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Review

Beyond proliferation—cell cycle control of neuronal survival and differentiation in the developing mammalian brain

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Abstract

Cell cycle proteins are critical regulators of proliferation in dividing cells. Paradoxically, accumulating evidence supports the view that core components of the cell cycle also play key roles in the development of terminally differentiated postmitotic neurons. Distinct cell cycle proteins including cell cycle-dependent kinases may contribute to naturally occurring programmed neuronal cell death in the developing mammalian brain. In addition, recent studies have uncovered a novel role for the cell cycle-associated ubiquitination machinery in the control of axonal growth and patterning in the developing brain. The underlying molecular mechanisms regulating these distinct cell cycle-based developmental events in neurons are just beginning to be understood.
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Contents

1. Introduction

During the course of their development, neurons exit the cell cycle and enter a postmitotic and terminally differentiated state [1]. Although recent studies demonstrate that neurogenesis persists in the adult brain, the birth of new neurons is restricted to pools of neural stem cells that are enriched in only a few regions of the brain [2]. Thus, neurons that compose our brain are born to last a lifetime.

Paradoxically, although neurons are terminally differentiated cells, they do not desist permanently from cell cycle processes. Growing evidence indicates that neurons do express cell cycle proteins. However, in contrast to proliferating cells, engagement of the cell cycle machinery rarely leads to proliferation.

Over the past few years, studies on cell cycle proteins in postmitotic neurons have focused on the role of these proteins in apoptosis. Cell cycle-based mechanisms have been

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shown to contribute to neuronal cell death in response to stimuli relevant to developmentally regulated apoptosis including neurotrophic factor deprivation [3–5] and neuronal activity withdrawal [6–8].

Interestingly, both cell proliferation and cell death are highly conserved processes that display similar morphological changes including cell rounding and detachment, chromosome condensation, and membrane blebbing [9]. Furthermore, both processes involve common regulators including cyclin-dependent kinases (CDKs) and E2F transcription factors [9–13]. Together, these observations suggest that cell proliferation and apoptosis might be regulated by similar molecular pathways and are consistent with the intriguing hypothesis that neuronal apoptosis is the result of an abortive attempt of neurons to enter the cell cycle [14].

The function of cell cycle proteins in postmitotic neurons is not restricted to apoptosis, as cell cycle proteins may regulate other essential processes in neurons. Recent experiments have elucidated a critical role for the cell cycle-associated ubiquitin machinery in the control of axonal growth and patterning in the developing mammalian brain [15]. This finding broadens our view of the function of cell cycle proteins in neurons beyond apoptosis to developmental processes that are unique to neurons.

In this review, we will discuss the molecular mechanisms that control the activity of cell cycle proteins in postmitotic neurons and by which cell cycle proteins in turn regulate developmental events in the brain including neuronal survival and differentiation. First, a brief overview of cell cycle control in dividing cells will be presented.

2. Cell cycle control in proliferating cells

The cell cycle is a complex and tightly regulated process by which cells duplicate their contents and divide into daughter cells. Cell cycle regulation in proliferating cells is the subject of a number of excellent reviews [16–19] and will be only briefly introduced here.

The cell cycle is typically divided into four phases: G1 (first gap), S (DNA synthesis), G2 (second gap), and M (mitosis). Progression through these phases is coordinated by the sequential activity of cyclin-dependent kinases (CDKs) and their activating subunits, the cyclins [17,20]. At least seven CDKs and eight cyclins have been identified in mammalian cells [16,20–22]. Distinct pairs of CDKs and cyclins drive cells through different phases of the cell cycle. Progress through the cell cycle is controlled by checkpoints that ensure critical events of one phase of the cell cycle are completed before the next phase can be entered. Besides their dependence on association with specific cyclins, the different CDKs are regulated by phosphorylation events as well as ubiquitination and degradation [20,22,23]. In addition, the activity of cyclin–CDK complexes is subject to control by two families of CDK inhibitors (CDKIs). Members of the Kip/Cip family of proteins (p21, p27 and p57) inhibit the activity of all G1 cyclin–CDK complexes and to a lesser extent cyclin B/CDC2, while members of the INK4 family (p16, p15, p19, and p18) specifically inhibit CDK4 and CDK6 [20,24–26].

In response to mitogenic stimulation, D-type cyclins are transcriptionally induced and subsequently activate CDK4 and CDK6 thereby allowing cells to leave the quiescent phase and enter G1. The retinoblastoma protein Rb and its related proteins (p107, p130) represent critical substrates of cyclin D-CDK4/6 and are thought to act at the G1/S checkpoint in proliferating cells [27–29]. In its active state, Rb is hypophosphorylated and interacts with members of the E2F family of transcription factors. The association of Rb with E2F shuts off transcription of E2F-regulated genes either by inhibiting the transcriptional activity of E2F or by recruiting a repressor complex to the promoters of E2F-target genes [30,31]. Upon mitogenic stimulation, Rb is phosphorylated by CDK4/6 and released from E2F, thereby promoting the derepression and transactivation of E2F-target genes [30,31]. E2F-regulated genes encode proteins required for cell cycle progression including cyclins, CDKs, and DNA replication proteins [32,33].

Later in G1 phase, cyclin E is induced and associates with CDK2. The cyclin E/CDK2 complex is necessary for transition into S phase. During S phase, an active cyclin A/CDK2 complex drives DNA replication. When DNA synthesis is completed, cyclin A forms a complex with CDC2, also termed CDK1, and drives the cell through G2 phase.

At the G2/M transition, cyclin A is degraded and CDC2 associates with newly synthesized cyclin B. Before its biochemical identification, the cyclin B/CDC2 complex was termed maturation or M-phase promoting factor (MPF) based on its ability to drive cells through mitosis [34–36]. Targets of cyclin B/CDC2 activity include enzymes regulating chromatin condensation, nuclear membrane breakdown, and actin and microtubule reorganization [37]. The activity of the cyclin B/CDC2 complex is controlled at several levels. CDC2 expression is relatively stable throughout the cell cycle, but CDC2 kinase activity is regulated by multiple phosphorylation events [38–40]. The obligate CDC2 activating factor cyclin B is transcriptionally induced and imported into the nucleus during early mitosis [39,41].

Inactivation of the cyclin B/CDC2 complex at the end of metaphase is required for mitotic exit and cytokinesis to proceed. This is achieved through ubiquitination and consequent proteasomal degradation of cyclin B [42–44]. Cyclin B is ubiquitinated by the anaphase-promoting complex (APC), a multiprotein complex that contains E3-ubiquitin ligase activity [45,46]. APC is regulated by phosphorylation [47] and becomes fully active through interaction with the adaptor protein Cdc20 or Cdh1. Whereas the Cdc20–APC complex functions in early mitosis, the association with Cdh1 is required for APC activity during late mitosis and G1 [48]. In addition to cyclin B and other cyclins, APC targets other proteins for destruction including securin, protein kinases, motor, spindle,

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