

CHAPTER 2

Paved with Good Intentions:

The Link between Cell Cycle and Cell Death in the Mammalian Central Nervous System

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Cell Division

Cell division is among the most basic of biological processes. All life forms, from blue-green algae to human hepatocytes, ultimately depend for their survival on the ability of one cell to create two. In keeping with the centrality of this process, the component enzyme systems have been well conserved in evolution. But while unicellular creatures such as bacteria, protozoa and yeast are free to divide whenever the nutrient source is adequate, multicellular organisms must tightly regulate the division of their constituent cells if they are to maintain their correct size and shape. Given this requirement, it is not surprising that the activities of the various cell cycle enzymes are regulated by a large and complex network of gene products. Indeed since life itself depends on the existence of a vigorous cell division process, it is nearly axiomatic that complex organisms must have an equally robust series of mechanisms to hold the cell cycle in check. Nowhere is this need for cellular restraint more crucial than in the adult central nervous system.

The mitotic cell cycle has four recognized phases. G1 phase is a period of variable length during which a single cell grows to a point where cell division is called for. After the commitment to begin division is made, G1 is followed by S phase in which the DNA synthetic machinery replicates the cell's genetic material and chromosome number doubles. The cell then prepares for division in a period known as G2 phase. Finally, during M phase, the chromosomes move to opposite poles of the cell; the cytoplasm is split and two daughter cells emerge. The proteins that regulate this process are diverse in both form and function. The central players are a series of protein kinases known as cyclin dependent kinases, or Cdks. The activities of these proteins vary with the phase of the cycle according to their own state of phosphorylation as well as their binding to a series of regulatory proteins known as cyclins. Additional levels of regulation are added by a number of cell cycle inhibitors (such as the cyclin D inhibitors p16 and p27) that act by binding to and blocking the action of various cyclins. Further, peptide destruction (targeted by ubiquitination and effected by specific peptidases such as cdc25) is yet another level of both positive and negative cell cycle regulation.

Cell Cycle Events in the Cell Death Process

Until recently, cell division and cell death seemed not only separate, but polar opposite concepts. The former would seem a generative process that favors growth and development while the latter is a destructive event that favors atrophy and loss. A substantial body of evidence now suggests, however, that the two processes are intimately related and use many of the same mechanisms for their execution. The idea that reactivation of the machinery of cell division in a mature neuron might to death rather than division, though paradoxical, fits well with an oft-observed but poorly understood phenomenon: there are almost no examples of tumors that are founded by CNS neurons. With very few exceptions,* the cancers that we refer to as "brain" tumors originate from nonneuronal cells such as astrocytes, oligodendrocytes, and cells of the meninges.

Some of the first direct hints of the cell cycle/cell death linkage came from the analyses of transgenic mice in which oncogenes such as SV40 T-antigen were driven with neuron-specific promoters. When T-antigen is expressed under the control of a rhodopsin promoter, the result is the loss of photoreceptor cells.¹ When it is expressed under a N-methyltransferase promoter retinal amacrine and horizontal cells die.² Finally, when the Purkinje cell-specific promoter of the *pcp2* gene is used to drive T-antigen expression, cerebellar Purkinje cell death rather than cell division is the unexpected result. Careful study of this latter situation revealed that the dying Purkinje cells were labeled by the DNA precursor, bromodeoxyuridine (BrdU) before their demise.³ This suggests that the T-antigen oncogene had successfully initiated a cell cycle but for some reason the Purkinje cell could not complete it. T-antigen functions in part by binding the endogenous cellular protein, retinoblastoma (RB).⁴ RB is a nuclear protein that regulates a key point in the cascade of events that initiates cell division.^{5,6} The activity of RB is normally inhibitory (hence its classification as a tumor suppressor gene) but it can be modulated through protein phosphorylation; higher levels of phosphorylation inactivate RB and release the cell cycle. By binding and sequestering RB, the effect of T-antigen is to functionally mimic the effects of phosphorylation.

