Cell cycle reactivation in mature neurons: a link with brain plasticity, neuronal injury and neurodegenerative diseases?

Karina Hernández-Ortega¹, Ricardo Quiroz-Baez^{1,2}, Clorinda Arias¹

¹*Department of Genomic Medicine and Toxicology, Institute of Biomedical Research, National University of Mexico, Mexico City, Mexico*

²*Department of Basic Research, Research Division, Geriatrics Institute, National Institute of Health, Ministry of Health, Mexico City, Mexico*

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Abstract: Although the cell cycle machinery is essentially linked to cellular proliferation, recent findings suggest that neuronal cell death is frequently concurrent with the aberrant expression of cell cycle proteins in post-mitotic neurons. The present work reviews the evidence of cell cycle reentry and expression of cell cycle-associated proteins as a complex response of neurons to insults in the adult brain but also as a mechanism underlying brain plasticity. The basic aspects of cell cycle mechanisms, as well as the evidence showing cell cycle protein expression in the injured brain, are reviewed. The discussion includes recent experimental work attempting to establish a correlation between altered brain plasticity and neuronal death, and an analysis of recent evidence on how neural cell cycle dysregulation is related to neurodegenerative diseases especially the Alzheimer's disease. Understanding the mechanisms that control reexpression of proteins required for cell cycle progression which is involved in brain remodeling, may shed new light into the mechanisms involved in neuronal demise under diverse pathological circumstances. This would provide valuable clues about the possible therapeutic targets, leading to potential treatment of presently challenging neurodegenerative diseases.

Keywords: Alzheimer's disease; cell cycle; neurodegeneration; brain plasticity

1 Cell cycle machinery and neuronal function

Fine regulation of cell cycle is critical for a wide range of cellular processes such as proliferation, differentiation, apoptosis and cancer. It is now accepted that in mature neurons, many signaling pathways, transcriptional programs and an elaborate orchestration of cell cycle exit are required for a variety of brain functions. Quiescent neurons reside in the G0 phase until mitogenic signals activate the

cell cycle machinery. In general, the cell cycle involves 4 phases: first gap (G1), DNA synthesis (S), second gap (G2) and mitosis (M) phases. Additionally, cells that exit the cell cycle may remain in the quiescent G1 state for a long period. In fact, during the G1 gap, cells may face many metabolic, environmental or stress signals, which may influence their future fate: proliferation, differentiation or death.

Progression along the cell cycle phases is regulated by the sequential expression, activation and inhibition of cell cycle proteins including cyclins, cyclin-dependent kinases (Cdks), and cyclin-dependent kinase inhibitors (Cdkis)^[1,2]. By binding to cyclins, Cdks become catalytically competent. The transition between one cell cycle phase and another is

Corresponding author: Clorinda Arias
Tel: +52-55-56229215; Fax: +52-55-56229182
E-mail: carias@servidor.unam.mx
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regulated by check-points, better described as molecular switches which ensure that essential events of each phase are completed before the cell enters the next phase.

During the G1 stage, cells incorporate environmental signals that lead them to progress through the first restriction point, after which cells are committed to divide. G1 progression is promoted by D-type cyclins, which bind and activate Cdk4 and Cdk6. Phosphorylation of the retinoblastoma protein (Rb) by Cdk4, Cdk6 and cyclin E/Cdk2 along G1 progression inhibits its affinity to the E2F transcription factors. Derepressed E2F proteins can induce the expression of downstream target genes necessary for subsequent cell cycle progression, including those encoding cyclins D, E and A, DNA polymerase, Cell division control protein 6 (Cdc6), mini-chromosome maintenance (MCM) proteins and origin recognition complex (ORC) proteins^[3].

The activity of the cyclin E/Cdk2 complex allows the G1/S transition, and DNA duplication begins. In the early S phase, cyclin E is degraded concomitantly with the binding of Cdk2 to cyclin A. At the end of DNA duplication, cyclin A forms a complex with Cdk1 (or Cdc2) and leads the cell cycle to the G2 phase, during which cells verify the fidelity of DNA replication prior to mitosis. Once DNA duplication fidelity is confirmed, cells undergo mitosis, which implies division of the genomic material into 2 daughter cells. During the G2/M transition, cyclin A is degraded, and now Cdk1 is joined to cyclin B. The activity of cyclin B/Cdk1 is essential for progression along mitosis. Towards the end of the M phase, cyclin B is degraded and thus the cyclin B/Cdk1 complex is inactivated^[1].

