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"CELL CYCLE RE-ENTRY AND ITS PHARMACOLOGICAL IMPLICATIONS IN NEURODEGENERATIVE DISEASES."

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MASTER OF SCIENCE

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Pharmacological intervention in oxidative stress as a therapeutic target in neurological disorders

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Objectives: Oxidative stress is a major cellular burden that triggers reactive oxygen species (ROS) and antioxidants that modulate signalling mechanisms. Byproducts generated from this process govern the brain pathology and functions in various neurological diseases. As oxidative stress remains the key therapeutic target in neurological disease, it is necessary to explore the multiple routes that can significantly repair the damage caused due to ROS and consequently, neurodegenerative disorders (NDDs). Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is the critical player of oxidative stress that can also be used as a therapeutic target to combat NDDs.

Key findings: Several antioxidants signalling pathways are found to be associated with oxidative stress and show a protective effect against stressors by increasing the release of various cytoprotective enzymes and also exert anti-inflammatory response against this oxidative damage. These pathways along with antioxidants and reactive species can be the defined targets to eliminate

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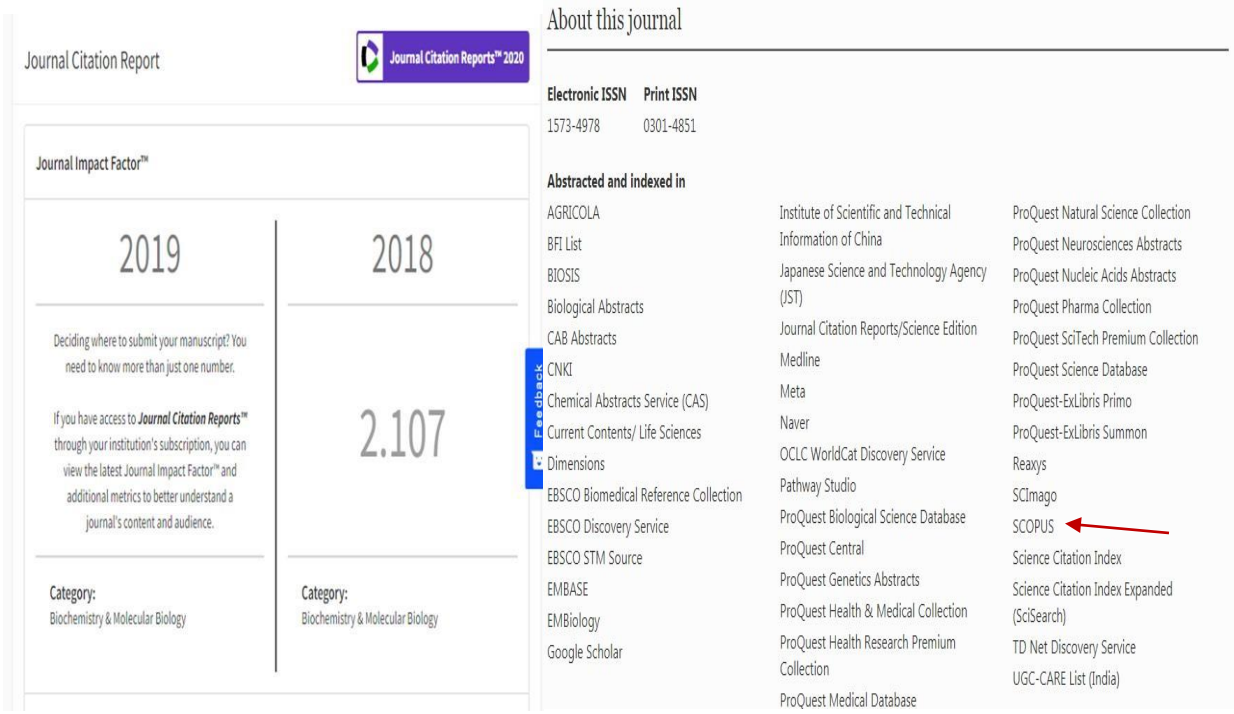

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ABSTRACT

Neurodegenerative diseases (NDDs) are one of the most frightening medical disorders that affect the brain and the nervous system. The limited amount of understanding of the NDDs makes the treatment difficult. In the pathogenesis of many neurodegenerative diseases oxidative stress, considered to play an important role and can also induce DNA damage and later cell cycle re-entry of neuronal cells. Along with oxidative stress, endoplasmic reticulum (ER) stress affects various cellular functions, which also includes cell cycle progression. Research performed for several years has discovered that cell cycle reentry may be abortive, causing neuronal cell death, or non-abortive, leading to DNA synthesis followed by cell death in neurodegenerative diseases. Therefore, aberrant cell cycle reentry is probably a contributing factor in disease progression rather than a secondary phenomenon. In the brain of AD patients with mild cognitive impairment, cell cycle reentry can be seen in the early stage of the disease. In the brain of PD patients, response to various neurotoxic signals, the reentry cell cycle of post-mitotic has been observed, which leads to neuronal death. On the other hand, the primary reason for the initiation of the cell cycle in neurons and the future of dedifferentiating neurons in the pathology of HD and ALS brain is yet unclear. There is the various pharmacological drug that has been developed to reduce the pathogenesis of several NDDs, but they are still not helpful in eliminating the cause of these NDDs. Thus, a major focus of neuroscience research is to examine the mechanism involved in aberrant cell cycle reentry and cell death in neurons to find potential drug targets to treat NDDs.

CONTENT

List of figures

ABBREVIATION

CCR: Cell cycle reentry;

NDDs: Neurodegenerative diseases;

AD: Alzheimer's disease;

PD: Parkinson disease;

HD: Huntington disease;

ALS: Amyotrophic lateral sclerosis;

O.S: Oxidative Stress

ppRb: Hyperphosphorylated pRb

Cdks: cyclin-dependent kinases

MAPK: Mitogen-activated protein kinases

MPTP: 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine

BrdU: Bromodeoxyuridine/5-bromo-2'-deoxyuridine

PCNA: Proliferating cell nuclear antigen

BNDF: Brain-derived neurotrophic factor

HSPs: Heat shock proteins

NMDA: N-methyl-D-aspartate

UPR (Unfolded protein response)

NGF: Nerve Growth factor

DDR: DNA damage response

ATM : Ataxia telangiectasia mutated

CHAPTER 1

1. INTRODUCTION

Aberrant cell-cycle trials have been considered to be connected with several neurodegenerative diseases. Aberrant appearance of cell-cycle proteins along with DNA-replication can be detected in the aging brain. As supreme of these neurons have been lethally discriminated throughout progress and also been inactive for years, cell-cycle reentry in the neuron is both unexpected and perplexing. The cell cycle activity seems to be failed, and the authentic partition of neurons cannot occur. Ironically, growing proof recommended the departure of inactive neurons, that is actively participate in the cell-cycle reemergence upon conveyance mitogenic boosts, fabricated DNA and were then outcome in cell demise [1]. Along with AD [2] strange cell-cycle action has been seen in other neurodegenerative sicknesses like PD [3] and HD [4] as well. Aberrant cell cycle reentry has also been stated in amyotrophic lateral sclerosis (ALS) [5], and ischemia.

sNuclear growth of hyper-phosphorylated pRb & adjusted confinement for E2F-1 happens in ALS affected people in motor neurons (above and below), showing involved neurons return into the predetermined phase of cycle that is G1 phase. [5]. In Parkinson's sickness, ppRb and E2F-1 additionally are extended [6][3] as can be observed bountiful ppRb and E2F-1 based staining of substantia nigra, hippocampus and mid-cerebrum by immunological techniques. For control, against ppRb inexactly nuclear staining of neuronal cells at the core nigra which displayed 0 perceptible stained midfrontal hippocampus and cortex. Inside core nigra and additional to ppRb restricted to Lewy bodies, sign of PD. Additionally, infusion of neurotoxin that is dopaminergic like 1- methyl-4-phenyl-1,2,3,6-tetrahydropyridine when injected to the mouse, can be developed as PD model organism for research, impels the retinoblastoma-E2F based mechanism in dopaminergic neuronal cells after mitosis [3]. It is critical to take note of that, E2F(1)- insufficient mouse models were fundamentally highly impervious by MPTP-actuated cells

that are dopaminergic passing in other wild type forms demonstrating a significant piece of cell phases reemergence in this mouse based system.

