Review

Aberrant Neuronal Cell Cycle Re-Entry: The Pathological Confluence of Alzheimer's Disease and Brain Insulin Resistance, and Its Relation to Cancer

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Abstract. Aberrant neuronal cell cycle re-entry (CCR) is a phenomenon that precedes and may mechanistically lead to a majority of the neuronal loss observed in Alzheimer's disease (AD). Recent developments concerning the regulation of aberrant neuronal CCR in AD suggest that there are potential intracellular signaling "hotspots" in AD, cancer, and brain insulin resistance, the latter of which is characteristically associated with AD. Critically, these common signaling nodes across different human diseases may represent currently untapped therapeutic opportunities for AD. Specifically, repurposing of existing US Food and Drug Administration-approved pharmacological agents, including experimental therapeutics that target the cell cycle in cancer, may be an innovative avenue for future AD-directed drug discovery and development. In this review we discuss overlapping aspects of AD, cancer, and brain insulin resistance from the perspective of neuronal CCR, and consider strategies to exploit them for prevention or therapeutic intervention of AD.

Keywords: Alzheimer's disease, amyloid, cell cycle re-entry, tau

Alzheimer's disease (AD) is the sixth leading cause of death in the US, yet it may actually represent the third overall cause of death in the elderly [1]. AD causes irreparable neurodegeneration that destroys memory and cognition. Although extracellular amyloid plaques, intraneuronal neurofibrillary tangles, and significant synaptic and neuronal loss in the brain define AD [2], the pathogenesis of AD is complex and its dysfunctional metabolic pathways continue to be mapped [3, 4]. Two such seminal pathways are

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those for aberrant neuronal cell cycle re-entry (CCR) [5] and reduced insulin signaling [6], which together form the focus of this review.

NEURONAL DEATH IN AD

In the brain regions affected by AD, neuronal death is a massive, irreversible pathological feature. Indeed, up to 65% of hippocampal CA1 neurons and 90% of the neurons in select neocortical areas degenerate and die in typical AD cases [7, 8]. There is substantial evidence that most of the neuron death in AD is prompted by aberrant cell cycle re-entry (CCR), which is typified by the re-expression of signaling effectors commonly associated with cell cycle progression and cell proliferation [9, 10]. While neurons generally are considered post-mitotic, and permanently arrested in the G0 phase of the cell cycle (Fig. 1), in vulnerable brain regions, roughly 10% of the neurons exhibit biochemical and histological evidence of CCR beginning in presymptomatic AD stages. However, the neurons never complete cytokinesis and their gradual disappearance from the brain parallels a commensurate net loss of neurons in the same regions [10–12].

The precise signaling mechanisms propelling this neuronal loss are not well defined, although our deeper understanding of the molecular pathogenesis of an array of human diseases, including AD, indicates that many seemingly unrelated pathologies share common aberrant pathways. For example, IκB kinase (IKK) and c-Jun N-Terminal kinase (JNK) have been linked to cancer, diabetes, and inflammation [13–15]; serine/threonine glycogen synthase kinase 3 (GSK3) has been implicated in bipolar disease, AD, type II diabetes, cardiac hypertrophy, and cancer [16–18]; and both the PI3 kinase-mTOR and Erk1/2 pathways have been linked to cancer, type II diabetes, and AD [19–23]. Likewise, insulin resistance and reduced glucose uptake are pathological phenomena that link diabetes with AD [24]. Thus, signaling convergence points among seemingly unrelated diseases may provide opportunities for accelerated approaches to prevent and treat AD.

