CHAPTER 6

Alzheimer Disease:

A New Beginning or a Final Exit?

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Abstract

Today, a new chapter is being written in the book of Alzheimer disease, one that is challenging the longstanding view that adult neurons are incapable of division, remain nonproliferative, and are terminally differentiated. Here, we review the provocative notion that, in Alzheimer disease, whole populations of nonstem cell neurons leave their quiescent state and re-enter into the cell cycle. However, such neuronal re-entry into the cell cycle is futile and ultimately leads to the neurodegeneration that typifies Alzheimer disease.

Introduction

It is perhaps ironic to discover that neurodegenerative diseases, such as Alzheimer disease (AD), where cell loss is a key feature, may provide clues to understanding the plasticity of the adult central nervous system. In AD, there is accumulating evidence that susceptible neuronal populations exhibit a de-differentiated phenotype likely representative of a reactivated cell cycle. This exit from a quiescent state is manifested in several ways, including:

1. The ectopic expression of cyclins along with their cognate cell cyclin-dependent kinases (CDKs) and their inhibitors (CDKIs);
2. Recruitment of mitogenic signal transduction pathway components; and
3. The increased transcriptional activation of a variety of mitosis-related proteins.

While the cause of this apparent neuronal re-entry into the cell cycle is not known, the consequences for these terminally differentiated cells are disastrous leading to oxidative stress, cytoskeletal abnormalities, mitochondrial dysfunction and, ultimately, neuronal death. In other words, the re-emergence into the cell cycle by neurons accounts for many of the cardinal features of the disease. In this review, we explore some of these mitotic alterations including the recruitment of mitogenic factors and oxidative stress. Further, we speculate on the nature and the source(s) of mitogenic factors, which underlie the pathological events observed in this dreaded disease.

Pathological Hallmarks of Alzheimer Disease

As an insidious and progressive neurodegenerative disease, AD affects up to 15% of individuals over the age of 65 and nearly half of all individuals aged 85 and above.[1] The disease is quickly becoming one of the most serious health problems in the U.S. and has a dehumanizing

nature that involves destruction of higher-order brain function leading to dementia, disability and, finally, death. Two pathological lesions, namely the neurofibrillary tangle (NFT) and the senile plaque, are hallmarks of the disease and these neuritic plaques and NFT are largely associated with dementia. NFT, which contain a highly phosphorylated form of the microtubule associated protein tau, is the major intracellular pathology of AD, while senile plaques are extracellular and are primarily composed of amyloid-β.[2,3] The mechanisms involved in the formation of these lesions or neuronal death are largely unknown although recent findings indicate a key role for the aberrant re-entry of neurons into the cell cycle.

A Mitotic Phenotype Appears in Alzheimer Disease

A growing number of cell cycle-related proteins are found associated with the susceptible and vulnerable neurons of AD (Table 1) that, from their temporal and pathological distribution, are indicative of an early and fundamental role in the pathogenesis of AD. This cycling phenotype, rather than a phenotype of cells in a terminally differentiated state, has been reviewed elsewhere.[4] Nonetheless, it is important to note that cell growth changes ultimately occur through signal transducers that activate specific transcription factors and modulate cell cycle control proteins.[5] These proteins themselves are also regulated in a cell cycle-dependent manner[6,7] and are listed in Table 2. Perhaps of greatest import, however, as regards disease pathogenesis, all of the major genetic and protein elements dysregulated in AD, including tau, amyloid-β precursor protein (AβPP), presenilin1/2, and, possibly, apolipoprotein E (ApoE), are also altered during the cell cycle.[4]

Tau Phosphorylation

Since increased phosphorylation and decreased microtubule stability are coincident during progression through the cell cycle[8,9] and these cell cycle-related protein alterations are found in AD, it is not surprising that microtubular abnormalities and tau phosphorylation are associated with AD.[10] While the kinases responsible for tau phosphorylation in AD are not completely characterized, increased residue-specific phosphorylation of tau occurs in mitotically active neurons where phosphorylation is driven by CDKs.[11-15] Of note, in AD, CDKs, such as CDK2 and CDK5, as well as Cdc-kinases and MAP2 kinases, are increased in AD in a topographical manner that completely overlaps with phospho-tau[16,17] and also have been shown to hyperphosphorylate tau in in vitro assays.[18-22] In addition, we recently demonstrated that CDK7, an age-dependent CDK-activating kinase, also associates phospho-tau in AD and may be essential to all other mitotic alterations since CDK7 plays such a crucial role as an activator of all the major CDK/Cyclin substrates.[23] Finally, we have shown that cell cycle re-entry leads to tau phosphorylation in primary neurons (McShea and Smith, unpublished data).

