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Breakthroughs and Views

Cdh1-APC/C, cyclin B-Cdc2, and Alzheimer's disease pathology

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Abstract

The anaphase-promoting complex/cyclosome (APC/C) is a key E3 ubiquitin ligase complex that functions in regulating cell cycle transitions in proliferating cells and has, as revealed recently, novel roles in postmitotic neurons. Regulated by its activator Cdh1 (or Hct1), whose level is high in postmitotic neurons, APC/C seems to have multiple functions at different cellular locations, modulating diverse processes such as synaptic development and axonal growth. These processes do not, however, appear to be directly connected to cell cycle regulation. It is now shown that Cdh1-APC/C activity may also have a basic role in suppressing cyclin B levels, thus preventing terminally differentiated neurons from aberrantly re-entering the cell cycle. The result of an aberrant cyclin B-induced S-phase entry, at least for some of these neurons, would be death via apoptosis. Cdh1 thus play an active role in maintaining the terminally differentiated, non-cycling state of postmitotic neurons—a function that could become impaired in Alzheimer's and other neurodegenerative diseases.

Keywords: Anaphase-promoting complex/cyclosome; Alzheimer's disease; Cell cycle; Cdh1; Cyclin B; Neuron

The mammalian cell cycle stage transitions are temporally regulated by two key ubiquitin ligase complexes, the Skp/Cullin/F-box (SCF) complex and the anaphase-promoting complex/cyclosome (APC/C) [1,2]. The SCF complex targets the Cdk inhibitors p21 and p27 for degradation [3]. The APC/C is an E3 ligase acting on B-type cyclins, several mitotic kinases, and proteins associated with chromatid separation [4,5]. Neurons are postmitotic, and any functions of these cell cycle component specific ubiquitin ligases in these cells are therefore not particularly anticipated. This view is now changing very quickly. In *Caenorhabditis elegans*, a novel F-box protein, FSN-1, was recently found to be required for the restriction and/or maturation of synapses [6]. FSN-1 associates with the *C. elegans* homologues of Skp1 and Cullin to form novel SCF-like complexes that are neuronal specific. Recent findings have also illuminated novel and interesting roles for APC/C in postmitotic neurons, particularly in the modulation of synaptic functions and axonal growth. Pertaining to the former, mutants of *Drosophila morula* (Mr), the fly orthologue of APC2 (a subunit of APC/C), showed a marked increase in the number of synaptic boutons (twice that of heterozygote controls) [7]. This phenotype of increased synaptic bouton number was reversed by targeted expression of Mr in all postmitotic neurons of the fly. *Drosophila* APC/C also has a role at neuromuscular junctions, as both spontaneous and evoked junction potentials are increased in the *Mr* mutant. This increase corresponded to an up-regulation of postsynaptic glutamate receptors. APC/C also has a role in determining the abundance of glutamate receptors in the postsynaptic termini of *C. elegans* [8]. In this report, temperature-sensitive mutants of various APC/C subunits were shifted to the restrictive temperature at the fourth larval stage to bypass possible gross mitotic defects. The distribution of GFP-tagged glutamate receptor GLR-1 in wild type and mutants was then compared by quantitative fluorescence microscopy. All mutants showed an increase in the abundance of GLR-1 in the ventral nerve cord. Again these increases could be reverted by the expression of the respective wild type subunits driven by the promoter of *glr-1* itself, which illustrated the cell autonomous effect of the mutations.

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There is further evidence to suggest that APC/C might in fact regulate some aspect of GLR-1 recycling between the postsynaptic plasma membrane and the endosome, as mutations that block clathrin-mediated endocytosis suppress the effects of APC/C mutations.