In fact, although the sequential activation of different Cdks (Cdks4, 6, 2 and 1) in mammalian cell cycle progression is well established, a recent report indicates that Cdk1 is the only essential factor for cell cycle progression. Moreover, in mice embryos lacking Cdks2, 3, 4 and 6, Cdk1 can still bind to all cyclins and execute all the events necessary for cell division during organogenesis^[4].

The activity of the cyclin/Cdk complexes is inhibited by 2 families of proteins, the Kip/Cip inhibitors and the Inhibitors of Cdk4 (INK4) family. The members of the Kip/Cip family (p21, p27 and p57) mainly regulate the activity

of the G1 cyclin/Cdk complexes, and to a lesser extent, the activity of the cyclin B/Cdk1 complex. In contrast, the INK4 family (p16, p15, p19 and p18) specifically inhibits Cdk4 and Cdk6. The expression and content of cell cycle proteins are regulated by transcription, translation and degradation, specifically by ubiquitination in proteasomes^[1,5,6]. Progression along the cell cycle phases can be prevented by pharmacological inhibitors such as flavopiridol which inhibits all Cdks and arrests cells at the G1/S or G2/M transition, and roscovitine which displays selectivity toward Cdks1, 2, 5, 7 and 9, competing for the ATP-binding site^[7-9].

2 Significance of cell cycle marker expression in mature neurons

Numerous studies have provided evidence that cell cycle-associated mechanisms contribute to neuronal death in various pathological conditions including target deprivation^[10,11], DNA damage^[12], excitotoxicity^[13] and exposure to amyloid β protein (A β)^[14-16]. Furthermore, aberrant cell cycle reentry has been implicated in neuronal death during stroke and trauma^[17,18], epilepsy^[19], amyotrophic lateral sclerosis (ALS)^[20], Parkinson's disease (PD)^[21] and Alzheimer's disease (AD)^[22-30].

For a long time it was thought that neurons would cease going through the cell cycle process lastingly once they have differentiated. However, certain evidence has suggested the neuronal ability of reactivating the cell cycle machinery along cellular life^[10-30], although some studies have shown that in post-mitotic neurons, experimentally driving the cell cycle results in cell death rather than in cell proliferation^[10,12-15]. This late attempt to bring about cell cycle reentry has frequently been found to be associated with neuronal death. Rb, a tumor suppressor typically arresting the cell cycle at the G1 phase, is expressed during pathological neuronal death. Studies in transgenic Rb^{-/-} mice have shown that DNA synthesis is accompanied by neuronal apoptosis in the central nervous system (CNS) and the peripheral nervous system (PNS)^[31-33]. In fact, Rb is proposed as an essential gatekeeper of cell cycle reactivation and possibly neuronal apoptosis in the CNS^[34]. Cell cycle-related proteins are expressed in neurons exposed to

repairable DNA damage, implying a relationship between the cell cycle machinery and DNA repair processes in post-mitotic neurons^[35]. Terminally differentiated neurons are highly susceptible to oxidative DNA damage, and repair of double-strand breaks in neurons exposed to H₂O₂ is accompanied by phosphorylation of Rb protein by cyclin C-associated kinase, which induces the transition from G0 to G1 phase. In other words, cell cycle reentry represents the need of resting cells to activate DNA repair mechanisms^[36].

Although in most cases, cell cycle reactivation in mature neurons leads to apoptosis, differentiated neurons have recently been revealed to be capable of undergoing sustained cell division while maintaining typical features of mature neurons including synaptic contacts. This particular process seems to be involved in the origin of highly aggressive metastatic retinoblastoma in mice and is achieved in horizontal interneurons from a *Rb*^{-/-}; *p107*^{+/-}; *p130*^{-/-} background^[37].

