THE NEURONAL CELL CYCLE AS A MECHANISM OF PATHOGENESIS IN ALZHEIMER'S DISEASE

NEVRONSKI CELIČNI CIKLUS KOT PATOGENETSKI DEJAVNIK PRI ALZHEMERJEVI BOLEZNI

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Abstract *Differentiated neurons display specific biochemical, physiological and morphological properties that apparently prevent them from further cell division. Nevertheless, expression of cell cycle modulators persists after neuronal differentiation and is upregulated under stress conditions, such as trophic factor deprivation, oxidative stress and the presence of DNA damaging agents. This apparent reactivation of the cell cycle has been postulated as a sine qua non for neuronal death in response to those stress conditions, particularly in Alzheimer's disease. However, the physiological and pathogenic implications of a putative neuronal cell cycle are far from clear. Here, we discuss the notion of the neuronal cell cycle as a mediator of cell death in Alzheimer's disease.*

Key words *Alzheimer's disease; cell cycle; neurodegeneration; apoptosis; catenin; presenilins*

Izvleček *Specifične biokemične, fiziološke in morfološke lastnosti diferenciranih nevronov preprečujejo njihove nadaljnje celične delitve. Vendar pa nevroni ohranijo izražanje modulatorjev celičnega ciklusa, ki se dodatno poveča ob prisotnosti škodljivih dejavnikov, kot so odtegnitev trofičnih faktorjev, oksidativni stres ali prisotnost snovi, ki poškodujejo DNK. Čeprav vloga reaktivacije celičnega ciklusa in njene fiziološke ter patološke posledice ostajajo v veliki meri nepojasnjene, je reaktivacija celičnega ciklusa verjetno nujen dogodek na poti do smrti nevrona pod vplivom škodljivih dejavnikov, kar še posebno drži za Alzheimerjevo bolezen. Namen podanega pregleda je osvetliti vlogo celičnega ciklusa kot posrednika celične smrti nevronov pri Alzheimerjevi bolezni.*

Ključne besede *Alzheimerjeva bolezen; cellični ciklus; nevrodegeneracija; apoptoza; katenin; presenilini*

Introduction

Once a neuron is born, it loses its capacity for cell division and differentiates, contributing uniquely to the plasticity of the basic wiring pattern that defines a neuronal system. The preservation of this pattern is necessary for the overall generation and storage of memories, as well as the acquisition of other higher brain skills. Differentiated neurons appear to be irreversibly post-mitotic, perhaps because a hypothetical cell division would result in cytoskeletal and synaptic disruption in order to prepare the cell for mitosis and cytokinesis, which would in turn impair neuronal connectivity and function. Hence, it is reasonable to think that, once a neuron differentiates, it resides out of the reach of cell division control. However, this notion was first questioned when some researchers surprisingly observed that neuronal programmed cell death was accompanied by the expression of cell cycle markers. Specifically, cyclins and cyclin-dependent kinases (CDKs), key components of the cell cycle machinery (see Figure 1) were found upregulated after exposure to severe conditions, such as oxidative stress and trophic factors deprivation.[1–8] Based on the premise that »neurons do not divide«, the notion that has emerged from this evidence is that activation of a neuronal cell cycle does exist but it is abortive, the final result being the initiation of apop-