In the same year that the T-antigen transgenics were published, several cell cycle labs announced the creation of engineered null mutations in the mouse *retinoblastoma* gene.⁷⁻⁹ The three labs were undoubtedly expecting to find unregulated cell division in the embryo; instead all three reported the occurrence of massive amounts of cell death in the central nervous system. All three groups noted the implication of this discovery: loss of cell cycle control in a newly generated neuron leads to cell death. One might have imagined that the curious cooccurrence of cell cycle anomalies and neuronal cell death was limited to artificial genetically engineered systems and somehow perhaps to other functions of the RB protein itself. Yet, shortly after these findings were announced, Freeman et al.¹⁰ showed that the death of sympathetic neurons following trophic factor deprivation led to the up-regulation of cyclin D1 (a G1 phase cyclin). This finding was of particular interest as the message levels for most of the other genes examined decreased. Following these observations in PNS neurons, our laboratory investigated several instances of target-related cell death in the CNS.¹¹

Taken together, these early findings suggest a model of cell division in the mature nervous system that is the central hypothesis of this chapter:

Once a neuroblast makes the commitment to stop dividing and begin differentiation, any event that forces it back into the cell cycle will result in its death. This prohibition against cell division begins early in development and persists for the life of the organism.

* Retinoblastomas, medulloblastomas and multiple endocrine neoplasias

The Cell Biology of Cell Cycle Induced Cell Death

Since these first studies there has been a growing recognition of the wide spread applicability of this principle. Tissue culture model systems have been developed and have provided some of the most detailed evidence establishing a linkage between cell cycle and cell death. These data come from analyses of cell lines such as PC12 cells¹²⁻¹⁶ as well as primary neuronal cultures.^{13,15,17-20} The role of cell cycle processes is noted in a number of different experimental situations in which neuronal cell death is observed. For example, trophic factor withdrawal can induce a cycle-associated death in primary neurons and PC12 cells cultured in vitro.^{15,17-19} Using pharmacological approaches, the laboratories of Greene and colleagues have shown that drugs block cell cycle advancement are efficient at preventing the death of both PC12 cells and sympathetic neurons.¹⁷⁻²⁰ Molecular genetic approaches have also been used. Dominant negative forms of the Cdk4 and Cdk6 proteins have been engineered and these too are effective in blocking the cell death process.¹⁹ In addition, neurons subjected to DNA damaging agents such as UV irradiation or camptothecin (a topoisomerase inhibitor) require cyclin D1 and CDK4/6 activity to induce neuronal death.²¹ These in vitro models are significant since many of them provide direct experimental evidence that, rather than merely being associated with cell death, an ectopic cell division is both necessary and sufficient to produce the death of neurons. An excellent review of this entire topic can be found in Liu and Green.²²

The tissue culture studies and the observations in the RB mutants and T-antigen transgenics are strong evidence in support of the cell cycle and cell death connections. And this linkage is found a number of other in vivo situations of neuronal cell death. Recently, Chen et al^{22a} have shown that in mice lacking the cell cycle inhibitor, p19^{Ink4d}, hair cells die post-natally. Their death is clearly cell cycle related as BrdU is incorporated into the normally post-mitotic cells. An additional example mentioned briefly above is the phenomenon of naturally occurring cell death. In normal development, most neurons go through a 'critical period' during which they have an acute dependency on contact with their target. If the contact is insufficient, the presynaptic neurons will rapidly die. It is believed that this pruning mechanism allows the different interconnected parts of the CNS to achieve a functional numerical balance that is optimum for adult function. One of the regions where target-related cell death has been studied most extensively is in the developing cerebellum. This is because many of the 'classic' neurological mutations of the mouse such as *lurcher* and *stagger* lose large numbers of granule cell and inferior olive neurons due to the mutations' destructive effects on their target, the cerebellar Purkinje cell.^{23,24} The presynaptic granule and olivary neurons are not themselves intrinsically compromised by either mutation; the Purkinje cells in both mutants are.²⁵⁻²⁸ In both mutants the discovery of BrdU incorporation as well as immunocytochemical evidence for the reexpression of cell cycle proteins (Fig. 1A)¹¹ demonstrates that both neuronal cell types reenter an unscheduled cell cycle before their demise. This point is further underscored by the situation in the wild type mouse where even the normal pruning of the granule cell population that occurs during postnatal cerebellar development is found to proceed by the same reengagement of the cell cycle (Fig. 1B).¹¹

