degenerate only at final stages of the disease.[83]

Not so much information is available about the mechanism that lead to cell cycle reactivation and *de novo*-generated tetraploidy in the diseased brain. In this regard, a recent study has reported that cell cycle re-entry in AD may be regulated by MiR-26b, a microRNA whose levels are elevated in relevant pathological areas from early stages of the disease.[95] MiR-26b induces cell cycle re-entry through an Rb1/E2F dependent mechanism that leads to upregulation of cyclin E1 and downregulation of p27[Kip1].[95] It is also worth to note that p75[NTR] becomes upregulated in response to stress in AD-affected neurons.[96] Moreover, p38[MAPK] has been linked with AD as well[97] and its active form can be detected in the brain of AD patients from the very early stages of the disease, becoming increased with age.[98,99] In addition, E2F4 can also be detected in the normal brain[100] (**Table 1**), suggesting that the p75[NTR]/p38[MAPK]/E2F4 pathway may also participate in this neurodegenerative process.

Cell cycle markers in neurons can also be found in neural tissue subjected to ischemia/hypoxia,[101-103] suggesting the existence of DNA replication in these cells. In this regard, Burns et al.[104] have demonstrated this notion since the vast majority of neurons that incorporate BrdU in response to ischemia/hypoxia do it once they are differentiated, indicating that they had not been generated by adult neurogenesis. Importantly, those neurons that incorporate BrdU remain alive 7 d after stroke.[104]

Cell cycle reactivation, evidenced by BrdU incorporation and FISH, has also been observed in the affected neurons of patients suffering PD.[105] In this regard, different cell cycle markers including pRb, E2F1 and PCNA, associated with DNA replication, can be detected in affected neurons from the PD brain.[106] Cell cycle markers, including E2F1, were also found by

immunohistochemistry in animal models of PD.[105,107] Furthermore, inhibition of Cdk4 by flavopiridol and removal of E2F1 have neuroprotective effects for PD as have been demonstrated by in vivo and in vitro studies.[105,108] These studies suggest that in PD, post-mitotic dopaminergic neurons can re-enter the cell cycle, cross the G1/S checkpoint, and then become blocked in G2/M transition. This suggests that tetraploid neurons could be generated during the course of PD, as occurs in AD.

G2/M transition in neurons and neuronal death

Although AD-affected neurons can re-enter into the cell cycle, mitosis is rarely observed in these cells.[109] Therefore, neurons that undergo S-phase block cell cycle progression at the G2/M transition, acquire a tetraploid condition, and survive for long time in the affected brain. This situation is reminiscent of what occurs in neurons becoming tetraploid during normal development, which block the cell cycle at G2/M, and die if they trespass this checkpoint.[69,74,110] This suggests that in neurodegenerative diseases where neurons become tetraploid, G2/M transition blockade likely plays a key role for the survival of the affected neurons.

Blockage of G2/M transition in newly formed, tetraploid neurons seems to be independent of DNA damage response,[111] the canonical cause for cell cycle arrest at this stage of the cell cycle.[18] Indeed, the mechanism that prevents G2/M transition in differentiating tetraploid RGCs is based on the capacity of BDNF to block this particular stage.[69,110] This process is crucial for the removal of tetraploid RGCs from the central retina.[69,112] Indeed, the use of BDNF blockers results in a significant increase of ectopic mitoses and cell death in the differentiating chick retina.[69] A similar mechanism is likely to occur in the developing mouse retina, whose neuroepithelium also contains ectopic mitoses in a small proportion of β3 tubulin-positive cells,[72] likely those fated to p75[NTR]-dependent death.[113] BDNF prevents G2/M transition in tetraploid neurons through its neurotrophic receptor TrkB, due to its capacity to decrease the expression of both cyclin B and Cdk1 in differentiating retinal neurons.[74,110] In addition, BDNF leads to a further decrease of Cdk1 activity triggered by the phosphorylation of this kinase in Tyr15,[110] thus blocking G2/M transition in tetraploid neurons.