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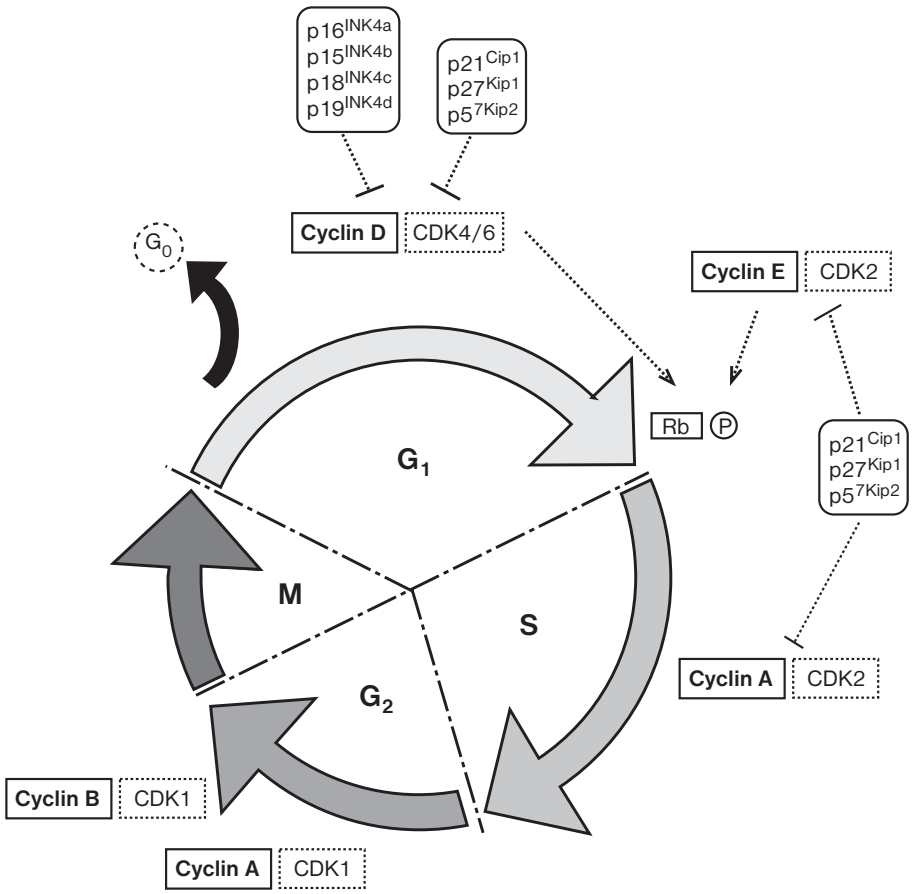

Figure 1. *Schematic representation of the eukaryotic cell cycle. See main text for details.*

tosis. As we discuss below, this aberrant phenotype has also been postulated as a mechanism of neuronal loss in neurodegenerative diseases, particularly Alzheimer's disease (AD).

Regulation of the cell cycle

The cell cycle of eukaryotic cells comprises four main successive phases: G1 phase (first gap), S phase (DNA synthesis), G2 phase (second gap) and M phase (mitosis) (Figure 1). Transition between the different phases and subsequent progression through the mitotic cycle is driven by a group of protein kinases whose activity is central to this process, the cyclin-dependent kinase (CDKs), and requires the binding of their activating partners cyclins, whose levels of expression varies throughout the cycle.

During G1 phase, mitogenic signals, such as extracellular growth factors or intercellular contact, trigger the activation of D-type cyclins that, jointly with CDK4 or CDK6, phosphorylate the retinoblastoma protein (Rb), inhibiting its affinity to bind the transcriptor factor E2F-1. E2F-1 is released and directs the transcription of specific genes that code for proteins required in the next stages of the cell cycle. In late G1, an increase in cyclin E-CDK2 activity ensures the G1/S transition by completing Rb phosphorylation and irreversibly committing cells to enter the division process. Throughout S phase, cyclin A-CDK2 phosphorylates various substrates allowing DNA replication. After completion of S phase, DNA replication ceases and cells enter the G2 phase of the cycle. CDK2 is then replaced by CDK1 that associates with cyclin A and regulates the phosphorylation of proteins specific to the G2 and M phases of the cell cycle together with cyclin B-CDK1, that appears in late G2 and triggers the G2/M transition. Cyclin A is degraded and the system is reset, re-establishing the requirement for mitogenic cues to induce D-type cyclins for the next cycle. In M phase, cells physically divide originating two separate daughter cells.[9]

CDK activity is regulated through posttranslational modifications and subcellular translocations of specific CDK inhibitors (CDKIs), which are organized in two families, INK4 and Cip/Kip. The INK4 (inhibitors of cyclin D-dependent kinases) consists of four members: $p16^{INK4a}$, $p15^{INK4b}$, $p18^{INK4c}$ and $p19^{INK4d}$, and the Cip/Kip family (inhibitors of cyclin D-, cyclin E-, and cyclin A-dependent kinases) comprises $p21^{Cip1}$, $p27^{Kip1}$ and $p57^{Kip2}$.

