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Cell Cycle Phase Transitions: Signposts for Aberrant Cell Cycle Reentry in Dying Mature Neurons

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The last two decades have brought forth compelling new findings showing that aberrant cell cycle reentry results in death of mature neurons [1-3]. The cell cycle is an irreversible, ordered set of events [4], that normally leads to cellular division [5-7]. The release of cells from a quiescent state (G0) results in their entry into the first gap phase (G1), during which the cells prepare for DNA replication in the synthetic phase (S). This is followed by the second gap phase (G2) and mitosis phase (M). After the cell has split into its two daughter cells, the cell enters either G1 or G0.

Mature neurons normally maintain themselves in G0 resting phase. Although they are unable to divide once differentiated, mature neurons do reenter cell cycle in certain pathological conditions. However, these mature neurons that reenter cell cycle neither revert to the earlier G0 nor advance to a new G0 phase. This presents a critical dilemma from which death may be an unavoidable, but necessary, outcome for these critical cells [3].

Postmortem studies have revealed pathological evidence of aberrant cell cycle reentry occurring in neurons of patients with Alzheimer's disease (AD) [8-12], epilepsy [13], Parkinson's disease (PD) [14] and amyotrophic lateral sclerosis (ALS) [15]. This phenomenon has been further experimentally confirmed in primary neuron cultures exposed to amyloid beta (Aβ) and thrombin [16-20] and animal models of neurological diseases including AD [2,21,22], ALS [23], stroke [24,25], traumatic brain injury (TBI) [26] and cerebral hypoxia-ischemia [27].

The observable events in these death-bound mature neurons include elevated expression of cell cycle proteins and DNA replication. However, these events are controversially taken as direct evidence for aberrant cell cycle reentry in dying neurons. This is because the elevated cell cycle proteins could also be a sign for neuronal differentiation [28-30], and DNA replication could be a sign for other synthetic events such as DNA repair [31].

We and others reported that sporadic expression of cyclin D (a G1 cyclin) without cyclin-dependent kinase 4 (Cdk4, a G1 kinase) can be activated in unperturbed normal primary neurons [16,17]. However, once the expression of cyclin D and activation of Cdk4 co-occurred (cyclin D/Cdk4 complexes formed), the neurons pass G0/G1 transition, reenter the cell cycle, and ultimately die via apoptosis [16,17].

The formation of cyclin D/Cdk4 complexes (G0/G1 transition) is the first step leading to neuronal cell cycle reentry. This is followed by several waves of cyclin/Cdk complexing in mature neurons that reenter cell cycle, including cyclin E/Cdk2 (G1/S transition), cyclin A/Cdk2 (S/G2 transition) and cyclin B/Cdc2 (G2/M transition) [32-35]. Since cyclin/Cdk complexes are characteristic of cell cycle phase transitions, the presence of these complexes is a hallmark of non-G0 resting phases, indicative of aberrant cell cycle reentry in dying mature neurons.

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