In the mammalian brain, core components of APC/C and one of its activators, Cdh1, are in fact present in good abundance in postmitotic neurons [9], and multiple Cdh1 homologues have been identified in chick brain [10]. In dividing cells, APC/C is activated in a cell cycle stage-dependent manner by either Cdc20 or Cdh1 [4,5]. However, in both mammals and fly, it appears that only Cdh1 and its orthologues, not Cdc20, activate APC/C function in neurons [7,11]. Cdh1 silencing by siRNA turns out to have a fairly specific effect on the morphology of the neuronal processes of primary cerebellar granule neurons. The rate of axonal growth and its final length are increased (but dendritic growth is not affected), an effect that is also mimicked by APC11, a dominant-negative APC/C component, and Emi1, an APC/C inhibitor protein [11]. Cdh1-silenced axons extended across different layers of the cerebellar cortex when cultured on organotypic cerebellar slices, and a good fraction of these extended long axons over the cerebellar white matter. Cdh1 silencing thus appear to attenuate the inhibitory activity on axonal growth by myelin-associated inhibitors in an apparently cell autonomous manner. In brief, Cdh1-APC/C appears to have a role in both the presynaptic and postsynaptic compartments of the neuron, as well as a rather unique function in modulating axonal growth. We have previously discussed these roles in connection with a novel APC/C substrate, liprin-α, a member of a family of multidomain scaffolding proteins [12,13]. The latter appears to provide a link for the manifestation of APC/C's activities in postmitotic neurons described above [14].

It is, however, notable that none of the activities of Cdh1-APC/C in postmitotic neurons described has an apparent connection to the control of cell cycle staging, of which Cdh1-APC/C is primarily known to regulate in dividing cells. This, therefore, does not intuitively provide a physiological explanation for the rather persistent high levels of Cdh1 in neurons. A very recent report now suggests that the sustained Cdh1 level serves a more basic function—as a survival factor.

Silencing of Cdh1 in postmitotic neurons induces apoptosis

In their article, Almeida et al. [15] had first reaffirmed that Cdh1 and Cdk1 levels of E16 rat cortical neurons remained high after 7 days of plating. This contrasted with the levels of Cdc20, which diminished after day 3 as the neurons in culture gradually become fully differentiated in vitro. Interestingly, cyclin B1 protein levels, initially high, also decline by day 3 and diminished to undetectable levels by day 7. This occurs in spite of sustained cyclin B1 mRNA levels. When Cdh1 levels are depleted by using small hairpin (sh)RNA-mediated silencing after 4 days in culture, these neurons exhibit apoptotic cell death. Inhibition of Cdh1-APC/C activity by exogenously expressed APC/C inhibitor Emi1 likewise induced cell death. Neuronal death is associated with an elevation in cyclin B1 protein levels, which appeared to be stabilized as a consequence of diminished Cdh1. These phenomena are not only peculiar to primary neurons, but are also readily observed with the human neuroblastoma cell line SH-SY5Y.

To ask if the elevation in cyclin B1 levels and its accumulation are directly responsible for neuronal death resulting from Cdh1 silencing, the authors co-expressed Cdh1 shRNA and cyclin B shRNA, and noted that the latter rescues the death inducing effect of the former. Cdh1 silencing also appears to drive S-phase entry by the neuronal cells as indicated by an increase in bromodeoxyuridine incorporation. Importantly, S-phase entry, like neuronal death, is also attenuated by co-silencing of cyclin B. In addition, Cdh1 over-expression, although by itself did not affect neuronal survival, markedly attenuated apoptotic cell death caused by exogenously added amyloid-β (Aβ).

The results of Almeida et al. above are significant in at least two ways. First, they provide a tentative explanation as to why Cdh1 is found at high levels in postmitotic neurons. Second, they provide experimental support that cyclin B accumulation resulting from deficient Cdh1-APC/C activity could cause neuronal death by driving aberrant S-phase entry of postmitotic neurons. This is interesting from a neuropathological point of view, especially with regard to neuronal death associated with Alzheimer's disease.

It should be noted that the findings of Almeida et al. using embryonic day 16 (E16) cortical neurons are slightly at odds with that described earlier by Konishi et al. [16] using postnatal day 6 (P6) cerebellar granule neurons, where axonal growth was actually enhanced by Cdh1 silencing and no apoptosis was reported. The main difference in terms of experimental protocol is the timing of Cdh1 silencing. In the case of the P6 cerebellar granule neurons, transfection with the shRNA generating construct was performed 8 h after plating, a time when cell adherence to the substratum was just completed and neurite sprouting was just beginning. The E16 cortical neurons, on the other hand, were transfected after 4 days in culture—a time when axonal identity has long been established and the neuron approaching as terminally differentiated a phenotype as it could be achieved in vitro (but probably still short of elaborate synapse formation). The difference in the type of neuron (cerebellar granule versus cortical) and their relative ages (P6 versus E16) notwithstanding, it would appear that Cdh1 silencing induced apoptosis only in "fully" terminally differentiated neurons, but in not growing neurons (whose axonal identity has not yet been established). Importantly, this observation correlated well with the changes in cyclin B levels, which had remained high for up to 2 days after plating but declined at the third day and became much lower by the fourth. Therefore, at least for the first 2–3 days