NEURONAL CCR AND AD

Proliferating eukaryotic cells have readily detectable mitotic (M) and DNA synthesis (S) phases separated by two gap (G1 and G2) phases.
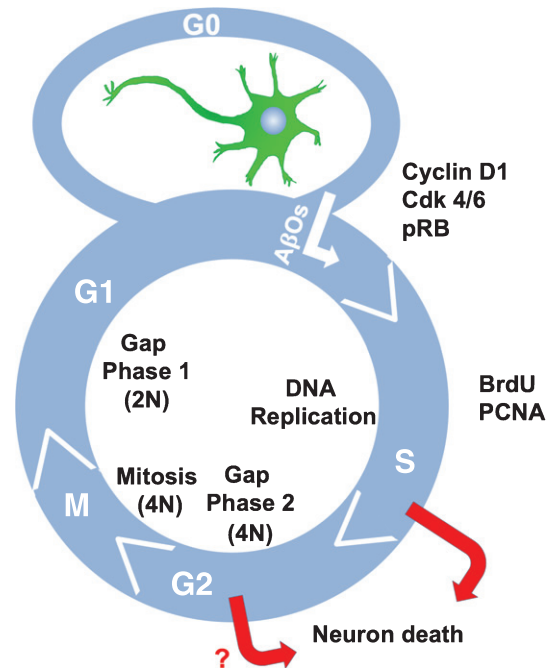

Fig. 1. Cell cycle re-entry in AD neurons. AβO exposure induces neurons to exit G0 and proceed through the cell cycle at least as far as S phase. Markers of AβO-mediated CCR include Cyclin D1, Cdk4/6, phosphorylated retinoblastoma (pRB), BrdU incorporation, and PCNA expression. Neurons never complete cytokinesis, but instead eventually die. N refers to the haploid DNA content in the cell.

In contrast, terminally differentiated neurons have permanently exited the cell cycle and thus reside as mitotically quiescent cells in a phase called G0 (Fig. 1). Classically, it was thought that exposure of neurons to various stresses can cause their re-entry back into G1, although recent results surprisingly indicate that some neural stem cells in *Drosophila* exit the cell cycle from G2 in response to nutritional cues using the insulin signaling pathway [25].

In the brains of individuals with AD, re-expression of several cell cycle or proliferation-associated proteins is indicative of neuronal exit from G0. Examples of such cell cycle proteins include cyclins B, D, and E [26–28], cyclin-dependent kinases 1 and 4 (Cdk1 and Cdk4) [29, 30], PCNA [26, 31], Ki67 [27, 31], and Cdk inhibitors, such as p16 and p21 [32, 33]. Cell cycle-related protein overexpression has been observed in the brains of individuals with mild cognitive impairment, which is a clinical predecessor of AD, and in brain regions that experience substantial neuronal loss in AD [12]. DNA replication was also observed using fluorescence *in situ* hybridization of four different loci on three chromosomes.

In this study, DNA replication was detected in a significant fraction of neurons in the "at risk" regions of the brains of individuals with AD, but not in non-demented aged-matched controls [34]. Furthermore, in AD model mouse brains, abnormal increases in cell cycle markers and DNA replication have been detected in regions corresponding to sites where there is neuronal loss in humans with AD [35, 36]. These findings imply that aberrant neuronal CCR precedes neuronal loss in AD. Notably, there is growing evidence that several other neurodegenerative conditions, including stroke, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease, exhibit extensive neuronal CCR [37–40], suggesting that CCR is a common pathological feature of neurodegeneration.

AMYLOID-β OLIGOMERS AND TAU AS MEDIATORS OF NEURONAL CCR IN AD

Amyloid-β (Aβ) peptides and tau protein, which are the main components of the amyloid plaques and neurofibrillary tangles that respectively accumulate in AD brain, are considered to be central to AD pathogenesis [2]. Although poorly soluble amyloid plaques are hallmarks of AD, soluble Aβ oligomers (AβOs) correlate much better with cognitive impairment in AD and are early drivers of AD pathogenesis [41]. Aβ peptides are generated from amyloid-β protein precursor (AβPP) by sequential cleavage mediated by β- and γ-secretases. The Aβ peptides are variable in length, but those that end with a C-terminal valine ($A\beta_{40}$) or alanine ($A\beta_{42}$), and are typically 40 or 42 amino acids long, respectively, are among the principal Aβ species that increase over time in AD brain [2, 42]. Aβ peptides and aberrant neuronal CCR were first detected in the brains of an AD mouse model (R1.40) expressing Swedish mutant human *APP* [43]. However, direct genetic evidence that amyloidogenic cleavage of AβPP and subsequent Aβ peptide generation is required for CCR induction was provided by crossing R1.40 and Bace1 knockout mice. The resulting β-secretase-deficient, mutant *APP*-positive mice did not exhibit CCR [43]. Moreover, CCR was detected in R1.40 mouse brains long before deposition of the poorly soluble Aβ fibrils that populate plaques, suggesting that the trigger for neuronal CCR is soluble AβOs. Consistent with that notion is the observation that AβOs, but not monomeric or fibrillar Aβ, potently induce CCR in primary neurons *in vitro* [43]. All of these findings support the proposition that soluble AβOs are the inducer of aberrant neuronal CCR within the context of AD.