The principle of cell cycling as a correlate of the cell death process has recently been extended further. When a neuron is deprived of oxygen, even for relatively short periods of time, it will die. This is true both in tissue culture and in vivo during disease related or experimentally induced ischemic incidents. Both situations have been examined for the evidence of cell cycle processes and in both situations such evidence has been found. In rats, focal ischemic insults as short as 30 min induce Cdk2 and Cdk4 as well as their associated cyclins, cyclin D1 and cyclin A and in response the levels of phosphorylated RB increase and E2F appears to be released.^{29,30} As if to protect itself from the ill effects of the cell cycle, the Cdk inhibitors p21 and cyclin G1 also appear to be induced in the neurons bordering the ischemic core region after middle cerebral artery occlusion in rats.³¹ The significance of the elevations in cell cycle

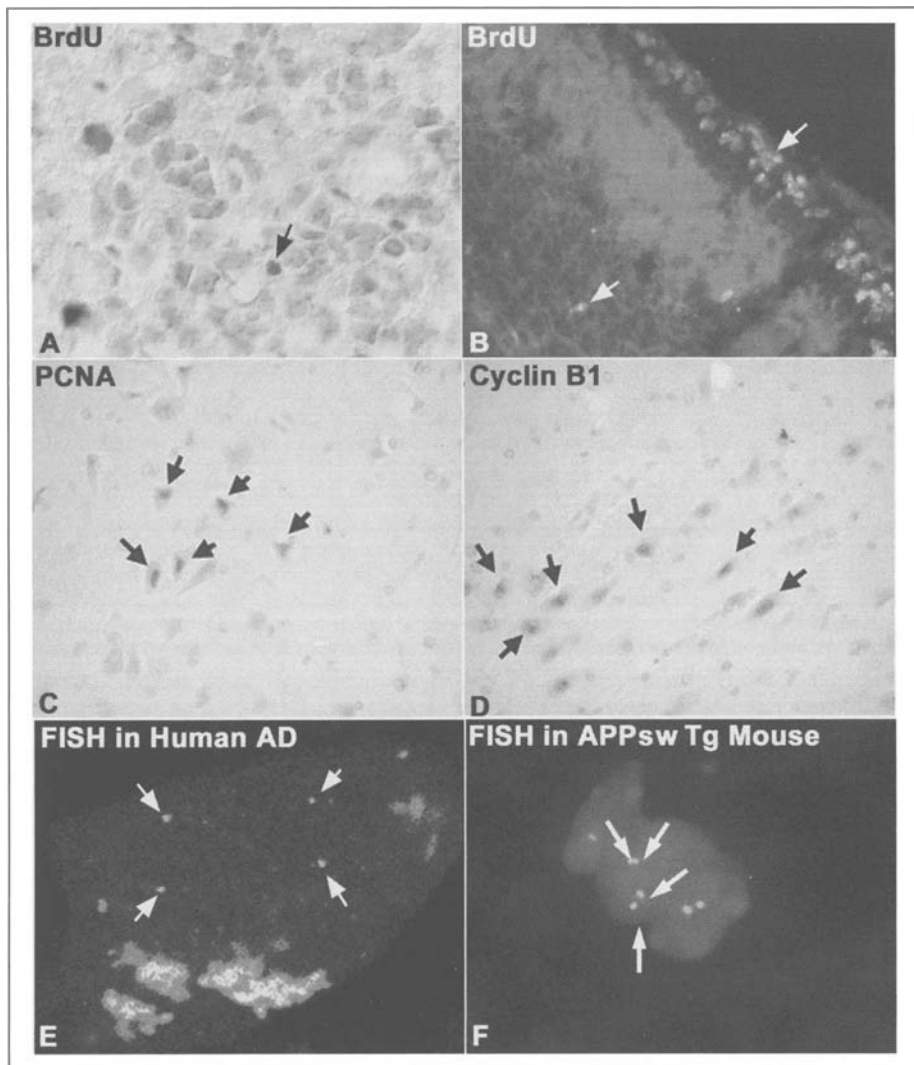


Figure 1. Immunocytochemical evidence for cell cycle events in models of neurodegeneration in mouse and man. BrdU is incorporated into post-mitotic cerebellar granule cells (arrows) if they are deprived of their target. Such a situation is found in mutations (A) such as staggerer and also during normal development in the wild type (B). Neurons in populations at risk for cell death in Alzheimer's disease (such as hippocampal pyramidal cells) also reexpress cell cycle markers such as PCNA (C) or cyclin B (D) before their death. These cell cycle proteins lead to a well regulated S-phase as illustrated by the incorporation of BrdU (A, B) or the use of fluorescent in situ hybridization to detect the duplication of specific loci in both human (E) and mouse (F). The probe shown in the human hippocampal neuron is a probe to a region of the human genome containing the end of the long arm of chromosome 11. The probe shown in F recognizes a long stretch of unique genomic sequences surrounding the aldolase C gene.

protein content is clear since administration of flavopiridol prevents neuronal death in the vulnerable CA1 region neurons,³² and intraventricular administration of flavopiridol in the focal ischemia reduced the size of infarct.

Human Disease

The studies cited above provide solid evidence for the role of cell cycle events in the prosecution of neuronal cell death. What these studies also reveal is that a wide range of insults is able to induce a neuronal death that is associated with cell cycle reactivation. It seems only logical, therefore, that several neurodegenerative diseases have been found associated with an apparent induction of a cell cycle in the areas where neurons are lost.

Alzheimer's Disease