Amyloid-β

The major protein component of senile plaques, amyloid-β, is derived from a larger precursor AβPP encoded on chromosome 21[24] and is upregulated secondary to mitogenic stimulation.[25] Further, AβPP metabolism is regulated by cell cycle-dependent changes[7] and has neurotrophic effects at low (nM) concentrations[26] consistent with its mitogenic activity in vitro.[27,28] Presumably, the effect of amyloid-β is mediated through mitogen activated protein kinase (MAPK),[29] and therefore may play a direct role in the induction or propagation of cell cycle-mediated events in AD. Therefore, amyloid-β, along with oxidative stress[30] and cell cycle re-entry, may have common etiologies. However, it is notable that, while amyloid-β-mediated cell death, at least in vitro, is dependent on the presence of various cell-cycle-related elements,[31] in vivo analysis of the basal nucleus of Meynert and the locus ceruleus, where amyloid-β is rarely seen, found little or no topographical relationship between amyloid-β and the ectopic expression of cell cycle markers in diseased brains.[23,32-38] Thus, amyloid-β may only become

toxic in vivo when the neuronal cell cycle machinery is activated or when levels exceed the body's ability to regulate its turnover.

Presenilins

Mutations in the human presenilin genes 1 and 2 (PS-1/2) found on chromosomes 14 and 1, respectively, are linked to early onset AD.[1] The association of presenilins with centrosomes and centromers, and the link between PS-1/2 and Notch-based signaling through cadherin-based cell-cell adherence junctions,[39] indicates that PS-1/2 may play critical roles in cytoskeletal anchorage, cell division, chromosome segregation,[40] cell fate,[41-43] early embryonic development,[44] and tumorigenesis.[45] In this regard, we and others have shown that overexpression of PS-1/2 leads to cell arrest in the G_1 phase of the cell cycle, an effect that is potentiated by expression of the PS-2 (N141I) mutation.[46] Overexpression also yields a loss of calcium homeostasis, increased oxidative stress, and increased susceptibility to apoptotic death,[47] with AD-linked mutations of presenilins showing greater effect.[46,48] Further, PS-1 mutations destabilize beta-catenin and can potentiate neuronal apoptosis,[49] by reducing the capacity of neurons to induce endoplasmic reticulum chaperones.[50] Alternatively, induction of apoptotic systems via PS-1/2 and AβPP mutations, could also lead to the upregulation of CDKs since expression of Cyclin/CDKs, in addition to driving cell proliferation and growth control, are also implicated in neuronal death signaling and apoptosis (see Fig. 1).[31,51,52] Indeed, the differential activity of AD-linked PS-1 in the beta-catenin-signaling pathway indicates a key role for cadherins in the pathogenesis of AD. Therefore, one would also expect the subsequent induction of p27 (Ogawa et al, submitted) and inhibition of Cyclin E/CDK2, while increasing expression of p21[53] and consequently an inhibition of proliferation. In addition, a block from progression at the G1/S phase boundary, by PS (and possibly AβPP) mutations, would likely result in the accumulation of cell cycle control proteins as is seen in AD. Therefore, PS mutations confer a contracted time course to the underlying pathophysiology of AD.

AβPP, through the stimulation of Ras-dependent MAPK cascade in vivo, is correlated with highly phosphorylated tau.[54] The early p21Ras expression pathway is activated during the posttranslational modification of AβPP and tau phosphorylation, which precedes neurofibrillary degeneration and amyloid-β formation.[55] Additionally, the presence of p21, highly phosphorylated tau, Ki-67, and cell cycle-associated nuclear antigen protein (PCNA), may have a role in the production of abnormally phosphorylated tau which then leads to the formation of cytoskeletal derangements in susceptible neurons.[56] This strong link points to cell cycle reactivation and the upstream ectopic expression of cell cycle markers as a critical, and common, early event in AD pathogenesis.