after plating, high cyclin B levels do not result in apoptosis. Beyond that period, Cdh1 silencing builds up cyclin B levels again after it had dropped, and only then would cyclin B elevation lead to apoptosis. In conjunction with the fact that co-silencing of cyclin B levels protects against apoptosis, this points to a direct role for cyclin B and its associated activity (or activities) in driving apoptosis in terminally differentiated neurons.

There are two (non-mutually exclusive) possibilities as to how elevation of cyclin B could induce neuronal apoptosis. The first is that cyclin B activates proapoptotic components or suppresses an anti-apoptotic survival factor. In this regard, it has been previously shown that the cyclin B-dependent kinase Cdc2 (or Cdk1) is expressed in postmitotic cerebellar granule neurons, and could mediate apoptosis of these cells upon the suppression of neuronal activity by phosphorylating the proapoptotic protein BAD at a distinct site, serine-128 [17]. Growth factor survival signaling typically phosphorylates BAD at serine-136, which enhances its interaction with 14-3-3 proteins [18]. The latter sequester BAD away from the mitochondria, where it functions to promote apoptosis. Phosphorylation of BAD at serine 128 apparently inhibits this BAD–14-3-3 interaction. Another possibility is that cyclin B induces terminally differentiated neurons (in a permanent G_o-like phase) to re-enter the S-phase. Such an aberrant forced re-entry into the cell cycle is known to lead not to cell proliferation, but cell death by apoptosis.

Neuronal apoptosis is known to be associated with aberrant cell cycle re-entry

The association between neuronal apoptosis and re-entry or reactivation of the cell cycle is a well-known phenomenon (see [19] for an extensive recent review), although the underlying mechanism in each case is not always clear. Such an association had been observed in vitro as well as in vivo, and in both neuronal death during development or when subjected to apoptotic stimuli. A common observation in line with the inability of neuronal cell to tolerate cell cycle re-entry is that neurons are particularly resistant to oncogenic transformation, and brain tumors of neuronal origin are exceptionally rare [20]. Cell cycle re-entry of G_o-arrested fibroblasts upon mitogenic stimulation is typically mediated by D-type cyclins, whose activation of the cyclin-dependent kinases (Cdk) Cdk4 and Cdk6 leads to G_1 entry. Cyclin E-Cdk2, which is induced later, is necessary for G_1–S transition while cyclin A-Cdk2 is associated with DNA synthesis in S-phase [21]. Accordingly, the cyclins D and E as well as their associated G1 and S-phase Cdks 4, 6, and 2 are those most often implicated in various experimental models of neuronal apoptosis.

Cyclin D1-dependent Cdk activity is clearly stimulated during several models of neuronal apoptosis, a direct result of an elevation in cyclin D1 levels. In fact, exogenous elevation of cyclin D1 levels is sufficient to induce apoptosis in both neuronal and non-neural cell types [22]. This cyclin D1-induced apoptosis can be inhibited by over-expressed Bcl-2 and importantly, the cyclin D-dependent kinase inhibitor $p16^{INK4}$—the latter a clear demonstration that activation of endogenous cyclin D1-dependent Cdks could drive neuronal apoptosis. In fact, chemical blockers of G_1–S progression, as well as over-expression of G_1–S Cdk inhibitors or dominant-negative forms of Cdk4 and Cdk6, have all been shown to attenuate apoptosis induced by a range of stimuli ranging from genotoxic drugs to neurotrophin deprivation in model systems such as PC-12 cells and sympathetic neurons [23–25]. In another experimental model, chemical inhibitors of Cdk also protect cerebellar granule neurons from KCl withdrawal-induced apoptosis [26]. In this model, apoptosis is apparently preceded by an increase in the level of both cyclins D and E protein, with enhanced activity of cyclin D1- and E-associated Cdks, accompanied by a significant decrease in the level of the Cdk inhibitor p27.