1.1 Relevance of cell cycle proteins

The proper functioning of the cell requires proper management and working of cell cycle proteins. These cell cycle proteins regulate various functions inside the cell such as DNA replication and various other cell cycle events. These proteins control the cell starting with one stage then onto the next which prompts the multiplication of cells, needed for the appropriate cell development. Proteins such as cyclin and the cyclin dependent kinases (Cdks) varies in their activity as the neuronal cell advances from S-stage to M-stage [7]. The presence of mitotic development factor set off the outflow of cyclin D/cdk4,6 complex, which controls the reemergence of G0 neuronal cells to the G1 stage of the cell cycle [8]. Enactment of cyclin E/cdk2 complex control the G1/S progress [8]. Without protein cyclin A, neuronal cells reverse back to the G0 stage and again seperate while, within the sight of cyclin A, the cells are resolved to gap and come up short on the capacity to re-separate. On the off chance that on the off chance that they can't finish the cell cycle, they kick the bucket through an apoptotic pathway [9].

Accordingly, when cyclin A is actuated in the late G1 stage, a capture will prompt cell passing. The guideline of the Cyclin–CDK edifices is accomplished through cyclic proteolysis [10]. The appropriate working of cells is controlled through the reasonable articulation of cyclins proteins and restraint of different proteins. Furthermore, to work with the finishing of initial stage and the transition to another, the organized proteolysis of the previous cyclins productively deregulate the incident of the primary stage to an extent following stage continue over the accompanying upregulated of cyclins. The attributes of neurodegenerative problems are not the consequence of its diminished movement but rather enacted withdrawal through from G0 to G1 which starts the tragic passing of the cell [11][12].

1.2 Inducer of neuronal Cell Cycle Reentry

There are various factors such as environmental stress, genetic factors, and cellular stress that trigger the neuronal cell cycle reentry. Reactive oxygen species leads to DNA damage, chromosomal breaks, and aborts the movement of DNA repair protein related with the process of DNA replication in Alzheimer's disease. Other than DNA damage, oxidative stress is proposed to expand the cell cycle reemergence in outcome to UPS (ubiquitin-proteasome system) dysregulation [13]. Also, deposition of DSB intervened practically accounted for the Alzheimer's cerebrum [14]. Moreover, E2F1 are related histone alterations, in this way, fundamental for cell cycle reentry as they may assume an important part in DNA repair or apoptosis [15]. Be that as it may, barely any research have detailed the part of microRNA in the cell cycle reentry, yet microRNA research is still at a starter stage. Furthermore, over-activation of miR26b has also provoked Cdk5 intermediated increased tau phosphorylation in both vivo and in vitro studies. Also in a recent research, induced cyclin E1 up-regulation get induce due to an increase in miR-26b level and p27kip1 expression downregulated facilitated, suggesting important part of the cell cycle [16]. In the same manner disturbance of other miRNA had associated in Alzheimer and other neurodegenerative diseases. Example, amyloid beta facilitated destruction of miRNA gives rise to an spontaneous cell cycle re-entry and death through the MAPK pathway that facilitated the deprivation of tumor suppressor TAp73 in a Alzheimer's disease mouse model .

CHAPTER 2

ROLE OF OXIDATIVE STRESS AND ER STRESS IN NEURONAL CELL CYCLE REENTRY

The question which arises in front of us is that can the stress which is oxidative and at somewhere in molecular level the reactivation of neurons has a slight possibility of being connected. The basic connection in between the cell cycle re-entry as well as oxidative stress can have mitogenic signaling pathways stimulations. The oxidative stress signals in the rising form of ROS level have been somewhere resulted in the increase in the oxidative stress signals which is the effect of taking or having low level of ozone doses, also the reactivation of the cell cycle in rats, in the transcription factors we can also introduce the FoxO family with FoxO3 and FoxO 1a. The level of SOD is increased on the activation of FoxO in the system of antioxidant which causes the repeated manifestation of cyclin D1 which leads to the demise of apoptotic [17]. On the note of same manners, the impairment of mitochondria can somewhere operate the oxidative stress which leads to the neuronal passing and the re-entry of the cell cycle. [18] Interpreted the cycle of the cell reactivation and the death of the neurons, leading to H_2O_2- in nerve extension where the induced stress in the extension of the nerve which is the differentiated factor of the ROS.

H_2O_2 leads for the treatment to decline in the mitochondrial potential typed membrane, the cyclin D1 up-regulation, the pRb is also phosphorylated, also the phosphorylation of the inhibitor of the cycle of the cell which is p27 (kip1). In addition, the regulation of oxidative stress acquires a unique design of the responses of the mitogenic as a side consequence of the impairment of the mitochondria. Which somehow rely on the intensity of the stimuli that is the str4ess stimuli or on the basis of the growth factor of the nerve. Endoplasmic reticulum (ER) stress impacts different cellular functions, which includes the progression cycle of the cell. Several studies have shown that the implication of the stress of the ER stops the progression of the cycle of the cell but thinking

of the mechanism behind all this that is the molecular mechanism and how it stimulates or causes cell cycle arrests. Studies have shown how the stress of ER the induction of the other subsequent of the unfolded protein responses can lead to the cycle of the cell which can lead to the arrest at the earliest phase of M/G2 cycle arrest by lowering the number or quantity of the cyclin B1 which is present [19].

CHAPTER 3

DNA DAMAGE AND CELL CYCLE REENTRY

Proof for a connection between the DNA harm reaction and cell-cycle reemergence comes from the presence of cell-cycle reemergence in neurodegenerative conditions instigated by transformations in DDR (DNA harm reaction) qualities [20]. In the event that in neurodegenerative sickness, bit by bit gathering assortment of demonstrating of DNA harm is noticed, for reference, upregulation of DNA strand break in neurons have been seen in AD [21] and HD [22] while rising 8-oxoguanine sores has been seen in ALS [23] and ischemia [24]. Harm to mitochondrial DNA has been accounted for in PD [25]. Stunningly it was showed that oxidative DNA harm amassed in the human cerebrum with age, and could be answerable for the consistent loss of neuronal capacity saw with more established age. Being a neurodegenerative infection, for example Promotion, PD, and ALS are incredibly age-reliant, this discovering featuring the odds that increments of DNA harm structure the subtle "age part" that may initiate, award to, or award neuronal pathogenesis. As demonstrated in the conversation, cell cycle reemergence and DNA harm are qualities of different neurodegenerative conditions that may act in a show to actuate neuronal end. In any case, just recently have a connection between the two marvels been educated in the appearance concerning neurodegeneration. It was seen that DNA harm can convince cell cycle reemergence in essential neurons [26].

Cell cycle enactment identified with neuronal cell demise began by DNA harm. Moreover, DNA harm and cell cycle reemergence are being seen going with in culture and mouse models showing neuronal passing [27][28] As noticed, DNA harm may enact neuronal cell cycle action and demise, however conflictingly, in a registration way [29]. Contrariwise, cell cycle action, specifically DNA replication action, in neurons could prompt DNA harm. It is predominant that

the S stage is a time of explicitly high powerlessness to DNA strand breaks, for reference through slowing down or falling of replication forks [30]. Tumor silencer/DNA destruct reaction qualities could be related with degenerate cell cycle action and DNA harm at the atomic level. To cite the model, ATM (Ataxia telangiectasia transformed) and p53 can prompt DNA harm designated spots and repress cell cycle activities because of DNA harm yet could trigger DNA fix instruments [31]. Both freak cell cycle action and DNA harm can be initiated by liberation of principal cell measures that are essential for both DNA respectability and legitimate charge of cell cycle quality articulation are one of the potential outcomes. Of late, it has been tracked down that an obsessive pathway which remains with this idea. In the p25 overexpressing model for neurodegeneration, p25/Cdk5 containing HDAC1(Histone deacetylases 1) action, bringing about degenerate cell cycle action and formation of DNA twofold strand breaks, and neurodegeneration [32]. Liberation of HDAC1 by p25/Cdk5 in neurotoxicity. HDAC1 inactivation-actuated cell cycle protein articulation has been seen to be an immediate yield of transcriptional despondency; different examinations are expected to guarantee how HDAC1 inactivation yield in twofold strand breaks. Shows by this investigation is that neurotoxic upgrades can influence chromatin guideline to prompt neurodegeneration. The other chromatin modulators that convincingly may be liberated in neurodegenerative problems and different sicknesses fuse the other HDACs and histone methylases/demethylases. In the finishing up outcome, the point and principal systems of neuronal cell cycle action and DNA harm are still wondering that are still halfway saw, yet they can be said to work in show to prompt neuron demise in numerous neurodegenerative conditions. The acknowledgment of regular key instruments may have fundamental helpful outcomes.

