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Cyclin Dependent Kinase 11, Neuroinflammation and Alzheimer's Disease: A Review

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Abstract

Aging is the main risk factor for Alzheimer's disease (AD). With aging, inflammation has been recognized as potential trigger for starting the neurodegenerative cascade leading to neuronal death. Before Aβ and tau accumulation, evidence has put alterations of the cell cycle at the core of these processes.

Still, a number of features of the cell cycle re-entry phenotype have remained elusive to the role of ectopic protein expression in the process of neuroinflammation and consequently neuronal cell death. Recently, a novel cyclin dependent kinase CDK11 has been found to be involved in astrocyte mediated inflammatory response and Alzheimer's disease.

In this review, we aim to establish the missing part of the puzzle between neuroinflammation and APP / Aβ deregulation in AD by evaluating the role of a cyclin, CDK11.

CDK11 may play a vital role in cell cycle re-entry in AD neurons in an APP-dependent manner, thus presenting an intriguing novel function of the APP signaling pathway in AD.

Keywords: Neuroinflammation; Alzheimer's disease; Inflammation; CDK11

Introduction

Aging is an unavoidable process during the course of our lifetimes. Among the most vulnerable cells affected by aging are our brain cells [1]. Cells in the brain experience oxidative stress, accumulation of damaged proteins, alterations in energy homeostasis, immunological and inflammatory response [1] and this is characterized by impaired function of signaling mechanisms and altered gene expression [2]. Still, these changes during aging are exacerbated in the vulnerable area of the brain in which cells may fail to respond adaptively to changes resulting in neurodegenerative disorders.

The most prominent type of dementia today is Alzheimer's disease, exceeding 5 million cases in US alone [3]. Two types of AD are recognized, one that is less prevalent, the familial type or FAD which comprises about 1 to 5% of all cases and the more prevalent or sporadic form of AD (SAD) for which no certain etiological factors can be named for the occurrence of the disease.

Neuroinflammation invariably accompanies aging and has been shown to be a strong contributing factor of AD [4-6]. Pathological markers of inflammation are enriched in brain areas affected by AD [7,8]. When analyzed in individuals with high plaque content and no sign of dementia investigators found also no trace of inflammation [9].

These two features made neuroinflammation an area of interest for finding novel ways in developing a therapy for AD [10]. Cell cycle cyclins should be taken into account when conceptualizing new strategies for AD treatment [11]. Here in this mini review we will elaborate the role of CDK11 in inflammation and its relevance to AD.

CDK 11

Post-mitotic neurons are typically terminally differentiated and in a quiescent state. For some time there has been a notion that altered cell cycle events in vulnerable neurons precede the occurrence of amyloid-β (Aβ) and neurofibrillary tangles, the hallmarks of AD [1,12,13], and lead to degeneration of selected neuronal populations in the hippocampus and other cortical brain regions. Ectopic expression of a number of mitosis-specific proteins has been reported in susceptible neurons in AD leading to neuronal cell death in the G2/M phase of the cell cycle [14-22]. Also, an interesting view has emerged based on new data concerning APP signaling processing [23-25], i.e. Aβ in an oligomeric form may push neuronal cells into the cell cycle, opening the door to neurodegeneration and consequently cell death [24]. Except for CDK5 [26], CDK11 shows an altered expression in AD vulnerable neurons which may be related to APP signaling processes [27].

CDK11 is found to regulate the G2/M phase of the cell cycle by interacting with cyclin D3 [28]. In humans, CDK11 is encoded by two highly homologous genes; named Cdc2L1 and Cdc2L2 (cell division

control 2 like). The CDK11 is also named PITSLRE for its conserved motif in its kinase domain and involves major isoforms from a number of splice variants (at least 10 CK11 isoforms have been cloned in eukaryotic cells, with their molecular weight varying from 46 to 110 kDa [29]. Major isoforms are the CDK11 p110, CDK11 p58 [30,31], and CDK11 p46 [32]. The largest CDK11, CDK11 p110 is a 779-amino-acid containing protein, representing the whole gene, and is ubiquitously expressed in all cell lines and constantly through the cell cycle [30]. CDK11p110 localizes to both splicing factor compartments (SFC-s) and to the nucleoplasm [33]. Recently Yokoyama et al. [34] reported that CDK11 p110 is a Ran GTP-dependent microtubular stabilization factor that has an essential role in spindle assembly formation.