Cell cycle progression at the G_1–S checkpoint involves two other important proteins, the retinoblastoma susceptibility gene product (Rb), a tumor suppressor which regulates the G_1–S checkpoint progression [27], and E2 promoter binding factor (E2F), a family of transcription factors whose activities are regulated by interaction with Rb [28]. In quiescent cells, hypophosphorylated Rb binds to E2F and represses the transcription activity of the latter. Mitogenic stimulation results in Rb phosphorylation by cyclin D-Cdk4/6, E2F dissociation, and activation of its transcriptional activities (functioning as dimers with another molecule DP-1) that are required for S-phase entry [29]. Targeted disruption of the *rb* gene resulted in early embryonic lethality and massive cell death in the central and peripheral nervous systems, and an increase in Rb phosphorylation had been observed in various models of neuronal apoptosis [30]. E2F is known to function in apoptosis in response to DNA damage and regulates, amongst others, the expression of components of cellular apoptosis machinery including the apoptotic protease-activating factor 1 (Apaf1) and some caspases. E2F is induced in neurons exposed to apoptotic stimuli. Over-expression of E2F promotes apoptosis, while dominant-negative forms of E2F and DP-1 could attenuate apoptosis (extensively reviewed by [31–33]). A recent report had revealed that an important neuronal proapoptotic molecule, Bcl-2 interacting mediator of cell death (Bim), is a key target of a cell-cycle-related apoptotic pathway in neuronal cells [34]. Bim is induced in nerve growth factor (NGF)-deprived cells. This induction requires Cdk4-mediated activation of E2F and consequently, members of the Myb transcription factor family. The Bim promoter has two Myb binding sites, and Myb's elevation during NGF deprivation increases Bim expression.

Are Cdh1 and cyclin B involved in cell cycle re-entry?

However, is Cdh1-APC/C involved in preventing, or is cyclin B1 functional in inducing, cell cycle re-entry in the first place? Although the APC/C is best known for its function in the M-phase, mounting evidence suggests that Cdh1-activated APC/C also has a function at the G1 phase of the cell cycle. Important findings published last year are indeed supportive of its role in S-phase entry [35,36]. As mentioned at the beginning, the SCF ubiquitin ligase complex regulates S-phase entry by inducing the degradation of the Cdk inhibitors p21 and p27. It was found that subunits of the SCF complex Skp2 and Cks1 are unstable in G_1, and their degradation is mediated by Cdh1-APC/C. Cdh1 silencing of HeLa cells at G_1 has the effect of stabilizing the SCF complex, increase degradation of p21 and p27, with a consequential increase in cells at S-phase. Loss of Cdh1-activated APC/C activity, therefore, could potentially result in aberrant S-phase re-entry.

In the classical depiction of mammalian cell cycle regulation, cyclin B is required only for progression through the M-phase, as a component of the maturation promoting factor in complex with Cdc2 (or Cdk1). At late M-phase, cyclin B is degraded by APC/C, thus allowing exit from mitosis, with the cells entering G_1. In *Xenopus* egg extracts, cyclin B-Cdc2 catalyzes entry into mitosis but cannot trigger DNA replication. However, it has cryptic S-phase-promoting abilities that can be unmasked by relocating it from the cytoplasm to the nucleus. This was done experimentally by deletion of its nuclear export signal and adding instead a nuclear localization signal [37]. In light of the above, it is notable that the cyclin B accumulated as a result of Cdh1 silencing in the work of Almeida et al. [15] is apparently nuclear localized.

