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Alzheimer's disease and the cell cycle

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Review

Abstract. Current views associate the reappearance of cell cycle markers with early events in Alzheimer's disease. Even though, the cell cycle was implicated early in the study of this disease, only recently has it been associated with selective early vulnerability of neurons. The pathological hallmarks of Alzheimer's disease namely tau and amyloid have been associated with having effects on or being affected by cell cycle progression. Indeed the mitogenic component looms large early in the onset of Alzheimer's disease. Although quite a number of markers of reentry have been catalogued, the common denominator is abortosis, the unalterable march towards neuronal dysfunction, stasis and eventually death. We feel that complete understanding of the mechanisms, acting either positively by stimulation or through removal of inhibitory signals will provide promising molecular targets for pharmacological interventions which have been static for a number of years by being relegated to inhibition of the enzyme cholinesterase. In our opinion, investigating more proximal mechanisms will provide answers to changing the natural course of this illness.

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INTRODUCTION

Alzheimer's disease (AD) is a progressive insidious dementia that continues to severe debility and finally ends with death. It affects up to 15% of people over the age of 65 and nearly half of all individuals by the age of 85 (Smith 1998). There is selective loss of cortical neurons within the hippocampus, temporal and frontal lobes. Depending upon the symptoms, onset and regional histopathology many variants of AD have been catalogued thus far. However, the resolution of early mechanisms will have to await a better understanding of the neuronal environment that allows for re-entry into the cell cycle.

The two lesions that form the *sine qua non* of Alzheimer's disease are the neurofibrillary tangle (NFT) and the senile plaque whose distribution is parallel and is present with neuronal loss (Smith 1998). Given that occurrence of these two phenomena are distal as compared to oxidative stress and cell cycle events, we believe that they are are both secondary to an underlying primary event in AD. Hence, the pathology represents successive neuronal compensations. Of course we do not know which of these compensations marks irreversibility in the disease process.

Periodically we see new markers of cell cycle entry being associated with either neuronal pathology present in AD or present in neurons that are vulnerable to changes that lead to AD such as p27 and histone H3 (Ogawa et al. 2003a,b). This accumulating evidence helps cement the early and possibly irreversible fate of these vulnerable neurons. It is fascinating that neurons that have been in a phase called G_0 for nearly 50 to 60 years make compensations that includes among others, an attempted reentry into the cell cycle. This ectopic cell cycle activation is also seen in mitotically active cells such as those seen during neoplastic transformation and neurogenesis (Smith 1998). The mechanisms of cell cycle activation probably do differ at many levels between the above three, but in AD this reentry is incomplete and results in stasis, dysfunction and death, a process that we term abortosis (Raina et al. 2000b).

In AD there in addition to the activation of a number of markers that signal cell growth prior to mitosis including surge in mitochondrial activity, activation of cyclin dependent kinases and signal transduction cascades that lead to tau phosphorylation (Raina et al. 1999a, Zhu et al. 1999). The conclusion is that the susceptible neurons in AD have proceeded to the G_1 phase.

AD PROTEINS ARE ASSOCIATED WITH THE CELL CYCLE

The pathological proteins that are seen in AD along with genetic factors are sensitive to changes in the cell cycle. These include the tau protein, β-protein precursor (βPP) and presenilins. All of these proteins that are associated with increased susceptibility to AD are sensitive to changes in the cell cycle. We will begin with a general introduction to the association of cell cycle with AD.

CYCLING IN ALZHEIMER'S DISEASE

The phenotype of vulnerable primary neurons in AD suggests cycling, rather than being terminally differentiated (Arendt et al. 1995, 1996, 1998, Gerst et al. 2000, Harris et al. 2000, McShea et al. 1997, 1999a,b, Nagy et al. 1997a,b, Smith and Lippa 1995, Vincent et al. 1996, 1997, Zhu et al. 2000a,b). Exit from senescence is seen by the presence of positive modulators of the cell division cycle such as CDK4 and CDK2 (Arendt et al. 1996, McShea et al. 1997). We believe that this is an early feature of the disease and is minimally coincident with oxidative stress which is the earliest feature of the disease to date (Pogocki 2003, Smith 1998). To date, there is no evidence that a nuclear division has been completed in these vulnerable neurons although there is circumstantial evidence of increased DNA, in certain vulnerable neuronal populations (Yang et al. 2003). However, the significance and interpretation of these data needs further investigation since it may in fact represent a completely separate phenomenon (unpublished observation). Additionally to confuse the picture further, proteins associated with putting the brakes on the cell cycle such as p16, are upregulated (McShea et al. 1997). What seems to be plausible given this scenario is that these terminally differentiated neurons in the adult CNS are inherently restricted in their ability to divide. Hence, even though these neurons enter the cell cycle they do not go beyond G_1 and stop short of actual division. Therefore, the neuron is arrested in an "intermediate state" of the cell cycle. However, we think that in fact there may be loss of the normal synchrony that is seen in the cell cycle. Normally during the cell cycle the subsequent phase does not begin until the prior phase has completed (Bowser and Smith 2002). This will account for markers being present from the different phases of the cell cycle without the presence of cell division or even 4n DNA.