Another attractive hypothesis concerning an alternative role of cell cycle machinery links cell cycle protein expression with brain plasticity. In this regard, formation and continuous reshaping of synapses are necessary events in neurons that have withdrawn from the cell cycle. Expression of cell cycle-related proteins in terminally differentiated neurons has been associated with physiological functions beyond cell cycle particularly in the control of microtubule-based mechanisms of neuroplasticity^[38]. Schmetsdorf *et al.*^[39] have demonstrated constitutive neuronal expression of Cdks 1, 2 and 4, as well as their activators (cyclins D, A, B, and E) and inhibitors within the neocortex of adult mice. More recently, the same research group has shown an association of cyclins and Cdks with the microtubule network. Cyclins D, E, A and B as well as Cdks1, 2 and 4 are associated with the axonal microtubule-associated protein tau, and these cyclin/Cdk complexes exhibit kinase activity towards tau^[38]. These findings suggest that the presence of cyclin complexes with CDKs in mature neurons may reflect their role in network stabilization and regulation of cytoskeleton dynamics during morphogenetic adaptation, and that tau, in addition, may act as an important phosphorylation target. Moreover, it has been

proposed that to maintain synaptic connections, neurons must permanently withdraw from the cell cycle to activate molecular mechanisms primarily developed to control proliferation, in order to influence synaptic plasticity^[40]. Thus, many external signals that influence concentrations of cyclins and their inhibitors are mitogenic signals involved in brain plasticity. The mitogenic-activated protein kinase (MAPK) signaling pathway plays a key role in promoting Cdk activation. The classical cascade involves the sequential activation of Ras, Raf-1, MEK and the extracellular-signal-regulated kinase (ERK)^[41]. ERK phosphorylates and stabilizes c-Myc, a transcription factor that induces the expression of cyclin D1 and suppresses expression of Cdkis^[42]. Over-expression of Ras in mature cortical pyramidal cells results in significant enlargement of pyramidal neuron size and increases in the complexity and spine density of dendritic trees leading to cortical expansion^[43]. These results suggest that the mitogenic Ras pathway not only controls proliferation in cycling cells but also regulates neuronal plasticity in differentiated neurons.

Cell cycle progression depends on a precise control of the oscillatory expression of cyclins and cyclin inhibitors. This temporal precision of protein expression also depends on the proteasomal machinery and its associated accessory and regulatory proteins involved in protein degradation. Two ubiquitin ligase complexes are responsible for the control of protein degradation during the cell cycle: the SCF family of ubiquitin ligases and the anaphase-promoting complex/cyclosome (APC/C)^[6,44]. Interestingly, APC/C^{Cdh1} and APC/C^{Cdc20} are recently implicated in axonal growth and dendrite morphogenesis, respectively. Since plasticity events in the CNS depend on *de novo* protein synthesis and protein degradation, APC/C complex is also shown to be involved in learning and memory function^[45]. Other pioneering studies have shown that *Cdh1* knock-in in cultured cerebellar granule neurons causes a specific increase of axonal growth without affecting the size of dendrites^[46].

Thus, novel and unusual biological functions of proteins in cell cycle regulation and progression in post-mitotic neurons have been described. These essential cell cycle

regulators participate at different developmental stages, including neuronal migration, axonal elongation, dendrite morphogenesis, synaptic maturation and adaptation of neuronal networks.

Long-term changes of synaptic strength in response to neuronal activity require active transcription and protein synthesis, and may be controlled by Cdh1, Cdc20, ORC, and the Polo-like kinases (PLKs) that participate in cell cycle progression^[3]. Moreover, Cdk5, a kinase highly active in post-mitotic neurons, seems to be involved in cell cycle suppression when it is located in nucleus^[47], and controls a variety of complex neuronal functions such as learning and memory-associated synaptic plasticity^[48].

Taken together, the present evidence indicates that the main molecular components that control the orderly progression along the cell cycle may participate not only in the dynamic organization of neuronal networks and DNA repair mechanisms of damaged neurons, but also in the erroneous conversion of plasticity and repair signals into pathological cell cycle reactivation processes and neuronal death.

3 Mechanism of cell death during cell cycle activation

As mature neurons do not divide, activation of a neuronal cell cycle seems to be abortive in many cases, with a final outcome being the initiation of apoptosis or of neuronal dysfunction. The association between an apoptotic stimulus and the reactivation of cell cycle machinery in mature neurons remains to be elucidated, although the activation of Cdk4, a Cdk involved in the G1 stage, seems to be essential for neuronal death^[49]. Recently, 3 different models of apoptotic neuronal death have shown the involvement of the transcriptional co-regulator Sertad 1 in Cdk4 activation to initiate the cascade that causes Rb hyperphosphorylation and of proapoptotic genes^[50]. On the other hand, cytoplasmic Cdk5 appears to retard neuronal death by a mechanism probably involving the anti-apoptotic protein Bcl2. Cdk5 may act in 2 ways depending on its location within neurons: in the nucleus it suppresses the cell cycle, and in the cytoplasm it transiently delays cell death^[51].