Two important checkpoints (G1/S and G2/M) coordinate CDKs activity and control the order and timing of cell-cycle transitions ensuring that DNA replication and chromosome segregation are completed correctly before allowing further progress through the cycle. The checkpoints allow alternative decisions between progression, growth arrest or induction of apoptosis. (See[10] for a detailed review addressing the regulation of the cell cycle in proliferating cells)

Differentiated neurons express cell cycle proteins

Every story has a beginning. For a functional neuron it is termed neurogenesis, and takes place at two germinal compartments that line the lateral ventricles – the ventricular zone (VZ) and the subventricular zone (SVZ). Most neurons are originated prenatally through a process of migration to shape a complex pattern of layers. The deep layers are formed from earlier-born neurons originated in the VZ, while later-generated neurons from the SVZ occupy higher layers.[11] The journey is meant to cease proliferation and start neuronal differentiation. However, although terminally dif-

ferentiated neurons seem to irreversibly withdraw from division, expression of cell cycle proteins is not completely silenced. Thus, cytoplasmic cyclin D1 was detected in mature neurons associated to the CDKIs $p21^{Cip1}$ and $p27^{Kip1}$, suggesting an impairment of its nuclear transport and a possible role in cell cycle withdrawal.[12–14] Indeed, cyclin D1 is downregulated,[15] but also becomes predominantly cytoplasmic, in neuronal progenitor cells undergoing terminal differentiation.[16] Similarly, cyclin E expression was identified in the cytoplasm of postmitotic neurons.[17, 18] More recently, Thomas Arendt's lab reported that, within the neocortex of the adult mouse, there is constitutive expression of cyclins D, E, A and B; of CDKs 4, 2 and 1; and of their inhibitors $p16^{INK4a}$, $p15^{INK4b}$, $p18^{INK4c}$, $p19^{INK4d}$, $p21^{Cip1}$, $p27^{Kip1}$ and $p57^{Kip2}$.[19] Furthermore, CDKs were found to be properly complexed to cyclins and exhibit kinase activity.

These findings have led to speculate that, in the absence of detectable neuronal cell division, there may be additional, cell cycle independent roles for cell cycle regulators in adult neurons. Indeed, there is evidence to suggest that cyclins and CDKs may participate in synaptic plasticity[20, 21] and neuronal differentiation.[22, 23] Similarly, CDH1 and APC (anaphase-promoting complex), which are found ubiquitously expressed in the nuclei of terminally differentiated neurons,[24] and form a complex involved in cellular division at the end of mitosis and G1 through cyclin B degradation, also appear to play a role in regulating axonal growth and patterning in the developing brain.[25] Furthermore, CDK5, a cyclin-dependent kinase whose exact role in the cell cycle, if any, still remains elusive, is highly active in postmitotic neurons and is involved in the coordination of complex neuronal properties including synaptic plasticity, learning and memory (reviewed in[26]).

Thus, the presence of cell division mediators in differentiated neurons where the cell cycle is absent is well documented, and it does not appear to be the consequence of abnormal regulatory events. Rather, it appears as if at least some cell cycle proteins have adapted to life in a non-dividing neuron by taking up additional, cell cycle-independent roles that are presumably crucial to neuronal function. The use of mouse conditional knockout models of these proteins should help us to unveil both the identity and importance of these putative functions.