G_0 Exit, G_1 Entry, and Mitogenic Drivers in Alzheimer Disease

Quiescence, cell division, and differentiation are states central to the regulation of growth and development. Increased growth stimuli, as in extrinsic mitotic pressure, activate key factors for G_0 exit and G_1 progression, including the complex-forming CDKs, i.e., CDKs 4, 5, 6, 7 (see Table 1), and their cognate activating cyclins, i.e., Cyclin D1, D3, E and B1 (see Table 1). These complexes are able to phospho-regulate a wide variety of relevant substrates.[57] Together, they orchestrate DNA replication, cytoskeletal re-organization, and cellular metabolism required for proliferation, development, and cell cycle progression. While it has been argued that a number of the cell-cycle related phenomena found in AD can also occur as sequelae to other processes, such as apoptosis, trophic-deprivation, and DNA repair (see Table 2),[52,58-62] we propose that the re-emergence of, or sensitivity to, extrinsic signals initiates an attempt to re-enter into the cell division cycle, with progression being limited by the degree of mitotic competence of the adult neuron.
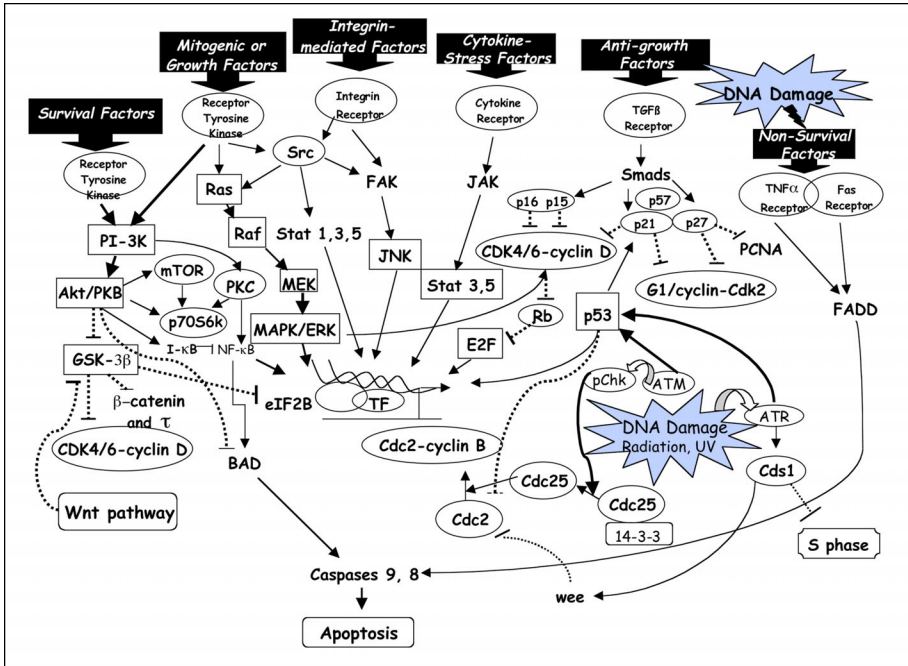
Figure 1. The complex relationship between cell survival and cell death pathways.

The identity of the signal(s) that lead the neuron to attempt exit from a quiescent state and re-enter the cell cycle remains yet to be determined. However, a number of growth factors and mitogens are elevated in the AD brain and may drive cell cycle re-entry. Re-sensitization to these exogenous or surface-derived signals can lead to the activation of the mitotic engine and drive cell proliferation as seen in AD. Candidate growth factors, elevated in the AD brain include, but are not limited to, neurotrophic factors, nerve growth factor (NGF), transforming growth factor beta-1 (TGF-β),[63] platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and basic fibroblast growth factor (bFGF).[64-67] Additionally, insulin-like growth factor-1, which has been shown to mediate transient site-selective increases in tau phosphory-lation in primary cortical neurons,[68] is involved in axonal growth and development and can mediate the cytoskeletal reorganization that occurs during neurite outgrowth and, perhaps, in aberrant neuronal sprouting.[69]

Apoptotic Avoidance in Alzheimer Disease

Apoptotic avoidance by itself can be viewed as both sufficient and necessary for transfor-mative processes. Therefore, we made a systematic study of the caspase cascade proteins in AD by evaluating the presence and/or absence of central initiator (caspases 8 and 9) and the execu-tioner (caspases 3, 6 and 7) proteins of apoptosis.[165] Our study revealed that although up-stream initiator caspases were present in association with the pathological lesions in all cases of AD, downstream executioner caspases, including 3 and 7, that signal the onset of the execution phase of apoptosis, remained at control levels in vulnerable populations indicating an absence of effective distal propagation of the caspase-mediated apoptotic signal(s). This lack of down-stream amplification of signaling via the caspase pathway may well account for the lack of an apoptotic phenotype but the development of a mitotic phenotype in AD. Notably, expression