A key feature of the working hypothesis concerning the prohibition against a neuron reentering a cell cycle is that it applies from the moment a developing neuron leaves its neurogenic phase and persists until the death of the organism. This has led many laboratories to investigate the involvement of cell cycle events in a variety of neurodegenerative diseases. Of these, by far the best studied is sporadic Alzheimer's disease. Beginning with immunocytochemical evidence for the ectopic expression of a variety of cell cycle enzymes, nearly half a dozen laboratories have proposed that the neurons at risk for cell death in Alzheimer's disease reenter a cell division process before their death. The cell cycle proteins whose levels have been reported to increase include cyclin D,^{33,34} cdk4,³³ PCNA,^{33,35} cyclin B,³³ cdc2³⁶⁻³⁸ and Ki67.^{34,35} In addition to these proteins whose presence is usually found only in actively cycling cells a number of studies have pointed out that several of the Cdk inhibitors are also present. These include p16^{ink4},³⁹ p21^{ras}³⁹ and p105.⁴⁰

As is often the case with post-mortem human studies the available tissue is derived predominantly from individuals who died with advanced, if not end stage disease. This leaves open the possibility of several types artifact. For example, it is possible that the observed cell cycle changes are a rare but stable event that collects throughout the 10-year disease course and the quantitative prevalence that is seen in end-stage material is not representative of the contribution of cell-cycle events to the overall disease pathology. Alternatively, it could be that cell cycling is only prevalent at the very end of the illness, once again leading to a false impression of its importance. To address this problem,⁴¹ have done a detailed quantitative analysis of the prevalence of cell cycle events in individuals who die with a diagnosis of mild cognitive impairment (MCI). We adopted this approach because several studies have shown that a high percentage of individuals with MCI will progress to Alzheimer's disease (AD) within 3-5 years of diagnosis.⁴² Thus many researchers view MCI as a prodromal stage of Alzheimer's disease.^{43,44} Using a battery of cell cycle protein antibodies, we found that in both hippocampus and basal nucleus there is a significant percentage of cell cycle immunopositive neurons in all MCI cases (Fig. 1C, D). Indeed, the percentages turn out to be very similar to those found in Alzheimer's disease cases, and significantly higher than in cognitively intact controls. This means that cell cycle-related cell death is not a peculiarity of late stage disease and suggests that it represents a unifying disease mechanism.