Cell cycle abnormalities in differentiated neurons

There is a substantial body of evidence pointing to a role for neuronal cell cycle proteins in the modulation of stress-induced apoptosis through a mechanism involving the initiation of a cell cycle. For example, rat cerebellar granule neurons plated in culture medium without trophic factors, such as brain-derived neurotrophic factor (BDNF), undergo apoptosis but also present up-regulated expression of both mRNA and protein levels of cyclin D1. Immunostaining confirmed cyclin D1 immunoreactivity prior to cell shrinkage and nuclear condensation. Furthermore, blocking the cell cycle with the CDKs inhibitors ciclopirox, mimosine and olomoucine was sufficient to suppress immunoreactivity and, more importantly, cell death.[6] Herrup et al. showed that two mouse neurological mutants, staggerer (sg/sg) and lurcher (+/Lc), that model the absence of trophic support in the brain, present significant numbers of cerebellar granule cells and inferior olive neurons degenerating after elevation of Cyclin D and proliferating cell nuclear antigen (PCNA) levels and bromodeoxyuridine (BrdU) incorporation.[1] RNA alphavirus Sindbis-driven expression of $p16^{INK4a}$, $p21^{Cip1}$ and $p27^{Kip1}$, and of dominant negative forms of CDK4 and CDK6, protected rat primary neuronal cultures from apoptosis evoked by withdrawal of nerve growth factor (NGF)[2] and neuronal death as a result of DNA-damaging agents treatment, such as camptothecin, AraC and UV radiation.[3] The CDK inhibitors flavopiridol and olomoucine also protected the neurons from these conditions, suggesting that these cell cycle elements might mediate death signalling as a result of DNA-damaging environments.[4] Kruman et al. hypothesized that cell cycle reentry is a critical component of the DNA damage response in postmitotic neurons. Suppression of ataxia telangiectasia mutated (ATM), a component of DNA damage-induced checkpoint, by caffeine and wortmannin, attenuated both cell cycle reentry and apoptosis triggered by the genotoxic compounds etoposide, methotrexate, and homocysteine.[7]

Oxidative stress-related cell death has also been associated with apparent cell cycle induction in postmitotic neurons. Induction of cyclin B prior to the commitment of neurons to both dopamine- and peroxide-triggered apoptosis was reported in primary cultures of post-mitotic sympathetic neurons. Both neuronal death and rise in cyclin B were inhibited by antioxidant treatment.[5]

In summary, the evidence available to us suggests that exposure of post-mitotic neurons to a wide range of stress stimuli triggers the expression of cell cycle proteins as part of a well regulated programmed cell death response. The most widely accepted scenario is that, in response to stress signals, neurons can be driven into the cell cycle but their array of cell cycle proteins may not suffice to allow for its completion, leading to a situation in which the cell cannot reverse course or complete division, rendering it non-functional and ready to trigger a programmed cell death response. In other words, neurons may have learned to translate stress signals into an irreversibly damaging incomplete cell cycle from which the cell has no choice but to trigger apoptosis.

Additional support for this notion is provided by the demonstration of a direct causality link between overexpression of cell cycle mediators and neuronal death. Kranenburg et al. showed that artificial elevation of cyclin D1 was sufficient to induce apoptosis and could be inhibited by the CDKI $p16^{INK4}$.[27] More recently, McShea et al. used adenoviral-mediated expression of c-myc and mutationally active ras oncogenes to force non-dividing cortical neurons into the cell cycle leading to their death.[28] Transgenic mouse mo-

dels characterized by conditional expression of the simian virus 40 T antigen oncogene in postmitotic neurons clearly presented a neurodegenerative phenotype, consequence of forced cell cycle activation.[29]

Nevertheless, even if cell cycle activation is a *sine qua non* for apoptosis in neurons, we still do not know whether the low constitutive levels of cell cycle proteins in neurons may exist to facilitate a fast response to stress or their presence simply reflects their role in unrelated functions.