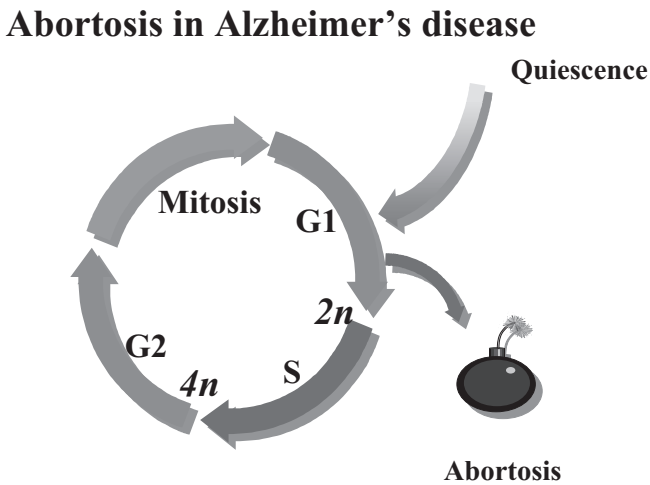

Fig. 1. In Alzheimer's disease the vulnerable neuron enters the cell cycle and then is unable to progress through it with loss of the synchronous nature of the cycle and concomitant dysfunction and neuronal loss. This phenomenon we term abortosis.

The end result is neuronal dysfunction and neuronal loss a phenomenon we term abortosis (Fig. 1).

BOTH AD AND MITOTICALLY ACTIVE CELLS SHARE HYPERPHOSPHORYLATED TAU

The hyperphosphorylated form of the microtubule associated protein called tau (τ) forms the core of NFTs the central intracellular pathological protein seen in AD (Grundke-Iqbal et al. 1986, Iqbal et al. 1984). Thus at this amount of hyperphosphorylation tau cannot participate in microtubular dynamics in the neuron. This inability to participate in the stability of microtubules leads to neuronal dysfunction (Alonso et al. 1996, Lindwall and Cole 1984). Physiological hyperphosphorylation of τ driven by cyclin-dependent kinases (CDKs) occurs when cells are mitotically active (Brion et al. 1985, 1994, Goedert et al. 1993, Kanemaru et al. 1992, Pope et al. 1994). Thus, it shouldn't be a surprise that we find CDKs localized to the intraneuronal compartment in AD. This *in vivo* finding is further supported by *in vitro* assays which show that CDKs can also phosphorylate τ similarly (Arendt et al. 1995, 1996, Nagy et al. 1997a,b Vincent et al. 1996). Since increased phosphorylation and altered microtubule stability are seen during progression through the cell cycle, predictably microtubular abnormalities are also seen in AD (Terry et al. 1964). CDKs are highly sensitive to regulation by growth factors (Raina et al. 2000a). The reactivation of these mitogenic kinases in the AD neuron means that at the least, there is resensitization to the growth factors in the neuronal environment which was not present before (Raina et al. 2000b).

AMYLOID-β, A MITOGENIC FACTOR

At the center of the senile plaque is amyloid-β, a 4.2 kDa polypeptide, the subtractive product of a precursor called βPP, who's gene is encoded on chromosome 21 (Smith 1998). Familial AD is linked to mutations in the *βPP* gene. What is interesting is that βPP is upregulated secondary to mitogenic stimulation (Ledoux et al. 1993). Furthermore, cell cycle-dependent changes regulate βPP metabolism (Suzuki et al. 1994). This is interesting given the role of amyloid and reentry in AD. Also since amyloid-β is mitogenic *in vitro* it can induce and indeed maintain cell cycle events in AD (Pyo et al. 1998, McDonald et al. 1998). Amyloid-β mediates cell death, *in vitro.* This cell death is dependent on the presence of various cell cycle-related elements (Giovanni et al. 1999). Therefore the activation of cell cycle machinery *in vivo* in the neuron could also similarly mediate its toxic effects.