Several membrane receptors have been proposed to bind AβOs (reviewed in [44, 45]); however, only NMDA receptor (NMDAR) has been shown to be involved in AβO-induced CCR. In cultured mouse neurons, NMDAR antagonists or knock down of NMDAR subunit NR1 prevents AβO induced CCR [46]. Moreover, treatment of Tg2576 AD mice model with an NMDAR antagonist, memantine, prevented neuronal CCR in the mice brains [46]. Possible contribution of other receptors on AβO-induced neuronal CCR and subsequent cell death remains to be an intriguing question.

Significantly, almost all of the known adverse effects of AβOs depend on the presence of tau, which is the other protein most conspicuously associated with AD [3]. We found that AβO-induced neuronal CCR requires site-specific tau phosphorylation at Y18, S262, S409, and S416 (relative to the largest human CNS tau isoform), and that phosphorylation at those sites is dependent on Fyn, mTORC1, cAMP-regulated kinase A (PKA), and calcium-calmodulin-dependent kinase II (CaMKII), respectively [46–48] (Fig. 2). Additional tau phosphorylation sites and tau kinases that are required for neuronal CCR may also exist, but as yet have not been identified. While our findings firmly place tau in the AβO-mediated neuronal CCR pathway in AD (Fig. 2), the mechanism of this tau dependence is incompletely understood.

PARALLELS WITH CANCER BIOLOGY

The CCR observed in AD prompts comparison with the major proliferative pathways that are hyperactive in cancers [20, 23, 49], although the fate of cancer cells is significantly different than that of neurons. Whereas cancer cells entering the cell cycle evade cell death and continue to proliferate [50], in AD, neurons degenerate and die in a manner reminiscent of oncogene-induced cell death [34]. Studies have shown that aberrant activation of oncogenes, such as Ras, initially induce CCR in cancer, but eventually the DNA damage response becomes activated and cells are arrested in the cell cycle prior to mitosis, and eventually die via apoptotic or senescence pathways [51]. Similarly, ectopic expression of Ras and/or Myc in neurons triggers CCR, but in both cases neurons eventually degenerate
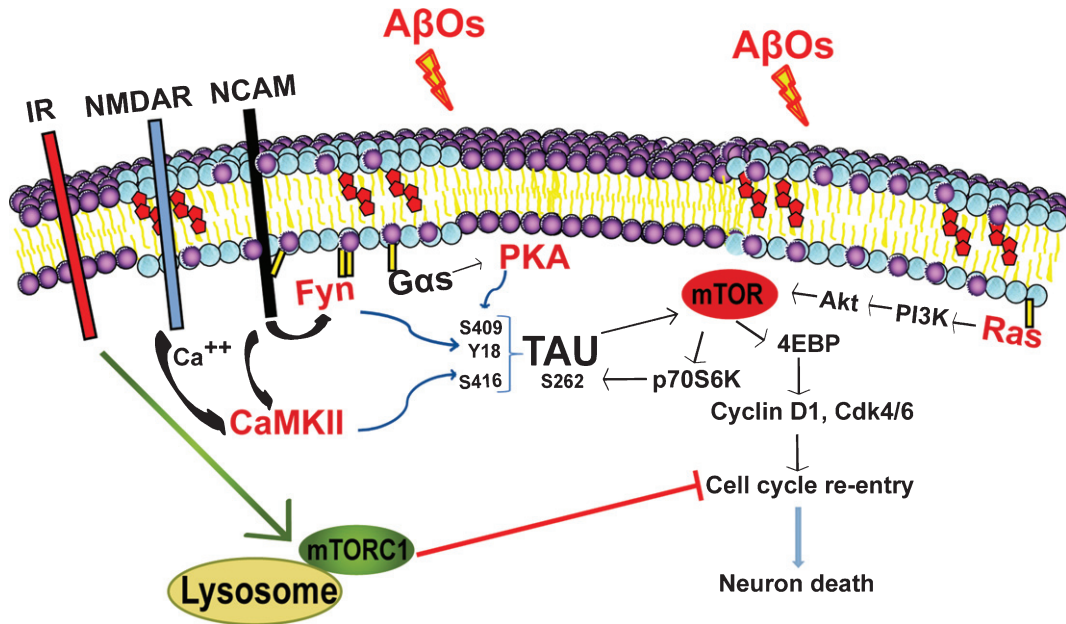
Fig. 2. AβOs trigger several parallel events that cumulatively induce cell cycle re-entry (CCR) in AD. While inhibiting insulin signaling, AβOs induce mTORC1 activation at the plasma membrane, which triggers neuronal CCR. AβO-induced tau phosphorylation at multiple sites is required for neuronal CCR. IR (insulin receptor), NCAM (neuronal cell adhesion molecule); all other abbreviations are defined in the main text.

