Available online at www.sciencedirect.com
ScienceDirect
Biochimica et Biophysica Acta 1772 (2007) 484–493
Biochimica et Biophysica Acta
BBA
www.elsevier.com/locate/bbadis

Review

# Cell cycle machinery and stroke

J. Rashidian [1], G.O. Iyirhiaro [1], D.S. Park *

*Ottawa Health Research Institute, Neuroscience Group, Centre for Stroke Recovery, University of Ottawa, 451 Smyth Road, Ottawa, ON, Canada K1H 8M5*

Received 30 August 2006; received in revised form 22 November 2006; accepted 29 November 2006
Available online 5 December 2006

**Abstract**

Stroke results from a transient or permanent reduction in blood flow to the brain. The mechanisms involving neuronal death following ischemic insult are complex and not fully understood. One signal which may control ischemic neuronal death is the inappropriate activation of cell cycle regulators including cyclins, cyclin dependent kinases (CDKs) and endogenous cyclin dependent kinase inhibitors (CDKIs). In dividing cells, activation of cell cycle machinery induces cell proliferation. In the context of terminally differentiated-neurons, however, aberrant activation of these elements triggers neuronal death. Indeed, there are several lines of correlative and functional evidence supporting this "cell cycle/neuronal death hypothesis". The objective of this review is to summarize the findings implicating cell cycle machinery in ischemic neuronal death from in vitro and in vivo studies. Importantly, determining and blocking the signaling pathway(s) by which these molecules act to mediate ischemic neuronal death, in conjunction with other targets may provide a viable therapeutic strategy for stroke damage.


*Keywords:* Stroke; CDKs; Cyclins; Cell cycle; Apoptosis

## 1. Introduction

Stroke occurs primarily as a result of a transient or permanent interruption of blood supply to the brain. This condition can stem from an occluded or ruptured blood vessels and in some cases cardiac arrest. Consequently, neurons in the affected brain region, or the whole brain in the case of a cardiac arrest, are deprived of oxygen and glucose. This sets in motion a cascade of cellular activities that ultimately culminate in neuronal cell death [1–3].

Presently, stroke is a leading cause of death and permanent disability in industrialized nations. Stroke occurs on average every 45 seconds in the USA (www.strokecenter.org). The American Heart Association (AHA) estimates the cost of treating stroke related injury and disability at $58 billion for 2006 alone (www.americanheart.org). Currently the treatment of stroke is mainly reliant on the use of thrombolytics such as tissue plasminogen activator (TPA), which themselves can pose an inherent risk of intracerebral hemorrhage. This limits the use of TPA to only certain cases of stroke. Furthermore, the efficacy of TPA depends on timely presentation of <3 h which excludes 95% of stroke patients [4,5]. Thus there is a need to develop new and efficacious neuroprotective strategies for the treatment of stroke.

The development of new strategies for stroke hinges on better understanding of the complex cellular and molecular interplay that ensue following stroke. A maelstrom of dyregulated molecules and potential perpetrators of ischemic neuronal death have been recently suggested. One of these exciting new developments involves the role of cell cycle molecules such as the cyclin dependent kinases. The notion that cell cycle machinery may mediate ischemic neuronal death is not unique to stroke. Indeed research evidence from numerous labs have demonstrated correlative relationship between the dysregulation of cell cycle machinery and neuronal death models of neurodegenerative diseases such as Parkinson's disease (PD) [6,7], Alzheimer's disease (AD) [8–10], amyotrophic lateral sclerosis (ALS) [11,12], and Niemann–Pick type C disease [13,14]. Whether or not cell cycle mechanism is similar in neurodegenerative diseases and acute conditions such stroke is unknown. This review will focus only on evidence implicating cell cycle molecules in ischemic neuronal death. We will also briefly discuss the potential involvement of other members of the CDK family not directly involved in cell cycle

* Corresponding author. Tel.: +1 613 562 5800x8269; fax: +1 613 562 5403.
*E-mail address:* dpark@uottawa.ca (D.S. Park).
[1] J.R. and G.O. contributed equally to this review.

0925-4439/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbadis.2006.11.009

control, but only as potential activators of cell cycle machinery in stroke.

## 2. Ischemic neuronal death

The mechanism(s) of ischemic neuronal death is complex and may be determined by factors such as the location, severity and duration of insult. For example, neuronal death in the ischemic core, the region most severely affected by the lack of blood flow, occurs within minutes to a few hours and is marked predominantly by necrotic and excitotoxic cell death. Neuronal death in the ischemic penumbra, the region less severely affected by ischemia, is marked mainly by delayed apoptotic-like death that can progress over a period of days.