Loss of neuronal cell cycle control in AD

If exposure to stress may trigger an abortive cell cycle in neurons, it is reasonable to ask whether such mechanism may exist in the AD brain, which is exposed to a wide range of stress stimuli. Substantial, although mostly descriptive, evidence suggests that this is indeed the case. Cyclins, CDKs and other cell cycle proteins are expressed in the AD brain.[30–34] In addition, Ranganathan et al. reported high levels of hyperphosphorylated Rb and observed altered subcellular distribution of E2F-1 to the cytoplasm[35] in brain and spinal cord tissues from Alzheimer's disease (AD). In another study, phosphorylated histone H3, a key component involved in chromosome compaction during cell division, was found increased in the cytoplasm of hippocampal neurons in AD, rather than within the nucleus as in actively dividing cells.[36] Cdk7, an activator of major cyclin-CDK complexes, constantly expressed during the cell cycle and indispensable for cell cycle progression, is also upregulated in susceptible hippocampal neurons of AD patients.[37]

Further experiments from the Herrup's lab went further in their approach to the study of the neuronal cell cycle and, using fluorescent in situ hybridization, demonstrated that a significant fraction of the hippocampal pyramidal and basal forebrain neurons in AD have fully or partially replicated four separate genetic loci on three different chromosomes.[38] Mosch et al.[39] also quantified the DNA amount of identified cortical neurons in AD and reported a population of cyclin B1-positive tetraploid neurons that had entirely passed through a functional interphase with a complete DNA replication. These experiments are particularly important because, unlike evidence showing the presence of cell cycle markers in neurons, which could be dismissed as epiphenomena of no physiological relevance, they demonstrate that the DNA replication machinery is functional and capable of completing S phase in post-mitotic neurons.

Interestingly, CDK inhibitors $p16^{INK4a}$, $p15^{INK4b}$, $p18^{INK4c}$ and $p19^{INK4d}$ have also been found abnormally expressed in the temporal cortex and in pyramidal neurons of the hippocampus of AD patients.[40–42] An increase in the cytoplasmic levels of $p27^{Kip1}$ was also identified in vulnerable neurons from individuals with histopathologically confirmed AD.[43] The significance of these findings is not immediately obvious. One could argue that expression of these inhibitors occurs as a defence mechanism against the untimely activation of cell cycle initiators. However, that would run counterintuitive to the notion that initiation of an abortive cell cycle is an adaptive response to stress. Clearly, much of the nature of cell cycle events in neurons, whether in response to stress situations or in basal conditions, is far from being understood.

Interestingly, although DNA replication and entry into S phase can be demonstrated to occur in dying neurons, progression through M phase has never been reported. No condensed chromosomes, formation of a mitotic spindle-like structure or cytokinesis have ever been reported, consistent with the idea that susceptible neurons may be arrested at the G2/M transition before they die. Therefore, activation of CDK1 at G2 might be a rate-limiting step before neurons undergo apoptosis. Indeed, activated CDK1 can phosphorylate and activate the pro-apoptotic BAD protein,[44] thus providing a direct link between the cell cycle apparatus and the cell death machinery in neurons. It is also reasonable to suggest that neuronal apoptosis at the G2 stage may simply be the result of permanent loss of ability to undergo chromosome segregation and cytokinesis due to a highly specialized cytoskeleton. In other words, cytoskeletal commitment to the plasticity of neuronal shape may come at the expense of its inability to dismantle dendrite and axonal structures to commit to mitotic spindle formation and cytokinesis. Indeed, the microtubule associated protein tau, which is phosphorylated during this phase of the cell cycle in a mitotic-competent cell, has also been consistently reported to be abnormally phosphorylated in AD and colocalizes with cell cycle regulators.[29, 30, 43, 45–47] Moreover, tau can be phosphorylated by CDK1[48] and CDK1-like protein.[49–50] Therefore, abnormally increased levels of tau phosphorylation could be explained in the context of an unsuccessful attempt to modulate G2 neuronal architecture and prepare it for mitosis, leading to programmed cell death.