As has been mentioned, high expression levels of cell cycle Cdks, their cyclin partners and Cdkis have been detected in several neurodegenerative conditions. Furthermore, expression of these cell cycle proteins is not a direct consequence of death because the specific inhibition of Cdks can prevent death of cultured neurons induced by DNA-damaging agent exposure, trophic factor deprivation^[52] and ischemic damage *in vivo*^[53].

At the G1/S transition, for instance, E2F1 is able to initiate the apoptotic mechanism of cell death, directly activating the expression of the human tumor-suppressor protein p14^{ARF}, which binds to the Mouse double minute-2 (MDM2)–p53 complex and prevents p53 degradation, leading to cell cycle arrest or apoptosis^[54]. In another case, unrestrained E2F1 activity forces cell entry to the S phase and promotes apoptosis-upregulating death effectors such as the apoptotic protease-activating factor (Apaf)^[55] and several caspases^[56]. Contrariwise, a dominant negative form of E2F1 can block the activity deprivation-induced *cdc2* transcription and thus prevent apoptosis in cerebellar granule cells^[57].

Recently, the mitotic kinase Cdk1 has been implicated in neuronal apoptosis in postmitotic neurons through the phosphorylation of the forkhead transcription factor (FOXO1), a protein involved in cell death and DNA repair^[58]. Moreover, the proapoptotic protein Bcl-2 antagonist of cell death (BAD) has been identified as a direct target of Cdk1-mediated phosphorylation and activation^[59].

The aforesaid evidence supports the proposition that neuronal cell cycle reentry is also a component of a well-regulated response to stress signals, which may ultimately lead to neuronal death.

4 Activation of cell cycle regulators in apoptosis mediated by the lack of neuronal activity and/or deprivation of neurotrophic support

During normal brain development, the absence of trophic signals derived from either lack of neuronal activity or deprivation of neurotrophic support is a major cause of neuronal apoptosis. In cultured neurons, apoptosis induced by nerve growth factor (NGF) deprivation is accompanied

by changes in cyclin expression and Cdk activity^[60,61]. Besides, the use of cell cycle inhibitors promotes cell survival in sympathetic neurons deprived of serum and in PC12 cells lacking NGF but only before the G1/S transition point^[62].

The *staggerer* mouse is a useful model for the study of neuronal death induced by lack of trophic signals. The *staggerer* mutation consists of a deletion in *RORα* gene, which encodes the retinoic acid-related orphan receptor alpha. As a result, Purkinje cells do not develop completely, nor do they form synapses with cerebellar granule neuron axons^[63]. In consequence, the inferior olive population of cerebellar granule cells and neurons die, almost certainly resulting from the loss of target-dependent trophic signals from the Purkinje cells^[64]. Apoptosis of the inferior olive granule neurons is preceded by increased expression of cyclin D, the proliferating cell nuclear antigen (PCNA), and cell cycle markers of the G1 and S phases, respectively^[10].

In relation to activity deprivation, it is known that cerebellar granule neurons undergo apoptosis when they lack

membrane-depolarizing concentrations of KCl. In 2003, Konishi *et al.*^[57] defined a novel apoptotic mechanism whereby E2F1 selectively couples an activity deprivation-induced signal to Cdk1 transcription in the absence of stimulating DNA synthesis, thus culminating in Cdk1-mediated apoptosis of post-mitotic granule neurons in the developing cerebellum. These findings suggest that the lack of neuronal activity or deprivation of neurotrophic support leads to the activation of cell cycle regulators and thus culminates in apoptosis of post-mitotic neurons (Fig. 1).

5 Cell cycle reactivation in AD

AD is the most frequent dementia in the old and is characterized by a progressive cognitive deficit. The main neuropathological markers include synaptic loss and neuronal death, with extracellular accumulation of Aβ and intraneuronal presence of neurofibrillary tangles composed of a biochemically modified tau protein. Several causes have been implicated in the pathological mechanism of AD, including Aβ cascade, tau phosphorylation, oxidative

Fig. 1 A schematic description of neuronal cell cycle progression. During G1 phase, many metabolic, environmental or stress signals represent mitotic stimuli for mature neurons. At G1 phase, neurons can redifferentiate, progressing into the cell cycle or undergoing apoptosis. The G1/S arrest may be a state to develop age-related neurodegenerative pathology. If the neuronal cell cycle progresses to G2 phase, many components of the Alzheimer's-related pathology (Aβ and phosphorylated tau) may be expressed. Oxidative or mitotic insult may alter the outcome of cell cycle progression and induce neuronal apoptosis.

stress, and most recently, cell cycle reactivation. However, the initial events that precipitate neurodegeneration during AD are still under debate.