Nuclear localization of cyclin B-Cdc2 does not mean that it is necessarily active. For dividing cells, it is crucial to arrest those with DNA damage at G_2 and preventing their entry into mitosis, as these could lead to oncogenic transformation. In addition to inhibiting nuclear import of cyclin B, fibroblasts have an additional mechanism to block activation of cyclin B1-Cdc2. Exposure to non-repairable DNA damage actually leads to nuclear retention of inactive cyclin B1-Cdc2 complexes by the Cdk inhibitor p21, thus preventing activation of cyclin B1-Cdk1 by Cdc25 and Cdks, as well as its recruitment to the centrosome [38]. Therefore, in addition to blocking Rb phosphorylation, p21 acts directly in preventing mitosis of damaged cells by inactivating and maintaining the inactive state of mitotic cyclin B-Cdc2 complexes. As noted above [35,36], however, Cdh1 silencing has the effect of stabilizing the SCF complex, resulting in increased degradation of p21. Therefore, Cdh1 silencing of postmitotic neurons could potentially, in more ways than one, result in active cyclin B-Cdc2, which could potentially drive these cells into S-phase.

Cyclin B-Cdc2 and neuronal death in Alzheimer's disease

Neuronal apoptosis associated with aberrant cell cycle re-entry has been documented for ischemic brain injury [39] and neurodegenerative diseases like amyotrophic lateral sclerosis [40]. Of particularly relevance to cyclin B-Cdc2, however, is Alzheimer's disease (AD). There is abundant evidence for aberrant cell cycle reactivation in AD neurons, with evidence of induction of G_1–S cyclins and Cdks [41–46] as well as indication of S-phase entry and DNA replication [47]. Induction of cell cycle markers was already apparent in early stages of AD clinically categorized under mild cognitive impairment [48].

Induction of cyclin B and Cdc2 in AD neurons was documented years ago [42,43]. Both proteins were enriched in neurons with one of the histopathological hallmarks of AD, neurofibrillary tangles (NFT), and in neurons susceptible to NFT. Cdc2 activity in fact appears to play a pathophysiological role in tau phosphorylation [42,49]. Elevated Cdc2 activity had indeed been reported in other tauopaties such as Down's syndrome [50]. These observations provide a direct link between cyclin B-Cdc2 and AD pathology. Another possible link comes in the form of CIP-1-associated regulator of cyclin B (CARB), a protein that associates with both p21 and cyclin B. Increased CARB localization to NFTs and granulovacuolar degenerative structures was observed in susceptible hippocampal and cortical neurons in AD samples, but was found only at background levels in the same neurons in non-diseased age-matched controls [51].

Aβ's ability to induce neuronal apoptosis in vitro is well known [52,53]. It was shown that both $A\beta_{40}$, $A\beta_{42}$ and the active fragment $A\beta_{25-35}$ could drive differentiated cortical neurons into the cell cycle, with an induction of cyclin D1, E, A, and the phosphorylation of Rb, but these cells did not progress beyond S-phase [54]. Inactivation of Cdks 2 or 4 prevented both S-phase entry and apoptosis. Aβ also induces, in a Cdk-dependent manner, the expression of DNA polymerase-β, proliferating cell nuclear antigen, and the p49 and p58 subunits of DNA primase [55]. Surprisingly, knockdown of the DNA polymerase-β or the p49 primase subunit prevents Aβ-induced neuronal DNA synthesis and apoptosis to some extent. With particular relevance to cyclin B-Cdc2, there is some evidence of Aβ phosphorylation by the Cdc2 kinase activity, with the phosphorylated Aβ showing increased neurotoxicity [56]. It is therefore interesting to note that over-expression of Cdh1 protected against the neurotoxicity of Aβ in cortical primary neurons [15]. It is too early to say if a difference in Cdh1 levels could underlie the difference in susceptibility of different neurons to Aβ toxicity. However, the above, and the possible usefulness of Cdh1-based therapeutic interventions, are both worth further experimental explorations.

Epilogue

Some recent findings implicating important functions of Cdh1-APC/C in postmitotic neurons have been described above. It is quite clear that other than modulating processes that are specific to postmitotic neurons (such as synaptic junction development), this E3 ubiquitin ligase complex may also be required for sustenance of neuronal survival and maintenance of neurons in their terminally differentiated state. It should be fruitful to explore other neuronal functions of Cdh1, and it would perhaps be more prudent to try and understand if Cdh1 activity is required (and to what extent are they required) for different types of neurons, particularly those with known susceptibility to neuropathological diseases. A particular question that could be asked is whether cyclin B induction in AD neurons is a result of loss of Cdh1-APC/C activity. Investigations along this line may yield new knowledge that could be directly applicable to AD therapeutics.

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