Mechanisms of neuronal cell cycle reentry. Lessons from familial AD

Taken together, the available evidence pointing to a role for an abortive cell cycle in neurodegeneration in AD is reasonably strong. Nevertheless, the question remains: what mechanisms do neurons use to enter the cell cycle in the first place in response to a stress signal? If this is an adaptive response, there must be a well-defined molecular pathway that triggers an entry into an apoptotic cell cycle. Although nothing is known in this respect, some clues can be obtained from studies of familial AD (FAD) cases which, perhaps not surprisingly, also display cell cycle abnormalities.[51–53]

Mutations in the genes for amyloid precursor protein (APP) and presenilins (PS1, PS2) associated to FAD lead in all cases to aberrant production of Aβ peptides,[54] which in turn exacerbate cycle-related neuronal death.[55–57] In addition, increased Rb phosphorylation and E2F1 levels are measurable in areas sur-

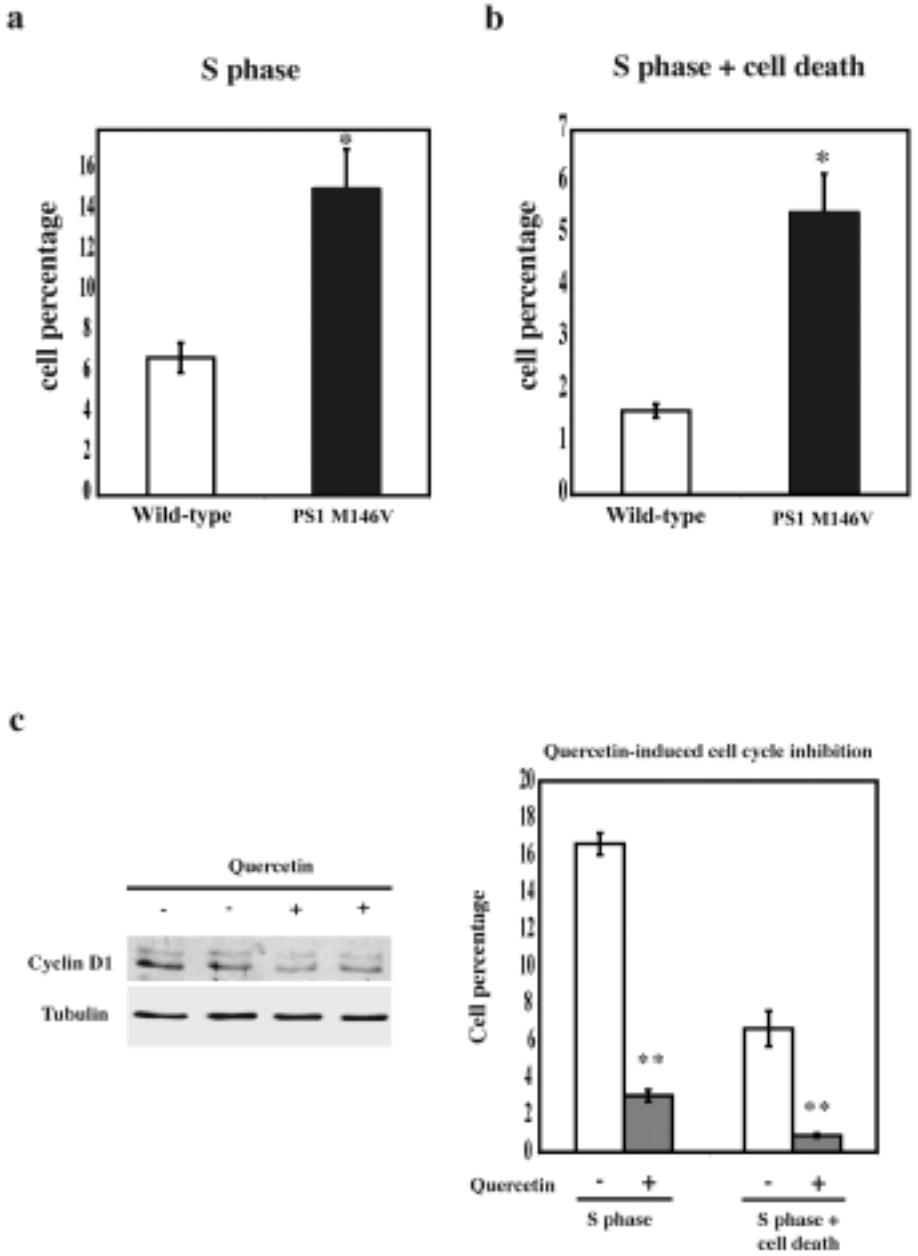

Figure 2. *The presence of the PS1 KI^{M146V} mutation in cortical neurons increases entry into the cell cycle (a), and cell death in neurons that have entered the cell cycle (b). Entry into the cell cycle was measured as the fraction of neurons incorporating BrdU, and cell cycle-linked cell death as the number of neurons both incorporating BrdU and displaying fragmented and condensed nuclei or expression of activated caspase-3. *P < 0.05, t-test (n = 7). Values shown are the mean ± SEM. ≥ 500 cells per genotype were counted in each experiment. (c) Blocking β-catenin/TCF transcription in PS1 KI^{M146V} neurons with 10μM quercetin results in downregulation of nuclear cyclin D1 and, accordingly, into a decline in the number of neurons entering the cell cycle (S phase columns), and cell cycle-dependent cell death also decreases. **P < 0.01, t-test (n = 3). ≥ 500 cells per genotype were counted in each experiment. Statistical analyses was carried out using SPSS v15.*