without dividing, which resembles what is seen in the brains of individuals with AD [52, 53]. Significantly, Ras is overexpressed in the brains of AD patients [54, 55] and Ras activity has been shown to be required for AβO-induced CCR and subsequent death of differentiated neuroblastoma cells [49]. These data align with the intriguing hypothesis that neurons in AD patients undergo events similar to oncogene-induced cell cycle arrest, which eventually leads to neuron death, and suggest that Ras is a critical upstream regulator of AβO-induced neuronal CCR.

PI3K-AKT-mTOR

The PI3K-AKT-mTOR signaling pathway regulates the cell cycle and directly mediates cellular quiescence, proliferation, metabolism, motility, growth, and survival [56]. It also is one of the most frequently dysregulated pathways in human cancers [56]. Bhaskar et al. showed that the PI3K-Akt-mTOR pathway is also required for AβO-induced neuronal CCR and subsequent neurodegeneration. They demonstrated that AβO treatment activates Akt and mTOR, and that pharmacological inhibition of PI3K with wortmannin, of Akt with Akt inhibitor VIII, or of

mTOR with rapamycin prevents AβO-induced CCR [20].

ERK$_{1/2}$-MAPK

The Erk$_{1/2}$-MAPK circuit is hyperactive in almost one third of human cancers [57]. Overexpression and subcellular translocation of MAPKK and MAPK were detected in the brains of AD patients at the early stages, suggesting that MAPK pathway is active as an early feature of AD [58]. Intriguingly, the Erk$_{1/2}$ pathway has also been shown to be involved in AβO-induced neurotoxicity. Chong et al. [23] showed that the Erk$_{1/2}$ pathway mediates AβO-induced neuronal death. Specifically, exposure to low micromolar concentrations of AβOs induced cell death in rat organotypic hippocampal brain slices concomitantly with detection of phospho-activated ERK$_{1/2}$. Moreover, pharmacological inhibition of the ERK$_{1/2}$ signaling pathway with U0126 attenuated AβO-mediated neuronal toxicity, further supporting a role for ERK$_{1/2}$ in AβO-mediated effects on neurons. Significantly, Ras proteins are upstream of both the ERK$_{1/2}$ and PI3K-Akt-mTOR pathways [59]. Both genetic and chemical inhibition of Ras (i.e., salirasib) prevents neuronal CCR _in vitro_ [49] suggesting

that Ras is a nodal mediator of AβO-induced CCR.