In AD-affected neurons G2/M transition seems to be also blocked. Indeed, the Cdk1/cyclin B complex can be detected in neurofibrilary tangle-containing neurons.[89,92,114-117] However, this complex is not translocated to the nucleus, thus likely contributing to the arrest at the G2/M transition.[116] The mislocation of this complex likely facilitates the aberrant phosphorylation of proteins such as tau or other cytoskeletal proteins, which display many features of the mitotic phase and contribute to AD pathology.[118,119]

The molecular mechanism used to block G2/M transition in the tetraploid neurons that are generated during the course of neuropathological conditions could derive from the DNA damage response.[18] Alternatively, it could be reminiscent of the inactivation of Cdk1 induced by BDNF through TrkB.[110] In the absence of BDNF, differentiating tetraploid neurons try to divide and then they die.[74,110] A similar situation might occur in the AD brain. In AD, neurons show markers of deregulated G2/M transition. For instance, the Cdk1 activators Cdc25A and Cdc25B show higher activity in degenerating neurons in vivo,[120,121] while a lower activity of the Cdk1 inhibitor Wee1 can be observed in these neurons.[122] Moreover, pH3 phosphorylation, a marker of the G2/M transition, can be found in AD hippocampal neurons, but aberrantly localized in the cytoplasm, suggesting a mitotic catastrophe that leads to apoptosis.[123] This latter notion is consistent with the lack of chromatin condensation and spindle formation in AD-affected neurons, suggesting that mitosis cannot be completed.[115] BDNF increases neuronal survival in different neurodegenerative diseases.[124-126] Therefore, the decrease of both TrkB and BDNF, observed in the late stages of AD,[127] could participate in the induction of neuronal degeneration.[84]

Although the mechanisms leading to apoptosis in adult neurons that undergo G2/M transition are not fully understood, what is widely accepted is that Cdk1 is involved in different signaling pathways that lead to cell death. In this sense, Cdk1 can induce FOXO1 phosphorylation in Ser249, which disrupts its interaction with 14–3–3 proteins. This leads to its nuclear accumulation, where it triggers the expression of cell death genes in neurons.[58,128,129] Cdk1 also induces the phosphorylation and the activation of the pro-apoptotic protein Bad by inducing its phosphorylation in Ser128, which blocks the interaction of the Ser136-phosphorylated Bad, induced by growth factors, with 14–3–3 proteins.[57] Alternatively, apoptosis can be derived from unknown mechanisms induced by mitosis in postmitotic neurons.

Mitosis and proliferating neurons

Interestingly, mitosis in neurons does not necessarily represent a synonym of apoptosis. Indeed, there are examples of neurons capable of dividing without undergoing cell death. This is the case of retinal horizontal cells, which can proliferate in absence of Rb and p130 while maintaining its differentiated state.[130] Therefore, under certain circumstances horizontal cells, which have capacity to become tetraploid,[70] can undergo full cell cycle progression as other proliferating cells. This astonishing observation indicates that neurons can no longer be considered as pure postmitotic cells, and that they can potentially proliferate provided that specific conditions are met. It can therefore be concluded that it is only the particular phenotype and the environmental signals what determines whether neurons can overcome G1/S and G2/M checkpoints with or without dying.