CHAPTER 4

CELL CYCLE REENTRY AND NEURODEGENERATIVE DISEASES

4.1 Alzheimer's Disease and Cell Cycle Reentry

Alzheimer's infection is a improver neurodegenerative problem related with dementia, psychological capacity hindrance, conduct changes, lastly demise [33]. The pathophysiological signs of AD join the production of neurofibrillary tangles (NFTs) and β-amyloid (Aβ) plaques. One of the most seasoned cell measures saw in the AD cerebrum is cell cycle reemergence in neurons [34]. Examination performed during the most recent twenty years has found that phone cycle reemergence might be failed, setting off neuronal cell demise at the G1/S designated spot [35], or on the other hand non-unsuccessful, prompting DNA union followed by cell demise prior to going through G2/M change [36]. In AD, most neurons that return the cell cycle go through DNA blend and stay with hyperploid DNA content (for example above 2C)[37][38][39]. Cell cycle reemergence in these neurons (with hyperploid DNA content) could bring about practical modifications basic the etiology of AD [40]. Tragically, neurons that go through cell cycle reemergence and become hyperploid remained is obscure because of the absence of atomic markers to recognize these phones in vivo. To summarize, unusual cell cycle reemergence gives two decisions to neurons; possibly they can gap and kick the bucket in the S stage or stay bursting at the seams with twofold DNA content at G2/M change. Given that neurons distinctively lacking in mitotic capacity, and no verification of M stage segment has been represented in NDD, cell cycle reappearance in terminally, isolated neurons drive them to death after satisfyingly incorporating new DNA. Thusly, cell cycle reappearance into grown-up neurons set up an early signature of NDDs. The inception of cell-cycle marker proteins in the psyche of AD patients was

first depicted during the 1990s [41][42]. In the mind of AD patients with gentle intellectual debilitation cell cycle re-emergence happens in the beginning phase of infection[43]. Neurons typically stay in the G0 period of the phone cycle, and the variables that brief reemergence to the phone cycle are obscure [44][45]. Minds from AD patients show an abatement or decrease in neuronal DNA fix. The outflow of MRE 11 (meiotic recombination 11 homolog A) intricate which is needed for DNA harm fix, DNA replication, and cell cycle designated spots gest decreased [46]. DNA damage is mutated ataxia telangiectasia (ATM), ataxia-telangiectasia Rad 3 associated (ATR) and repair of DNA damage from post-division neurons similar to E2F1 induces other proteins that control cell decease.[15]. Kruman and colleagues providing proof of the acute part of DNA impairment in abnormal cell cycle reentry in neuronal culture. They demonstrated that neurotoxins such as colchicine, that do not encourage DNA damage and ROS, do not induce cell cycle protein expression / activation. His study showed a link between his β-amyloid along with activation of ATM in the cell cycle of neuronal cells. CDK5 irregular activity triggered by p25 is associated with neuronal fiber changes [47][48]. Lopes and colleagues demonstrate that in vitro treatment of cultured cortical neurons and treatment of rats in vivo with β-amyloid induce cell cycle re-entry regulated by activation of Cdk5 and its inhibitors also block this process, demonstrating the importance of the calpain / Cdk5 path during neuronal cell cycle reentry.[49][50][51]. Therefore, CDK5 inhibition in AD therapy is an attractive target for further study as it is involved in both oxidative stress generation and cell cycle reentry.[52]. Senescence Accelerated Mouse-Prone 8 (SAMP8) is a line of naturally occurring mice widely used in the study of aging because it exhibits an accelerated aging phenotype.

Recent studies have demonstrated that the CCR-mediated pathway of neuronal degeneration in AD is the result of a direct functional link between amyloid-β and tau, which is a major component of bringing both plaques [53]. CDK5 phosphorylates tau at sites that are most frequently overphosphorylated in the AD brain.[54]. In fact, the point of phosphorylation of tau during division was demonstrated by in vitro studies. [55]. Tau mutations from the Paris model Tau mutations induce cell cycle re-entry from the same neuron.[56]. A recent study done in the same way has shown that cell cycle re-entry regulated by simian virus 40 large T antigen (SV40T)

conditional expression causes excessive phosphorylation of tau and NFT formation.[57]. Neuronal CCR may also trigger APP phosphorylation in AD brain. Phosphorylation of T668 in APP695, the main form of neurons [56]. The latest study in a similar manner showed that cell cycle re-entry, conciliated by the conditional expression of the simian virus 40 large T antigen (SV40T), raised the hyperphosphorylation of tau and NFT formation [58]. The neuronal CCR might also lead to APP phosphorylation in AD brains. The phosphorylation of T668 on APP695, the major form in neurons [59], It is known to increase significantly in AD, accelerating the production of Aβ. Additional studies have demonstrated that phosphorylation of T668 to APP may be achieved during the cell cycle by the proteins CDK5 and CDC2 kinase.[60][61][62]. As important evidence, such phosphorylated APP accumulates significantly in neurons that tolerate phosphorylated tau [63]. We strongly suggest that CCR acts on mutual upstream inducers. CCR events are also observed in APP (amyloid-beta precursor protein) transformed mice approximately to 6 months of age in which significant amounts of fed Aβ peptide are expressed. [64]. In addition, three genes, the amyloid beta precursor protein (AβPP) and the homologous genes presenilin 1 and presenilin 2 , are associated with early onset of AD [65] and play an important role in the cell cycle and cell cycle control. It plays an important role in cell cycle and cell cycle regulation. AβPP, a single pass transmembrane protein, is proteolytically cleaved to produce Aβ peptides. Both proteins act as mitogens in the invitro [66][67]. Overexpression of AβPP-BP1 provides further neuronal cloning of the guiding DNA into the S-phase and expression of the cdc2/cyclin B cycle of the cell marker [68][37]. AβPP-BP1 is likely to trigger cell cycle reentry because these phenotypes are evident in AD neurodegeneration. In addition, Rb (retinalblastoma) deficient mice exhibit neuronal defects with reentry of the cells and death in the middle of pregnancy [69][70][71]. In the hippocampus of the AD brain, the phosphorylated histone H3 shows up in the nerve cytoplasm. Rather than their typical limitation in the mitotic cores of effectively partitioning cells, they demonstrate unusual divisions that happen in neurons [72]. In one study, soluble Aβ oligomers have also been shown to trigger neuronal CCR through tau phosphorylation [53]. Irritation is presumably the main causative injury other than amyloid course in the pathogenesis of AD and can cause cell cycle measures [73][74], Inflammation of the AD brain is most likely to start with the amyloid plaque, but is aggravated by the factors which are mostly possible, like persistent amassing of other unusual proteins, spillage of the blood cerebrum hindrance, and reactivation of inert organisms [75], might act major inducer for the lethal CCR in neurons. Possibly a major inducer of lethal

CCR in neurons. Since cell cycle initiation is stringently identified with cell expansion, which is a sign of tumor arrangement, acknowledgment of the part of aggravation in AD neuronal CCR can be acquired from its focal job in the advancement of disease [76]. Malignant growth and AD are two contradicting infections with a typical atomic premise. Loss of control of cell multiplication because of ongoing collection of organic changes [77]. Thus, the CCR of neurons can be observed as a product of the cessation of tumor formation. MYC overexpression is an oncogene and is often involved in tumorigenesis because it encodes a transcription factor that regulates cell growth and proliferation [78]. Elevated MYC protein levels have been observed in vulnerable neurons in AD patients [79]. In fact, under the control of the induced CaMKII gene, an inspiring bite lance-modified mouse (CaMKII-MYC) neuron-specific cell cycle reentry that overexpresses human c-Myc (MYC) neuronal degeneration and cognitive decline [80]. However, it is not known whether entry of the cycle of these cells which is the cell cycle through Rb somewhere initiate the process of degeneration of the neurons in the adult humans. The Rb protein is one of these cell cycle markers and plays an important role in lifelong cell cycle inhibition in adult neuron [81]. Because Rb directly modulates G1/S cell cycle transitions is more cell cycle explicit than other cell cycle controllers utilized in past examinations, the actuation of Rb is recognizable in AD-influenced neurons [82][83]. Understanding the impact of Rb inactivation in the adult CNS may provide more direct evidence of a role for cell cycle reentry in neurodegeneration and AD. Proof of Aβ-actuated cell cycle reemergence in neurons after mitosis is selected by the re-articulation of the presentation of the BrdU, cyclin D1, PCNA. Thus providing valid in order to know the proof or existence of the DNA cells. According to recent studies, the underlying U1 cytoplasmic appropriation design is like the intracellular movement of spliceosomes of cells that are causing mitosis. This recommends that mis-localization of U1 can possibly divert neuronal cell cycle reemergence (CCR), which has been broadly demonstrated in the AD cerebrum [84]. These studies strongly support the important role of abnormal, neuronal cell cycle reemergence in the pathogenic system liable for degeneration of neurons in Alzheimer's disease. (Figure 4.1)