Cell cycle and proliferation-associated proteins

Other cancer-associated proteins that may be involved in AβO-induced CCR and subsequent cell death include the cyclins, B, D and E; the protein kinases, Cdk 1, 2, 4, and 5 [26–28, 60]; and the dual specificity phosphatases, CDC25A, B and C, which dephosphorylate and active Cdks [60, 61]. Cdk4 and the closely related Cdk6 are key kinases that trigger CCR, whereas Cdk2 is responsible for S phase entry and progression and Cdk1 regulates cell entry into mitosis. The importance of some of these proteins has been documented in pharmacological and shRNA-based studies targeting Cdk4/6 or Cdk2, in which inhibition prevents AβO-induced CCR and neurotoxicity in human induced pluripotent stem (iPS) cell-derived neurons and primary mouse cortical neurons [23, 62, 63].

NEURONAL CCR AND BRAIN INSULIN RESISTANCE

The Rotterdam Study provided compelling epidemiological evidence for a correlation between diabetes and AD, but could not establish whether the two distinctive pathological conditions are mechanistically linked [64, 65]. While type II diabetes is a strong risk factor for AD, brain insulin resistance (BIR) is common among AD patients even in the absence of systemic diabetes, prompting the idea that AD is a brain-specific, or type 3 form of diabetes [6, 24]. Recent evidence strongly suggests that BIR, as defined by the failure of brain cells to respond to insulin, leads to compromised synaptic, metabolic, and immune response functions, but the mechanisms by which BIR leads to synaptic dysfunction and neuron death have been difficult to unravel [66]. Moreover, whether BIR reflects neurons being unable to respond properly to insulin due to deficiencies in insulin receptor expression or the failure of systemic insulin to infiltrate the brain is still under discussion [67]. Nonetheless, postmortem studies of AD patient brains have revealed dramatically reduced expression of receptors for insulin and insulin-like growth factor-1 (IGF1) in the hippocampus and hypothalamus [6], and BIR also impacts the brain independently of those receptors. For example, BIR alters membrane trafficking of the AMPA glutamate receptor subunit, GluA1, in the hypothalamus,

thereby hindering synaptic plasticity in that brain region, and impairs hippocampal-dependent memory as well. [68]. In addition, a recent study links BIR and AD through the use of the diabetes drug, liraglutide. Specifically, liraglutide, blocks AD phenotypes in mouse and non-human primate model systems [69].

Despite persistent mysteries about the diabetes-AD connection, recently reported evidence indicates that AβOs are responsible for two relevant phenomena: rapid downregulation of insulin receptors from the neuronal cell surface [70] and AβO-mediated activation of a signaling network that stimulates neuronal CCR [48]. The latter mechanism involves AβO-induced activation of mTORC1 at the plasma membrane, but not at lysosomes, whereas insulin preferentially activates lysosomal mTORC1 [48]. We have shown that AβO-induced CCR is functionally connected to insulin resistance as the process is blocked by rescuing lysosomal mTORC1 activity through genetic manipulations that bypass normal insulin signaling or by modulating insulin availability in primary neuron cultures [48]. The mechanism by which AβO-mediated dysregulation of mTORC1 leads to neuronal CCR remains to be fully understood, but interestingly, insulin and mTORC1 have also been shown to regulate mitochondrial biogenesis and metabolism [71, 72], and mitochondrial dysfunction has been linked to BIR [73].

In this line, we have recently shown that activation of lysosomal mTORC1 by insulin regulates mitochondrial activity not only in mouse and human neurons in culture, but also in the live mouse brain [73]. Strikingly, we also found that activation of lysosomal mTORC1 regulates mitochondrial DNA (mtDNA) synthesis. AβOs, which activate mTORC1 at the plasma membrane, but not at lysosomes, blocks this nutrient-induced mitochondrial activity (NiMA) pathway by a mechanism dependent on tau, and deregulates mtDNA replication [73]. Collectively, these results suggest that lysosomal mTORC1 couples nutrient availability to mtDNA replication and mitochondrial activity, thus functionally connecting these two organelles. As alterations in neuronal mtDNA maintenance account for brain energy metabolism deficiencies in AD [74, 75], the NiMA pathway might represent a mechanistic link connecting metabolic alterations, such as Type II diabetes (insulin resistance), to mtDNA maintenance and dysfunction in AD.