The implication of reactivation of the cell cycle in AD were initially obtained from the analysis of AD brain tissues, which showed expression and activation of cyclin B and Cdc2 in differentiated neurons^[24,25]. It has been proposed that Cdc2 activity contributes to the formation of amyloid plaques and neurofibrillary tangles. The cyclin B/Cdc2 complex derived from the AD brain can phosphorylate tau^[24], which is essential for neurofibrillary tangle formation. Moreover, it is known that amyloid precursor protein (APP) is phosphorylated *in vitro* by Cdc2, favoring the production of amyloid fragments^[65]. These data strongly support a direct link between cell cycle reactivation and the 2 major histopathological markers of AD.

In 1997, Nagy *et al.*^[23,66] described the expression of Ki-67 (a protein present in dividing cells along the G1, S and G2/M phases), cyclin E and cyclin B in vulnerable regions of AD brain, particularly in the hippocampus. Although cyclin E expression was also detected in some neurons from age-matched control subjects (suggesting that ectopic cell cycle markers occur even in neurons from healthy aged subjects), its increase was significantly accentuated in patients with AD. Moreover, cyclin B-reactive nuclei in neurons from AD were also positive for hyperphosphorylated tau in AD-related epitopes^[23]. Later, another study reported the presence of the cyclin D/Cdk4 complex, PCNA and cyclin B expression in regions with abundant neuronal loss such as the hippocampus and the entorhinal cortex (EC)^[25]. Thus, the lack of control of cell cycle regulators is postulated as a source of regionally specific neuronal death in AD.

Considering that A β seems to play an important role in AD, whether A β is involved in the abnormal cell cycle reentry observed in AD, and if the A β -induced oxidative stress and cell cycle activation are related to each other are interesting issues to be investigated. Recent evidence suggests that DNA oxidative damage induced by A β can lead to cell cycle reentry. Cultured neurons exposed to A β_{1-42} or its active fragment A β_{25-35} express G1 markers: phospho-Rb

and the complex Cdk4/6, which is accompanied by neuronal death^[15]. Another study reported that blocking the G₁/S transition by a cyclin D antisense or dominant-negative mutant of Cdk2 prevented A β -induced apoptosis^[14].

However, controversies exist on the significance of A β -induced cell cycle reactivation and whether cell cycle reactivation is a cause or a consequence of neuronal damage. A recent study in the triple transgenic mice model of AD reported no cell cycle reactivation induced by A β or tau pathology whereas in a model of neuronal death, cell cycle reactivation was linked to acute neuronal loss^[67]. On the other hand, intracerebroventricular injection of A β_{1-40} induced phospho-Rb and PCNA expression mediated by Cdk5 overactivation^[68].

Using the fluorescent *in situ* hybridization (FISH) technique, Yang *et al.*^[69] described that in brains of AD patients, hippocampal and basal forebrain neurons have 4 separate genetic loci replicated on 3 different chromosomes. They conclude that in AD neurons, mitosis is not initiated and cells remain aneuploid before they die, suggesting that this imbalance contributes to the neuronal loss in AD. This is the first report of DNA replication in a neurodegenerative condition. Recently, increased aneuploidy of chromosomes 17 and 21 has been also observed in buccal cells of AD patients, as well as in aged subjects over 64 years^[70].

Further evidence supports that neurons in AD reenter the cell cycle and progress through the S phase activating a specific component of the DNA replication machinery (MCM2 protein), producing cell cycle stasis with the consequent expression of AD markers and the subsequent neuronal degeneration^[71]. In AD, accumulating evidence indicates that although vulnerable neurons proceed as far as DNA replication and entry into the S phase can be demonstrated in dying neurons, progression through the M phase has never been reported. This incomplete process results usually in stasis, dysfunction and death, and has been called “abortosis”^[72]. Although the presence of binucleated neurons has been reported^[73], no cytokinesis has ever been described, consistent with the idea that susceptible neurons may be arrested at the G2/M transition before

they die. At this point, activated Cdk1 can phosphorylate tau^[24,74]. Therefore, abnormally increased level of phosphorylated tau may be explained in the perspective of an effort to modulate G2 neuronal architecture and prepare it for mitosis^[75]. In addition, Cdk1 can phosphorylate and activate the pro-apoptotic BAD protein, linking the cell cycle to the programmed cell death mechanisms^[59].