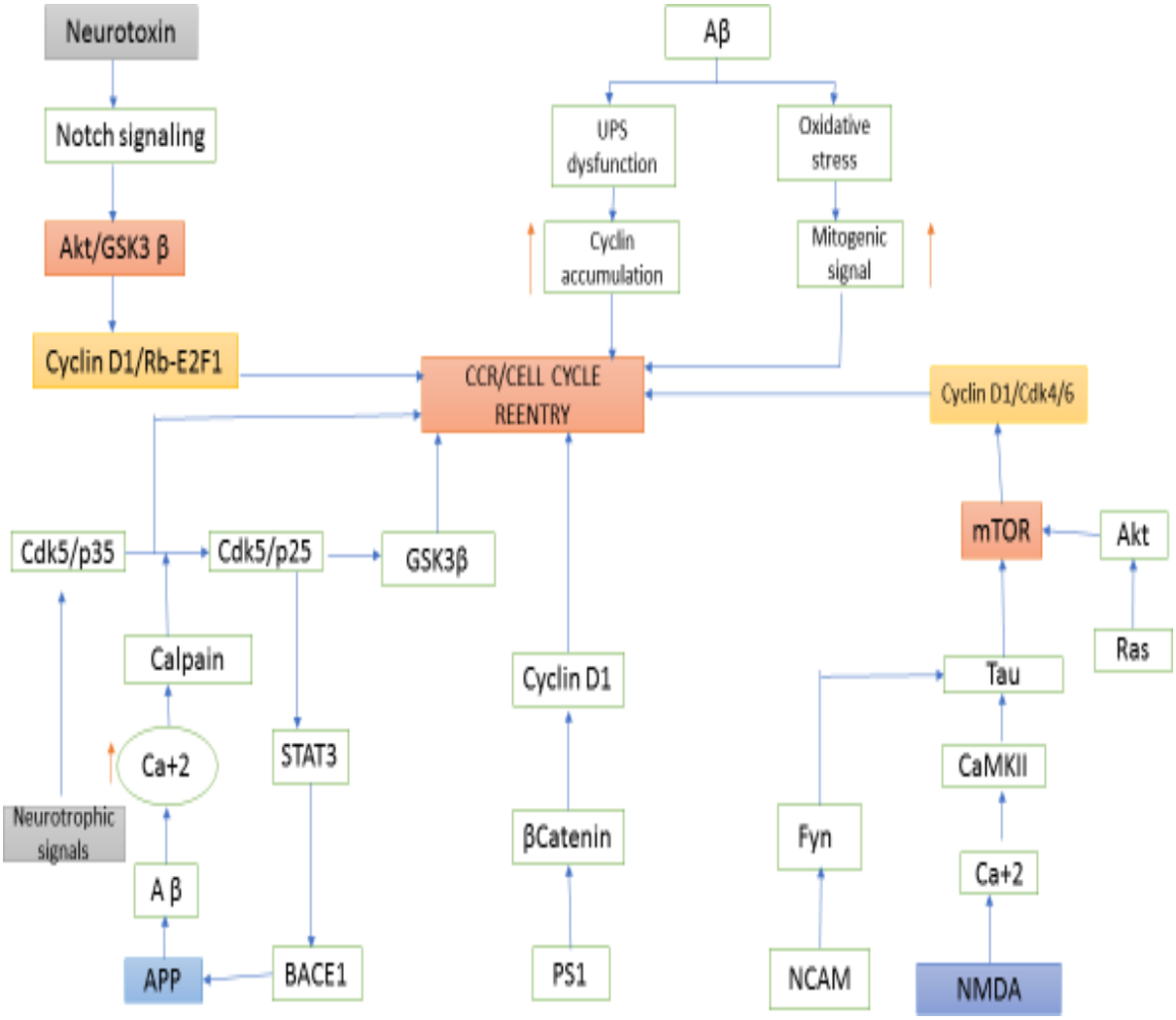

Figure 4.1.1: RELATIONSHIP BETWEEN CELL CYCLE REENTRY AND ALZHEIMER'S DISEASE

4.2 Parkinson's disease and the cell cycle reentry

Parkinson's disease (PD), it is the second most common neurodegenerative disease after AD in old people around the globe. It is categorized by the neuronal impairment of dopaminergic (DA) neurons in the substantia nigra pas compact (SNc) beside reduction in the level of DA in the nigro-striatal dopaminergic pathway inside the brain [85]. The occurrence of insoluble inclusions in neurons known as Lewy bodies, which consist mainly of alpha-synuclein acts as a major hallmark of this disease. Motor dysfunctions in PD are the consequence of subsequent death of dopaminergic neurons in the substantia nigra pars compacta (SNc), parkin, protein deglycase (DJ- 1), Leucine-rich repeat kinase 2 (LRRK2) and α-synuclein are the four major proteins responsible for the pathogenesis of PD [86].In reaction to numerous neurotoxic signals, postmitotic neurons reenter the cell cycle, which result in their death. Neurotoxic agents such as β-amyloid peptide leads to abnormal initiation of mitogen-activated kinase (MEK)–extracellular signal-regulated kinase (ERK) signaling, which reassures the admittance of neurons into the cell cycle, causing in their apoptosis [87]. CRNA is controlled by the MEK-ERK pathway by uplifting the levels of cyclin D1. The surge in cyclin D1 decreases the initiation of cyclin-dependent kinase 5 (cdk5) by its neuronal activator p35 [87]. These research display the role of neurotoxic signals in varying the neuronal signaling mechanism to arouse their entry into the cell cycle, which sooner or later leads to neuronal cell death. Recent studies have proposed that Cdk5 may be important for cell cycle arrest of post-mitotic neurons [88], and Aβ42 changes the localization of Cdk5, resultant in neuronal cell cycle reentry [89][90]. Jordan-Sciutto established an increase in pRb phosphorylation in the substantia nigra which was co-localized with Lewy bodies along with this they also witnessed proteins involved in the activation of cell cycle in the brain of PD patients [91][82][6]. Likewise, mutations in Parkin, prevent cyclin E deprivation and encourage cell cycle reentry in familial PD. Fascinatingly, PARK2 exhibited neuroprotective properties against excitotoxicity in neuronal cell cultures [92]. Thus, the potential neuroprotective mechanism of Parkin could be the lessening in cell-cycle protein expression [93].In addition, other genes intricate in PD such as DJ-1 and LRRK2 have been implicated in cancer, thus have a supporting role of the cell cycle in PD. Furthermore, Ho¨glinger and colleagues demonstrated that in dopaminergic neurons in Parkinson's patients the DNA is replicated [3]. Likewise, using the neurotoxin MPTP they verified an increase in neuron BrdU assimilation and an upsurge in cell cycle protein expression. Additional

significant point in this study was the observation that neurons with a greater expression in caspase-3 also showed an increase in BrdU incorporation. Interestingly, E2F-1 knock-out mice were protected from MPTP toxicity in vivo, so these data suggest that cell cycle re-entry is an important step in this model of neurotoxicity [3]. In addition, studies by Alvira and colleagues revealed that the neurotoxin MPP persuaded the expression of cell cycle proteins in neuronal cell cultures [94][95]. In addition, it has been also proven that oxidative stress-mediated by the MPP induces ROS production, cell cycle re-entry, and DNA damage linked to the initiation of ATM [96] (Figure 5.1).