Thus, BIR combined with the AβO-mediated activation of mTORC1 at the plasma membrane converge on mitochondria affecting their activity [76]. As

insulin and mTORC1 have been shown to regulate mitochondrial biogenesis and metabolism [71, 72], and mitochondrial dysfunction has also been linked to BIR [73, 76], we speculate that BIR combined with the AβO-mediated activation of mTORC1 at the plasma membrane alters neuronal energy metabolism by a mechanism that directly disrupts mitochondrial functions and thereby contributes indirectly to neuronal CCR. In fact, nucleotide biosynthesis necessary for DNA replication and CCR requires the coordinate action of mitochondria and mTOR [77, 78]. While the role of nucleotide biosynthetic pathways has not been comprehensively addressed in the context of either AD or BIR, these observations open the possibility that signaling pathways acting on lysosomal mTORC1 (i.e., insulin) directly regulate mitochondrial metabolic pathways involved in controlling cell cycle events. In this scenario, AβO-mediated activation of mTORC1 at the PM in neurons might disrupt proper nutrient signaling and mitochondrial metabolism. This process may also be relevant under other metabolic conditions. TNFα, a known proinflammatory cytokine, blocks insulin signaling through activation of JNK [79] and AβOs trigger the release of TNFα from microglia present in primary neuron cultures [80, 81]. In neurons, activation of TNFα receptors stimulate JNK-mediated phosphorylation of insulin receptor kinase substrate-1 (IRS-1), which inhibits IRS-1 activity and downregulates insulin receptor mediated activation of PI3K and Akt [80].

PHARMACOLOGICAL TARGETING OF NEURONAL CCR IN AD

The failure rate of clinical trials for AD during the past decade has been remarkable, particularly when one considers the preclinical evidence that formed the foundation for these trials [82]. A regrettable consequence has been the abandonment of efforts by several major pharmaceutical companies to develop new treatments for AD. It has been argued, for example, that broad knowledge gaps and poor clinical trial designs are responsible for the failures of γ-secretase inhibitors [83], and that cell-based and animal models of AD do not accurately recapitulate key features of *bona fide* AD in humans [84, 85]. Regardless of why so many potential AD drugs have failed, the fact remains that the last such drug to gain Food and Drug Administration (FDA) approval is memantine, in 2003, and the world still awaits regulatory approval

of any drug that actually prevents or slows symptom progression. It is notable that nearly all experimental drug development for AD has been focused on reducing the amyloid burden in brain, though some recent efforts have targeted tau. With these considerations in mind, alternative drug discovery and development strategies, including those directed at AβO-induced neuronal CCR, seem reasonable and timely.

In the past decade and a half, there has been a growing interest in formally investigating the repurposing of drugs that have already been approved by regulatory agencies, such as the FDA or the European Medicines Agency (EMA), for possible use against neurodegenerative diseases, such as AD [86–88]. Likewise, rescuing of experimental therapeutics that have failed their primary disease indication provides an additional pool of compounds for evaluation. One obvious benefit of the repurposing approach is the pre-existing body of knowledge about the safety and pharmacokinetics of approved compounds. One large class of drugs that might be repositioned for use against AD would be those currently used for solid and hematological malignancies [89, 90]. Other drugs that might be repurposed for AD prevention or therapy include those developed to treat diabetes.

Cancer drugs and CCR in AD

Most anti-cancer drugs have the capacity to block cell proliferation and, thus, would likely inhibit neuronal CCR. FDA-approved cytotoxic cancer chemotherapeutics with good (e.g., carmustine) or poor (e.g., paclitaxel) brain penetrance have been shown to have some potential positive effects, at least in existing preclinical AD models [89].

As has been already mentioned, newer, more targeted, anti-cancer drugs that inhibit PI3K, Akt, and mTOR have also been shown to prevent AβO-induced neuronal CCR (Fig. 3A) [20]. The investigational PI3K/mTOR inhibitor dactolisib has been observed to protect mice against Aβ$_{42}$-induced neurotoxicity and memory loss [91]. Similarly, pharmacological and genetic inhibition of Ras prevented AβO-induced CCR and subsequent cell death *in vitro* [49]. Finally, pharmacological and genetic inhibitors of Cdk2, Cdk4, and Cdk6 reduced AβO-induced CCR and neurotoxicity in human iPS-derived neurons and primary mouse cortical neurons [62, 63].