Interestingly, the brain regions with a high vulnerability to neuronal loss during AD and with marked re-expression of several cell cycle proteins are those with a high degree of plasticity, supporting a link between altered brain plasticity and neurodegeneration^[76].

Although significant progress has been made to understand the ethiopathological mechanisms of AD, there is still a lack of a comprehensive theory, and thus research has been conducted to unravel alternative hypotheses to gain insight into the mechanisms underlying neuronal differentiation and plasticity. As brain plasticity depends on continuous synaptic reshaping, plasticity molecules involved in this process are constantly secreted and may contribute to synaptic modifications and neuronal cell cycle reactivation^[77]. Loss of synaptic input reduces the activation of post-synaptic neurons which could be interpreted as a lack of trophic support, and drives neurons to exit from the G0 phase. This pathological cell cycle reactivation would be particularly frequent in circuits submitted to high rates of synaptic adjustments such as the perforant pathway that connects the EC with the dentate gyrus (DG) of the hippocampus, which is particularly vulnerable in AD.

However, the role of mitogenic stimulation may be interpreted in 2 facets: a transient lack of neuronal activity could turn on cell cycle and induce its progression to the G1 phase, while on the other hand, permanent mitogenic stimulation could induce cells to arrest the cell cycle in advanced phases such as G2 and S, and induce a hypermitogenic state in which AD markers (A β and phosphorylated tau) may appear and disseminate (Fig. 1).

Consistent with this hypothesis, our research demonstrated that after loss of synaptic contact between 2 interconnected areas, the EC and the DG, by excitotoxic dam-

age of the hippocampus, several cell cycle proteins of the G1, S and even G2 phases were found to be up-regulated in the EC. In addition, we described the progressive expression of 2 AD-related proteins, phospho-tau identified by PHF-1 and APP, which reached higher levels immediately after the increase in G1/S phase markers^[11]. Similarly, we found that after deafferentation of DG neurons by excitotoxic damage into the EC, numerous neurons expressed p-ERK 1/2, formerly to the gradual increases in cyclin D1 and cyclin B immunoreactivities in the DG (unpublished data). These findings suggest that the signals participating in the establishment of synaptic plasticity may also have a role in cell cycle reactivation in mature neurons (Fig. 2).

6 Cell cycle reactivation in other neurodegenerative conditions

Aberrant neuronal expression of numerous cell cycle markers is associated with many other pathological conditions and is inextricably linked to neuronal death. This is the reason why cell cycle reentry has been proposed to represent a general form by which post-mitotic neurons die during pathological aging. In fact, as neurons age, their ability to maintain the regulation of the G0 quiescent phase is compromised, probably due to inefficient energy metabolism, accumulative oxidative DNA damage and an imbalance in neurotrophic support. Mature neurons re-entering the cell cycle are neither able to advance to a new G0 quiescent state nor to revert to their earlier G0 state. Particularly in several stroke models, there is evidence that Cdks are activated and required to initiate the apoptotic cascade^[78].

Available data suggest that cell cycle-associated mechanisms are linked to the process of neurodegeneration in PD. Expression of cell cycle proteins such as phosphorylated Rb protein and E2F1, as well as DNA synthesis, has been observed in postmortem samples of PD patients^[21,79]. A mutation in the ubiquitin ligase Parkin is an identifiable cause of familial PD. Interestingly, Parkin deficiency increases the level of cyclin E and promotes apoptosis during kainate-mediated excitotoxicity in post-mitotic neurons^[80]. Other genes that underlie familial forms

Fig. 2 Expression of several markers of mitogenic pathway and cell cycle machinery after hippocampal deafferentation. Reduced activation of dentate gyrus (DG) neurons after damage to the entorhinal cortex (EC) could be interpreted as a lack of trophic support and drive neurons to exit from the G0 phase. Prior to the cell cycle reactivation, a rise in p-ERK 1/2 expression in a large number of granule neurons is observed. The progressive expression of cell cycle markers from G1 (cyclin D) and G2/M (cyclin B) phases reached higher levels immediately after the increase in p-ERK 1/2. Scale bar: 20 μ m (unpublished data).