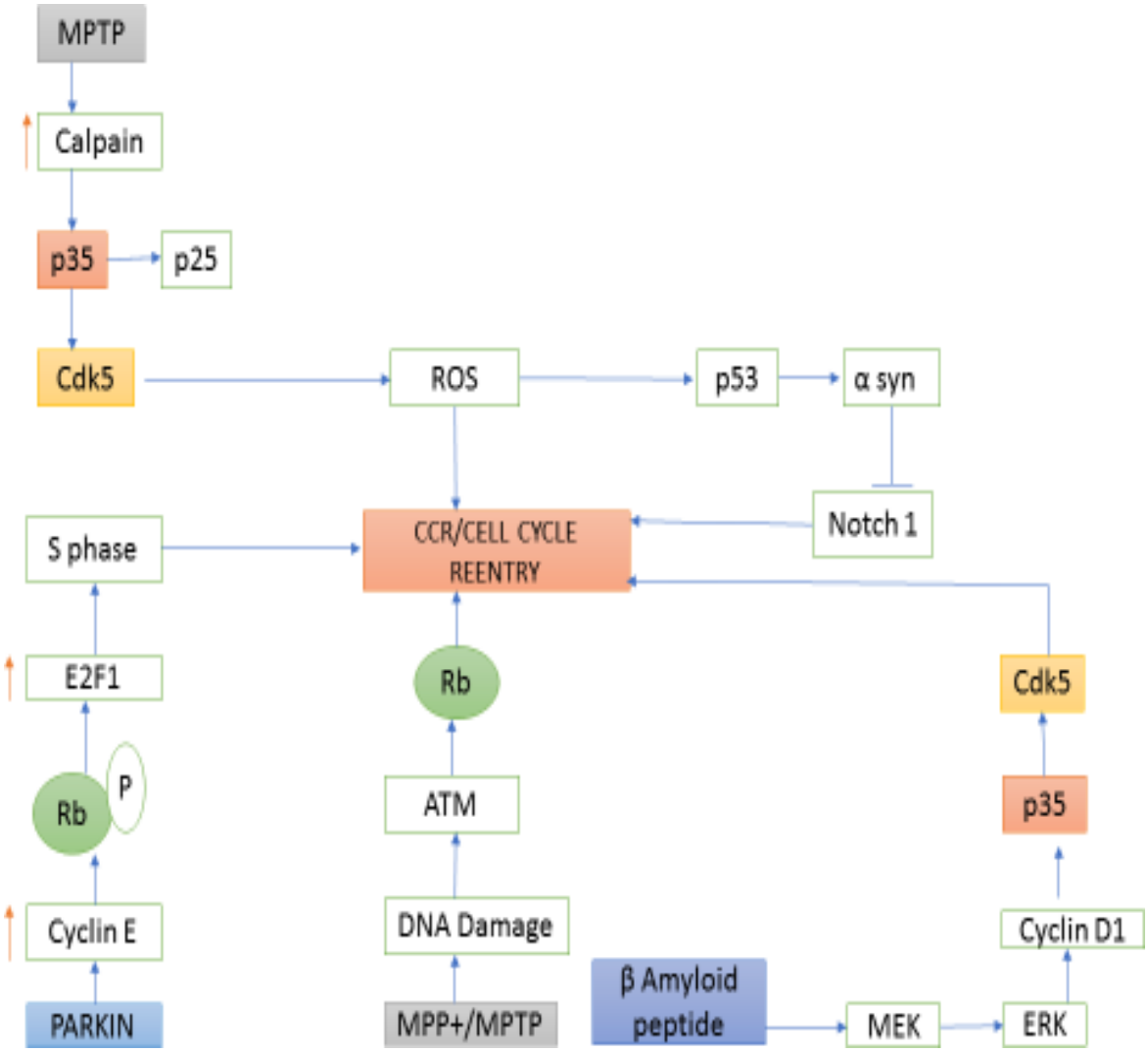

Figure 4.2.1: RELATIONSHIP BETWEEN CELL CYCLE REENTRY AND PARKINSON'S DISEASE

(ATM- AtaxiaTelangiectasia Mutated NOS- Nitric Oxide Synthase)

A better understanding of the complex role played by cell cycle reentry in the pathogenesis of Parkinson's may help to expose a different target for beneficial modifications and clinical treatment.

4.3 Cell Cycle Reentry and other Neurodegenerative disorders

Pathological proof related to cell cycle reentry has been observed in various neurodegenerative disease such as ALS, epilepsy, Huntington disease and ischemia. Through the development of D/CDK4 complexes cell cycle reentry has been observed in this neurodegenerative disease. The cycle of the reemergence was seen during the advancement G0/G1 in neurodegenerative disorders. Coworkers Ranganathan with Browser, worked on ALS patients, and recounted sign of the appearance of cell cycle proteins in the motor sensory cortex [5][97]. These scientists confirmed a nuclear deposition of ppRb, with a simultaneous surge in E2F1 cytoplasmic immunoreactivity, signifying the starring role of abnormal initiation of G1 to S phase controllers deprived of development to synthesis of DNA; precisely, they establish an surge in the intensities of cyclin D and cdk4 in motor neurons inside the motor neuron of ALS patients [5][97]. As of late, freak cyclin F, complex the cell which are seen in neurons are seen over ALS patients. Love affirmed articulation in neuronal cells of Cdk2, and Cdk4, in the cerebrum of diseased people with neurodegenerative issues [98]. Several data have shown that in ischemia most of the neurons in the mind reappear the cell cycle in post mitotic neuron. Wang and his colleagues together set forward signs multifaceted in the cell demise of neuron in ischemia disease, because of actuation of CDKs and cyclins [99][100].

CHAPTER 5

RESULT AND DISCUSSION

1. Evidences suggest that cell cycle markers and regulatory factors, are early signs in AD of cell cycle re-entry.

2. In Parkinson's disease various neurotoxic signals, makes post mitotic neurons in cell cycle to re-enter, which leads to their death.

3. Expression of the mHTT gene induces neurons of HD affected brains for re-entry.

Primary reason for initiation of the neuronal cycle for future of neurons that dedifferentiate pathology of the HD brain is still unknown.

4. Presently, to focus on CCRs which are random or reverses long lasting effects of these changes, several molecular based therapeutic approaches have been designed to remove the effects of disease.

5. Proper analysis based on cell cycle therapy are not assumed for the readings in clinical practice.

6. Study and understanding the mechanism of CCR diverse our scientific dimension and perception for the NDD in neuroscience.

7. The current research has recognized that the conflicts in many signaling mechanisms monitoring cell death and cell proliferation.

8. In conclusion, re-entry of cell cycle has a contributing role in pathogenesis of several NDDs. and therefore, can be used as a therapeutic target to treat NDDs.

CHAPTER 6

CONCLUSION

Knowledge into the fundamental basis for the suggested cell-cycle reentry in the brain or its biological part in neuro-degeneration may deliver a diverse methodical dimension and perception for the NDD in neuro-science and outspread our understanding to improved recognize the neuro-biology of NDD. The detailed understanding of such mitotic dysfunction is still not completely known, oxidative failings do offer the trails from which transformed cell-cycle resistor could ascend. Cell-cycle brokenness is a justification neuronal brokenness in neuro-degenerative disorder with plausible fulfilling ways for controlling the condition. The phone cycle pointers show a significant job in planning the phone for mitotic partition or for checking different purposes like neural connection rule and mischief the recuperating. Moreover, several activating influences forcing cell-cycle reentry have been acknowledged, which comprises, environmental factors, oxidative pressure. Also, the cell cycle variations have been generally concentrated in Alzheimer's disease, while its examination in other neurodegenerative issues like ischemia along with ALS is still at the underlying stage. As of now, to zero in on the variant CCR or converse the constant impacts of such irregularities, a few biomolecules interceded remedial methodologies have been embraced to eliminate the illness manifestations. Example are, Flavo-piridol, Rosco-vitine, and Olomo-ucineas. CDKs inhibitors are used as a medication for the handling of Alzheimer's, Parkinson's, and ALS. Similarly, the possible defensive part of the a few flavonoids, for example, Resveratrol, Apigenin, and Epigallocatechin-gallate has likewise been recognized in order to encourage at the cell-cycle arrest at numerous check-points at Alzheimer's, Parkinson's, and Huntington's disease. More, it is practical to declare that the recent information on the participation of abnormal CCR in the pathogenesis of NDDs is still at a basic phase. Nevertheless, with its continuous significant progression in together the clinical study and therapeutic claim, we look ahead to significant investigation endeavors being attracted this ground to formulate various methods in the near forthcoming future.

REFERENCES

[1] D. J. Bonda *et al.*, “Evidence for the progression through S-phase in the ectopic cell cycle re-entry of neurons in Alzheimer disease.,” *Aging (Albany. NY).*, vol. 1, no. 4, pp. 382–388, 2009, doi: 10.18632/aging.100044.

[2] D. J. Bonda, H. P. Lee, W. Kudo, X. Zhu, M. A. Smith, and H. G. Lee, “Pathological implications of cell cycle re-entry in Alzheimer disease,” *Expert Rev. Mol. Med.*, vol. 12, pp. 1–11, 2010, doi: 10.1017/S146239941000150X.

[3] G. U. Höglinger *et al.*, “The pRb/E2F cell-cycle pathway mediates cell death in Parkinson’s disease,” *Proc. Natl. Acad. Sci. U. S. A.*, vol. 104, no. 9, pp. 3585–3590, 2007, doi: 10.1073/pnas.0611671104.

[4] C. Pelegrí *et al.*, “Cell cycle activation in striatal neurons from Huntington’s disease patients and rats treated with 3-nitropropionic acid,” *Int. J. Dev. Neurosci.*, vol. 26, no. 7, pp. 665–671, 2008, doi: 10.1016/j.ijdevneu.2008.07.016.

[5] S. Ranganathan and R. Bowser, “Alterations in G1 to S phase cell-cycle regulators during amyotrophic lateral sclerosis,” *Am. J. Pathol.*, vol. 162, no. 3, pp. 823–835, 2003, doi: 10.1016/S0002-9440(10)63879-5.

[6] K. L. Jordan-Sciutto, R. Dorsey, E. M. Chalovich, R. R. Hammond, and C. L. Achim, “Expression patterns of retinoblastoma protein in Parkinson disease,” *J. Neuropathol. Exp. Neurol.*, vol. 62, no. 1, pp. 68–74, 2003, doi: 10.1093/jnen/62.1.68.