An important question raised by these studies is whether or not the appearance of this large collection of proteins has any functional meaning in terms of actual cell cycle progression. To date, only a single study has addressed this question in the human. Yang et al⁴⁵ performed fluorescent in situ hybridization using either large genomic probes to unique sites in the human genome or small probes to the highly repetitive DNA of the centromere of specific chromosomes. The study showed that in two populations of nerve cells that are at risk for cell death in the CNS of the Alzheimer's disease brain (hippocampal pyramidal cells and the cholinergic neurons of the basal nucleus of Meynert) there were significant numbers neurons that showed evidence for three or four copies of each of these probes (Fig. 1E), direct indication that DNA replication has occurred. This means that the ectopic expression of cell cycle protein was sufficiently coordinated that a well-regulated S-phase ensued. Recent unpublished evidence from our lab suggests that the same process of cell cycle initiation occurs in engineered mouse

models of AD (Fig. 1F). That said, recent data from⁴⁶ adds an unusual wrinkle to the story. In a comprehensive analysis of the identity of the DNA polymerases that are involved these authors found an induction of DNA polymerase-beta, typically associated with DNA repair, rather the replication polymerase, pol-delta.

Stroke and Other Human Diseases

As in the animal models of ischemia, postmortem studies of brain tissue in and around a stroke or ischemic event reveal evidence for the reexpression of cell cycle proteins such as PCNA, GADD34.^{47,48} The timing of the appearance of these proteins strongly suggests that the initiation of a cell cycle is an early event in the process leading to cell death. Cell cycle markers have also been detected in brains of patients with Parkinson's disease,⁴⁹ in spinal cord samples from amyotrophic lateral sclerosis cases,⁵⁰ in frontotemporal dementia, in Neimann Picks disease, in Pick's disease, and in progressive supranuclear palsy.⁵¹ In an experimental in vivo model of Parkinson's disease, dying neurons of the substantia nigra express factors specific for G2, S and M phase of cell cycle.⁵² Activation of cell cycle machinery has also been observed in vulnerable regions following a traumatic brain injury⁵³ as well as several examples of infection induced neuronal loss, and other instances of neurodegenerative disease.⁵⁴⁻⁵⁷ Finally, recent evidence implicates cell cycle anomalies in both amyotrophic lateral sclerosis^{50,58} and the related SOD-1 transgenic mouse model.⁵⁹

Conclusions

The cells of the adult central nervous system appear to be in a continual struggle to hold their cell cycle in check. This is evident both from the virtual absence of neuronal cell division in the adult and from the apparent fate of those neurons that do try to divide. The losses of nerve cells in a variety of neurodegenerative conditions, including several human diseases, seem to be related by this common theme of attempted neuronal cell division. At a superficial level, it is almost as if the neurons retain a developmental 'memory' of their epithelial origins and following stress or 'wounding' of the CNS, a suppressed urge to repair the 'wound' by cell division ensues. This attempt would seem laudable on its surface – in a situation where neurons are dying, any effort to create new nerve cells should be welcome. But these good intentions on the part of the mature neurons have unintended consequences, and in the final analysis end up paving a very famous road that leads only to a worsening of the brain's condition.

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Cell-Cycle Mechanisms and Neuronal Cell Death

Copani, A.; Nicoletti, F. (Eds.)

2005, IX, 102 p., Hardcover

ISBN: 978-0-306-47850-5