More than 35 tyrosine kinase inhibitors have been approved by the FDA or EMA for cancer and several
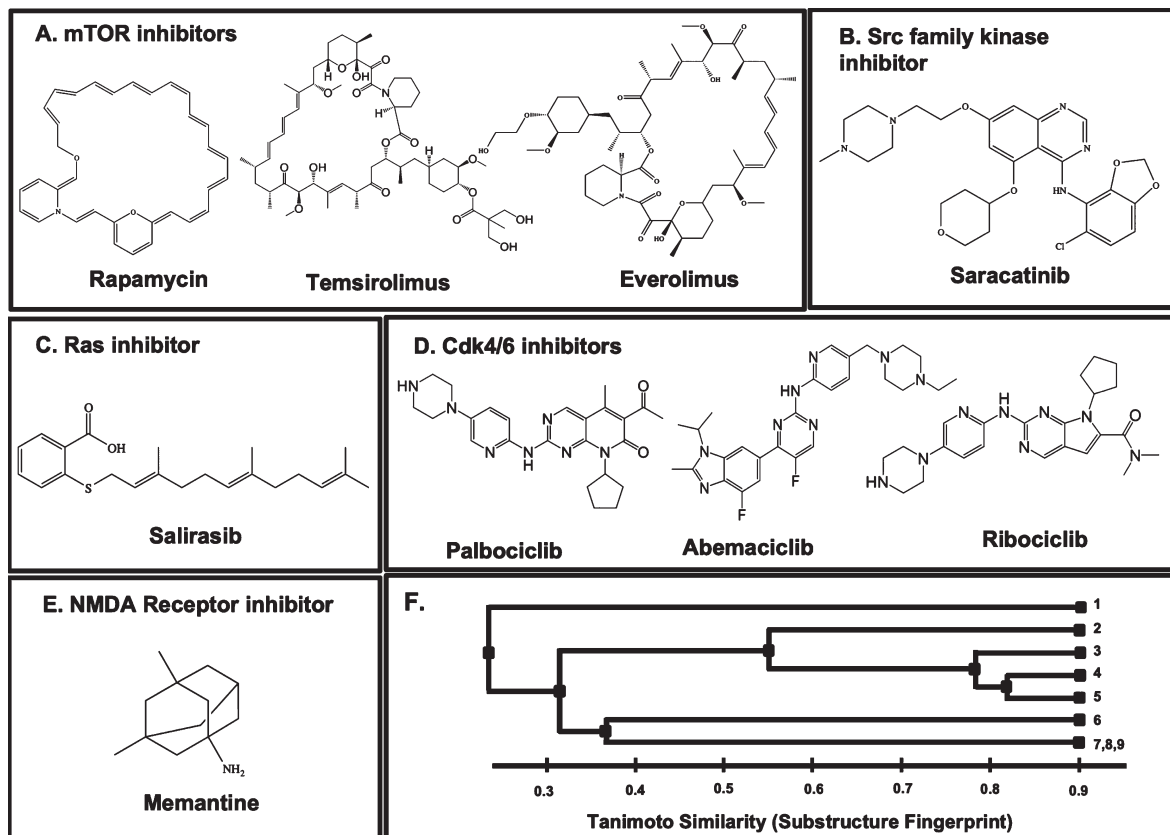
Fig. 3. Chemical structures of FDA-approved drugs that potentially can be re-purposed to target neuronal cell cycle re-entry in AD. A) Inhibitors of mTOR. B) Inhibitor of Src family kinases. C) Inhibitor of Ras. D) Inhibitors of Cdk4/6. E) Inhibitor of NMDA receptor. F) Tanimoto analysis of the two-dimensional similarity of the chemical structures of potential regulators of CCR. 1) Memantine. 2) Saracatinib. 3) Abemaciclib. 4) Palbociclib. 5) Ribociclib. 6) Salirasib. 7) Rapamycin. 8) Temsirolimus. 9) Everolimus. Tanimoto analysis was performed with PubChem software (https://pubchem.ncbi.nlm.nih.gov/assay/assay.cgi?p=clustering).