[7] X. Grana and E. P. Reddy, “Cell cycle control in mammalian cells: Role of cyclins, cyclin dependent kinases (CDKs), growth suppressor genes and cyclin-dependent kinase inhibitors (CKIs),” *Oncogene*, vol. 11, no. 2, pp. 211–219, 1995.

[8] C. J. Sherr, “G1 phase progression: Cycling on cue,” *Cell*, vol. 79, no. 4, pp. 551–555, 1994, doi: 10.1016/0092-8674(94)90540-1.

[9] W. Meikrantz and R. Schlegel, “Apoptosis and the cell cycle,” *J. Cell. Biochem.*, vol. 58, no. 2, pp. 160–174, 1995, doi: 10.1002/jcb.240580205.

[10] A. Udvardy, “The role of controlled proteolysis in cell-cycle regulation,” *Eur. J. Biochem.*, vol. 240, no. 2, pp. 307–313, 1996, doi: 10.1111/j.1432-1033.1996.0307h.x.

[11] A. McShea, P. L. R. Harris, K. R. Webster, A. F. Wahl, and M. A. Smith, “Abnormal expression of the cell cycle regulators P16 and CDK4 in Alzheimer’s disease,” *Am. J. Pathol.*, vol. 150, no. 6, pp. 1933–1939, 1997.

[12] Z. Nagy, M. M. Esiri, and A. D. Smith, “Expression of cell division markers in the hippocampus in Alzheimer’s disease and other nenrodegenerative conditions,” *Acta Neuropathol.*, vol. 93, no. 3, pp. 294–300, 1997, doi: 10.1007/s004010050617.

[13] S. Fulda, A. M. Gorman, O. Hori, and A. Samali, “Cellular stress responses: Cell survival and cell death,” *Int. J. Cell Biol.*, vol. 2010, 2010, doi: 10.1155/2010/214074.

[14] P. Katsel, W. Tan, P. Fam, D. P. Purohit, and V. Haroutunian, “Cycle Checkpoint Abnormalities during Dementia: A Plausible Association with the Loss of Protection against Oxidative Stress in Alzheimer’s Disease,” *PLoS One*, vol. 8, no. 7, pp. 1–11, 2013, doi: 10.1371/journal.pone.0068361.

[15] J. B. Paulina Tokarz1, Kai Kaarniranta2, “Role of the cell cycle re-initiation in DNA damage response of postmitotic cells and its implication in the pathogenesis of neurodegenerative diseases,” pp. 1–35, 2016, doi: 10.2136/vzj2013.08.0148.

[16] S. Absalon, D. M. Kochanek, V. Raghavan, and A. M. Krichevsky, “MiR-26b, upregulated in Alzheimer’s disease, activates cell cycle entry, Tau-phosphorylation, and apoptosis in postmitotic neurons,” *J. Neurosci.*, vol. 33, no. 37, pp. 14645–14659, 2013, doi: 10.1523/JNEUROSCI.1327-13.2013.

[17] N. P. Gómez-Crisóstomo, E. Rodríguez Martínez, and S. Rivas-Arancibia, “Oxidative stress activates the transcription factors FoxO 1a and FoxO 3a in the hippocampus of rats exposed to low doses of ozone,” *Oxid. Med. Cell. Longev.*, vol. 2014, 2014, doi: 10.1155/2014/805764.

[18] M. R. Bianco *et al.*, “Cross-talk between cell cycle induction and mitochondrial dysfunction during oxidative stress and nerve growth factor withdrawal in differentiated PC12 cells,” *J. Neurosci. Res.*, vol. 89, no. 8, pp. 1302–1315, 2011, doi:

10.1002/jnr.22665.

[19] D. Lee *et al.*, “ER stress induces cell cycle arrest at the g2/m phase through eif2α phosphorylation and GADD45α,” *Int. J. Mol. Sci.*, vol. 20, no. 24, pp. 1–13, 2019, doi: 10.3390/ijms20246309.

[20] Y. Yang and K. Herrup, “Loss of neuronal cell cycle control in ataxia-telangiectasia: A unified disease mechanism,” *J. Neurosci.*, vol. 25, no. 10, pp. 2522–2529, 2005, doi: 10.1523/JNEUROSCI.4946-04.2005.

[21] E. Adamec, J. P. Vonsattel, and R. A. Nixon, “DNA strand breaks in Alzheimer’s disease,” *Brain Res.*, vol. 849, no. 1–2, pp. 67–77, 1999, doi: 10.1016/S0006-8993(99)02004-1.

[22] S. L. Anne, F. Saudou, and S. Humbert, “Phosphorylation of huntingtin by cyclin-dependent kinase 5 is induced by DNA damage and regulates wild-type and mutant huntingtin toxicity in neurons,” *J. Neurosci.*, vol. 27, no. 27, pp. 7318–7328, 2007, doi: 10.1523/JNEUROSCI.1831-07.2007.

[23] R. J. Ferrante *et al.*, “Evidence of increased oxidative damage in both sporadic and familial amyotrophic lateral sclerosis,” *J. Neurochem.*, vol. 69, no. 5, pp. 2064–2074, 1997, doi: 10.1046/j.1471-4159.1997.69052064.x.

[24] T. Hayashi, M. Sakurai, Y. Itoyama, and K. Abe, “Oxidative damage and breakage of DNA in rat brain after transient MCA occlusion,” *Brain Res.*, vol. 832, no. 1–2, pp. 159–163, 1999, doi: 10.1016/S0006-8993(99)01409-2.

[25] J. Zhang *et al.*, “Parkinson’s disease is associated with oxidative damage to cytoplasmic DNA and RNA in substantia nigra neurons,” *Am. J. Pathol.*, vol. 154, no. 5, pp. 1423–1429, 1999, doi: 10.1016/S0002-9440(10)65396-5.

[26] B. A. Lu, T., Pan, Y., Kao, S.-Y., Li, C., Kohane, I., Chan, J., & Yankner, “Gene regulation and DNA damage in the ageing human brain,” *Gastroenterology*, vol. 135, no. 5, pp. 1794–1796, 2008.

[27] H. Laine *et al.*, “p19Ink4d and p21Cip1 collaborate to maintain the postmitotic state of auditory hair cells, their codeletion leading to DNA damage and p53-mediated apoptosis,”

J. Neurosci., vol. 27, no. 6, pp. 1434–1444, 2007, doi: 10.1523/JNEUROSCI.4956-06.2007.

[28] J. A. Klein *et al.*, "The harlequin mouse mutation downregulates apoptosis-inducing factor," *Nature*, vol. 419, no. 6905, pp. 367–374, 2002, doi: 10.1038/nature01034.

[29] I. I. Kruman *et al.*, "Cell Cycle Activation Linked to Neuronal Cell Death Initiated by DNA Damage," *Neuron*, vol. 41, no. 4, pp. 549–561, 2004, doi: 10.1016/S0896-6273(04)00017-0.

[30] D. Branzei and M. Foiani, "The DNA damage response during DNA replication," *Curr. Opin. Cell Biol.*, vol. 17, no. 6, pp. 568–575, 2005, doi: 10.1016/j.ceb.2005.09.003.

[31] A. Sancar, L. A. Lindsey-Boltz, K. Ünsal-Kaçmaz, and S. Linn, "Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints," *Annu. Rev. Biochem.*, vol. 73, pp. 39–85, 2004, doi: 10.1146/annurev.biochem.73.011303.073723.

[32] D. Kim *et al.*, "Deregulation of HDAC1 by p25/Cdk5 in Neurotoxicity," *Neuron*, vol. 60, no. 5, pp. 803–817, 2008, doi: 10.1016/j.neuron.2008.10.015.

[33] H. Förstl and A. Kurz, "Clinical features of Alzheimer's disease," *Eur. Arch. Psychiatry Clin. Neurosci.*, vol. 249, no. 6, pp. 288–290, 1999, doi: 10.1007/s004060050101.

[34] K. Herrup, "The involvement of cell cycle events in the pathogenesis of Alzheimer ' s disease," pp. 2–3, 2010, doi: 10.1186/alzrt37.

[35] D. X. Liu and L. A. Greene, "Neuronal apoptosis at the G1 / S cell cycle checkpoint," pp. 217–228, 2001, doi: 10.1007/s004410100396.

[36] C. Kuan *et al.*, "Hypoxia – Ischemia Induces DNA Synthesis without Cell Proliferation in Dying Neurons in Adult Rodent Brain," vol. 24, no. 47, pp. 10763–10772, 2004, doi: 10.1523/JNEUROSCI.3883-04.2004.