The precise sequence of events leading to neuronal death following stroke is at present not fully defined. However, a core picture is developing. Following the disruption of blood flow, the affected brain region(s) undergo a period of hypoxia resulting in a decrease in cellular ATP, due primarily to impaired mitochondrial oxidative respiration, a process that generates majority of the cellular energy required to maintain proper cell functions. The reduction of cellular energy results in the impairment of vital cellular functions such as the maintenance of the Na+/K+ pump, massive depolarization and excessive release of glutamate. Over activation of the glutamate channel particularly the *N*-methyl-D-aspartate receptor (NMDAR)-type channels mediates massive influx of Ca2+ resulting in cellular excitotoxicity and neuronal death. Increase in intracellular free calcium results in the activation of Ca2+ sensitive enzymes such as calpains proteases which then act to activate other molecules and cleave cellular structures. In addition to the events describe above other stressors such as oxidative stress, and DNA damage have been demonstrated to mediate ischemic neuronal death. Furthermore, extrinsic stressors such as the activation of glial cells and inflammation may impinge on ischemic neurons to mediate their demise. These later findings are particularly relevant when it comes to therapeutic interventions. In fact, cell cycle regulation may also play a critical role with these non-neuronal cell types in brain injury [15,16]. However, we will not mention this further in this review, but will instead focus on how the cell cycle machinery may impact neurons more directly.

## 3. Cell cycle regulation

Cell cycle is a highly regulated process. Timing progression of cell cycle through different phases, G0, G1 S, G2, and M requires an orchestrated functions of several elements, including cyclins, cyclin-dependent kinases (CDKs), retinoblastoma protein (Rb; pocket proteins) and E2F complex proteins [17]. Different complexes of cyclin-CDK drive each phase of cell cycle [18]. In this regard, the current model is that cyclin D–cdk4/6 and cyclin E–cdk2 complexes regulate G1/S progression, cyclin A–cdk2 complexes mediate S/G2 transitions, and cyclin B–cdc2 complexes mediate M-phase progression [19,20]. In addition, a recent report has suggested that cyclin C–cdk3 complexes also regulate G0/G1 transition [21] (Fig. 1). CDKs activity is regulated by binding to activating cyclin partners [22] as well as endogenous CDK inhibitors such as members of the INK4 (p15, p16, p18, p19) and Cip/Kip (p21, p27, p57) families [23,24]. Finally, phosphorylation also plays a critical role in CDK regulation. For example, cyclin H–cdk7–Mat1 (Cdk Activating Kinase; CAK complex) by phosphorylation of a central threonine [25] and cdc25 by dephosphorylation of thr14 (on cdc2) or tyr15 (on cdk2) modulate CDKs conformation to a fully active structure so they recognize their substrates more efficiently [23]. CDKs mediate cell cycle progression by phosphorylating downstream targets [26]. For example, an important target of G1 CDKs is the tumor

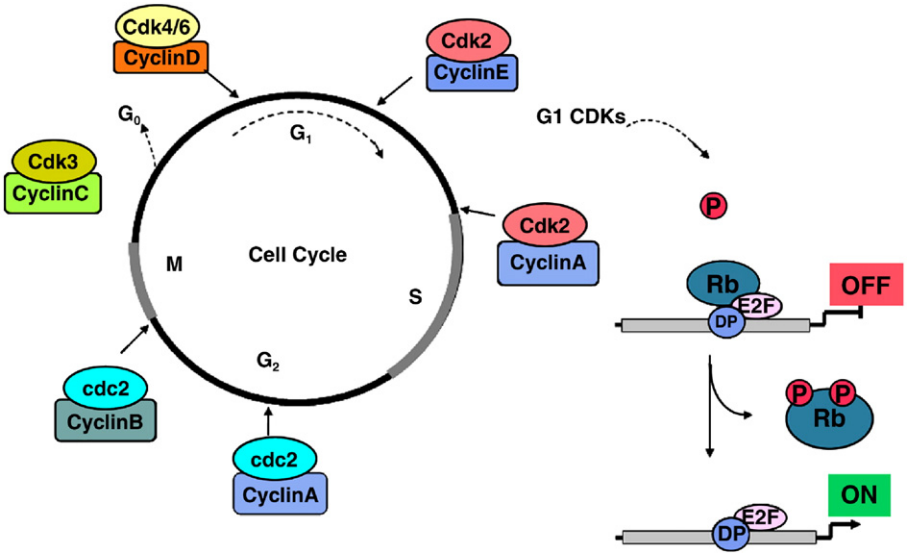


Fig. 1. Schematic representation of our current understanding of the mammalian cell cycle. The cell cycle is broadly divided into four phases culminating in cell duplication. Each phase of the cell cycle is regulated by different complement of cyclin dependent kinases together with a cognate cyclin. During the G1/S-phase, the downstream target, the retinoblastoma gene product. pRb is sequentially phosphorylated by the G1 CDKs resulting in the release of E2F transcription factor and DP. This results in the transcription of E2F responsive genes and those required for the progression thorough S-phase.