have the potential to inhibit neuronal CCR. The investigational tyrosine kinase inhibitor saracatinib (Fig. 3B) is known to be a potent inhibitor of the tyrosine kinase Fyn, which is expressed in the brain, phosphorylates tau, and mediates Aβ toxicity [92], including neuronal CCR [49]. In an initial repurposing Phase 1b clinical trial, saracatinib was found to be generally safe and well tolerated [92]. The National Center for Advancing Translational Sciences just completed a multicenter Phase IIa clinical trial with 159 participants called CONNECT (ClinicalTrials.gov Identifier: NCT02167256) to evaluate the clinical potential of saracatinib for AD. There is considerable interest in the results of this clinical trial. While CCR was not an evaluated endpoint, mechanistically it is reasonable to speculate that saracatinib can block neuronal CCR. Similarly, some of the tyrosine kinase inhibitors also have been investigated for use in diabetes [93] and some well-established

agents used for diabetes, such as metformin, are being examined for their potential use in cancer [94].

Rapamycin, which inspired approval by the FDA and EMA of the anti-cancer mTOR inhibitors, temsirolimus and everolimus (Fig. 3A), have been shown to reduce Aβ levels and cognitive loss in mouse AD models [95]. The authors linked the delay or inhibition of AD-like symptoms to an increase in autophagy but they did not exclude the possibility that inhibition of CCR was also involved.

The Ras inhibitor, salirasib (Fig. 3C), has been shown to inhibit AβO-induced CCR *in vitro* [49]. Salirasib passes through the blood-brain barrier and is neuroprotective in mouse closed head injury models [96, 97]. Furthermore, targeting Ras has shown to diminish excitotoxic stimulus-triggered brain damage. Salirasib has shown low efficacy against lung cancer in Phase II trial [98], but it has

potential to suppress AD pathogenesis by inhibiting AβO-induced CCR.

There have been reports of neuroprotective effects in Aβ-mediated *in vitro* models of Cdk4/6 inhibitors, including palbociclib, which is approved by the FDA and EMA [62, 63]. Considering the increasing numbers of next generation Cdk4/6 inhibitors that are emerging for use in cancer, including abemaciclib and ribociclib (Fig. 3D), and the apparent complexity of their actions, there may be an opportunity to exploit these agents for use in the treatment of AD [99].

Diabetes drugs and CCR in AD

Several diabetes drugs, including insulin itself, have been repurposed to treat BIR in AD [100, 101]. Our recent findings connect the insulin signaling to AβO-induced CCR as an important component of AD pathology. AβO signaling highjacks mTORC1 to the PM to trigger CCR, while the insulin pathway is diminished due to BIR [48]. Our findings suggest that targeting BIR with diabetes drugs, such as GLP-1 agonists, metformin, or insulin [100, 101], may inhibit CCR, which precedes most of the neuronal death in AD.

Other drugs targeting CCR

We recently showed that NMDA receptor antagonist, memantine, prevents AβO-induced CCR both *in vitro* and *in vivo* [46]. Memantine (Fig.3E) is an FDA-approved drug for modest symptom relief in moderate to severe AD, but our findings suggest that memantine can be a disease modifying drug to forestall AD progression if administered beginning at preysmptomatic stages of the disease. A chemoinformatics analysis of the chemical structures of these inhibitors of CCR reveals considerable diversity in their chemical fingerprint as measure by Tanimoto score (Fig. 3F). These results suggest multiple other chemotypes in chemical space could be available for exploitation as possible agents for use against AD and we believe this is worthy of further investigation.

CONCLUSIONS

The emerging findings about intracellular signaling of AβO-mediated neuronal CCR reveals convergence points among AD, cancer and BIR. This signaling pathway commonality that connects different diseases raises the possibility that

pharmacological tools developed to combat cancer or diabetes can be re-purposed for AD prevention or therapy by targeting AβO-mediated signaling, including that which leads to neuronal CCR.

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