[37] Y. Yang, D. S. Geldmacher, and K. Herrup, "DNA Replication Precedes Neuronal Cell Death in Alzheimer ' s Disease," vol. 21, no. 8, pp. 2661–2668, 2001.

[38] B. Mosch, M. Morawski, A. Mittag, D. Lenz, A. Tarnok, and T. Arendt, "Aneuploidy and DNA Replication in the Normal Human Brain and Alzheimer ' s Disease," vol. 27, no. 26,

pp. 6859–6867, 2007, doi: 10.1523/JNEUROSCI.0379-07.2007.

[39] N. López-sánchez *et al.*, “Neuronal tetraploidization in the cerebral cortex correlates with reduced cognition in mice and precedes and recapitulates Alzheimer’s-associated neuropathology,” *Neurobiol. Aging*, 2017, doi: 10.1016/j.neurobiolaging.2017.04.008.

[40] J. M. Frade, N. López-sánchez, J. M. Frade, and N. López-sánchez, “neuronal tetraploidy induced by p75 A novel hypothesis for Alzheimer disease based on neuronal tetraploidy induced by p75 NTR,” vol. 4101, no. March 2016, 2010, doi: 10.4161/cc.9.10.11582.

[41] K. Baumanna, E. Mandelkow, J. Biernata, and E. Mandelkow, “Abnormal Alzheimer-like phosphorylation of tau-protein by cyclin-dependent kinases cdk2 and cdk5,” vol. 336, no. 3, pp. 417–424, 1993.

[42] I. Vincent, M. Rosado, and P. Davies, “Mitotic Mechanisms in Alzheimer ’ s Disease ?,” vol. 132, no. 3, pp. 413–425, 1996.

[43] Y. Yang, E. J. Mufson, and K. Herrup, “Neuronal Cell Death Is Preceded by Cell Cycle Events at All Stages of Alzheimer ’ s Disease,” vol. 23, no. 7, pp. 2557–2563, 2003.

[44] Atabay, “No Title,” pp. 430–439, 2012, doi: 10.1111/j.1471-4159.2011.07259.x.

[45] T. Arendt, “Synaptic degeneration in Alzheimer ’ s disease,” pp. 167–179, 2009, doi: 10.1007/s00401-009-0536-x.

[46] E. Jacobsen, T. Beach, Y. Shen, R. Li, and Y. Chang, “Deficiency of the Mre11 DNA repair complex in Alzheimer ’ s disease brains,” vol. 128, pp. 1–7, 2004, doi: 10.1016/j.molbrainres.2004.05.023.

[47] J. C. Cruz, H. Tseng, J. A. Goldman, H. Shih, and L. Tsai, “Aberrant Cdk5 Activation by p25 Triggers Pathological Events Leading to Neurodegeneration and Neurofibrillary Tangles,” vol. 40, pp. 471–483, 2003.

[48] J. C. Cruz and L. Tsai, “Cdk5 deregulation in the pathogenesis of Alzheimer ’ s disease,” vol. 10, no. 9, 2004, doi: 10.1016/j.molmed.2004.07.001.

[49] J. P. Lopes, C. R. Oliveira, and P. Agostinho, “OS NO E . amyloid- b and prion peptides,” vol. 4101, no. September, 2015, doi: 10.4161/cc.8.1.7506.

[50] J. P. Lopes and C. R. Oliveira, “Alzheimer ’ s disease : the role of Cdk5,” pp. 64–77, 2010, doi: 10.1111/j.1474-9726.2009.00536.x.

[51] J. P. Lopes and P. Agostinho, “Progress in Neurobiology Cdk5 : Multitasking between physiological and pathological conditions,” *Prog. Neurobiol.*, vol. 94, no. 1, pp. 49–63, 2011, doi: 10.1016/j.pneurobio.2011.03.006.

[52] J. O. F. Neurochemistry, “* Department of Chemistry and Purdue Cancer Center, Purdue University, West Lafayette, IN 47907, USA Renovis, Inc., South San Francisco, California, USA,” pp. 265–278, 2008, doi: 10.1111/j.1471-4159.2008.05616.x.

[53] M. E. Seward *et al.*, “Amyloid- b signals through tau to drive ectopic neuronal cell cycle re-entry in Alzheimer ’ s disease,” pp. 1278–1286, 2013, doi: 10.1242/jcs.1125880.

[54] T. Kimura, K. Ishiguro, and S. I. Hisanaga, “Physiological and pathological phosphorylation of tau by Cdk5,” *Front. Mol. Neurosci.*, vol. 7, no. JULY, pp. 1–10, 2014, doi: 10.3389/fnmol.2014.00065.

[55] S. Illenberger *et al.*, “The endogenous and cell cycle-dependent phosphorylation of tau protein in living cells: Implications for Alzheimer’s disease,” *Mol. Biol. Cell*, vol. 9, no. 6, pp. 1495–1512, 1998, doi: 10.1091/mbc.9.6.1495.

[56] V. Khurana, Y. Lu, M. L. Steinhilb, S. Oldham, J. M. Shulman, and M. B. Feany, “TOR-mediated cell-cycle activation causes neurodegeneration in a Drosophila tauopathy model,” *Curr. Biol.*, vol. 16, no. 3, pp. 230–241, 2006, doi: 10.1016/j.cub.2005.12.042.

[57] A. Mcshea *et al.*, “Neuronal cell cycle re-entry mediates Alzheimer disease-type changes,” vol. 1772, pp. 467–472, 2007, doi: 10.1016/j.bbadis.2006.09.010.

[58] K. H. J. Park, J. L. Hallows, P. Chakrabarty, P. Davies, and I. Vincent, “Conditional Neuronal Simian Virus 40 T Antigen Expression Induces Alzheimer-Like Tau and Amyloid Pathology in Mice,” vol. 27, no. 11, pp. 2969–2978, 2007, doi: 10.1523/JNEUROSCI.0186-07.2007.

[59] Yusuf, “No Title終末論的永劫回帰とモダニズムの弁証法,” 日本ワーグナー協会編『年刊ワーグナー*1990*』, vol. 4, no. 1, p. 東京：音楽之友社：pp. 56-79, 1990.

[60] T. Suzuki, M. Oishi, D. R. Marshak, A. J. Czernik, A. C. Nairn, and P. Greengard, "protein," vol. 13, no. 5, 1994, doi: 10.1002/j.1460-2075.1994.tb06360.x.

[61] K. Iijima *et al.*, "Neuron-Specific Phosphorylation of Alzheimer ' s □ -Amyloid Precursor Protein by Cyclin-Dependent Kinase 5," 2000.

[62] F. Liu *et al.*, "Regulation of amyloid precursor protein (APP) phosphorylation and processing by p35 / Cdk5 and p25 / Cdk5," vol. 547, pp. 193–196, 2003, doi: 10.1016/S0014-5793(03)00714-2.

[63] M. Lee *et al.*, "Article phosphorylation," pp. 83–95, 2003, doi: 10.1083/jcb.200301115.

[64] N. H. Varvel, K. Bhaskar, A. R. Patil, S. W. Pimplikar, K. Herrup, and B. T. Lamb, "Neurobiology of Disease A □ Oligomers Induce Neuronal Cell Cycle Events in Alzheimer ' s Disease," vol. 28, no. 43, pp. 10786–10793, 2008, doi: 10.1523/JNEUROSCI.2441-08.2008.

[65] M. I. Prat *et al.*, "Presenilin 1 overexpressions in Chinese hamster ovary (CHO) cells decreases the phosphorylation of retinoblastoma protein: Relevance for neurodegeneration," *Neurosci. Lett.*, vol. 326, no. 1, pp. 9–12, 2002, doi: 10.1016/S0304-3940(02)00298-7.

[66] D. C. Greg Schuberta and T. O. Tilman Saitoh, "Amyloid beta protein precursor is a mitogen," *Biochem. Biophys. Res. Commun.*, vol. 165, no. 29, pp. 1155–1161, 1989.

[67] E. A. Milward *et al.*, "The amyloid protein precursor of Alzheimer's disease is a mediator of the effects of nerve growth factor on neurite outgrowth," *Neuron*, vol. 9, no. 1, pp. 129–137, 1992, doi: 10.1016/0896-6273(92)90228-6.

[68] X. Zhu, A. K. Raina, and M. A. Smith, "Cell cycle events in neurons: Proliferation or death?," *Am. J. Pathol.*, vol. 155, no. 2, pp. 327–329, 1999, doi: 10.1016/S0002-9440(10)65127-9.

[69] A. R. Clarke *et al.*, "Requirement for a functional Rb-1 gene in murine development," *Nature*, vol. 359, no. 6393, pp. 328–330, 1992, doi: 10.1038/359328a0.