The smaller CDK11 p58 isoform is cell-cycle regulated, and its synthesis occurs through internal ribosome entry site (IRES), which is used only in the G2/M transition [35]. Although CDK11 p58 and CDK11 p110 share many of the same sequences, including the kinase domain, the two isoforms are involved in different regulatory pathways in eukaryotic cells. CDK11 p58 is closely associated with cell cycle arrest and apoptosis in a kinase dependent manner by caspase cleavage, producing an apoptotic kinase regulator, CDK11 p46 [36-38]. Recent studies also revealed that CDK11 is implicated in differentiation, neuronal physiology, androgen receptor attenuation [39] centrosome maturation, bi-polar spindle formation, centromere cohesion [34,38,40] and tumorogenesis [38,41,42] (Figure 1).

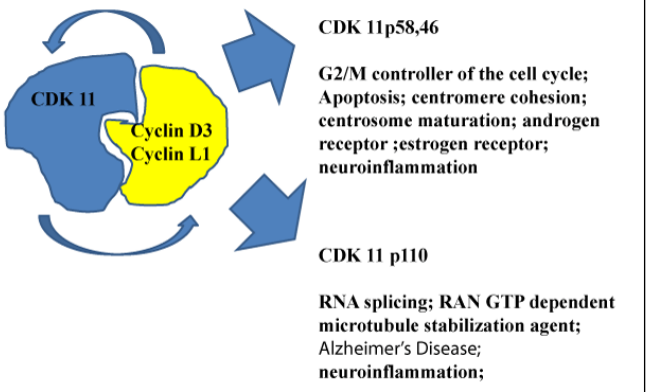

Figure 1: Diverse roles of CDK 11 and its isoforms.

CDK11 is ectopically expressed in AD [27]. By using a polyclonal antibody for CDK11, Bajic et al. [27] found that CDK11 was only expressed in the cytoplasm and cellular processes of the pyramidal neurons in many cases of AD, yet in most controls CDK11 was expressed specifically in the nuclei of post-mitotic neurons. CDK 11 has been found to be regulated by checkpoint kinase 2 (CHK2), a kinase with DNA damage and DNA damage independent functions [43].

This kinase has been also found to phosphorylate tau at an AD-related site enhancing tau toxicity, suggesting a potential role of this kinase in AD [44].

Inflammation, CDK 11 and AD

Astrocytes and microglia play an important role in the development and progression of Alzheimer's disease [8]. Astrocytes as neuronal support cells have a role in regulation of brain homeostasis and development thus providing metabolic and trophic support, promote repair processes and mediate brain inflammatory response through the secretion of various cytokines [45] and recently some cyclins such as CDK11 [46-48]. Activation of astrocytes in central nervous system inflammation leads to a disturbance of crosstalk between astrocytes and neurons, and that this may contribute to the death of neurons.

Liu et al. [48] showed LPS stimulated astrocyte condition medium causes PC 12 cells to upregulate CDK11 (p58) and consequently causes neuronal apoptosis. CDK11 (p58) knockdown in PC12 cells represses neuronal apoptosis. The AKT signaling pathway is involved in the CDK11 (p58)-induced neuronal apoptosis process.

Also, there has been a strong relationship of inflammatory responses due to astrocyte activation and neuronal death [46,47]. Astrocytes are the major glial subtype and are important effectors that participate in the pathogenesis of numerous neural disorders, including trauma, stroke, aging, development, genetic, idiopathic or acquired neurodegenerative diseases. Liu et al. [46] has found a correlation between the expression of CDK11 p58 in astrocytes that where activated by lipopolysacharide or LPS and inflammation markers. Knockdown of CDK11 p58 by small-interfering RNAs (siRNAs) reduced the LPS-induced astrocyte inflammatory response, while overexpression CDK11p58 enhanced the process. This process was in part mediated by the p38 and JNK MAPK pathways [46].

Disturbance of homeostasis can lead to instability, where glial cells that beneficially promote tissue repair and pathogen elimination in excessive activity may also have detrimental effects.