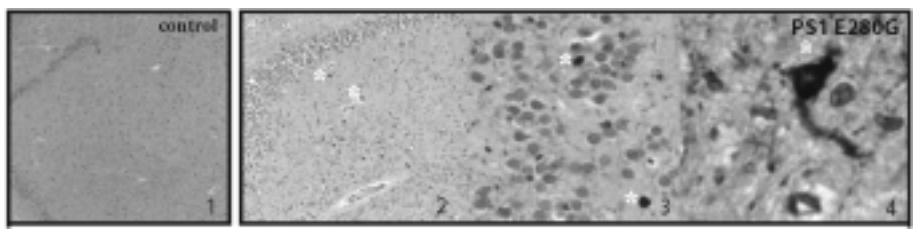

Figure 3. *Accumulation of cyclin D1 in the hippocampus of a PS1 FAD patient harbouring the PS1 E280G mutation relative to non-demented controls. 1: Panel 1 shows the absence of cyclin D1 in non-AD hippocampus, containing the CA4 segment and granule cell layer. 2: The same region in the PS1 E280G case shows the distribution and density of cyclin D1 expression. 3: The dentate fascia in the E280G case shows predominantly nuclear staining in granule cell layer neurons. 4: Immunolabelled neurons in the CA4 segment (end folium) were also readily detectable in the E280G case. Comparable overexpression levels and patterns of cyclin D1 were detected in the hippocampus of the PS1 FAD case expressing the Dexon4 mutation (not shown). White asterisks identify cyclin D1 immunopositive cells in panels 2–4. Post-mortem human temporal cortex of PS1 FAD and controls were obtained from the Institute of Psychiatry brain bank. Grey matter was dissected from temporal cortex of cases with the FAD E280G PS1 mutation (age 65 years, female) and a control non-AD case (age 68, female). Antibodies against tubulin, cyclin D1 and BrdU have been described.[61, 62] Original magnifications: 1–2: × 100; 3: × 200 4: × 400.*

rounding a subset of Aβ-containing plaques.[58] Interestingly, Copani et al. reported that, unexpectedly, the reparative DNA polymerase β may act as a death signal when erratically expressed by differentiated neurons exposed to Aβ.[59] In short, exposure of post-mitotic neurons to the Ab levels present in the AD brain may trigger a signalling pathway leading to the initiation of an abortive neuronal cell cycle.