[70] T. Jacks, A. Fazeli, E. M. Schmitt, R. T. Bronson, M. A. Goodell, and R. A. Weinberg, "Effects of an Rb mutation in the mouse," *Nature*, vol. 359, no. 6393, pp. 295–300, 1992, doi: 10.1038/359295a0.

[71] Lee E Chang C Hu N, "Mice deficoent for Rb are non viable and show defects in neurogenesis and haematupoiesis," *Nature*, vol. 359, pp. 710–713, 1992.

[72] O. Ogawa *et al.*, "Ectopic localization of phosphorylated histone H3 in Alzheimer ' s disease: a mitotic catastrophe?," pp. 524–528, 2003, doi: 10.1007/s00401-003-0684-3.

[73] T. Wyss-coray and J. Rogers, "Inflammation in Alzheimer Disease — A Brief Review of the Basic Science and Clinical Literature," pp. 1–24, 2012.

[74] F. L. Heppner, R. M. Ransohoff, and B. Becher, "Immune attack : the role of inflammation in Alzheimer disease," *Nat. Publ. Gr.*, vol. 16, no. 6, pp. 358–372, 2015, doi: 10.1038/nrn3880.

[75] C. K. Glass, K. Saijo, B. Winner, M. C. Marchetto, and F. H. Gage, "Review Mechanisms Underlying Inflammation in Neurodegeneration," *Cell*, vol. 140, no. 6, pp. 918–934, 2010, doi: 10.1016/j.cell.2010.02.016.

[76] S. M. Crusz and F. R. Balkwill, "Inflammation and cancer : advances and new agents," pp. 1–13, 2015, doi: 10.1038/nrclinonc.2015.105.

[77] M. A. Blasco, L. Partridge, M. Serrano, G. Kroemer, and C. Lo, "Review The Hallmarks of Aging," no. Figure 1, 2013, doi: 10.1016/j.cell.2013.05.039.

[78] C. V Dang, A. Le, and P. Gao, "MYC-Induced Cancer Cell Energy Metabolism and Therapeutic Opportunities," vol. 15, no. 21, pp. 6479–6484, 2009, doi: 10.1158/1078-0432.CCR-09-0889.

[79] I. Ferrer, R. Blanco, M. Carmona, and B. Puig, "Phosphorylated c-MYC expression in Alzheimer disease , Pick ' s disease , progressive supranuclear palsy and corticobasal degeneration," pp. 343–351, 2001.

[80] H. G. Lee *et al.*, "The neuronal expression of MYC causes a neurodegenerative phenotype in a novel transgenic mouse," *Am. J. Pathol.*, vol. 174, no. 3, pp. 891–897, 2009, doi:

10.2353/ajpath.2009.080583.

[81] K. Herrup and Y. Yang, “Cell cycle regulation in the postmitotic neuron : oxymoron or new biology ?,” vol. 8, no. May, 2007, doi: 10.1038/nrn2124.

[82] K. L. Jordan-Sciutto, L. M. Malaiyandi, and R. Bowser, “Altered distribution of cell cycle transcriptional regulators during Alzheimer disease,” *J. Neuropathol. Exp. Neurol.*, vol. 61, no. 4, pp. 358–367, 2002, doi: 10.1093/jnen/61.4.358.

[83] A. Thakur *et al.*, “Retinoblastoma protein phosphorylation at multiple sites is associated with neurofibrillary pathology in Alzheimer disease.,” *Int. J. Clin. Exp. Pathol.*, vol. 1, no. 2, pp. 134–46, 2008, [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/18784806%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC2480556.

[84] B. Bai, “U1 snRNP Alteration and Neuronal Cell Cycle Reentry in Alzheimer Disease,” vol. 10, no. March, pp. 1–10, 2018, doi: 10.3389/fnagi.2018.00075.

[85] D. J. Eve *et al.*, “Basal ganglia neuronal nitric oxide synthase mRNA expression in Parkinson’s disease,” *Mol. Brain Res.*, vol. 63, no. 1, pp. 62–71, 1998, doi: 10.1016/S0169-328X(98)00259-9.

[86] G. Abbruzzese *et al.*, “A pilot trial of deferiprone for neurodegeneration with brain iron accumulation,” *Haematologica*, vol. 96, no. 11, pp. 1708–1711, 2011, doi: 10.3324/haematol.2011.043018.

[87] P. K. Modi, N. Komaravelli, N. Singh, P. Sharma, and R. K. Assoian, “Interplay between MEK-ERK signaling , cyclin D1 , and cyclin-dependent kinase 5 regulates cell cycle reentry and apoptosis of neurons,” pp. 3722–3730, 2012, doi: 10.1091/mbc.E12-02-0125.

[88] J. Zhang, S. A. Cicero, L. Wang, R. R. Romito-digiacomo, Y. Yang, and K. Herrup, “Nuclear localization of Cdk5 is a key determinant in the postmitotic state of neurons,” vol. 105, no. 25, 2008.

[89] J. Zhang and K. Herrup, “a n d e s i o s c i e n c e o n o t d i s t r i b u t e a n d e s i o s c i e n c e o n o t d i s t r i b u t e,” vol. 10, no. 8, pp. 1208–1214, 2011, doi: 10.4161/cc.10.8.15328.

[90] J. Zhang, H. Li, O. Yabut, H. Fitzpatrick, G. D. Arcangelo, and K. Herrup, "Cdk5 Suppresses the Neuronal Cell Cycle by Disrupting the E2F1 – DP1 Complex," vol. 30, no. 15, pp. 5219–5228, 2010, doi: 10.1523/JNEUROSCI.5628-09.2010.

[91] K. L. Jordan-sciutto, G. Wang, M. Murphy-corb, and C. A. Wiley, "Induction of Cell-Cycle Regulators in Simian Immunodeficiency Virus Encephalitis," *Am. J. Pathol.*, vol. 157, no. 2, pp. 497–507, 2000, doi: 10.1016/S0002-9440(10)64561-0.

[92] S. Veeriah, L. G. Morris, D. Solit, and T. A. Chan, "The familial Parkinson disease gene PARK2 is a multisite tumor suppressor on chromosome 6q25.2-27 that regulates cyclin E," *Cell Cycle*, vol. 9, no. 8. pp. 1451–1452, 2010, doi: 10.4161/cc.9.8.11583.

[93] L. G. T. Morris, S. Veeriah, and T. A. Chan, "Genetic determinants at the interface of cancer and neurodegenerative disease," *Oncogene*, vol. 29, no. 24. Nature Publishing Group, pp. 3453–3464, 2010, doi: 10.1038/onc.2010.127.

[94] D. Alvira *et al.*, "Inhibition of cyclin-dependent kinases is neuroprotective in 1-methyl-4-phenylpyridinium-induced apoptosis in neurons," *Neuroscience*, vol. 146, no. 1, pp. 350–365, 2007, doi: 10.1016/j.neuroscience.2007.01.042.

[95] D. Alvira, I. Ferrer, J. Gutierrez-Cuesta, B. Garcia-Castro, M. Pallàs, and A. Camins, "Activation of the calpain/cdk5/p25 pathway in the girus cinguli in Parkinson's disease," *Park. Relat. Disord.*, vol. 14, no. 4, pp. 309–313, 2008, doi: 10.1016/j.parkreldis.2007.09.005.

[96] A. Camins *et al.*, "Activation of ataxia telangiectasia muted under experimental models and human Parkinson's disease," *Cell. Mol. Life Sci.*, vol. 67, no. 22, pp. 3865–3882, 2010, doi: 10.1007/s00018-010-0408-5.

[97] S. Ranganathan and R. Bowser, "p53 and Cell Cycle Proteins Participate in Spinal Motor Neuron Cell Death in ALS~!2010-02-16~!2010-02-19~!2010-04-14~!," *Open Pathol. J.*, vol. 4, no. 1, pp. 11–22, 2010, doi: 10.2174/1874375701004010011.

[98] S. Love, "Neuronal expression of cell cycle-related proteins after brain ischaemia in man," *Neurosci. Lett.*, vol. 353, no. 1, pp. 29–32, 2003, doi: 10.1016/j.neulet.2003.09.004.

[99] B. Wang, K. Liu, F. T. Lin, and W. C. Lin, "A role for 14-3-3τ in E2F1 stabilization and

DNA damage-induced apoptosis," *J. Biol. Chem.*, vol. 279, no. 52, pp. 54140–54152, 2004, doi: 10.1074/jbc.M410493200.

[100] Y. Wen, S. Yang, R. Liu, and J. W. Simpkins, "Cell-cycle regulators are involved in transient cerebral ischemia induced neuronal apoptosis in female rats," *FEBS Lett.*, vol. 579, no. 21, pp. 4591–4599, 2005, doi: 10.1016/j.febslet.2005.07.028.