Liu et al. [47] found that a key inflammatory mediator beta-1,4-galactosyltransferase 1 (beta-1,4-GT 1) has been associated with CDK11 p58 in LPS challenged rat primary astrocytes. This illustrates that CDK11 (p58) astrocyte activation promotion depends on β-1,4-GalT-I. Ji et al. [49] showed that CDK11 and its associated cyclin D3 are expressed in damaged spinal cord of the rat. The authors also reported co-localization CDK 11 with β-1,4-GalT-I in the damaged spinal cord suggesting an important role of CDK 11 in spinal cord physiology. The other partner of CDK11, beta-1,4-galactosyltransferase 1 (beta-1,4-GT 1) is regularly present in LPS induced inflammation in astrocyte primary cultures of rats [49] suggesting inflammation is key in the processes of neuronal cell death.

Schwann cell proliferation is also a sign of inflammation in the PNS. Duan et al. [50] presented that Schwann cell proliferation could be repressed by the complex CDK11 p58/cyclin D3, also leading to apoptosis.

The identification of factors that regulate reactive astrogliosis is of practical interest for the development of therapeutic strategies to reduce neural damage and promote regeneration after CNS injuries and decrease neuronal death in neurodegenerative disorders. It will be interesting in the future to identify and characterize whether CDK11 p58 produced by astrocytes can regulate neuronal death during pathological states in the CNS. Chronic inflammatory diseases and conditions such as atherosclerosis, diabetes, obesity, CVD, depression represent a risk factor leading to AD [51-54].

Concerning microglia, Hoozemans et al. [55] found that that there is an inversion of microglial activity and the time that has passed during process of the disease. Microglia cells go into senescence or become dysfunctional as disease progresses, suggesting first that neuroinflammation is an early, first hit in the process of

neurodegeneration that may take decades. Impaired microglia cells may act as nesting hot spots for non degraded and/or non cleared degenerate neurites and consequently accumulating aggregation of peptides that are aggregated further as plaques.

In regard to AD, stimulating the inflammatory response with LPS or IL-1β, results in an increase of APP synthesis in primary cortical neurons [56] in mice and rat brains [57].

Head injuries in mice models and humans are reported to be accompanied by an increase of APP, Aβ and plaque deposition [58-60]. Because of an appropriate response of the amyloid system in head injuries, research has questioned the assumption that Aβ is the sole toxic agent in its oligomeric form that accumulates intraneuronally but that APP is the main substituent of neuron demise [61].

The most promising hypothesis is that APP is accompanied by Aβ species in swollen axons in patients that have been found to have high levels of APP [8,62] and autophagy vacuoles that include PS 1 as well as other lysosomal proteins. The process of autophagy has also been linked to CDK 11 which is critically required for autophagic flux and cargo digestion [63].

Aberrant APP processing by accompanying axonal leakage are in agreement with the findings that Aβ plaques in AD contain not only Aβ 40 and 42 but also a substantial amount of truncated APP [8].

CDK 11 and APP

Previous results of the *in vitro* studies using M 17 cells suggest a new role of CDK11 in APP signal transduction processing as a dependent receptor [27]. For instance, there is a γ-secretase independent mechanism of signal transduction of APP, suggesting an alternative mechanism for APP signal transduction.

Has and Yankner [64] reported that in presenilin-1/2-deficient cells (PS-KO) APP retained the ability to activate Tip 60 suggesting that APP is able to activate transcription independently of γ-secretase cleavage. This is possible as Tip 60 is recruited to the membrane which leads to its activation through a cyclin-dependent kinase mediated phosphorylation process. This proposed mechanism would allow signaling to be regulated in multiple ways through CDKs [64].

Cyclin B1 and cyclin D1 are elevated in PC12 cells with APPswe mutation and this data has been substantiated in the brain tissues of Tg2576 mice which harbor the APPswe mutation [65]. As elaborated, PC12 cells when exposed to an inflammatory factor, LPS, upregulate CDK11 (p58) consequently leading to apoptosis [48].

AβPP-BP1, an adaptor protein involved in the cleavage of APP, is also a cell cycle protein that regulates mitotic transition from S to M phase. Overexpression of AβPP-BP1 may therefore push neurons into the S phase and cause DNA replication and expression of cell cycle markers like cdc2 or cyclin B [66].

APP is known to be phosphorylated at threonine residue Thr668 in the intracellular domain by several kinases including CDK5, c-Jun-terminal kinase 3 (JNK 3), and GSK3 β [67]. The growth promoting activity of APP is mediated by the ability of soluble APPα to down regulate CDK5 and inhibit tau phosphorylation [68]. Elevated levels of p25 relative to p35 cause dysregulation of CDK5 activity that lead to neuroinflammation and neurodegeneration [69].