Table 1. Cell cycle-specific markers found associated with Alzheimer disease

Marker	Role	Association with Alzheimer Disease
Cyclin A	S to G2/M	6,70
Cyclin B	G2/M	21,22,35,71
Cyclin C	No Known Role	
Cyclin D (D3)	G0/G1/ lateG1/S	35,71-73
Cyclin E	G1 to G1/S	21,22,74
p34cdc2/ cdk 1	Late G2/M	6,7,16,35,70,71,75
Cdk4/Cdk6	G1/ G1/S	31,32,35,75,76
Cdk5/p25/p35	G2 D1, D3 G1 Cyclins	17,76-83
Nclk cdc2-like kinase	Cyclin A kinase	17,20,76,84
Cdk7/MPM2	CDK activated kinase	23,72,73
Cdc42/rac	GTPase/cell division	36
p21ras	G protein/MAPK	46,54,55,70,85
MRG 15	M phase regulator	86
Ki-67	LateG1,S,G2,M	21,22,56,87
p105/pRb	G2/M TF	31,56,87
pCNA	Non cell-cycle specific	35
p107/pRb	Cdk2/4/6, check pt	31,46 (negative association)
c-myc	S to G2 checkpoint	46 (negative association)
p53/MDM2	Repressor complex	88,89
ATM	Check-point	46
Raf/Raf-1	Check point kinase	90
p16INK4a p18p15p19	CyclinD/cdk4/6 inhibitors of M phase	19,32,70,72,73,91
p27/Kip1	Cyclin D and E /cdk7 inhibitor	46 (negative association),72,73
WAF-1/ p21/Cip1	Multi-Cyclin /cdk-inihibitor (G1 and S)	92
Polo-like kinase	G2/M check point	93,94

of cyclin/CDKs, in addition to driving cell proliferation and growth control, has dual conserved roles as they are also implicated in apoptotic signaling.[31,51,52]

Redox Imbalance and Cell Cycle Re-Entry

Energy is an obligate requirement for dividing cells. Therefore, before mitosis, there is division and redistribution of cellular organelles such that during late S, G2 and mitotic phases, mitochondrial proliferation is most evident.[166] Notably, in AD, increases in the number of mitochondria are found in the same neurons that also exhibit cell cycle related abnormalities and undergo subsequent oxidative damage and cell death.[167] While in a normally mitotic cell, mitochondrial replication is imperative for providing the energy needed for cell division, in AD where neuronal cell cycle is interrupted or dysfunctional, we suspect that neurons incur a "phase stasis" with excessive mitochondria. Such "excess" mitochondria are then potent sources of free radicals and cause homeostatic and redox imbalances, especially in those redox reactions involving calcium metabolism.[168] Thus, cell cycle dysfunction, when mitochondrial mass is highest, poses an elevated, and possibly chronic, oxidative assault upon the cell, far beyond the blunting capacity of endogenous antioxidants.

Importantly, imbalances in redox homeostasis are also played out via numerous signal transduction cascades, which are also intimately linked to cell cycle control. Indeed, activation of p38 MAPK and ERK links tau phosphorylation, oxidative stress, and cell cycle-related events

Table 2. Cell cycle-associated proteins found in Alzheimer disease

Marker	Role	Association with Alzheimer Disease
PP2A or PP2B	Phosphatase (Cdk5, cdc2)	76,95-98
PP-1		81,95
Cdc25 Cdc25A	Phosphatase G2/M	99,100
PKC/ Wnt path	Translation control	101-109
PKA	Kinase	110,111
PKN	Kinase	112
PI3K	Kinase	113-116
AKT/PKB/RAC	Kinase	112,116-119
TGFBeta/ TAK	Kinase	120,121
p44/p42 MAPK (ERK1/2)	MAP kinase	16,38,54,70,122-135
CamK	Kinase Ca /Calmodulin regulated	136
p38 MAPK	Kinase	37,133,134,137-139
JNK/ (SAPK-2/3) - alpha gamma	Kinase (stress activated)	38,133,134,140
MEK	MAPK Kinase	70,126
GSK-3 and beta Catenin	Proline dependent protein kinase (PDPK)	17,49,76,77,80,81,109,113, 118,119, 122,133,137,141-151
P120/E-cadherin	Adhesion complex	152
c-fos	TF / regulator	153
14-3-3/14-3-3zeta	Adaptor protein	154,155
c-jun/p39, AP-1	TF component	101,153,156-159
Fyn	Transcription factor	160-162
p53	TF / DNA damage	21,22,163
Rho	G-protein	112,164
Rap Rab	G-protein	90
Sos-1	Guanine nucleotide exchange factor	33
Grb-2	Adaptor	33