Perspectives and Future Directions

Evidence described throughout this Review indicates that, under defined situations, neurons can activate the cell cycle and progress to the G1/S transition. If the proapoptotic signals associated with this stage are then prevented, they can undergo full DNA replication and remain in a G2-like state, or even divide without dying (**Fig. 2**). Several questions about the molecular mechanisms regulating this complex behavior remain to be responded, a constraint even stricter if one consider that most of
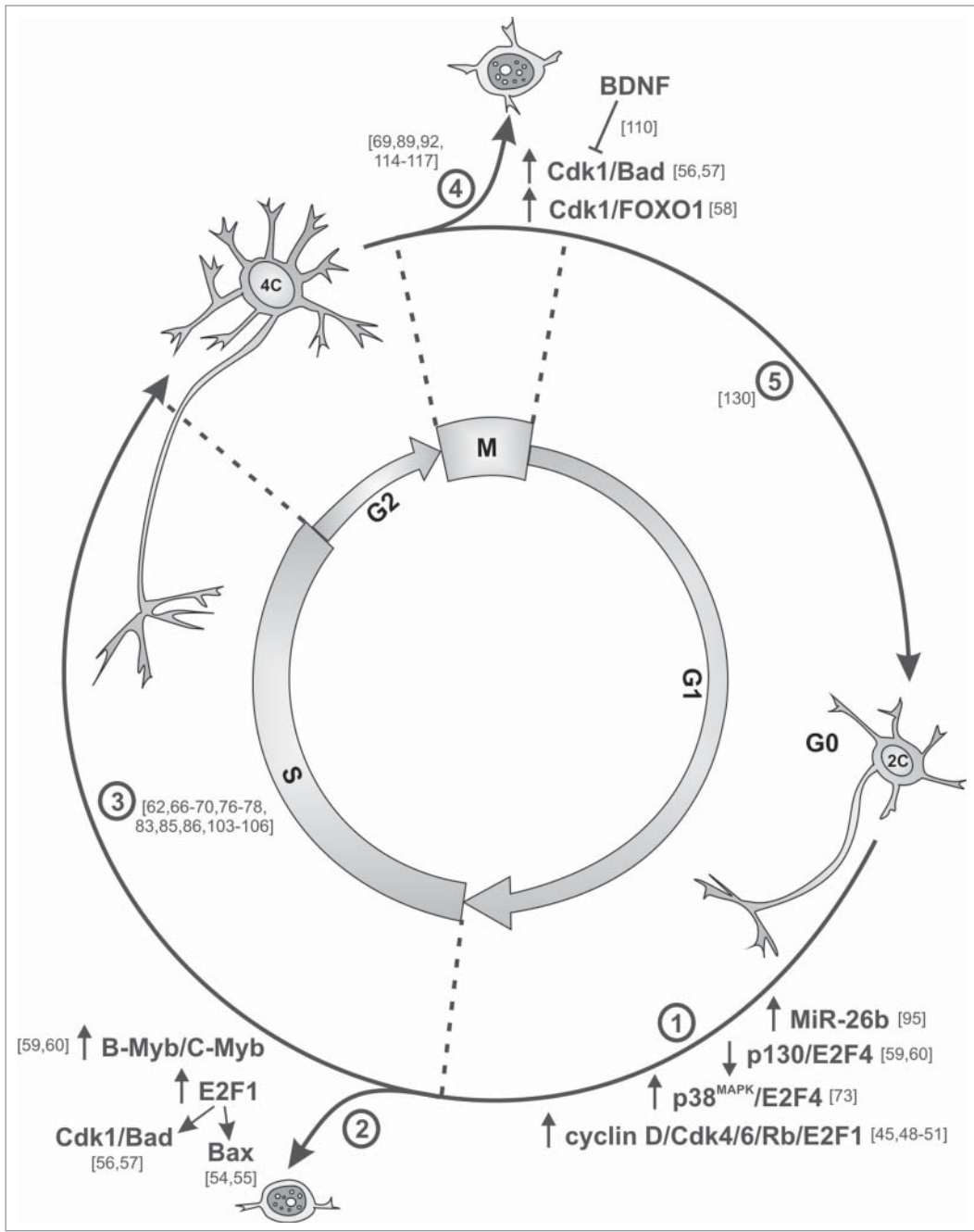
Figure 2. Scheme showing the evidence for cell cycle progression in neurons. Postmitotic neurons can reactivate the cell cycle (1) using the referred pathways. In many instances, this process is aborted at the G1/S transition and the neuron die through a number of pathways initiated by either E2F1 or Myb proteins (2). There are also examples of neurons that replicate their nuclear DNA and become tetraploid (3). These neurons die if they try to undergo mitosis, and evidence exists indicating that Cdk1 is involved in this process (4). In some instances, these neurons can divide and proliferate (5). References supporting the different steps are shown in brackets.

connection with the apoptotic machinery, as well as the molecular mechanisms leading to these cells to reactivate the cell cycle. This will facilitate our understanding of why some postmitotic neurons re-enter the cell cycle and survive as tetraploid neurons while other neurons die by apoptosis as soon as they reach the S-phase. The mechanism used by the adult brain to generate tetraploid neurons during the course of different neurodegenerative conditions, as well as the mechanism employed to prevent G2/M transition in these neurons during early stages of the disease has not yet been determined. Moreover, little is known about the proapoptotic pathways that are activated in the tetraploid neurons that are raised *de novo* in the diseased brain once they presumably cross the line defined by the G2/M checkpoint. Finally, nothing is known about the mechanism that prevents cell death in horizontal neurons that proliferate in the absence of Rb and p130 expression.[130] The answer to all these questions could help designing specific drugs for therapy against neurodegeneration. In this regard, different cell cycle modulators have been proposed as therapeutic strategies for neurodegenerative conditions such a stroke,[82,131] excito-

our current knowledge about cell cycle regulation comes from studies performed just in a few cell systems, including yeast, oocytes, fibroblasts, and cancer cell lines, and that little is known about the specific regulation of the cell cycle and its different checkpoints in most vertebrate tissues,[11] especially in neurons. Therefore, further studies are required to deeply understand the complexity of the G1/S and G2/M checkpoints in neurons, their

toxicity,[52] Alzheimer disease,[52] and brain trauma.[80] Preclinical experiments using cell cycle protein inhibitors such as flavopiridol, olomoucine or roscovitine demonstrated improved behavioral outcomes and increased neuronal survival in a series of CNS disease models such as AD,[79] PD,[108] and stroke.[82,131,132] We propose that modulation of G2/M transition can be a therapeutic approach to avoid neuronal apoptosis in advanced stages of

neurodegeneration, to prevent the death of *de novo*-generated tetraploid neurons.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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