Importantly, tau reduction prevents major Aβ-dependent cognitive deficits in hAPP mice [70]. On the other hand, APP reduction is associated with impaired neurite outgrowth and neuronal viability *in vitro* and synaptic activity *in vivo* [71,72]. APP undergoes rapid anterograde transport and is targeted to the synaptic sites [67], where the levels of secreted APP coincide with synaptogenesis [72,73] and is connected to toxic oligomeric forms of Aβ [74]. Thus, in our previous study we showed that elevated CDK11 expression in cellular processes may have an effect on APP, perhaps promoting cellular death [27].

Other critical associations of CDK11 and APP synaptic activity may be associated with reports showing CDK11 regulates microtubule stabilization in a Ran GTP (for RAs related nuclear protein) manner during spindle formation [34]. The Ran family further regulates nucleocytoplasmic transport [75].

The inappropriate localization of nuclear proteins in the cytoplasm of neurons in AD may lead us to suspect a dysfunction in the nucleoplasmatic transport mechanism of proteins, importins and congruently the engine that enables proteins to be imported in and out of the nuclei, the GTPase RAN.

In hippocampal neurons from AD patients, importin α is abnormally located in Hirano bodies [76] indicating impairment of transport. CDK11 localizes to spindle microtubules (MT) and centrosomes, there it may bind to MT through an inter-reaction with its substrate (not known). Moreover, we may hypothesize that CDK11 released from importins by RAN GTP-ase around chromosomes may form a soluble gradient of active kinase congruent with free NLS protein gradient. In the absence of CDK11, MT are shorter, whereas spindle assembly takes a longer time to organize [34]. It may further indicate a CDK11 non- amyloid β function, in which microtubule impairment, i.e. transport underlies the loss of neuronal connectivity and the basis of cognitive loss in AD. Cash et al. [77] showed that MT impairment in AD is not related to tau abnormalities. Concurrent with these findings, CDK11 in human brain is not co-localized to tangles or plaques suggesting again its role in MT and APP processing [27].

Based on new findings that cell cycle regulators of the metaphase-anaphase transition, such as cohesion proteins, have a role other than tethering sister chromatids and centromeres together in postmitotic neurons, and that Cdh-1/APC (anaphase promoting factor), a known E3 ubiquitin ligase known for its fundamental role in cell proliferation is a survival factor in neurons [78-80] we postulate that CDK11 is impiously not only primarily connected to cohesion dynamics [38,81], microtubule stabilization, centrosome dependent spindle assembly [34] and spindle assembly checkpoint control (SAC) but that CDK11 may have a role in active maintenance of the quiescent status the neuron probably through its role in RNA processing, in the regulation of transcription and in pre-mRNA splicing [82,83]. Ectopic expression of CDK11 in late phases of the AD disease and APPwt and APPswe type M17 cells may show some regulatory networks involving a new role of APP, as a dependence receptor that functions as a molecular switch in synaptic element interdependence on various trophic factors [84]. Our results strengthen the notion that Alzheimer's disease is not based on the toxic effects of Aβ [22] but on imbalanced signal transduction [64,65,84,85] that mediate synaptic maintenance vs. synaptic re-organization, mediated at least by APP.

Given the notion that CDK11 needs to be present in the nucleus of neuronal cells [28], the increased levels of CDK11 we observed in the cytoplasm in neurons may correlate to failed attempts of these neurons to maintain a differentiated or quiescent state.

Does CDK11 have a secondary role in post mitotic neurons in the case of microtubule integrity, as we see ectopic accumulation of CDK11 in cellular processes? One answer could come from the M17 cells showing that CDK11 in APPwt and APPswe mutant cells is concentrated in nuclei, not in the cytoplasm as seen in our AD cases [27]. Because insignificant changes in expression of CDK11 are found between APPwt and APPswe mutant phenotype, it suggests the changes in the AD brain are likely linked to APP signal transduction pathways [84,85].

Taken together with the finding that Aβ25-35, applied in a manner that does not cause cell death, resulted in increased CDK11 in a cell model, suggests there is an interplay between APP overexpression, APP processing, and cellular growth. Thus, the results of the present study showing elevated CDK11 expression in cellular processes may have an effect on APP perhaps promoting cellular death.