in AD.[37,38,128,169] MEK, ERK1/2, cyclins, cyclin-dependent kinases and their inhibitors, i.e., p16INK4a family, and p21Ras are elevated early in AD and co-localize in pyramidal neurons with NFT.[70] Neuronal ERK is increased in AD, and phosphorylation, as well as phosphorylation of p38 and CREB, by nerve growth factor or epidermal growth factor, is differentially modulated by oxidative and other stresses.[170] In support of this notion, compromised mitochondrial function was found to lead to increased cytosolic calcium and to the activation of MAPKs (ERK1/2).[127] Likewise, activated forms of ERK are found decreased in cells overexpressing heme oxygenase-1 (HO-1), indicating that tau and HO-1 both serve overlapping protective roles in regulating oxidative stress.[132] Importantly, there is abundant evidence that oxidative stress and free radical damage plays an essential role in the pathogenesis of AD.[38,171,172] Therefore, it is notable that free radicals, free-radical generators, and antioxidants also act as crucial control parameters of the cell cycle.[173,174]

Finally, there is abundant support for the notion that imperfect clearance of proteins, damaged or modified by oxidation processes, contributes to cell death by interfering with essential cell functions.[175] Impairments in the ubiquitin-dependent protein degradation system, which is aimed at clearing and preventing the progressive accumulation of misfolded or aggregated and ubiquitinated proteins, is a cytopathological feature in many neurodegenerative
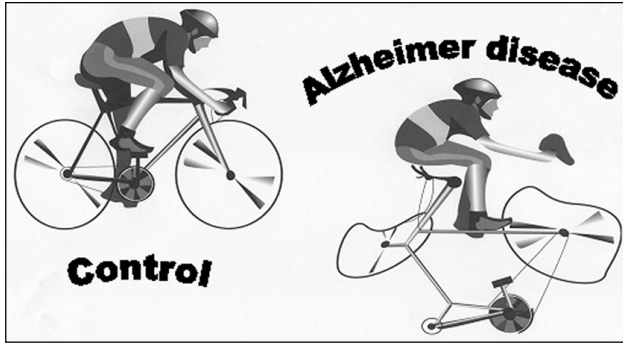
Figure 2. "Cycling towards dementia" involves cell cycle dysregulation in AD.

disorders, including AD.[176,177] In support of this notion, accumulation of phosphorylated neurofilaments and the increase in apoptosis-specific protein and phosphorylated c-Jun is induced by proteasome inhibitors.[178] This speaks to the importance of cellular context in this process, and the fact that the ubiquitin-proteasome pathway plays an important role in the regulation of critical cellular processes, which include the cell cycle, cytoskeletal organization, and gene transcription, e.g., c-fos, p53, p21 and p27. Such proteolysis is known to drive the cell cycle by regulating the oscillations in activity of CDKs and perturbations in this process also likely contribute to the dysregulated cell cycle seen in AD.[179] In this regard, any event that would also upset the balance between the signal transduction pathways for survival, or those for growth, as well as those for death or differentiation, would likely shift this delicate balance. Ultimately, this shift would determine the fate of select neuronal cells and population subsets by largely favoring one set of pathways over another. The net result of this cross table would impact survival or death to the cell and perhaps offer an explanation for the protracted time course, which is seen in most neurodegenerative diseases (see Fig. 1).

Other damaging factors like hyperglycemia, reducing sugars and the presence of reactive oxygen and nitrogen species can have a direct role in mediating protein crosslinking and, thus, the accumulation of undigested material in AD.[171,180,181] In support of this notion, caloric restriction has been shown to selectively modulate the age-associated induction of genes encoding proteins involved in inflammatory and stress responses.[182]

Conclusions

Cycling toward dementia requires an imbalance and despite their supposedly quiescent status, vulnerable neurons in AD display a cell cycle phenotype, albeit an aberrant one (see Fig. 2). Further, it is becoming increasingly apparent that an altered and protracted cell cycle stasis exists in susceptible neurons in AD. In fact, these "abnormalities" may be a partial response to the genotoxic stress and metabolic imbalance common in degenerating neurons. Therefore, any re-emergence of sensitivity to extrinsic signals, i.e., neurotrophic factors, may initiate an attempt to re-enter into the cell division cycle, with progression being limited by the degree of mitotic competence. Successful dysregulation of the cell cycle, coupled with a multilevel apoptotic avoidance system, fulfills both the sufficient and necessary criteria for the initiation of an oncogenic transformation and therefore, early in the course of AD, neurons likely face the recruitment of similar mechanisms,[4] i.e., AD is analogous to cancer. Unfortunate as it may be to our higher-order structures, this opera of cell cycle appears to be unsustainable in neurons and eventually leads to stasis in a specific phase of the cell division cycle, cellular dysfunction and in the end-death.

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