Mutations in Presenilin 1 (PS1) account for the majority of all FAD cases, and one of its functions is precisely the APP γ-secretase-dependent cleavage responsible for Aβ generation. However, PS1 is a multifunctional protein and participates in many other signalling pathways, involving Notch, MEK/ERK, PI3K/Akt, β-catenin and others (review by[60]). Relevant to the present discussion, PS1 is involved in β-catenin proteolysis, coupling its stepwise phosphorylation by PKA and GSK3-b prior to degradation.[61–63] Thus, in the absence of PS1 or in the presence of PS1 FAD mutations, this function is impaired and β-catenin is translocated to the nucleus, leading to hyperproliferation in mitotically competent cells,[62–64] and tumorigenesis in peripheral tissue lacking PS1.[65] Data from our lab points to a β-catenin-dependent aberrant cell cycle reactivation in cultured primary neurons from mice harbouring the knock-in PS1 mutation M146V (PS1 KI^{M146V}), as determined by increased BrdU incorporation (Figure 2a). This accelerated entry into the cell cycle appeared to be abortive, initiating an apoptotic response (Figure 2b). Treatment with quercetin, a disruptor of the β-catenin/TCF transcription complex, reduced cyclin D1 levels and reversed the cell cycle/cell death phenotype (Figure 2c), consistent with a role for β-catenin in this cell cycle-driven apoptosis. Thus, it is possible that the elevated levels of β-catenin that are present in the PS1 FAD brain accelerate cell cycle entry simply by upregulating cyclin D1 transcription. In further support of this notion, we found that levels of cyclin D1 are elevated in the hippocampus of PS1 FAD patients (Figure 3).

Recently, Repetto et al. demonstrated a critical role for PS1 in the trafficking and turnover of the epidermal growth factor receptor (EGFR), a key signaling receptor tyrosine kinase.[67] As with β-catenin, mutations that enhance EGFR expression can serve as oncogenic signals that promote hyperplasia and neoplastic transformation in human tissues, including skin. EGFR is important for development of the nervous system and maintenance of neural stem cells growth and differentiation. However, excess of EGF induces neuronal death, and strong EGFR immunoreactivity has been detected in neurites surrounding neuritic plaques in AD. Thus, the authors hypothesize that activation of EGFR and β-catenin pathways by the loss of PS1 can mutually reinforce each other and may contribute to neurodegeneration and aberrant cell cycle re-entry by stabilizing both EGFR and β-catenin while simultaneously driving Aβ42 deposition (discussed in [67]).

In summary, although the molecular events in a neuron converting a stress stimulus into a signal to enter an abortive cell cycle remain unknown, the use of PS1 FAD models point to the accidental triggering of oncogenic pathways (i.e. aberrant expression of cyclin D1 and EGFR). If this is representative of what occurs in the more widespread non-familial AD cases, one would favour the hypothesis that, rather than an abortive cell cycle being an early event in a regulated cell death response to stress, upregulation of cell cycle proteins in the AD brain may simply reflect the activation of oncogenic pathways that cannot be completed and leave the cell dysfunctional and ready to be eliminated by apoptosis. Clearly, more research is needed before a clearer picture of the nature and physiological significance of a neuronal cell cycle can emerge.

Concluding remarks

After differentiation, neurons become post-mitotic, acquiring a structural and functional plasticity at the apparent expense of a permanent exit from the cell cycle. Therefore, the expression of cell cycle markers in the adult brain has always been a subject of controversial debate. Clearly, although neurons are terminally differentiated cells, they do express a wide range of cell cycle proteins and are known to be capable of replicating their DNA, although no cases of a neuronal cell division have ever been reported. This, together with the finding that the expression of cell cycle proteins is necessary to execute apoptosis in response to certain stress signals, has lead to the proposition that a neuronal cell cycle does exist and is part of a well-regulated response to stress signals. Whether this interpretation is correct will probably depend on the nature of the initial signal triggering a neuron into the cell cycle in the first place. The fact that cell cycle proteins in neurons are capable of performing non-cell cycle functions and that, at least in PS1 FAD, oncogenic signals are readily generated, argue, in our opinion, for a neuronal cell cycle being no different from other oncogenic signals in different tissues. The reason for the absence of neuronal division and, indeed, tumors of neuronal origin, would simply reflect the impossibility of a fully mature neuronal cytoskeleton to revert to a mitosis-ready configuration. Clearly, more research is needed before we can begin to understand the physiological and pathogenic implications of a neuronal cell cycle.

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