of PD have also been linked to cancer or implicated in cell cycle regulation, such as ubiquitin C-terminal hydrolase (UCHL1) which presumably contributes to the degradation of Kip1, also known as cyclin-dependent kinase inhibitor 1 B (CDKN1B)^[81]. In a rat model of PD induced by 6-hydroxydopamine (6-OHDA), over-expression of Cdc2 was found in dopaminergic neurons of the substantia nigra^[82], and in PC12 cells, 6-OHDA-induced oxidative stress was accompanied by expression of several markers of cell cycle reactivation^[83]. In addition, in the 1-methyl-4-

phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD, the use of flavopiridol, a general Cdk inhibitor, or expression of a dominant-negative of Cdk5 can provide neuroprotection to some extent^[84].

Also worth mentioning is the finding of dysregulation of the cyclin system in postmortem human brain and spinal cord in ALS^[85]. More recently, using microarray analysis in single motor neuron in the SOD1 transgenic murine model of familial ALS, researchers found a significant increase in the expression of cyclins D2, E2, and I^[86]. Finally, over-

expression of cyclin D1 and the transcription factor E2F1 in striatal neurons has also been described in Huntington's disease^[87].

In order to determine the exact role of cell cycle reentry in neuronal dysfunction and death observed in many neurodegenerative diseases, Lee *et al.*^[88] developed a new transgenic mouse model in which forebrain neurons were induced to reenter the cell cycle by over-expression of the proto-oncogene *Myc* under the control of the *CAMKII* promoter. Research using this model has shown that the induction of ectopic cell cycle reentry (determined by the expression of PCNA, Ki-67 and cyclin D1, and BrdU incorporation) results in neuronal cell death, gliosis and cognitive deficit. These findings provide compelling evidence that dysregulation of cell cycle reentry results in neurodegeneration *in vivo*.

7 Conclusion

Expression of diverse cyclins, cyclin activators and inhibitors could constitute a final convergence point for all neurodegenerative diseases. This is based on the fact that several markers of the G1 phase and even the G2 and the S phases are present in adult neurons, in both human brain and in experimental models that exhibit neurodegeneration. Mitotic activation in mature neurons may be the result of extensive DNA damage, which ultimately triggers apoptotic mechanisms of cell death. Given that neurons are terminally differentiated, the role of cell cycle machinery activation along neuronal life is striking. Although the reexpression of cell cycle markers has been most frequently associated with extensive neuronal damage which ultimately leads to apoptosis, constitutive but subtle expression of Cdks and their respective cyclin activators and Cdkis has also been demonstrated under normal conditions. These facts support the idea that the transient expression of cell cycle proteins may be related to the mechanisms of neuroplasticity and/or the processes which maintain neuronal stability. In brain diseases associated with abnormal cell cycle reactivation, the mechanism of neuronal death may be linked to aberrant plasticity events. These findings provide new insights into therapeutic intervention to control neuronal

death that occurs in neurodegenerative conditions.

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成熟神经元的细胞周期再活化与大脑可塑性、神经元损伤和神经退行性疾病的关系

Karina Hernández-Ortega¹, Ricardo Quiroz-Baez^{1,2}, Clorinda Arias¹

¹ 墨西哥国立大学生物医学研究所, 基因组医学与环境毒理学研究室, 墨西哥城, 墨西哥

² 墨西哥国立卫生研究院老年医学研究所, 墨西哥城, 墨西哥

摘要: 细胞周期主要与细胞增殖有关。最近研究显示, 有丝分裂期后的神经元细胞死亡经常伴随有细胞周期调节蛋白的异常表达。细胞重新进入细胞周期以及细胞周期相关蛋白的表达是神经元对大脑损伤的应答, 也是大脑可塑性的一种机制。本文主要就此进行综述, 并对大脑可塑性变化与神经元死亡的联系, 以及神经元细胞周期失调与神经退行性疾病特别是阿尔茨海默病的关系进行了讨论。了解细胞周期进展过程中必需蛋白质的再表达, 将会帮助揭示不同病理环境下神经元凋亡的机制, 并提示神经退行性疾病的一些潜在治疗靶点。

关键词: 阿尔茨海默病; 细胞周期; 神经退行性病变; 大脑可塑性