PRESENILINS AND MITOSIS AND AD

The mutations of human presenilin genes *PSEN1* and *PSEN2* are linked to early onset AD. They are localized to chromosomes 14 and 1 (Smith 1998). Although the

function of human presenilins is not fully understood to date, their homologues are involved in Notch processing and signaling. These two proteins have redundant roles in cell fate determination (Struhl and Greenwald 1999, Wong et al. 1997, Ye et al. 1999). Additionally, presenilins interact with centrosomes and kinetochores, thus giving them a significant role during chromosomal segregation and mitosis (Li et al. 1997). Presenilin overexpression leads to G_1 arrest and this overexpression is potentiated by the PS2 (N141I) mutation (Janicki and Monteiro 1999).

Presenilin overexpression in the environment of the adult neuron leads to oxidative stress, loss of calcium balance and also to greater vulnerability to apoptosis (Mattson et al. 1998). Indeed, AD-linked presenilins show greater apoptotic effects (Janicki and Monteiro 1997, Wolozin et al. 1996). In our view, neurons that are vulnerable to AD have exited from G_0 and entered G_1 but are blocked from progressing into S phase at the G_1 /S boundary by the presenilin (and possibly βPP) mutations. This G_1 block would accumulate cell cycle regulatory proteins and produce the stasis as we see in AD. Hence these mutations yield a contracted time course of the basic pathophysiology in AD. Also the presenilin and βPP mutations may lead to the upregulation of cyclin-dependent kinases (CDKs), which can have dual roles in both cell cycle regulation as well as in death signaling (Giovanni et al. 1999, Park et al. 1998). Indeed, the role of the cell cycle braking proteins such as p16, p19 and p21 that also accumulate in AD can act to blunt possible apoptotic stimulation in early AD (Park et al. 1998).

OXIDATIVE STRESS IS CELL CYCLE REGULATED

The role of oxidative stress and free radicals in the pathogenesis of AD is well known (Markesbery 1997, Perry et al. 1998, Smith et al. 1995). Free radicals, free-radical generators and antioxidants function do also control the state of the cell cycle (Curcio and Ceriello 1992, Ferrari et al. 1995, Irani et al. 1997). It is not really a surprise that this is so, given that redox conditions were a crucial factor in cellular decision making early in evolutionary history. The accumulation of p53 secondary to oxidative stress inhibits the cell cycle at G1 (Stewart 1994, Sugano et al. 1995). The mitochondria are potent sources of free radicals and redox dysfunction (Sousa et al. 1997). Also, mitochondrial proliferation is most evident during late S, G_2 and mitotic phases (Barni et al. 1996). Increases in mitochondria number of are found in the same neurons that show cell cycle related abnormalities and undergo subsequent oxidative damage and cell death in AD (Hirai et al. 1998). Thus, cell cycle arrest, at a point when the mitochondrial mass is highest, poses an elevated, chronic, oxidative insult to the cell and quite possibly beyond the capabilities of the cell to abolish.

CONCLUSIONS

The state of the cell cycle in any given environment has unique spatial and temporal control mechanisms. This is very important when cells are terminally differentiated. This terminal differentiation is associated with an attenuation of sensitivity to growth signals, thus effectively following an internal program. The degree of mitotic competence within these neurons is probably vestigial (Raina et al. 1999b). Now in the face of loss of this attenuated sensitivity to extrinsic signals, i.e., neurotrophic factors, these vulnerable neurons attempt to re-enter into the cell division cycle. This reactivation of the cell cycle does not progress to completion but leads to stasis, dysfunction and cell loss. This phenomenon we term abortosis. With markers from various phases of the cell cycle present in these vulnerable neurons, it is our belief that the synchronous nature of the cell cycle must be undermined in AD. That is the onset of the subsequent phase only after the completion of the prior phase of the cycle has been lost in AD. It is interesting that successful dysregulation of the cell division cycle along with an overriding of apoptosis is also seen as the main feature of oncogenic transformation and both features are seen also in AD (reviewed in Raina et al. 2000b). Modulation of one or multiple targets aimed at restoring the previous state of differentiation may in fact alter the natural course of this disease.

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