Results from the *in vitro* studies using M17 cells suggest a new role of CDK11 in APP signal transduction processing as a dependence receptor. Using M17 cells as a model, expression levels of CDK11 were increased in the APPwt and APPswe mutant phenotype compared to empty vector as control. The finding of increased expression of CDK11 in cellular processes within the brain of AD cases may indicate that CDK11 is linked to APP signal transduction processing in neuronal synapses. A number of papers have proposed alternative roles for APP in AD pathogenesis in which the Aβ fibril formation is not the sole factor of neurodegeneration in AD [5,8,64,84,85].

These data, and the fact that in AD the neurons that display CDK11 in the cytoplasm remain viable, suggest that CDK11 may play a vital role in cell cycle re-entry in AD neurons in an APP-dependent manner.

Conclusion

The inflammation hypothesis proposed by Krstic and Knuesel [8] and others [6,86-90] come about from the findings that genetic etiology of FAD, such as mutations and their polymorphisms, in the APP and gamma secretase showed no correlation to SAD. In SAD the APOE 4 gene and genetic experiments found polymorphisms in genes that regulate innate immunity and inflammation are implicated as high risk factors for AD [91,92].

Inflammation mediators and the innate immune system in the brain are etiologically linked to AD. In a review laid out by Krstic and Knuesel [8] results are given in a line with the two hit hypothesis first proposed by Zhu et al. [93], updated by Zhu et al. [94] and Fiebich et al. [95]. Krstic et al. [5] showed that when animals where prenatally challenged by Poly (I:C) (polyribocytidilic acid) an accelerated deposition of aggregated proteins in brain of aged mice where found. When these mice where challenged later or the second hit, in adulthood, they found that mice had strikingly similarities and changes in the brain as do AD patients.

These reports show a link of inflammation, to oxidative stress, cell cycle re-entry and mitochondrial impairment (Figure 2).

Reactivation of the cell cycle, including DNA replication might play a major role in AD. This research will in a broad sense show us more precisely the specificity of the cell death trigger in AD, as all neuronal cells that enter the cell cycle, die. So, in regard to CDK11 we may offer an answer: is neurodegeneration a result of imbalance in physiological signaling events such as those that mediate synaptic maintenance and synaptic re-organization (APP, plus analogues what we have in neoplasia) or, as more commonly suggested, the result of nonspecific toxic effect of peptide or protein aggregate? Our work and that of others show that evidence on both sides exists. CDK11 p58 and p46 are implicated in apoptosis. Also, it is a well-established fact that key features of the Alzheimer's phenotype, at least in the standard transgenic mouse model, depend on the caspase cleavage site within APP and this trigger is critically dependent on Aβ, suggesting that the APP caspase site may lie downstream from Aβ accumulation. CDK11 p110 is expressed in processes of the AD brain and in M17 cells (swe mut phenotype). Also, we have found that Aβ given to M17 cells increases expression of CDK11, p110. Further experiment will tell us if CDK11 p58 and p46 are also connected to APP and how this implicates CDK-APP in neuronal cell death.

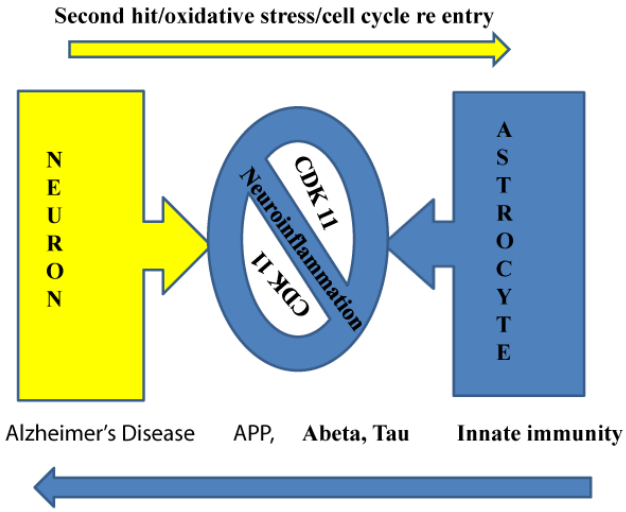

Figure 2: The complexity of the second hit-a possible role of CDK's in inflammation.

CDK11 may play a vital role in cell cycle re-entry in AD neurons after/or as an inflammation insult in an APP-dependent manner, thus presenting an intriguing novel function of the APP signaling pathway in AD.

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